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INTERNATIONAL LYMPHOMA
RADIATION ONCOLOGY GROUP

WELCOME

Third ESTRO – ILROG Course on Haematological Malignancies

Utrecht, the Netherlands, 5-8 September, 2018

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www.ilrog.com

Initiated 2010, Hodgkin Symposium in Cologne
First Steering Committee Meeting 2011 in Copenhagen

Goals:

- Advance optimal and evidence based care of lymphoma patients
- Improve the awareness of oncologists and patients of radiation benefits and reduce inappropriate scare from modern radiotherapy
- Improve the quality of radiotherapy for lymphoma patients
  - Guidelines, implementing modern radiation principles and techniques
  - Education of colleagues and trainees
  - Design and collaborate in research

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Multidisciplinary course

- Faculty medical oncologist/hematologists:
  - Professor Andreas Engert, University of Cologne, Chairman of the German Hodgkin Study Group, Honorary ILROG Steering Committee member
  - Dr. Andrew Davies, Cancer Research UK Senior Lecturer in Medical Oncology and Honorary Consultant, Southampton General Hospital

- Guest speaker, physicist:
  - Dr. Marianne Aznar, Associate Professor of Medical Physics, Christie Hospital, University of Manchester, Head of ILROG Physics Group

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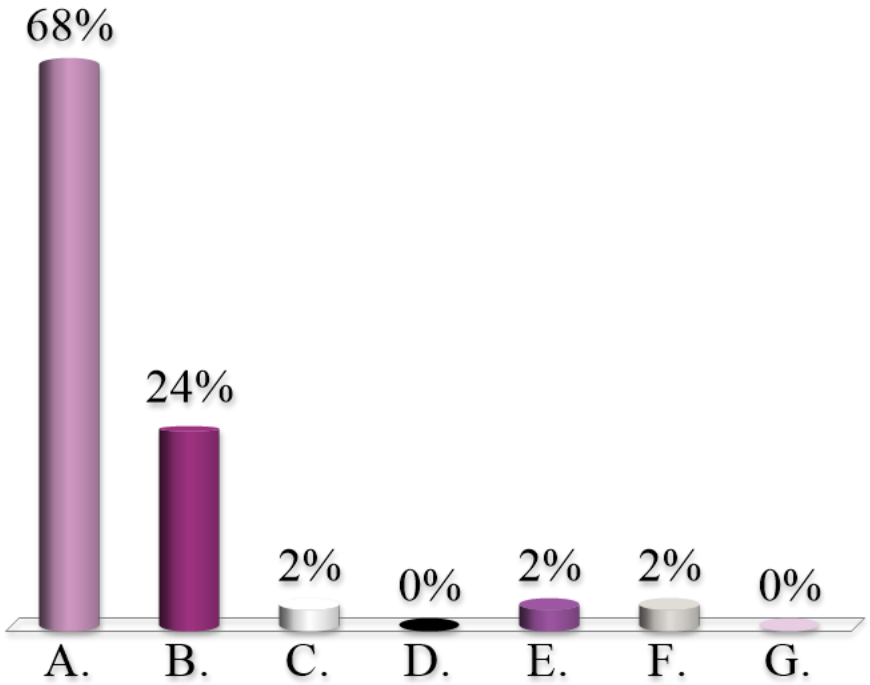
From ESTRO

- Miika Palmu, project manager
- Dr. Berardino De Bari, Radiation Oncologist, Centre Hospitalier Régional Universitaire "Jean Minjoz", Université de Bourgogne - Franche Comté, contouring administrator, FALCON

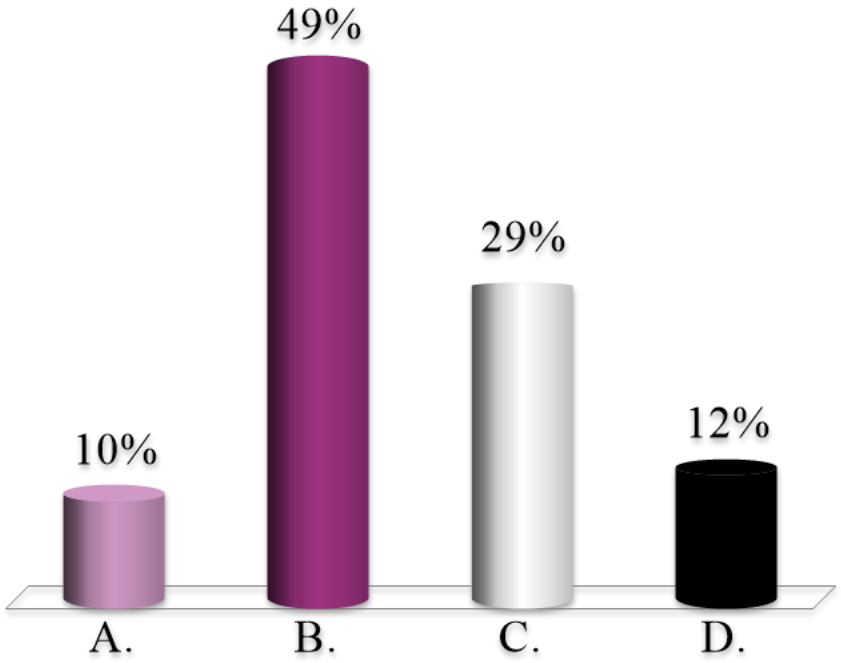
What is your specialty?

A. Radiation Oncologist
B. Clinical Oncologist
C. Medical Oncologist
D. Hematologist
E. Radiologist
F. Nuclear Medicine Specialist
G. Other



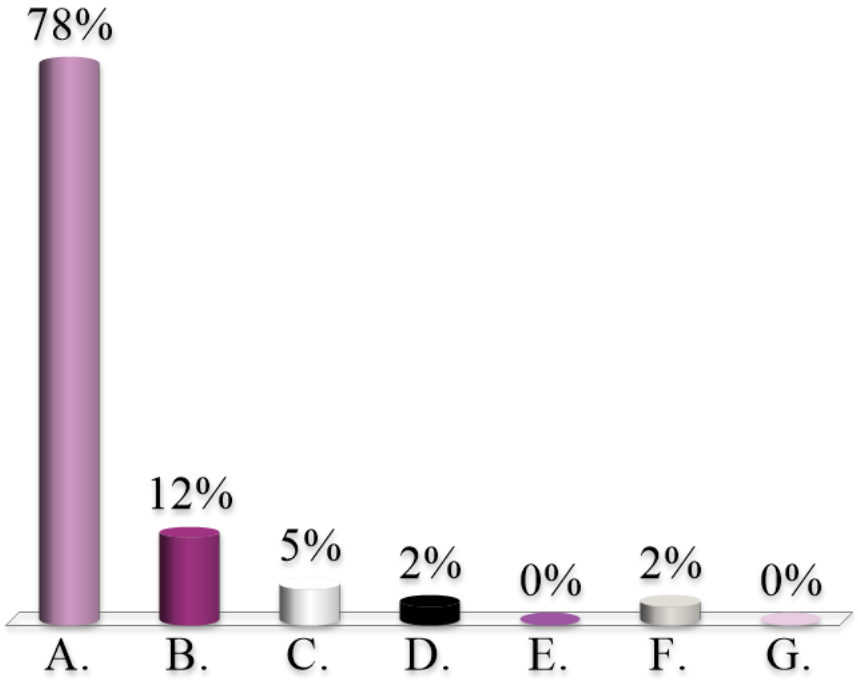
How long in practice?

A. Trainee
B. < 10 years after specialist recognition
C. 10 – 20 years after specialist recognition
D. > 20 years after specialist recognition



Where do you practice?

A. Europe
B. Asia
C. Middle East
D. North America
E. South America
F. Australia/New Zealand
G. Africa



For those who have brought cases for the case discussion sessions

- We will include as many as possible, but may not be able to include all
- 5 min. presentation of case, discussion with faculty and participants
- Contact Lena
- Bring case on USB stick

Join as Member! (Free)

Go to ilrog.com (membership tab) and register

Or write to shuttleworth@ilrog.com

Apply for ILROG Council Membership?

Special Interest in more involvement – Check the site or write to us

MODERN RADIOTHERAPY FOR HEMATOLOGIC MALIGNANCIES

February 16-17, 2019 • University of California, San Diego

CALL FOR ABSTRACTS OPENS LATE JUNE 2018.

REGISTRATION AND HOUSING OPEN LATE MID-AUGUST 2018.

www.astro.org/hematologic

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ILROG Educational Symposium

Radiotherapy in Modern Lymphoma Management

April 6-7 2019, Cancer Institute Hospital, Tokyo, JAPAN




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JROSG
Japanese Radiation Oncology Study Group

The Cancer Institute Hospital
Japanese Foundation for Cancer Research

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

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

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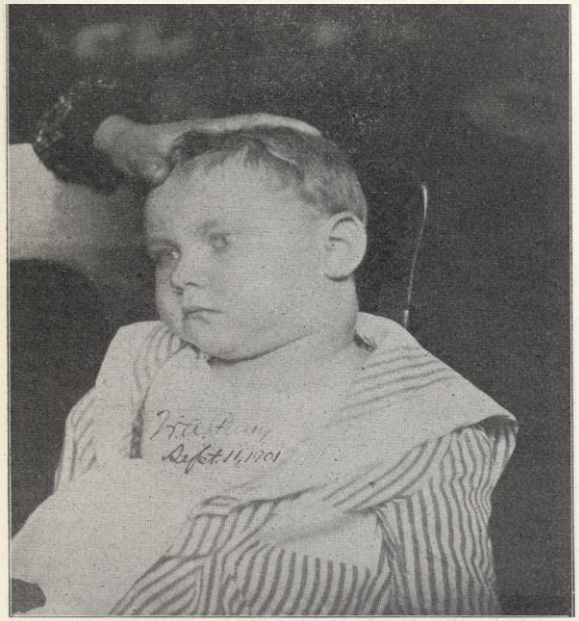

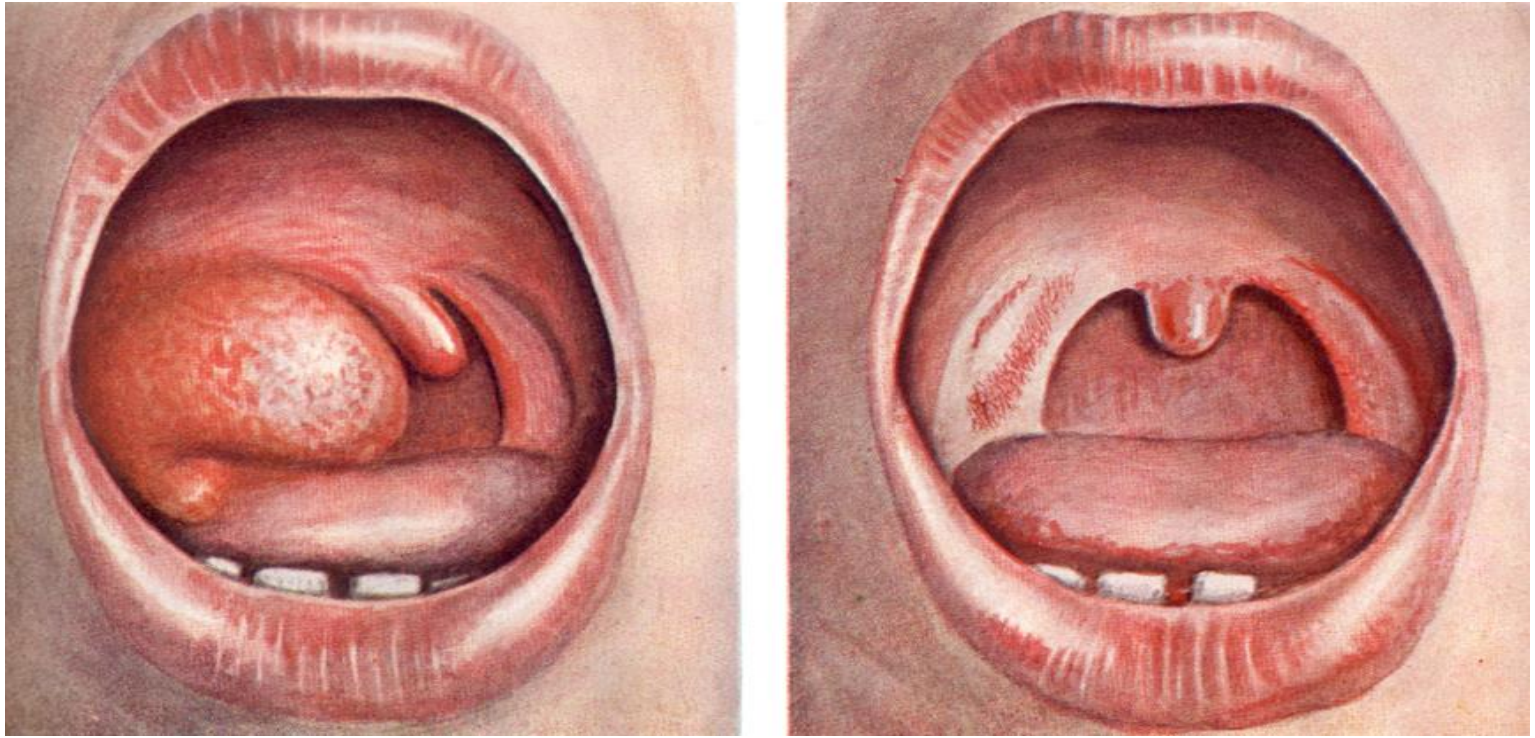

Lymphosarcoma of right tonsil, before treatment November 1916, alive and free of symptoms April 1930

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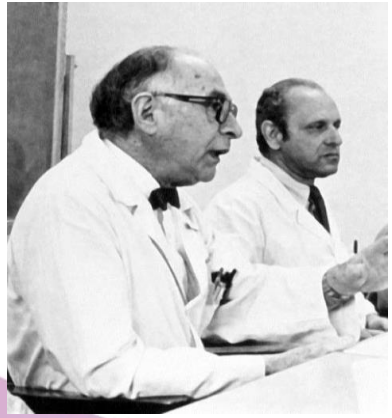
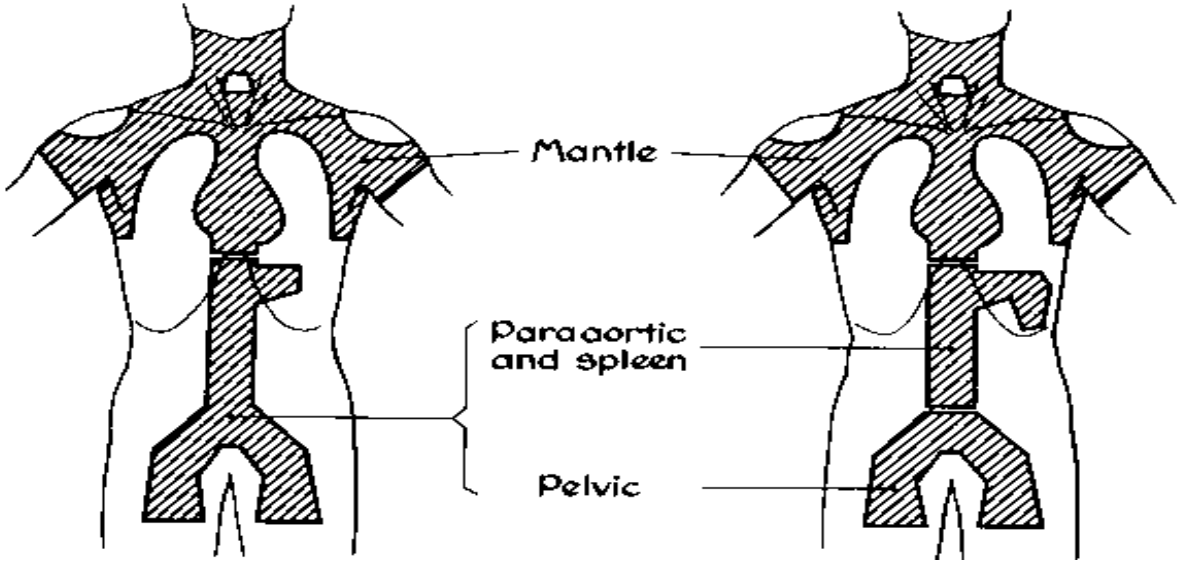
Prophylactic irradiation of clinically uninvolved regions → extended field RT





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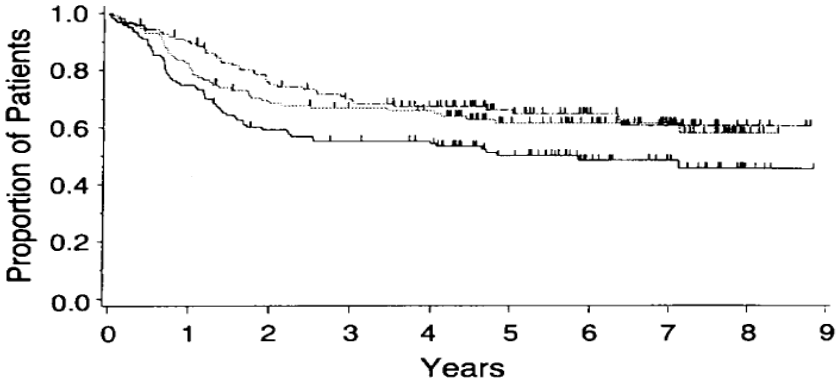
Effective chemotherapy was developed

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.

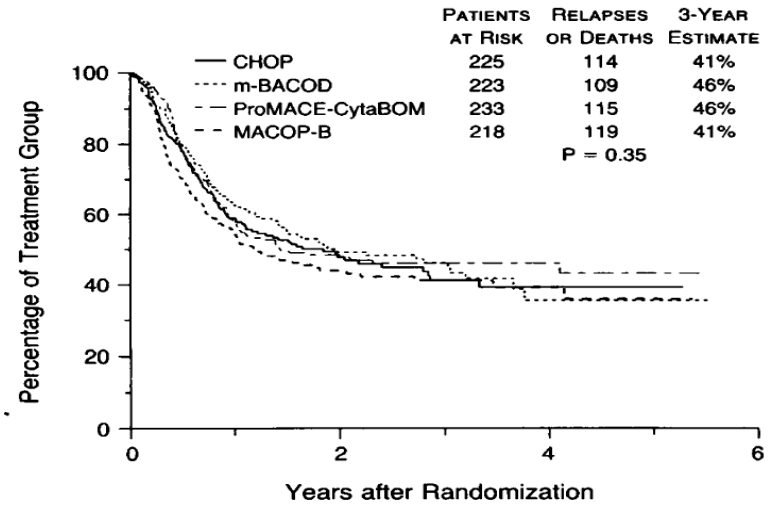


Figure 1. Time to Treatment Failure in the Treatment Groups. The three-year estimate is of survival without disease.

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

Challenges in lymphoma treatment

- > 100 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

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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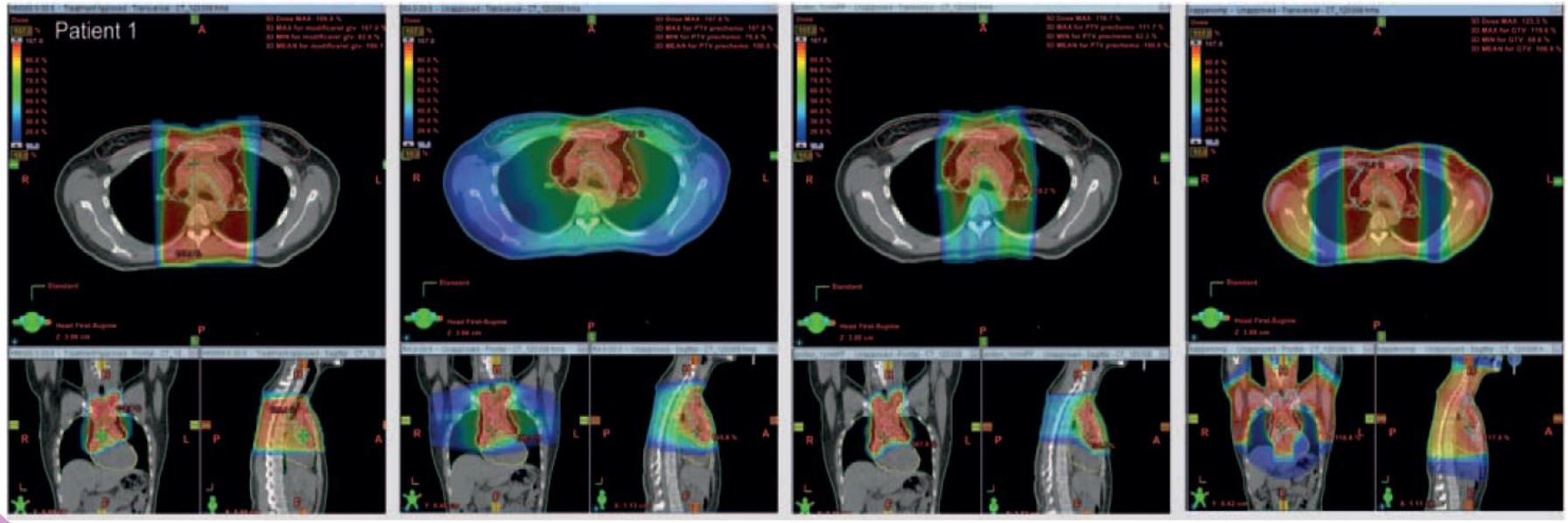
Different modern techniques vs. extended fields of the past

AP-PA IMRT IMPT Mantle field



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

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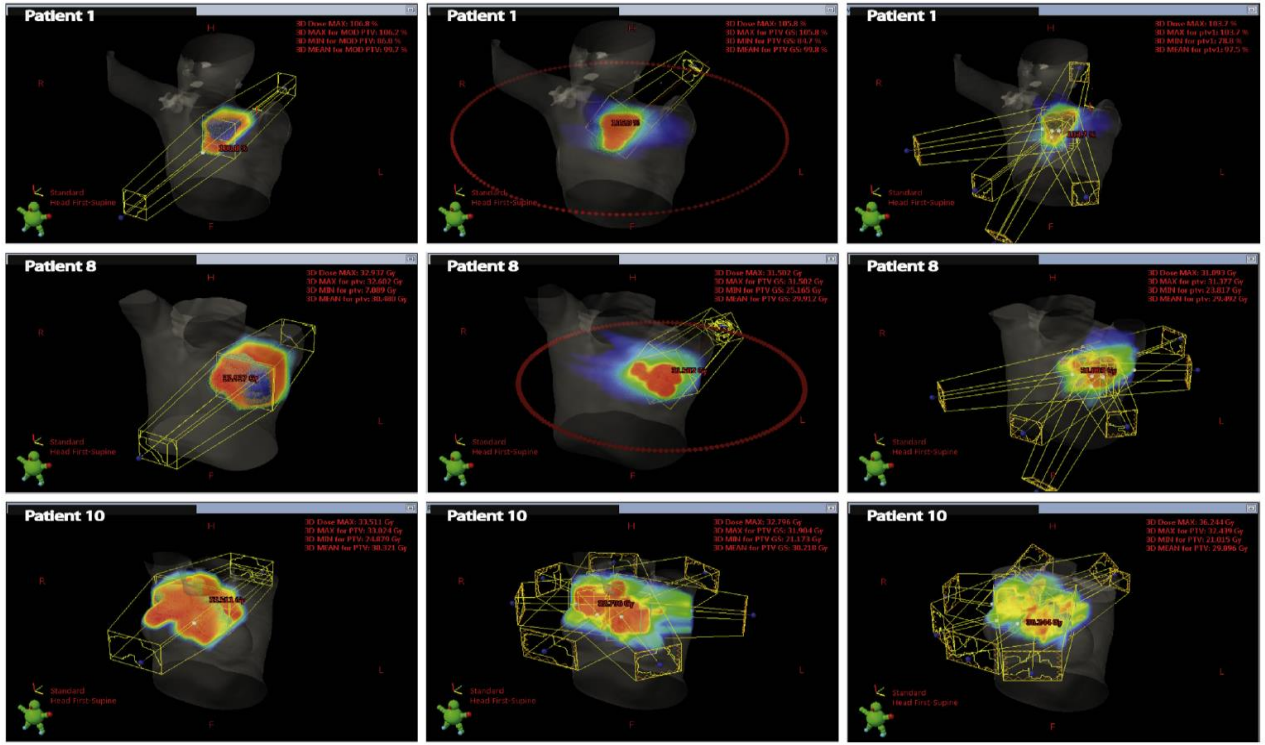
Same patient, different solutions



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

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ILROG Guidelines

INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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

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

IJROBP 2014; 89: 49-58

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

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

IJROBP 2014; 89: 854-62

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

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

IJROBP 2015; 92: 32-39

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

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

IJROPB 2015; 92: 11-31

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

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

Practical Radiation Oncology 2015; 5: 85-92

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INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Role of Radiation Therapy in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group

Andrea K. Ng, MD, MPH,* Joachim Yahalom, MD,† Jayant S. Goda, MD, DNB,‡ Louis S. Constine, MD,§ Chelsea C. Pinnix, MD, PhD,‖ Chris R. Kelsey, MD,¶ Bradford Hoppe, MD, MPH,# Masahiko Oguchi, MD, PhD,** Chang-Ok Suh, MD,†† Andrew Wirth, MBBS, MD, FRACP, FRANZCR,‡‡ Shunan Qi, MD,§§ Andrew Davies, MRCP, PhD,‖‖ Craig H. Moskowitz, MD,¶¶ Siddhartha Laskar, MD,‡ Yexiong Li, MD,§§ Peter M. Mauch, MD,* Lena Specht, MD, PhD,## and Timothy Illidge, MD, PhD***

IJROBP 2018; 100: 652-69

The Role of Radiation Therapy in Patients With Relapsed or Refractory Hodgkin Lymphoma: Guidelines From the International Lymphoma Radiation Oncology Group

Louis S. Constine, MD,*,† Joachim Yahalom, MD,‡ Andrea K. Ng, MD, MPH,§ David C. Hodgson, MD, MPH, FRCPC,‖ Andrew Wirth, MD,¶ Sarah A. Milgrom, MD,# N. George Mikhaeel, MD,** Hans Theodor Eich, MD, PhD,†† Tim Illidge, MD, PhD,‡‡ Umberto Ricardi, MD,§§ Karin Dieckmann, MD,‖‖ Craig H. Moskowitz, MD,¶¶ Ranjana Advani, MD,## Peter M. Mauch, MD,§,‡‡‡ Lena Specht, MD, PhD,*** and Richard T. Hoppe, MD†††

IJROBP 2018; 100; 1100-18

Radiation Therapy for Solitary Plasmacytoma and Multiple Myeloma: Guidelines From the International Lymphoma Radiation Oncology Group

Richard W. Tsang, MD,* Belinda A. Campbell, MBBS, MMed,† Jayant S. Goda, MD, MRes,‡ Chris R. Kelsey, MD,§ Youlia M. Kirova, MD,‖ Rahul R. Parikh, MD,¶ Andrea K. Ng, MD, MPH,# Umberto Ricardi, MD,** Chang-Ok Suh, MD, PhD,†† Peter M. Mauch, MD,# Lena Specht, MD, PhD,‡‡ and Joachim Yahalom, MD§§

IJROBP 2018; 101: 794-808

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Total Body Irradiation: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG)

Jeffrey Y.C. Wong, MD,* Andrea Riccardo Filippi, MD,† Bouthaina Shbib Dabaja, MD,‡ Joachim Yahalom, MD,§ and Lena Specht, MD, DMSc‖

IJROBP 2018; 101: 521-9

Use of Radiation in Extramedullary Leukemia/ Chloroma: Guidelines From the International Lymphoma Radiation Oncology Group

Richard L. Bakst, MD,* Bouthaina Shbib Dabaja, MD,† Lena K. Specht, MD, DMSc,‡ and Joachim Yahalom, MD§

IJROBP 2018; 102: 314-9

Radiation in Central Nervous System Leukemia: Guidelines From the International Lymphoma Radiation Oncology Group

Chelsea C. Pinnix, MD, PhD,* Joachim Yahalom, MD,† Lena Specht, MD, DMSc,‡ and Bouthaina Shbib Dabaja, MD*

IJROBP 2018; 102: 53-8

Lymphoblastic Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG)

Bouthaina Shbib Dabaja, MD, Lena Specht, MD, DMSc, Joachim Yahalom, MD

IJROBP (in press)

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More ILROG Guidelines

PROTON THERAPY FOR ADULTS WITH MEDIASTINAL LYMPHOMAS: THE INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP (ILROG) GUIDELINES

Running Title: ILROG Proton Guidelines

Bouthaina Shbib Dabaja[1], Bradford S. Hoppe[2], John P. Plastaras[3], Wayne Newhauser[4], Katerina Rosolova[5], Stella Flampour[2], Radhe Mohan[1], N. George Mikhaeel[6], Youlia Kirova[7], Lena Specht[8], Joachim Yahalom[9].

Blood (in press)

The optimal use of imaging in Radiation Therapy for lymphoma – Guidelines from the International Lymphoma Radiation Oncology Group (ILROG)

N. George Mikhaeel[1], Sarah A. Milgrom[2], Stephanie Terezakis[3], Anne Kiil Berthelsen[4], David Hodgson[5], Hans Eich[6], Karin Dieckmann[7], Shu-nan Qi[8], Joachim Yahalom[9], Lena Specht[4]

(Submitted)

Andrew Wirth et al. ILROG guidance on the Decision making process in the delivery of ISRT in NHL and HL

(In preparation)

Thank you for your attention

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RADIATION ONCOLOGY GROUP

General principles of treatment: Radiotherapy

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

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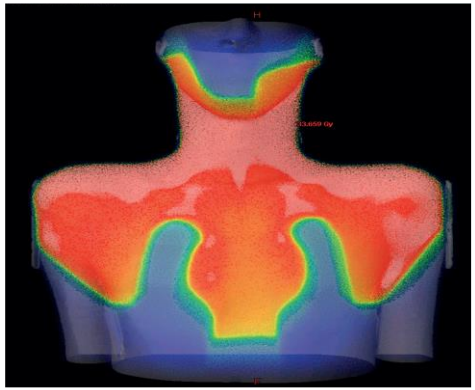
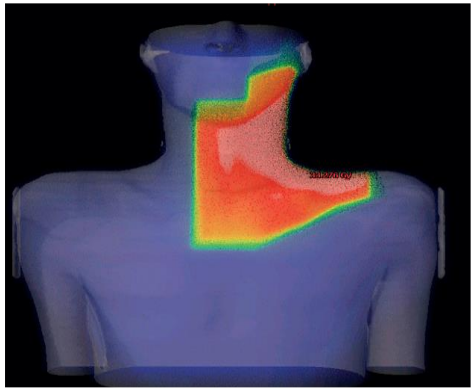
Facts about radiotherapy in lymphomas

- 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

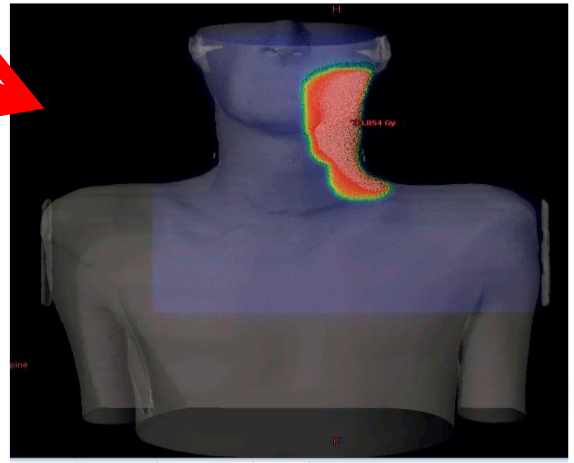
Mantle field (EFRT) or involved field (IFRT)





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

- 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 than necessary, replaced by lower doses in most lymphoma types

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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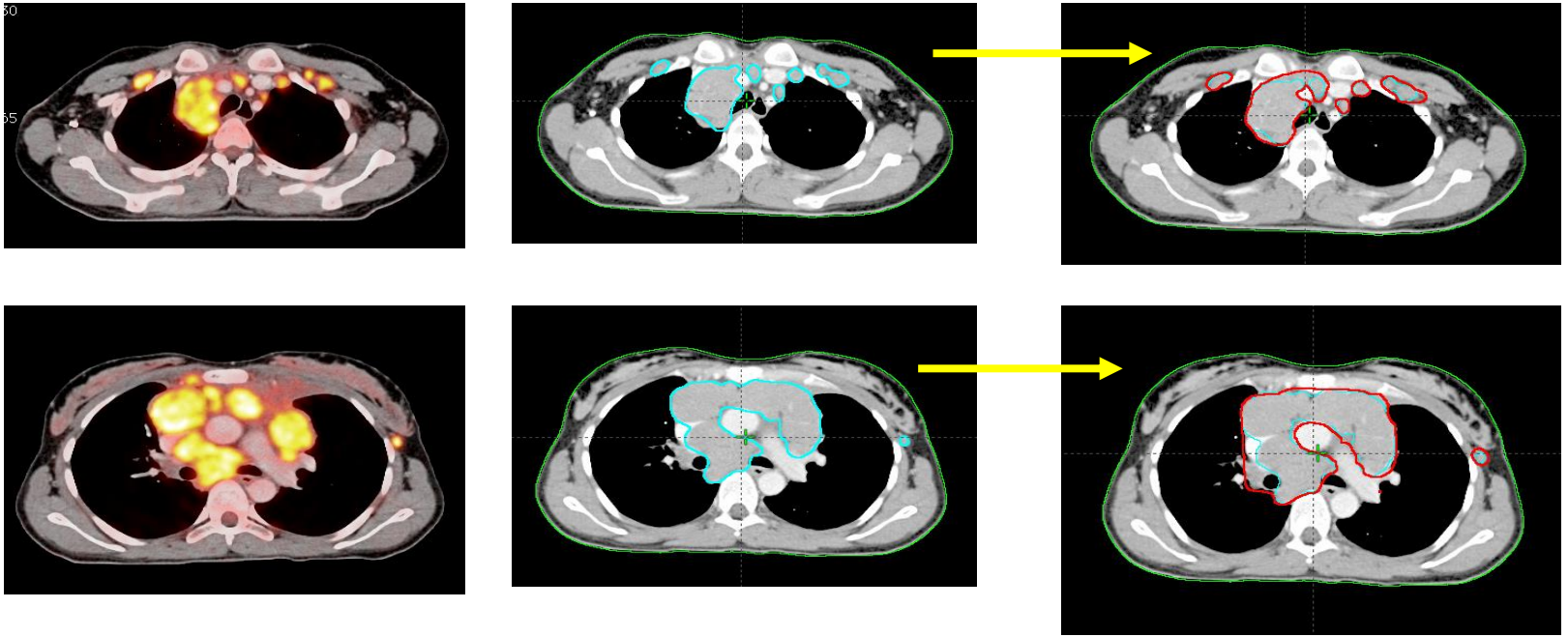
Pre-chemo PET/CT scan

PET+ volume

Gross tumour volume GTV
(pre-chemo)



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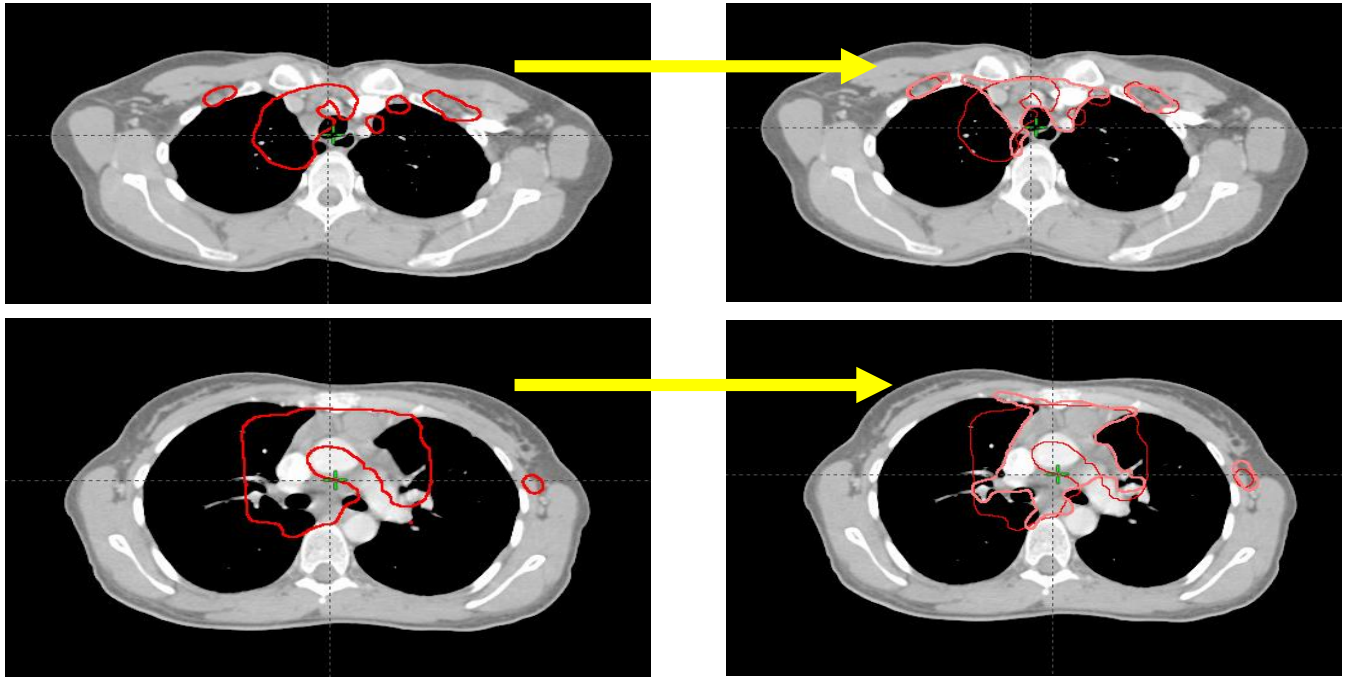
Post-chemo planning CT scan

Pre-chemo gross tumour volume

Post-chemo clinical target volume



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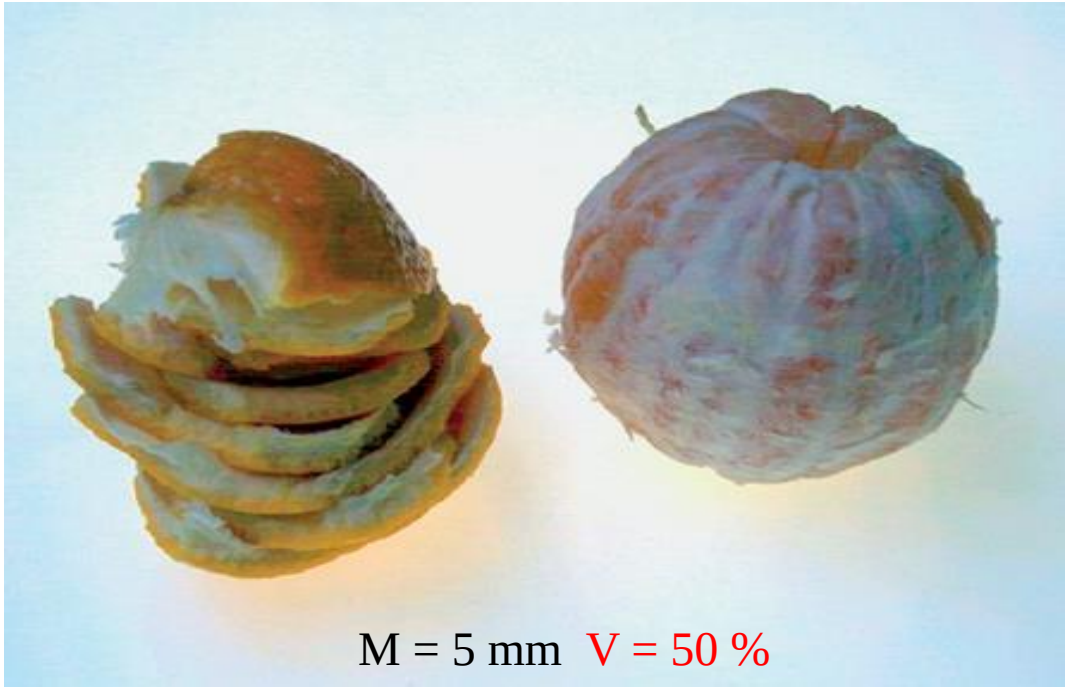
Margins and corresponding tissue volumes



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

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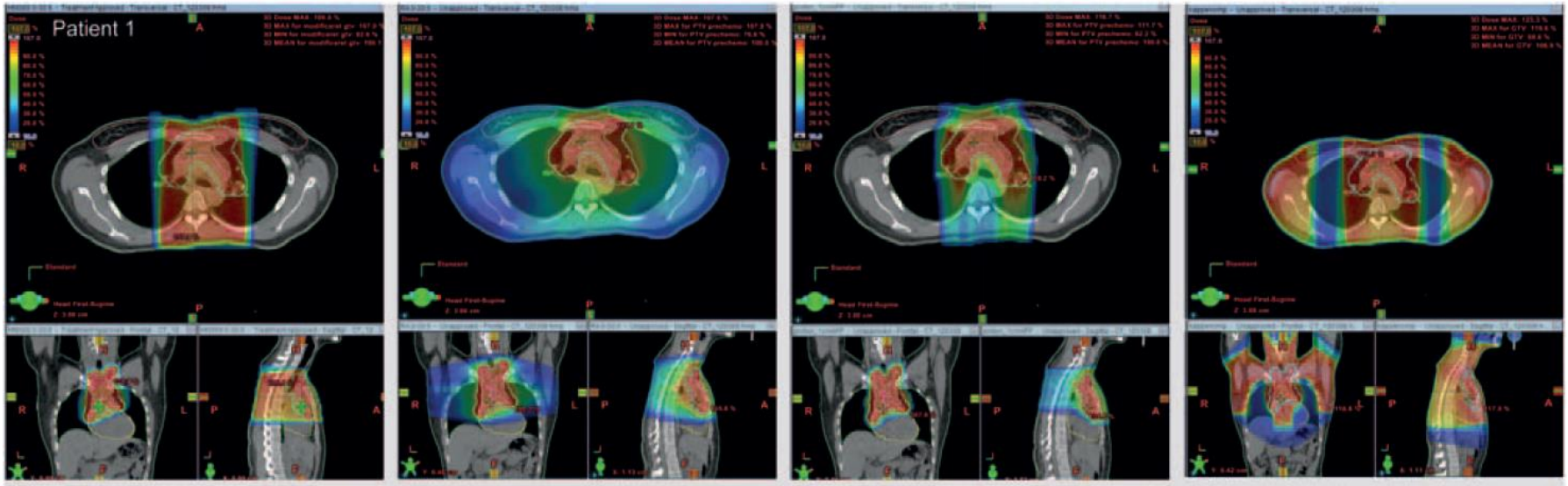
Different modern techniques vs. extended fields of the past

AP-PA IMRT IMPT Mantle field



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

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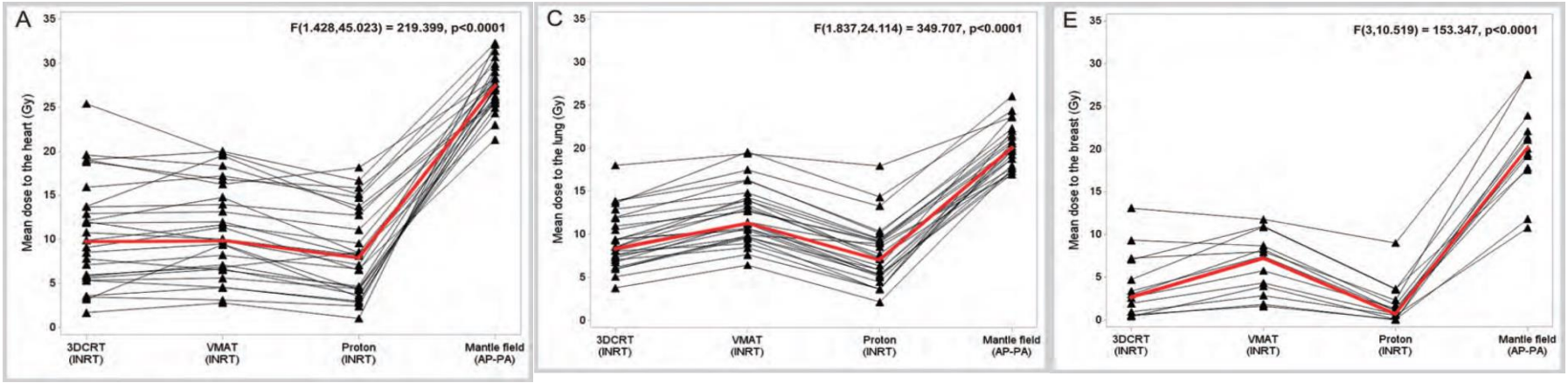
Mean doses to heart, lungs, and breasts in 27 early stage HL patients with mediastinal involvement with different techniques

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



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

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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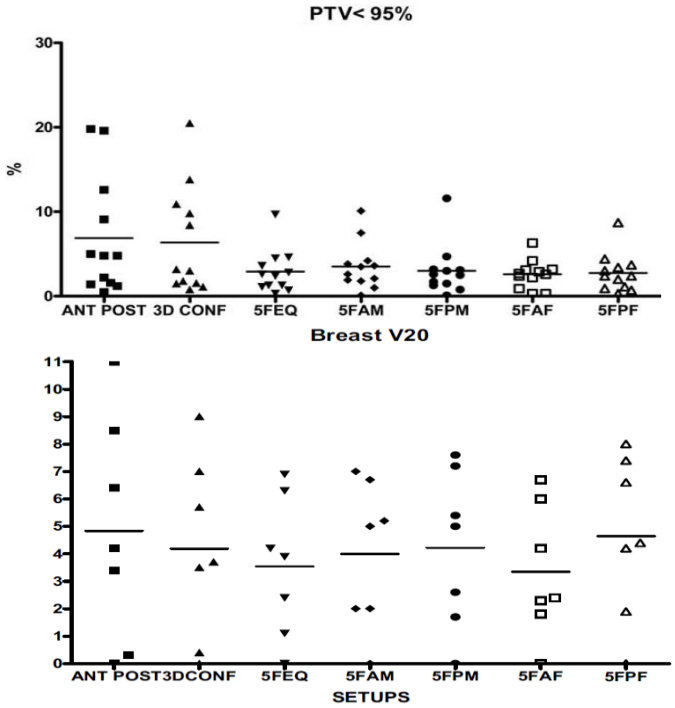
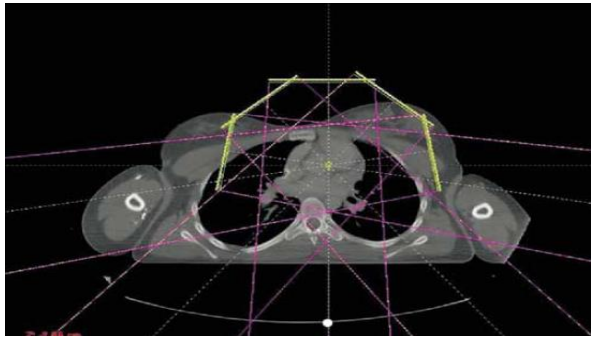
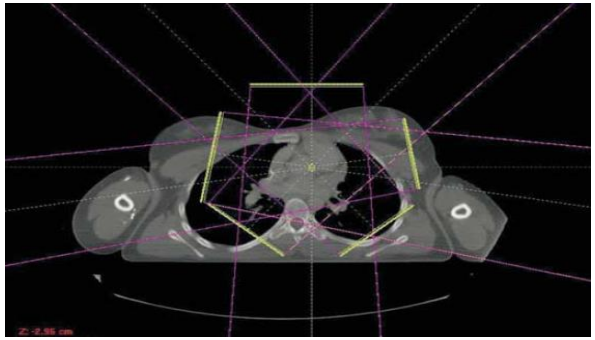
Optimizing IMRT with ”intelligent” beam orientation





Focus on anterior mass (FAM)



Avoid the breasts (FAF)

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

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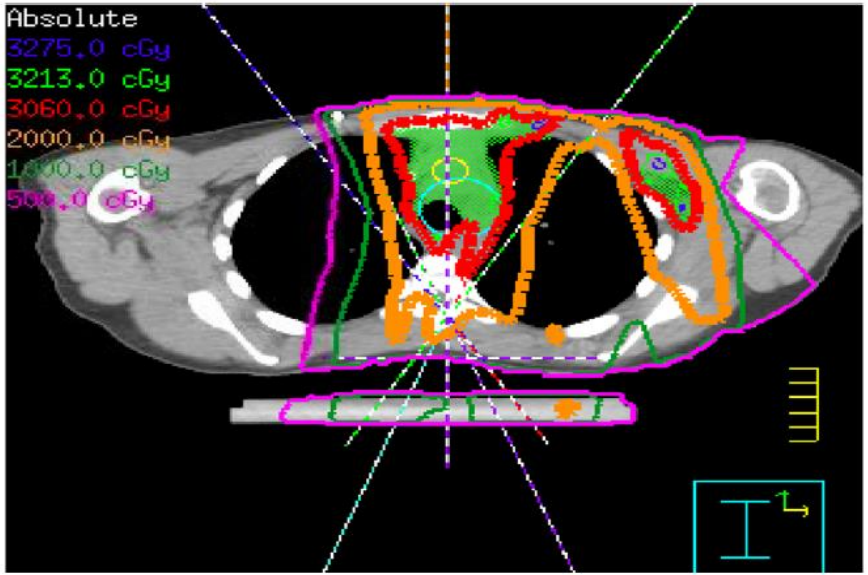
Optimizing IMRT with ”intelligent” beam orientation

”Butterfly technique”



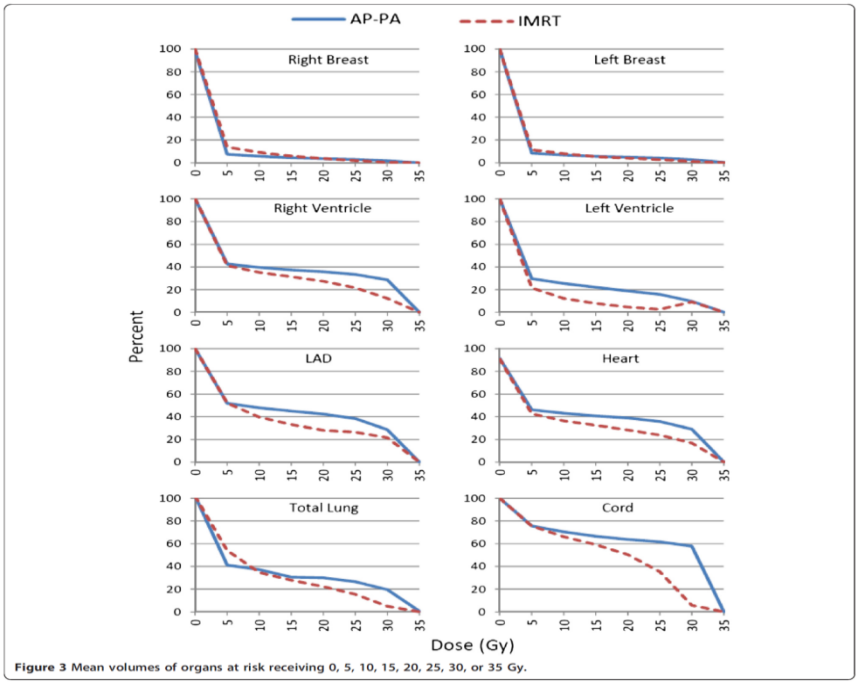


Figure 3 Mean volumes of organs at risk receiving 0, 5, 10, 15, 20, 25, 30, or 35 Gy.

Voong et al. Radiat Oncol 2014; 9: 94

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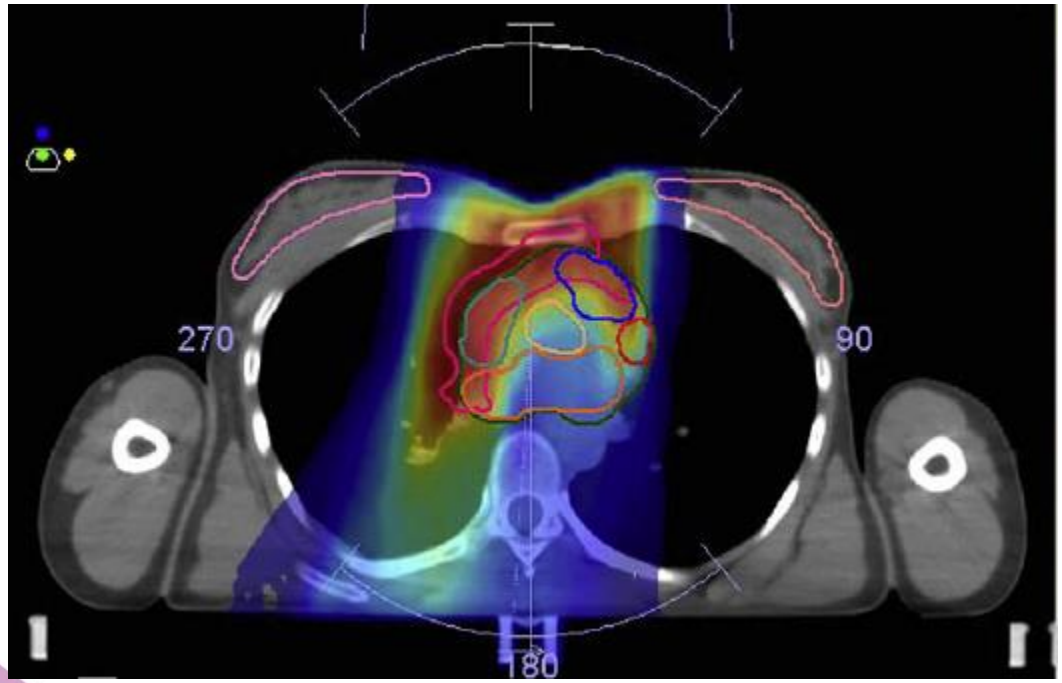
Optimizing IMRT with ”intelligent” beam orientation

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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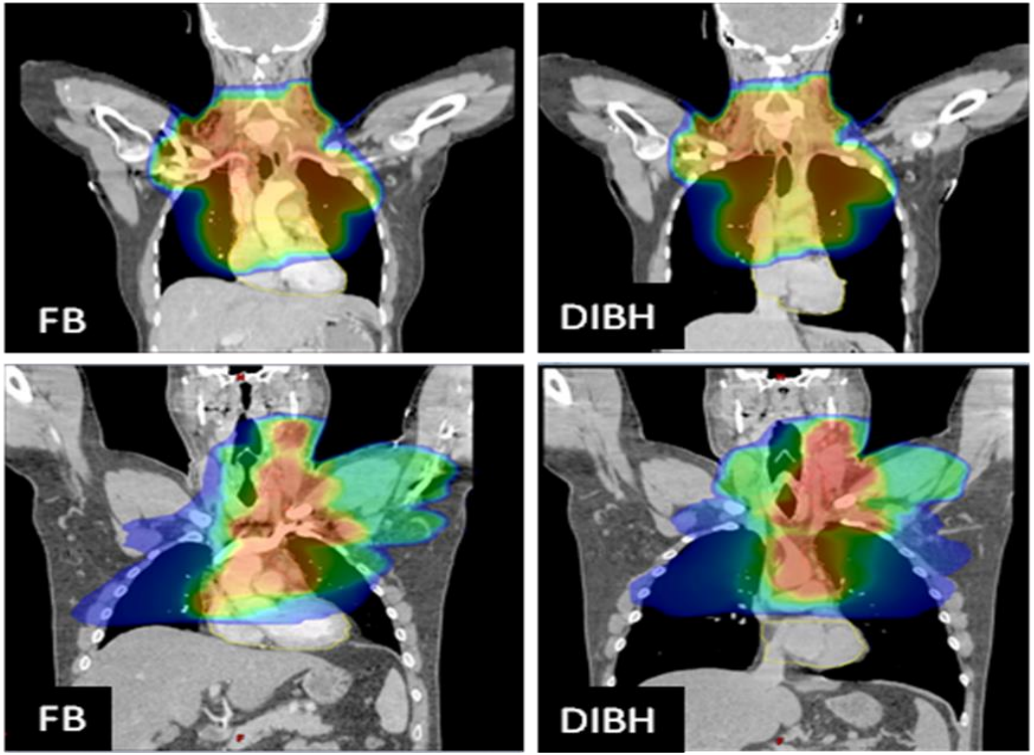
Breathing adapted RT



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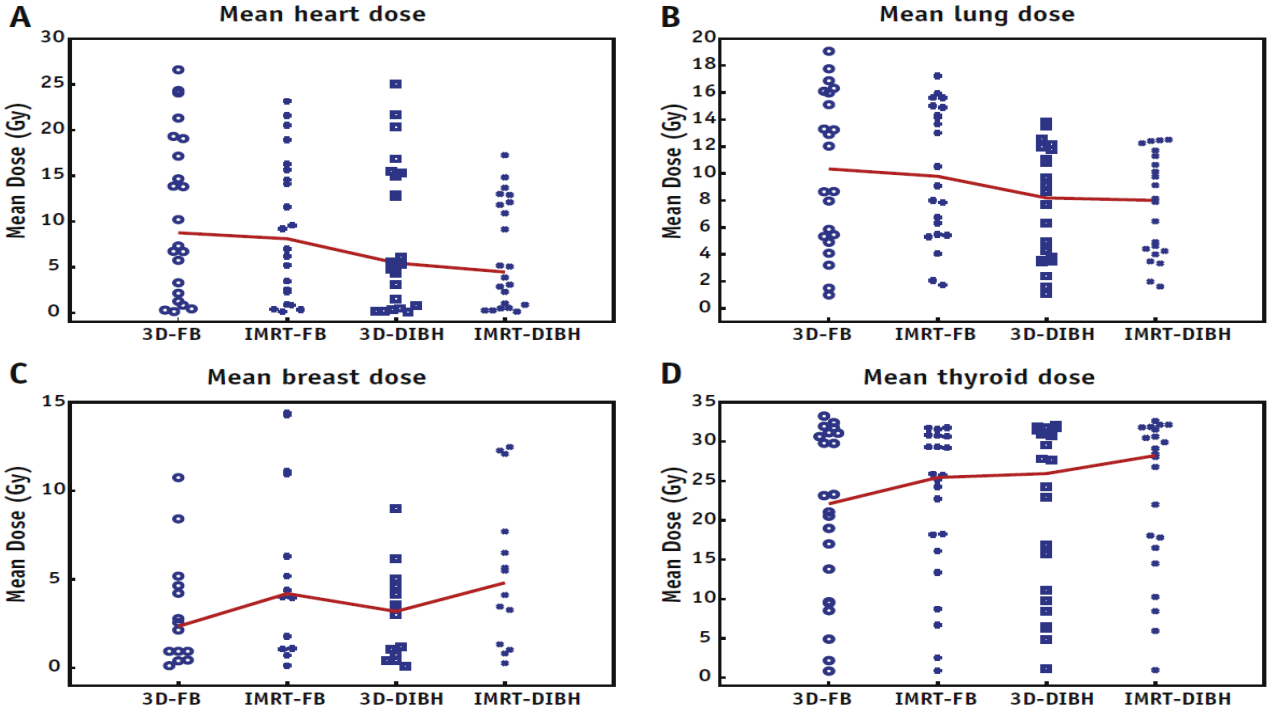
Breathing adaptation and highly conformal treatment (IMRT), what can we achieve?



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, why are they so difficult in lymphomas?

- The location of the target varies, may be located anywhere in the body
- The doses that we need are much lower than in solid tumours
- Acute toxicity is not a major problem
- Most patients may expect to become long-term survivors
- Late effects are a major issue
- Even the low doses used for lymphoma treatment cause serious late effects, there is no safe dose level

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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Dose constraints in lymphomas: Handle with care

- In some clinical situations (e.g., large mediastinal mass with involvement at heart level) it may be difficult/impossible to keep within reasonable constraints
- In other/most clinical situations (e.g., small, superior mediastinal mass) it may be very easy to keep within specified constraints
- This may not be good enough, since plans with even lower doses may be achievable

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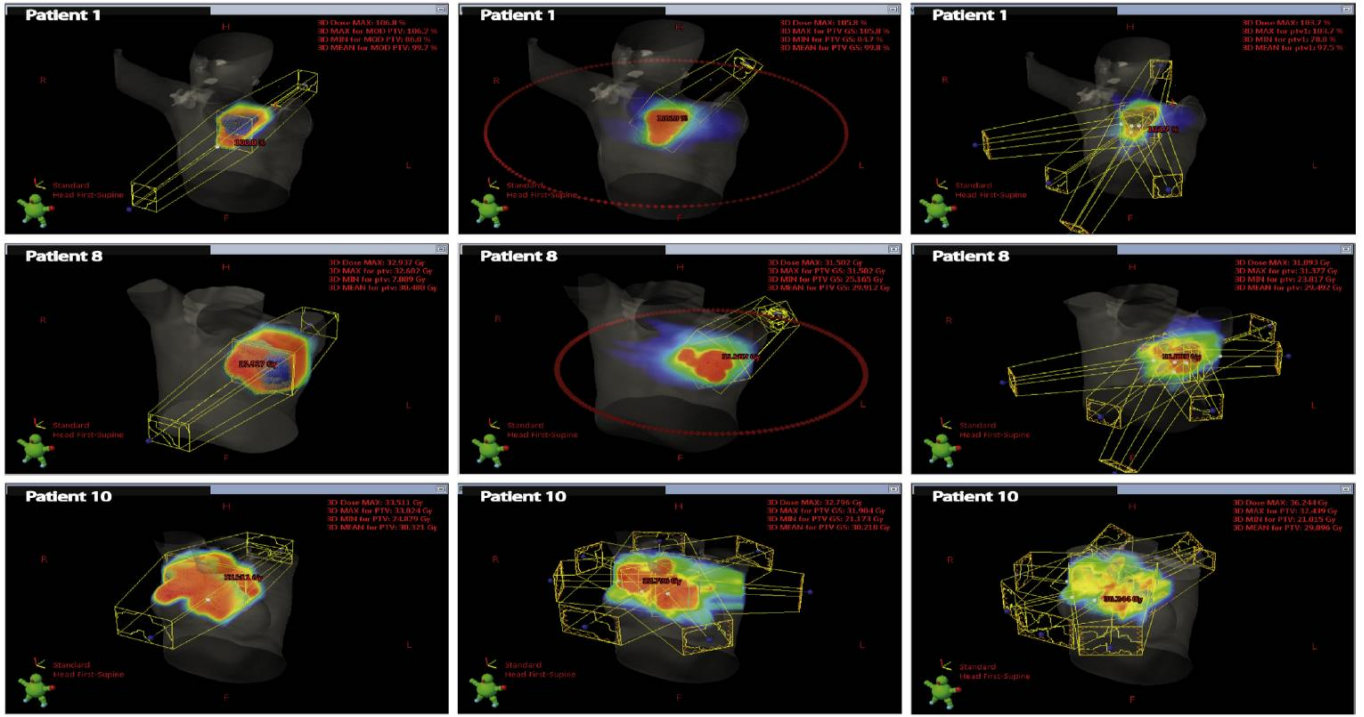
Same patient, different solutions



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

PROTON THERAPY FOR ADULTS WITH MEDIASTINAL LYMPHOMAS: THE INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP (ILROG) GUIDELINES

Running Title: ILROG Proton Guidelines

Bouthaina Shbib Dabaja[1], Bradford S. Hoppe[2], John P. Plastaras[3], Wayne Newhauser[4], Katerina Rosolova[5], Stella Flampour[2], Radhe Mohan[1], N. George Mikhaeel[6], Youlia Kirova[7], Lena Specht[8], Joachim Yahalom[9].

Blood, in press

Guide to acceptable dose, volume and field considerations

Structures	Ideal	Optimize Technique	Optimize Field (consider field reduction)	Unacceptable	Avoid Max Dose Landing in
Heart: left ventricle, coronary artieries, valves[1]	Mean <5 Gy	Mean 5-15 Gy	Mean >15 Gy	Mean >30 Gy	Coronaries
Breast (age-dependent)[2]	Mean <4 Gy	Mean 4-15 Gy	Mean >15 Gy	Mean >30 Gy	Glandular tissue
Lung[3]	V_5 <55% V_{20} <30% Mean <10 Gy	V_5 55-60% Mean 10-13.5 Gy	—	V_5 >60% Mean > 13.5 Gy	
Thyroid[4]	V_{25} <62.5%	V_{25} <62.5%			in the whole thyroid

[1] Based on Maraldo et al., Lancet Haematol 2015 [ref 33]; van Nimwegen et al., J Clin Oncol 2016 [ref 34]; and Cutter et al., J Natl Cancer Inst 2015;107(4) [ref 35].

[2]The importance of adhering to breast-dose restrictions is inversely related to patient age.

[3] Pinnix et al. IJROBP 2015 [ref 32]

[4] Pinnix et al. ASTRO annual meeting 2017, abstract.

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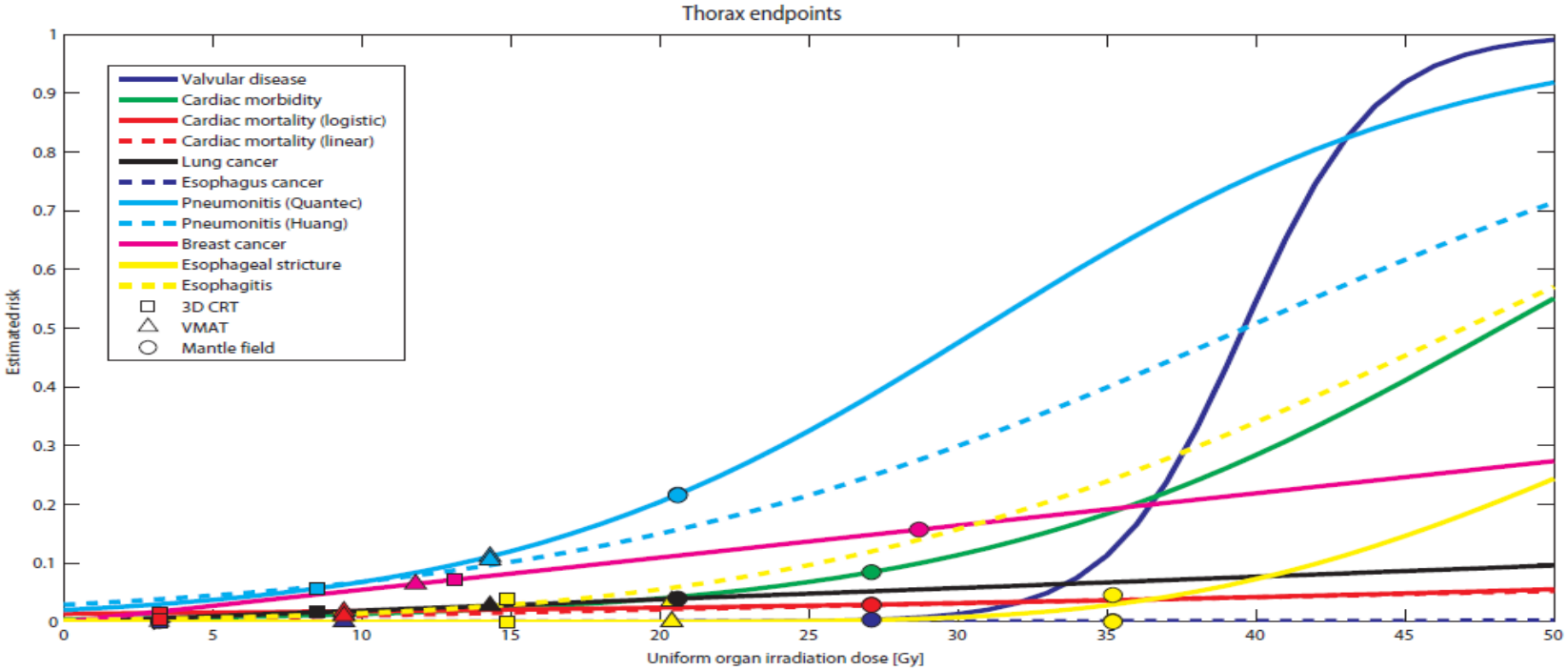
Ideally, normal tissue complication probability models for all relevant risk organs should be combined for each treatment plan



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

ALARA Principle

- Doses to all critical normal tissues should be kept

”As Low As Reasonably Achievable”

- I.e., a best common practice of judgement of the balance of risk and benefit for the individual patient

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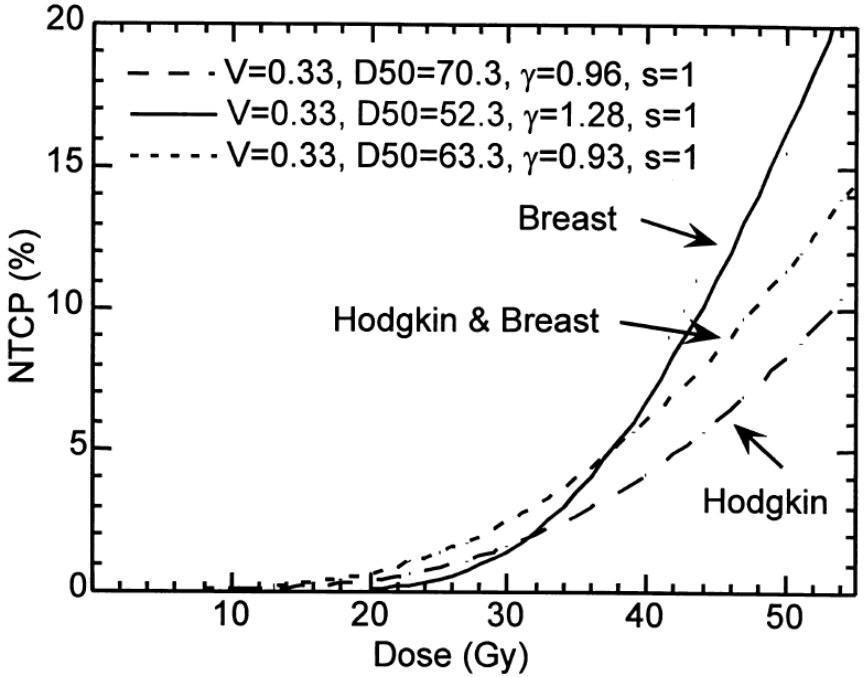
Cardiac late effects Quantec data: derived from retrospective data from pts treated with outdated techniques and target definitions
”Prudent to limit whole heart dose to 15 Gy” !!!!

Risk of cardiac mortality as a function of dose to 1/3 of the heart

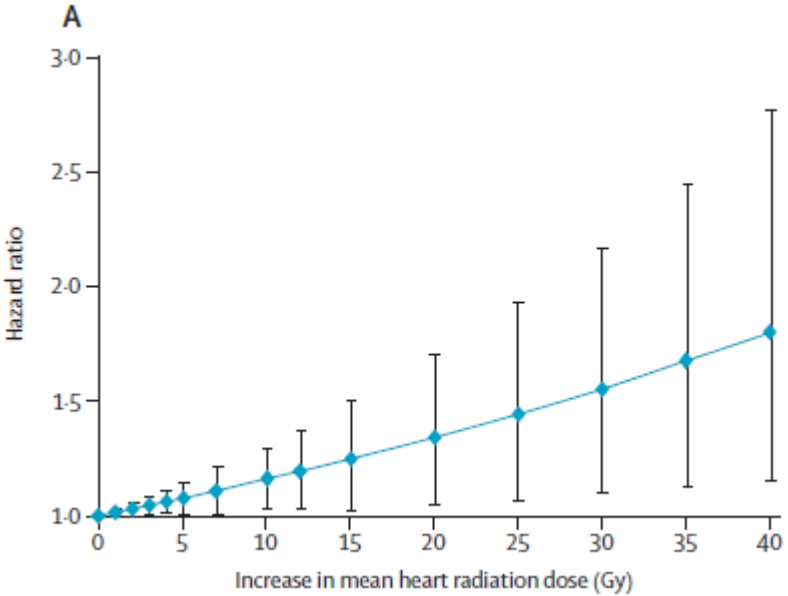
Eriksson F et al. Radiother Oncol 2000; 55: 153-62



Cardiac constraints

- Mean heart dose is the parameter most often used
- Other parameters (V_5, V_{10}, V_{20}, V_{25}, V_{30}, V_{40}) are highly correlated with mean heart dose
- The heart is evaluated as a single structure
- Very few data on toxicity according to where the high dose falls (e.g., cardiac valves, left ventricle)

Dose response relationship for cardiovascular event and mean heart radiation dose (from EORTC randomized trials in HL)



Maraldo MV et al. Lancet Haematol 2015; 2: e492-502

Suggested constraints:

≤ 4 Gy: should be obtained in all but the most challenging cases

5-15 Gy: acceptable

> 15 Gy: consider omission or modification of plan

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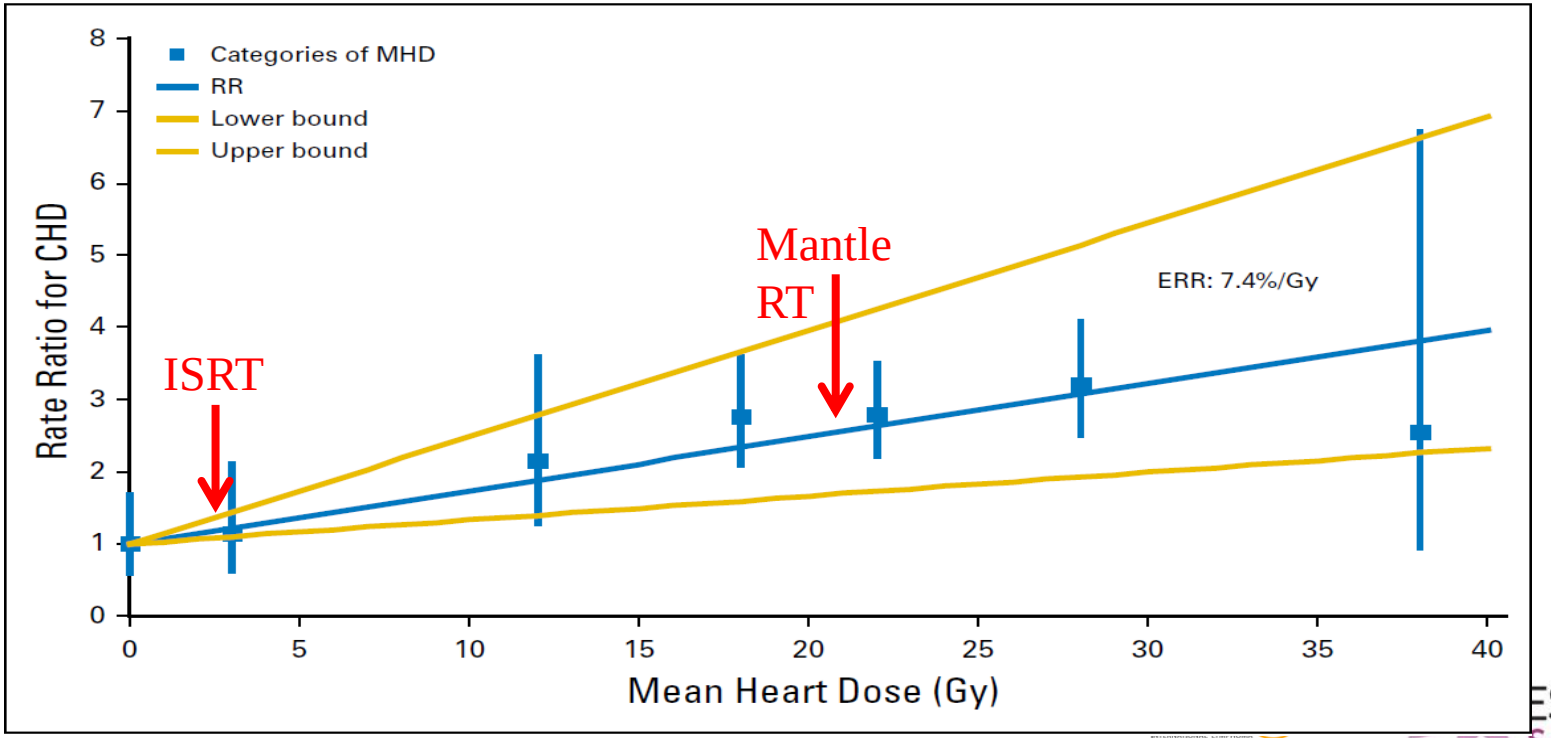
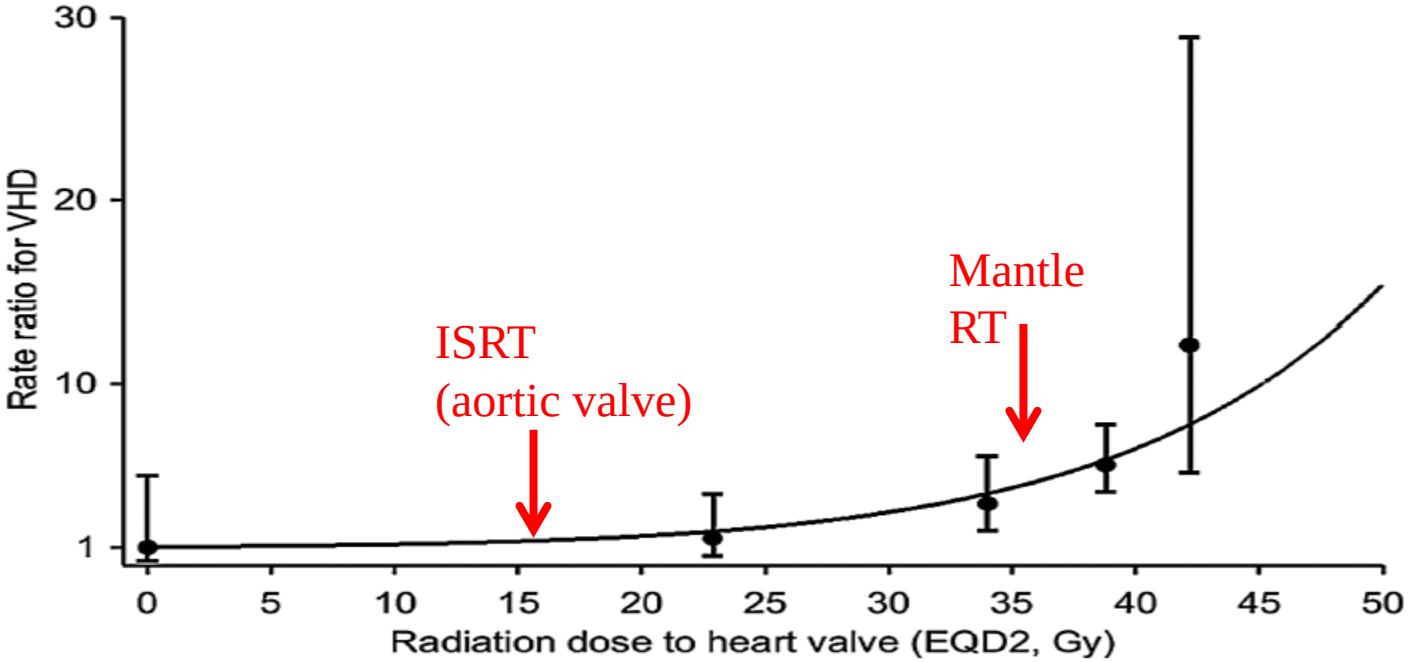
Radiation dose-response relationship for risk of coronary heart disease in Hodgkin lymphoma survivors



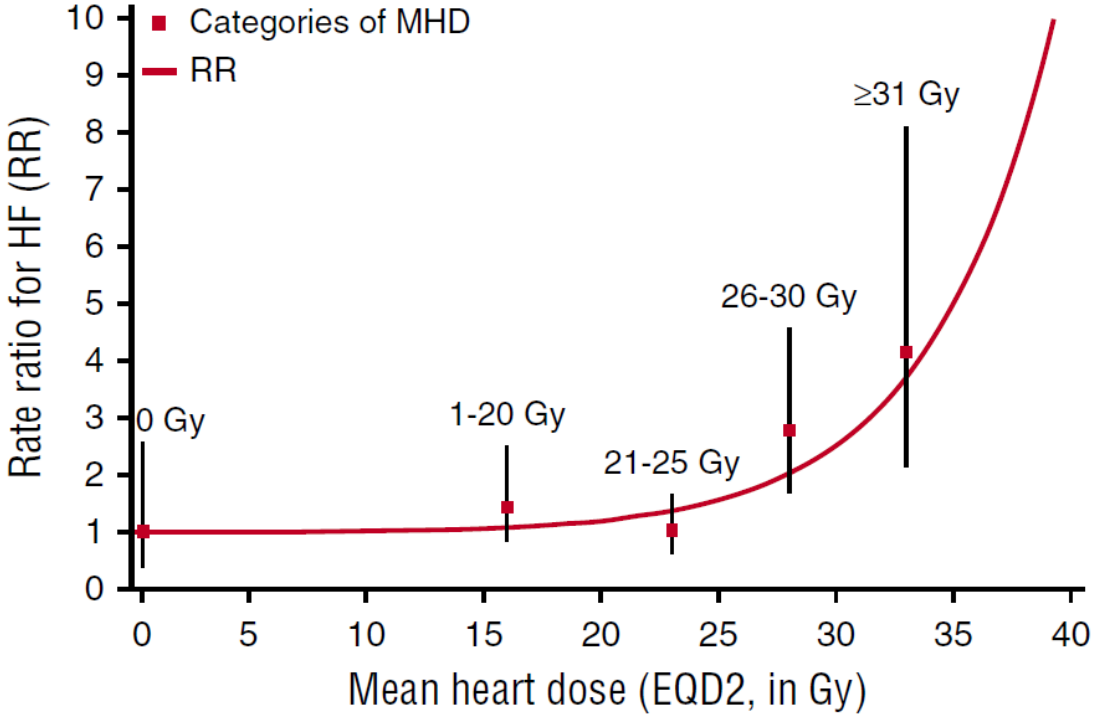
van Nimwegen FA et al. JCO 2016

Radiation dose-response relationship for risk of valvular heart disease in Hodgkin lymphoma survivors



Cutter DJ et al. JNCI 2015

Radiation dose-response relationship for risk of heart failure in Hodgkin lymphoma survivors



Not an issue

Van Nimwegen et al. Blood 2017; 129: 2257-65

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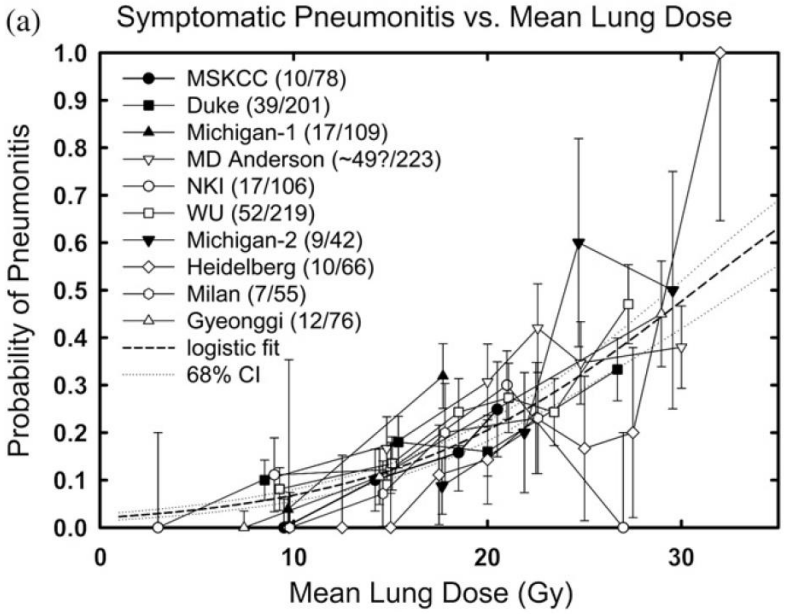
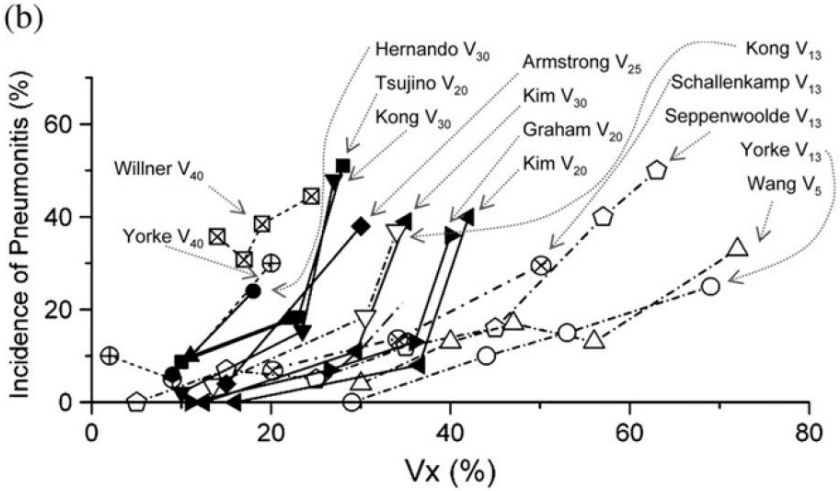
Pneumonitis, Quantec data





Dependent on dose, time, and fractionation

→ technique dependent

Marks LB. IJROBP 2010; 76 (3 Suppl.): 70-6

Table 6 Univariate analysis of potential clinical and dosimetric factors associated with radiation pneumonitis

Parameter	Odds ratio	95% CI	*P* value
Mean lung dose			
Continuous	1.46	1.17-1.83	.001
>12 Gy	1.91	1.19-3.07	.008
>13 Gy	2.43	1.47-3.99	<.001
>13.5 Gy	3.14	1.81-5.43	<.001
>14 Gy	3.12	1.63-5.99	.001
V_5			
Continuous	1.12	1.05-1.20	.001
>50%	4.08	1.48-11.22	.006
>55%	7.92	2.90-21.63	<.001
>60%	3.72	1.13-12.27	.031
V_{10}			
Continuous	1.12	1.04-1.20	.002
>35%	3.05	1.06-8.83	.039
>40%	4.54	1.73-11.90	.002
>45%	4.88	1.65-14.42	.004
V_{15}			
Continuous	1.13	1.05-1.22	.002
>25%	11.08	1.44-85.28	.021
>30%	3.47	1.27-9.53	.016
>35%	5.07	1.93-13.34	.001
>40%	2.61	0.47-14.43	.271
V_{20}			
Continuous	1.12	1.03-1.21	.005
>25%	2.41	0.93-6.21	.07
>30%	4.68	1.67-13.13	.003
>33%	4.73	1.38-16.22	.014
>35%	4.42	0.69-28.20	.116
V_{25}			
Continuous	1.12	1.03-1.21	.005
>20%	2.93	1.13-7.59	.027
>23%	4.81	1.84-12.56	.001
>25%	4.46	1.53-13.05	.006

Pulmonary constraints: pneumonitis

Ptts treated with mediastinal IMRT

To keep risk < 10 %:

Mean lung dose ≤ 13.5 Gy

$V_{25} \leq 23$ %

$V_{20} \leq 30$ %

$V_{15} \leq 35$ %

$V_{10} \leq 40$ %

$V_5 \leq 55$ %

Pinnix CC. IJROBP 2015; 92: 175-82

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Pulmonary late effects

- The constraints for pneumonitis will cover late effects as well
- Suggested constraints
  - ≤ 10 Gy mean lung dose should be obtained in all but the most challenging cases
  - 10 – 13.5 Gy mean lung dose: acceptable, but consider the risk of pneumonitis
  - > 13.5 Gy mean lung dose: consider omission or modification of plan

Second malignancies

- For many tissues the risk increases with increasing doses in the dose range used for lymphomas
- Exception: thyroid cancer has bell-shaped dose-risk curve, linear up to 29 Gy, then decreasing
- There is no safe dose level
- Doses to all organs should be kept ALARA

Second malignancies

- Other factors must be taken into account
  - Age: over 40 – 50 no longer significant increase
  - Underlying risk: some organs are more likely to be affected (breast, lungs)
  - Sex: Breast cancer
  - Individual risk: Smoking, family history
  - Prognosis of second cancer: E.g. breast cancer much better than lung cancer

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QUANTEC: Use of NTCP models in the clinic

- Historically, radiation therapy (RT) fields/doses were selected empirically, based largely on experience

- Physicians relied on clinical intuition to select field sizes/doses. They understood that these empiric guidelines were imprecise and did not fully reflect the underlying anatomy, physiology, and dosimetry

- For most cases, modern treatments will redistribute, not eliminate, the dose to normal tissue. The fundamental problem of treatment planning is how to balance exposure of one organ against that of another

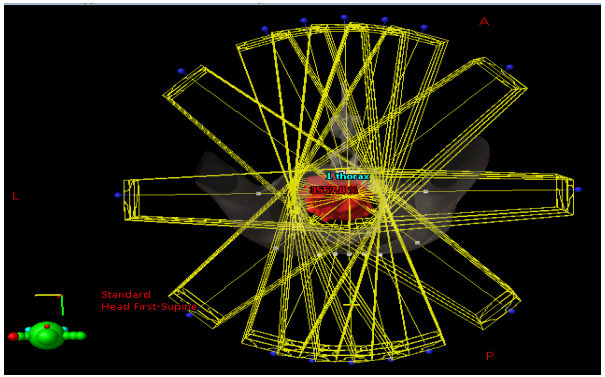
Goal : To give the patient the best deal

- Cure of the lympoma
- As little acute toxicity as possible
- The lowest possible risk of late effects in all the normal organs within the irradiated volume, taking into account
  - When is the late effect likely to occur
  - What is the prognosis of the patient if the late effect occurs

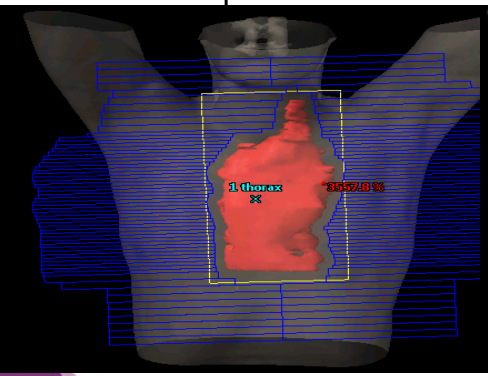
Dose effect relationships from clinical data

Endpoint	Assumptions	Source of data
Disease recurrence	-Mean dose is assumed to be predictive of disease control. - HR for 0 vs 20 Gy and HR for 20 vs 30 Gy from randomized trials. -A linear interpolation of the HR is performed for mean doses between 0,20 and 30 Gy. - Doses above 30 Gy assumed not to give benefit	Herbst C et al. Haematologica 2010;95:494–500 Engert A et al. N Engl J Med 2010;363:6430-5 Eich HT et al. J Clin Oncol 2010;28:4199–206.
Cardiac related mortality	- Mean dose to heart is assumed predictor of developing - Linear ERR: 7.4 %/Gy (male) 7.2%/Gy (female) - Background mortality as function of age from cdc data	Nimwegen et al 2016
Second breast cancer	- Mean dose to breast is assumed predictor of developing - ERR=14.9%/Gy - Assumed risk of dying after developing: 10.3% (SEER)	
Second lung cancer	- Mean lung dose is assumed predictor - ERR=14.1%/Gy - Background risk separate for men and women (SEER) - Assumed risk of dying after developing: 82.3% (SEER)	Travis et al 2002

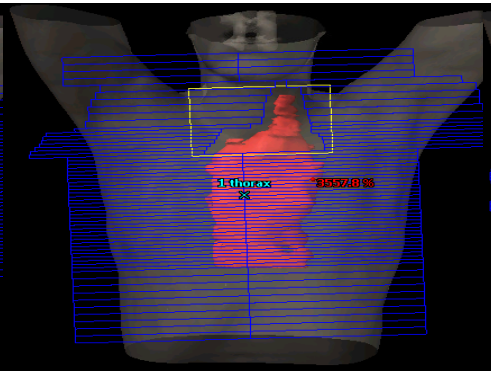
....Add large numbers of fields and let the computer minimize total risk...



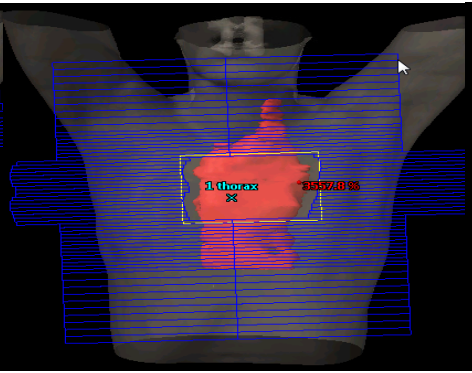
Open field



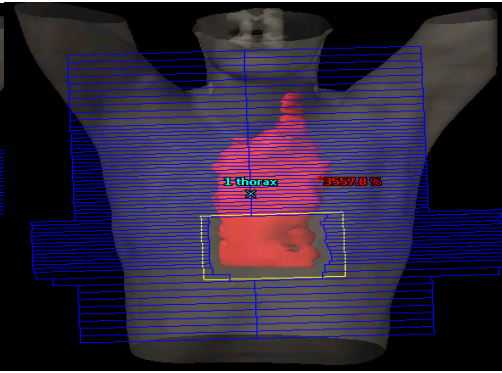
Subfield 1



Subfield 2



Subfield 3



Rechner LA et al, in preparation

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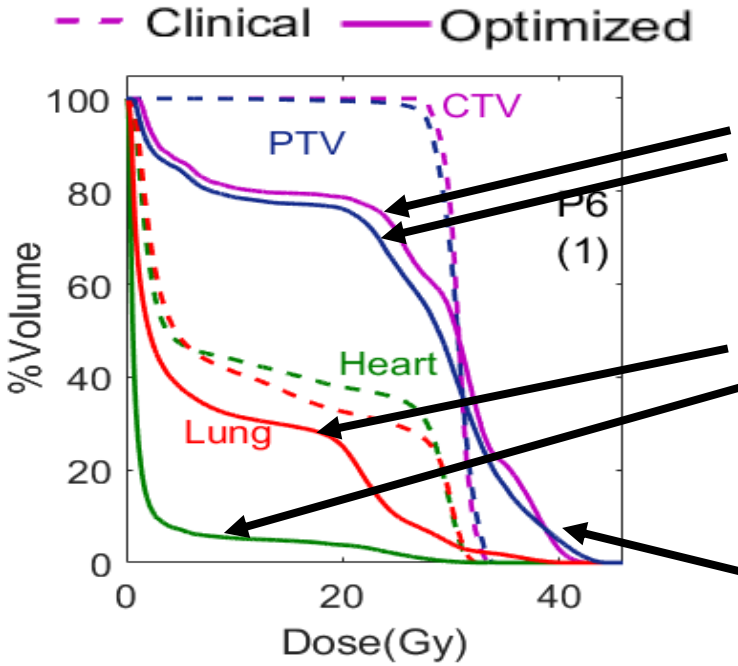
Preliminary results

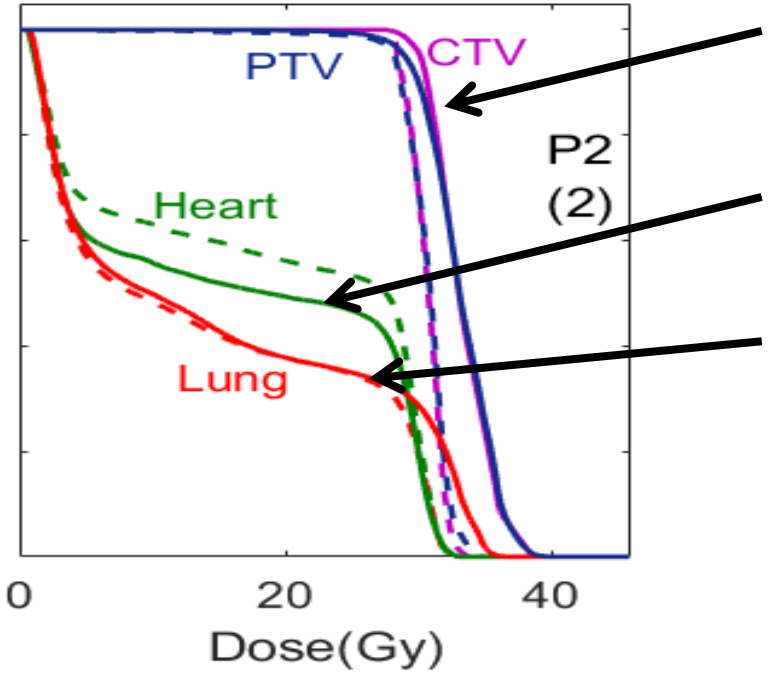


Target compromised

Substantial sparing of heart/lungs

OK, so this is a prototype...
Improvements necessary

Preliminary results

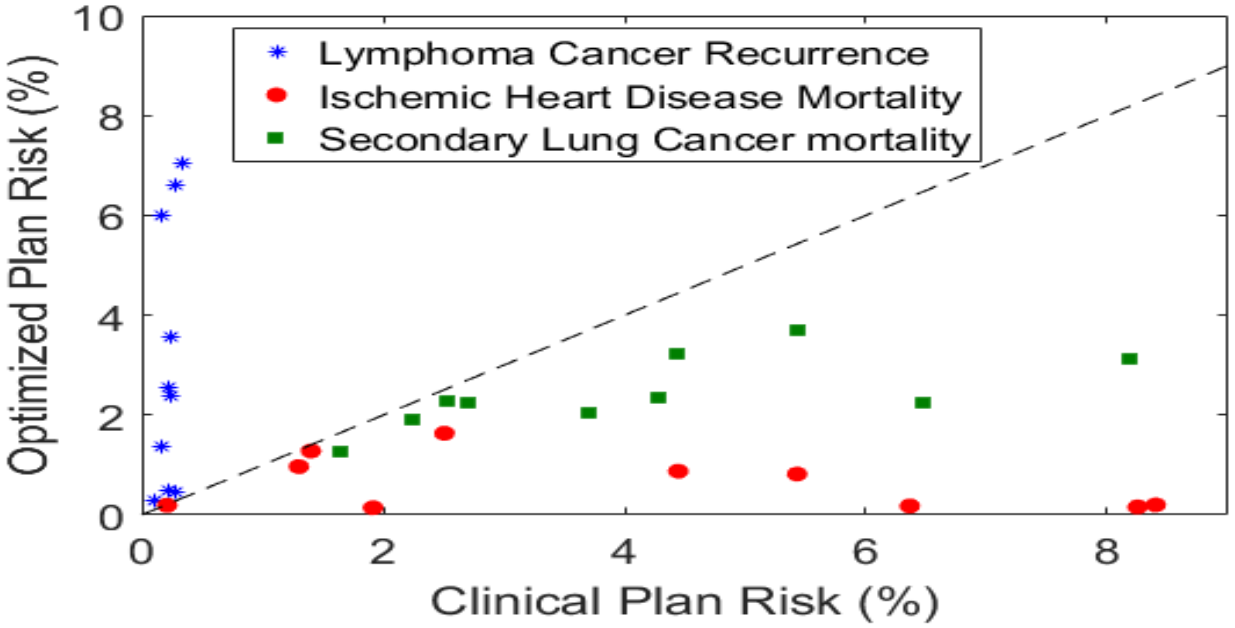


Target not compromised

Some sparing of heart

No Sparing of lung

Preliminary results



In current implementation, it appears sacrificing the target coverage is often chosen to spare late risk (note prelim. data)

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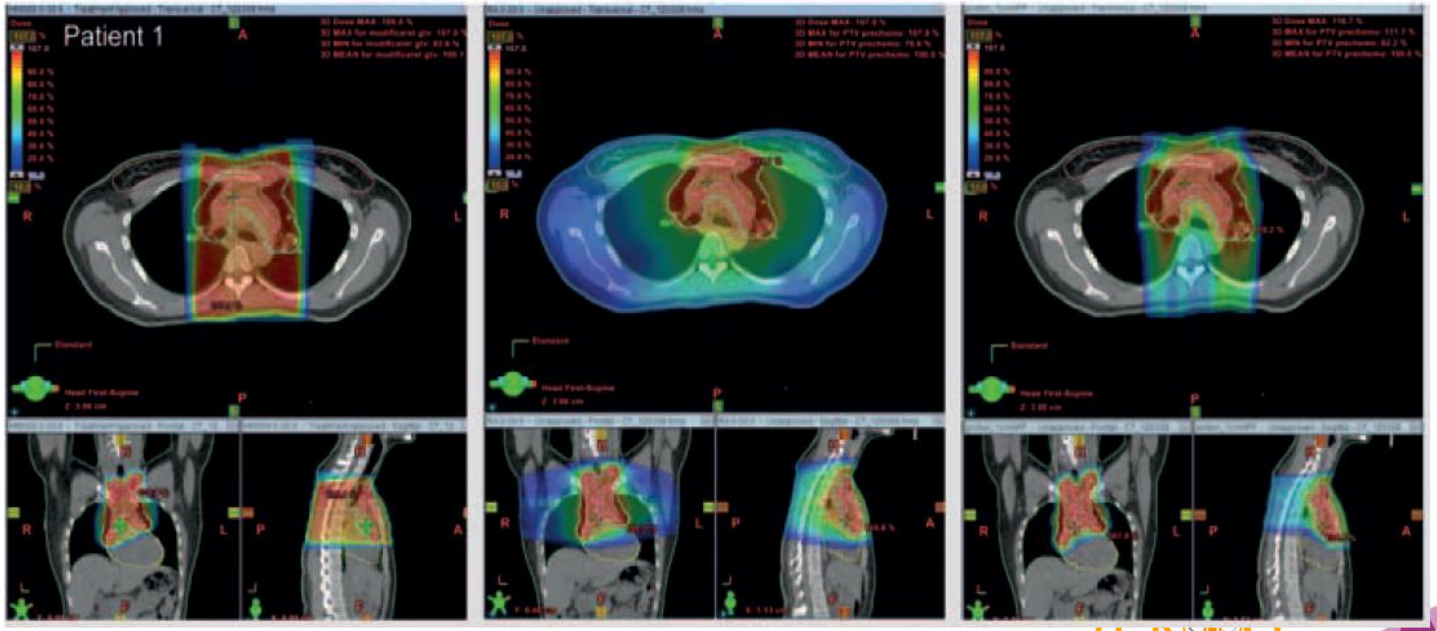
Which treatment plan should we choose for each individual patient?



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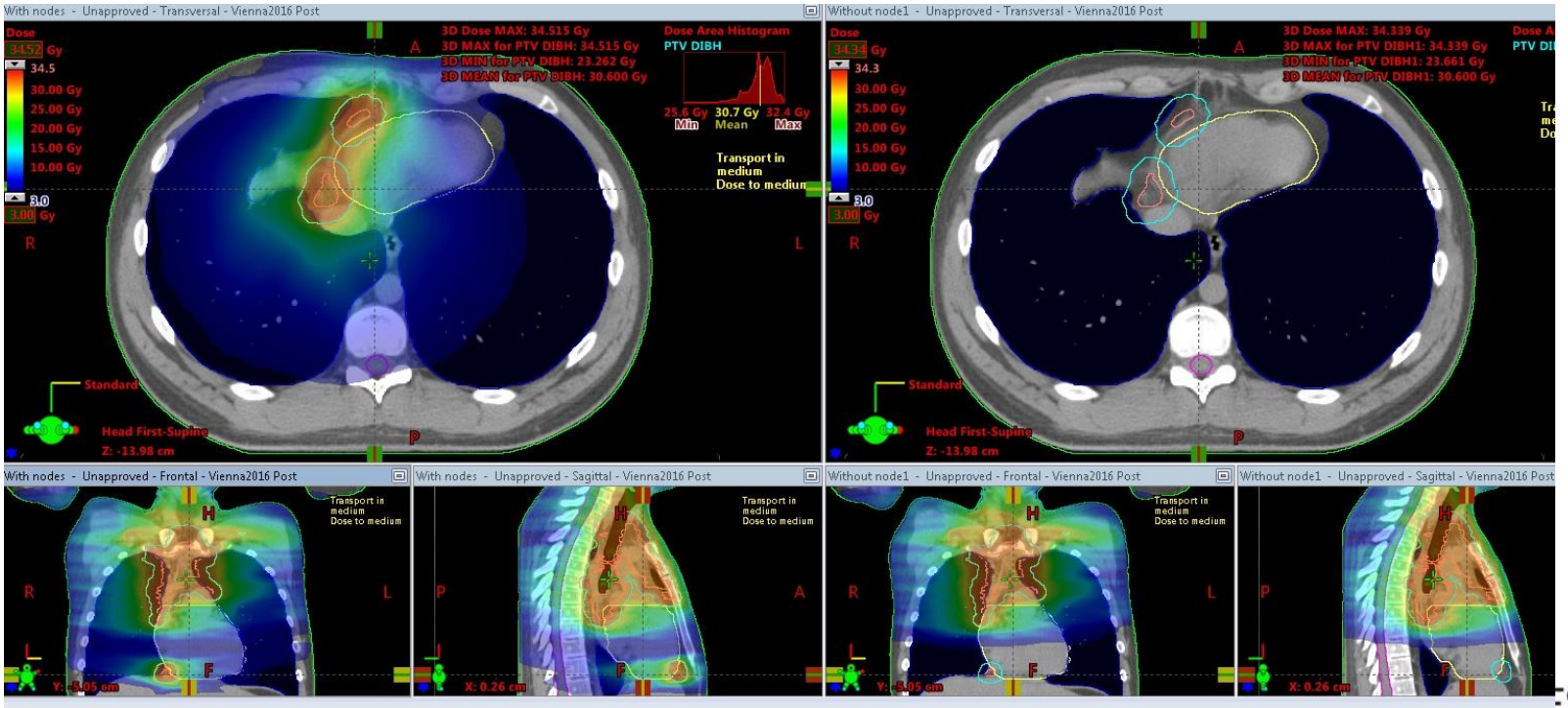
Should we or should we not include the small nodes in the inferior part of the mediastinum, considering the dose to the heart and the lungs?



Thank you for your attention

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MANCHESTER 1824
The University of Manchester
Manchester Cancer Research Centre

CANCER RESEARCH UK

Manchester Academic Health Science Centre

Tim Illidge

BSc PhD FRCR FCRP FRCPath

Immunotherapy and immunological approaches

Head of Cancer Sciences
University of Manchester
Manchester Cancer Research Centre
The Christie NHS Foundation Trust
Manchester, UK

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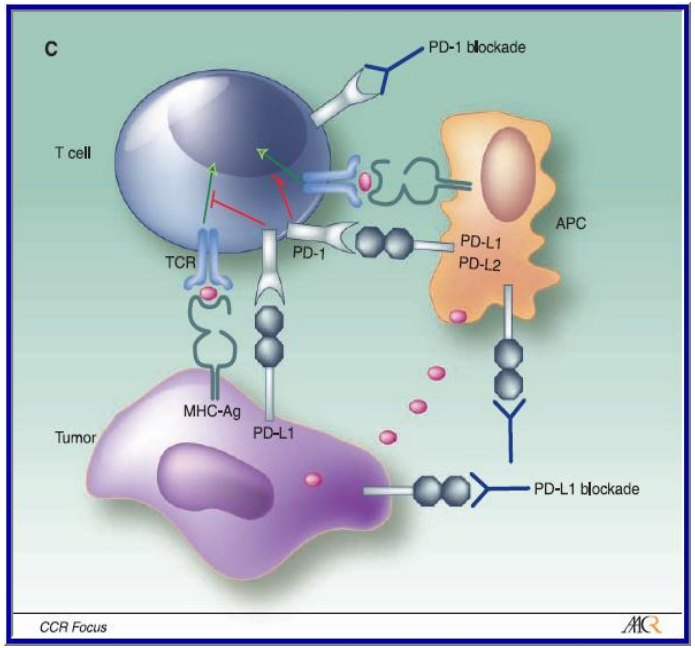
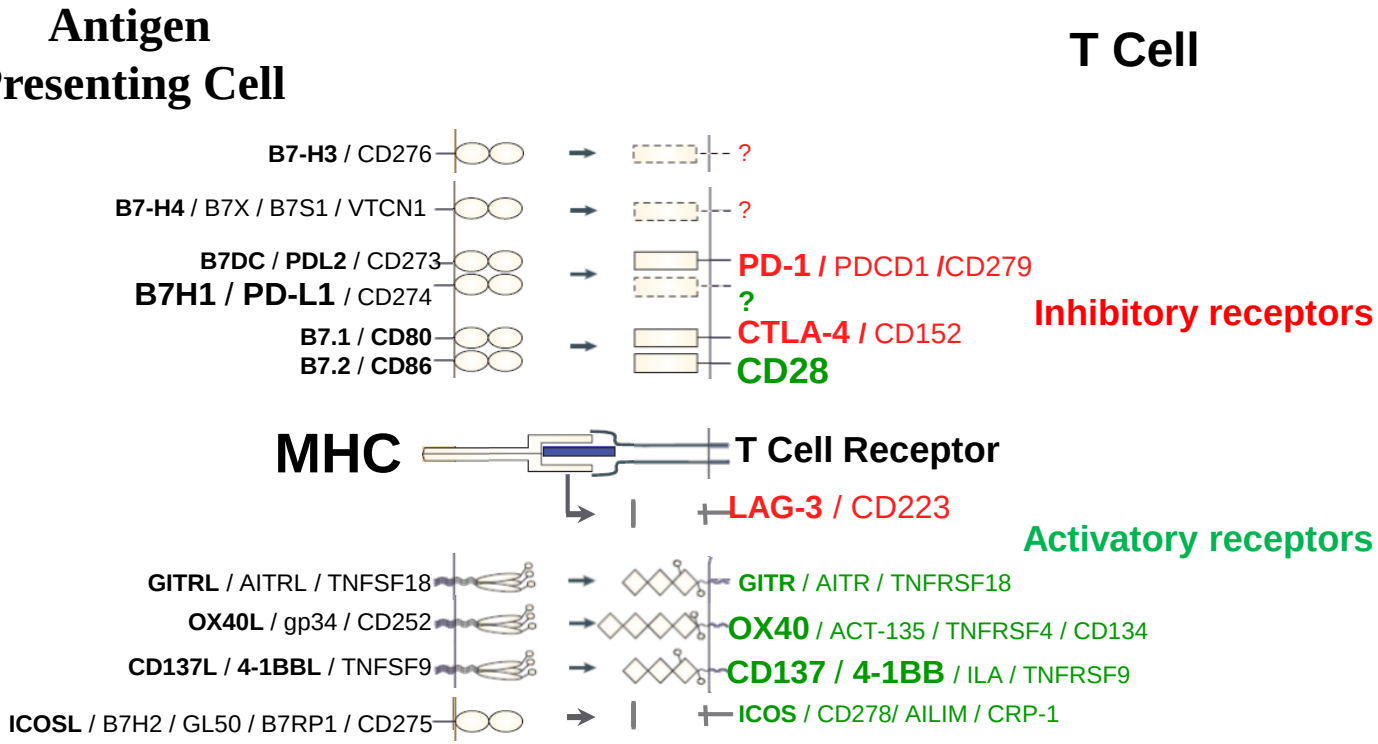
Exploiting Immune Checkpoints Inhibitors in cancer

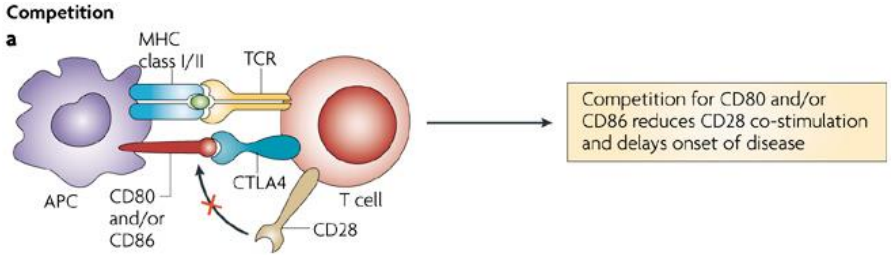


- Survival of cancer cells depends on their ability to evade the antitumor immune response initiated by the host
- A key mechanism of immune evasion - direct inhibition of cytotoxic T cells
- T-cell activation is two-step process:
- 1. **antigen recognition**
- 2**. antigen-independent co-regulatory signa**l that determines whether the T cell will be switched on or off in response to the antigen.
- This second step is overseen by the immune checkpoint pathways, which are either stimulatory or inhibitory

Understanding T- cell immune check-points in the tumour microenvironment and reversing immunosuppression



Anti-CTLA-4 (CD152) Ipilimumab first approved immunoregulatory mAb



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D.,

N Engl J Med. 2010 Aug 19;363(8):711-23.

Median OS 10.0 months - ipilimumab plus gp100, vs 6.4 months gp100 alone (HR for death, 0.68; P<0.001). Median OS with ipilimumab alone was 10.1 months.

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Durable benefit and the potential for long-term survival with immunotherapy in advanced melanoma

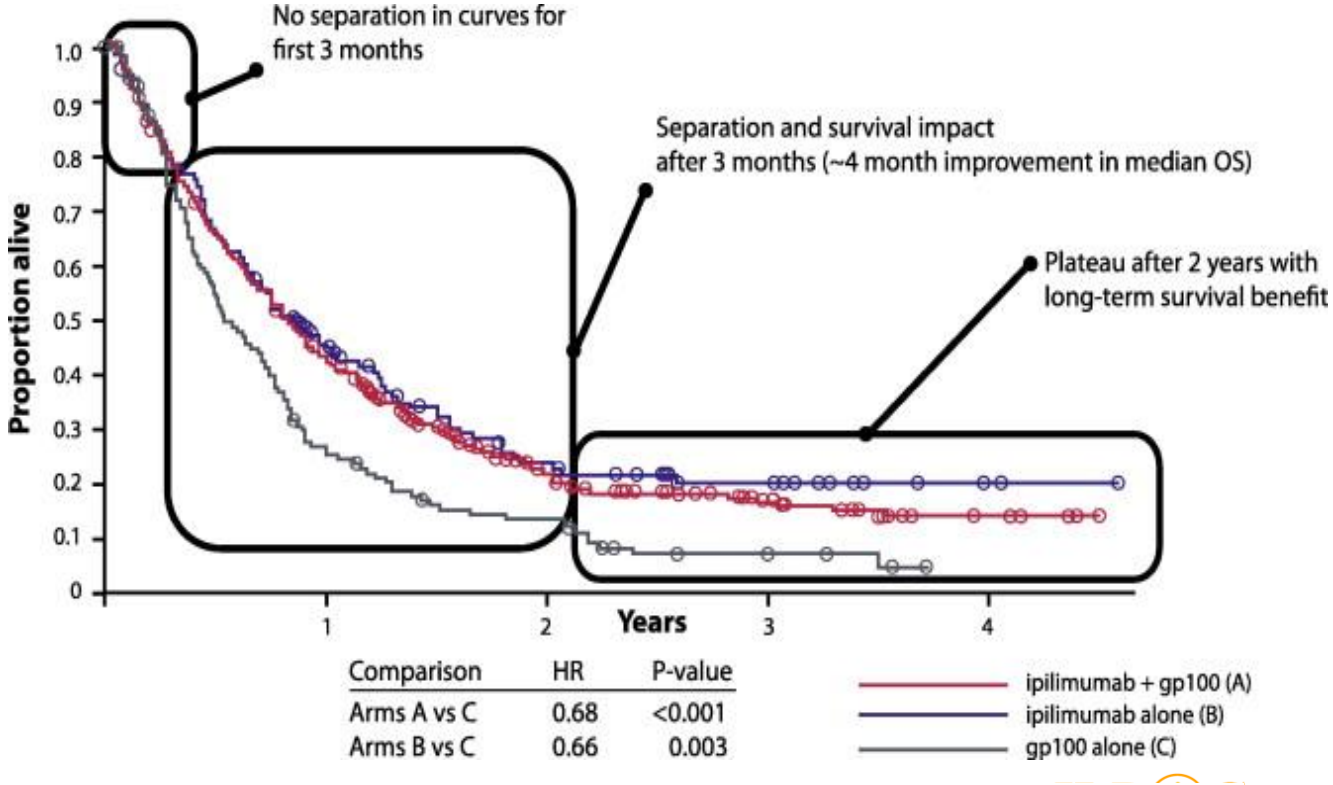

Fig. 2. Kaplan–Meier analysis of overall survival in study MDX010-20.

D McDermott, et al Cancer Treatment Reviews, Volume 40, Issue 9, 2014, 1056–1064

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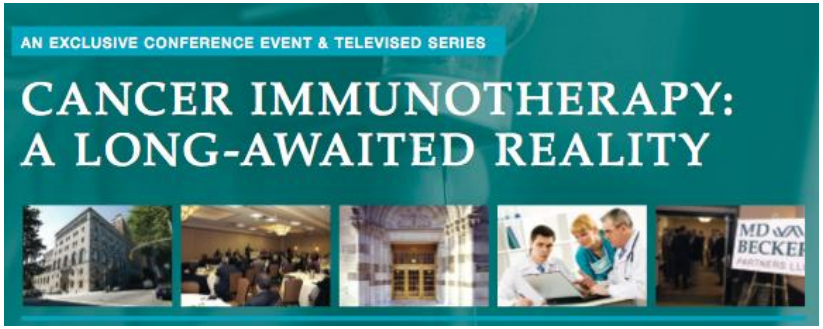
The immunotherapy revolution



Science
AAAS

Breakthrough of the Year 2013

Immunotherapy earns its spot in the ranks of cancer therapy

Feb. 2012

J. Exp. Med. Vol. 209 No. 2 201-209

Drew Pardoll and Charles Drake

Cancer immunotherapy comes of age

Ira Mellman[1], George Coukos[2] & Glenn Dranoff[3]

480 | NATURE | VOL 480 | 22/29 DECEMBER 2011

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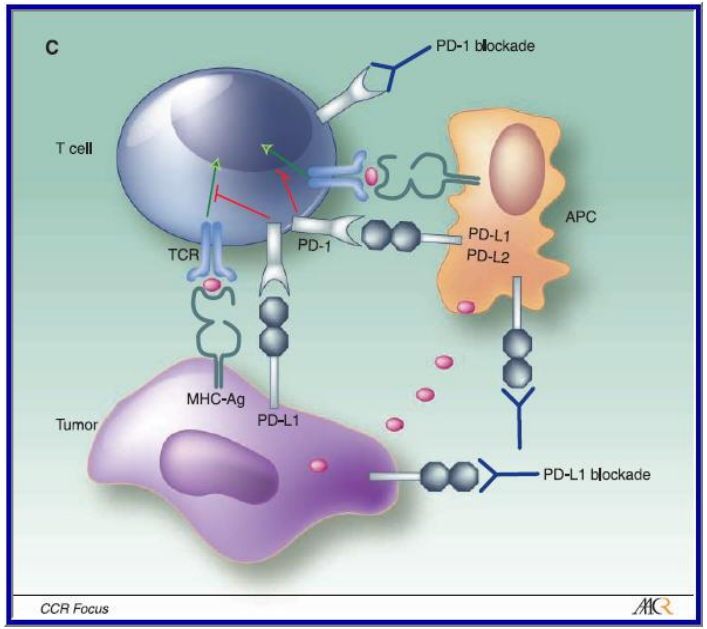
Rationale for Targeting PD1/PD-L1 Pathway in Cancer

- PD1 expressed by Tregs, activated T cells (CD4 and CD8), activated B cells, NK cells
- PD-L1 is expressed by APCs and several cancers



- Upon interaction with ligands, PD-L1 and PD-L2, initiates an inhibitory signaling network that switches off activated T cells
- Results in T cell exhaustion / anergy - poor effector function
- Anti-PD1/PDL1 mAb led to durable clinical responses in NSCLC, RCC, Melanoma, HL

PD1 – programmed death 1; PDL – programmed death ligand; NK – natural killer; APCs - antigen presenting cells

Shekhar S & Yang X. Cellular & Molecular Immunology 2012;9:380–5.

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Lesson learnt from immune check-point inhibition in solid tumours

Anti-CTLA-4

- Hard wired
- Targets CD28 pathway
- Works during priming

- Primarily effects CD4 T cells
- Can move T cells into Tumour
- Responses often slow
- Disease recurrence after response rare

Anti-PD1

- Induced resistance
- Targets TCR pathway
- Works on exhausted T cells
- Does not expand clonal diversity
- Primarily effects CD8 T cells
- Does not move T cells into tumours
- Responses usually rapid
- Disease recurrence after responses significant

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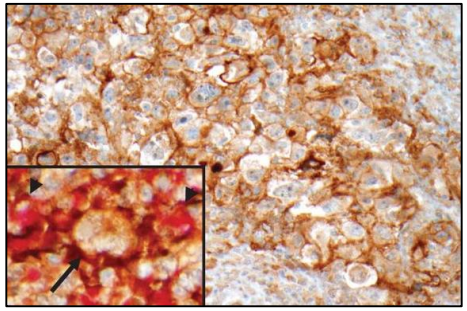
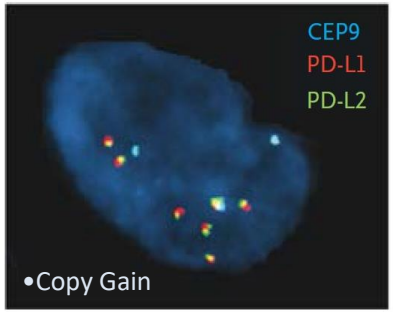
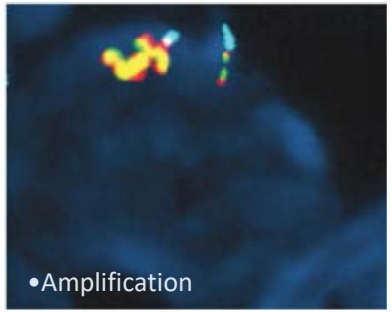
Anti-PD1 in Hodgkin Lymphoma

- **Classical Hodgkin lymphoma (cHL) is characterized by expression of PD-L1 and PD-L2 on malignant Reed-Sternberg cells and on inflammatory cells in the tumor microenvironment**
- **PD-L1 expression in cHL frequently occurs in the setting of genetic amplification of the 9p24.1 locus**
- **HL may have a genetically driven dependence on PD-1 / PD-L1 pathway for survival**







Ansell SM, et al. ***N Engl J Med.*** **2015;372(4):311-319.**

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Nivolumab in R/R HL (CA-209-039): Initial Responses and Response Duration

Phase I trial of nivolumab in patients with relapsed or refractory cHL

	cHL (n = 23)
	76 Weeks
Overall response, n (%)	20 (87)
Partial response rate, n (%)	15 (65)
Complete response rate, n (%)	5 (22)
24-week progression-free survival, %	87%
Duration of response, median (range)	NR (18–82+)

R/R, relapsed or refractory

Ansell SM, et al. ***N Engl J Med.*** **2015;372(4):311-319.**

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PD-1 Blockade With Pembrolizumab in Patients With cHL After BV Failure: Safety, Efficacy, and Biomarker Assessment

- **ORR 65% (n= 31), CR 16% (n=5), PR (48%) n=15, and SD (23%) n=7**
- **With a median follow-up of 9.7 (1.3-17.5) months, median DOR not been reached (0+ to 13.4+ months)**
- **As of the data cut-off, 14 patients (45%) remained on treatment; 2 (6%) patients discontinued for toxicity, 12 (39%) for progression, and 3 (10%) for other reasons**
- **Of the 20 responses, 14 are ongoing**

Armand P, et al. *Blood.* 2015;126:Abstract 584.

Immune-related adverse events

- Overall, grade 3 or 4 irAEs are observed in 7–12% of patients with solid tumors who receive single anti-PD-1 or anti-PD-L1 antibodies.
- A predictable pattern of irAEs has been observed in such patients; dermatologic and gastrointestinal toxicities appear early, and hepatic toxicities or endocrinopathies are seen later
- In patients with lymphoid neoplasms, irAEs of any grade appear in 72%-100% of patients.
- Common irAEs include thrombocytopenia, neutropenia, fatigue, infusion reaction, hypothyroidism, rash, diarrhea, nausea, pyrexia, pneumonitis, diarrhea, fatigue, back pain, decrease in platelets, dry skin, and cough.

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Immune-related adverse events

- Grade 3 or higher irAEs are observed in 11–22% of patients

- LUNG : includes interstitial pneumonia, pneumonitis,
- BOWEL colitis, gastrointestinal inflammation, stomatitis , increased alanine aminotransferase/aspartate aminotransferase levels, pancreatitis,
- RENAL nephrotic syndrome,
- PANCREAS fulminant type 1 diabetes mellitus,
- BONE MARROW : myelodysplastic syndrome, leukopenia, thrombocytopenia,
- OTHER : septic meningitis, pyrexia, infusion reaction, joint swelling, pain, tumor progression, and arrhythmia.

Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study.

Lesokhin A et al J Clin Oncol. 2016 Aug 10;34(23):2698-704.

- Phase 1 study, 81 patients with B-cell malignancies
- (NHL *n* = 31, including DLBCL [*n* = 11], and FL [*n* = 10]) other B cell NHL, T cell lymphoma (*n* = 23), and multiple myeloma (*n* = 27); treated with Nivolumab 3 mg/kg (NCT01592370).
- All patients had received prior systemic treatment regimens (median 3; range, 1–12).

Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study.

Lesokhin A et al J Clin Oncol. 2016 Aug 10;34(23):2698-704.

DLBCL

- N=11; ORR 36% (n=4), 2 CR, and 2 PR.
- Median follow-up duration of 22.7 weeks, response durations were 6 and 77.3+ weeks for CR patients and 12.1+ and 22.1 weeks for PR patents.

FL

- ORR 40% (n=4), including 1 CR and 3 PR.
- Median follow-up duration of 91.4 weeks, individual response durations were 81.6+ weeks for the patient with CR and 27.1+, 28.1+, and 32.1+ weeks for the patients with PR.

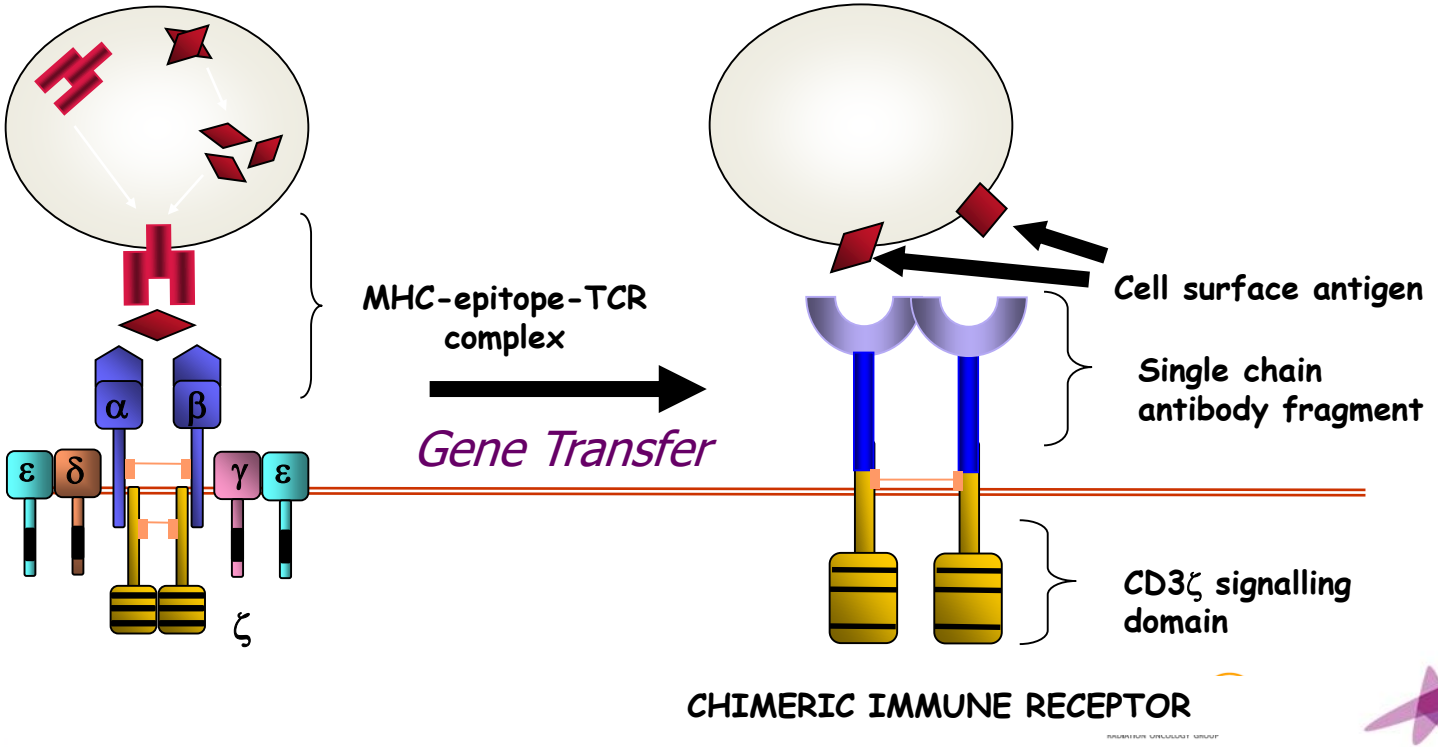
Chimeric Antigen Receptors T cells (CAR-T) in Cancer Therapy

- Adoptive cellular therapies such as tumour infiltrating lymphocytes and TCR gene-modified T-cells have demonstrated success in recent clinical trials

- Problem : Tumours often down-regulate MHC molecules and tumour specific antigens are often not known.

- Solution : Chimeric antigen receptors target cell surface proteins using antibody based recognition systems can overcome some of these problems.

CAR-T Technology



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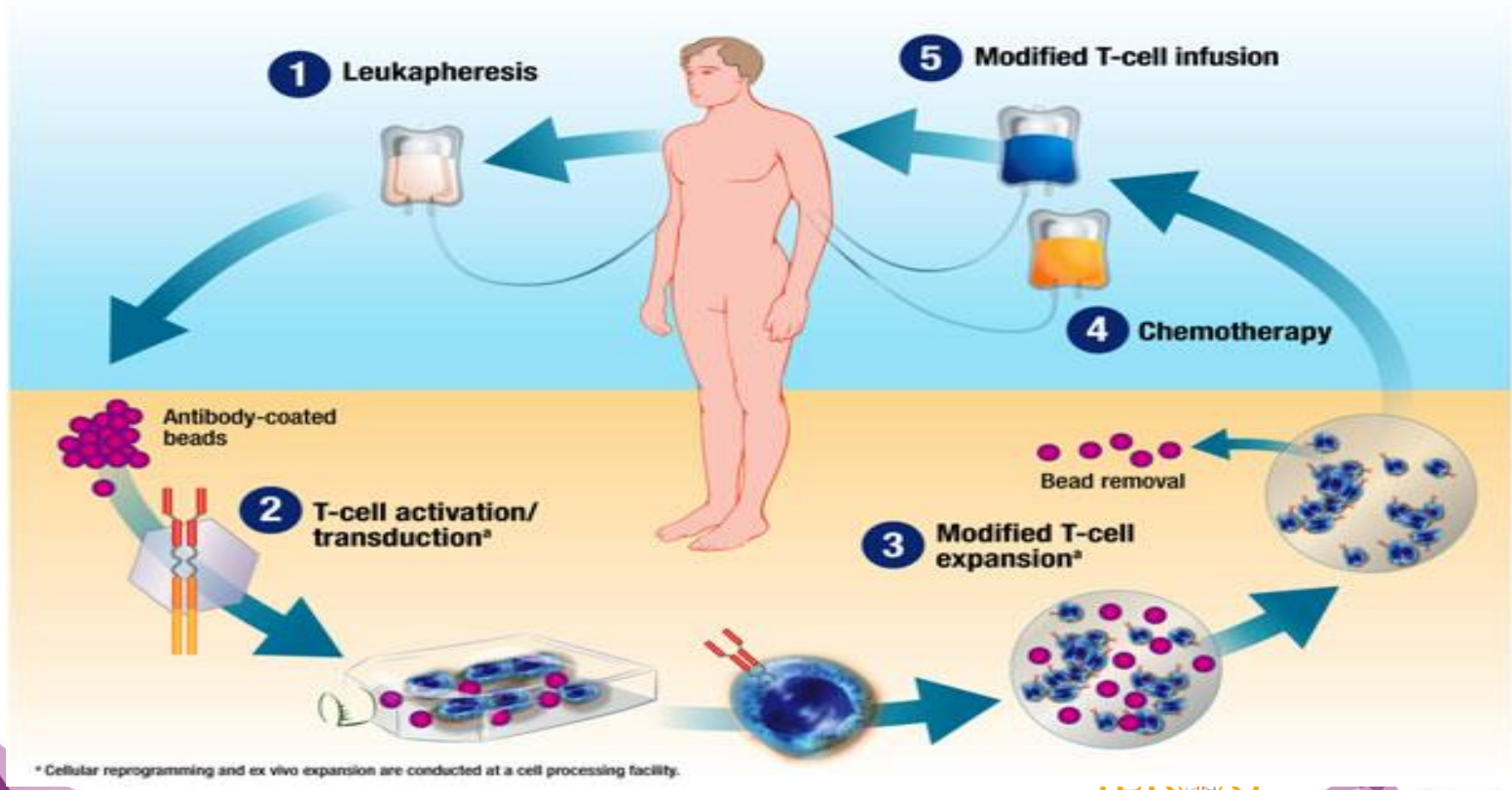
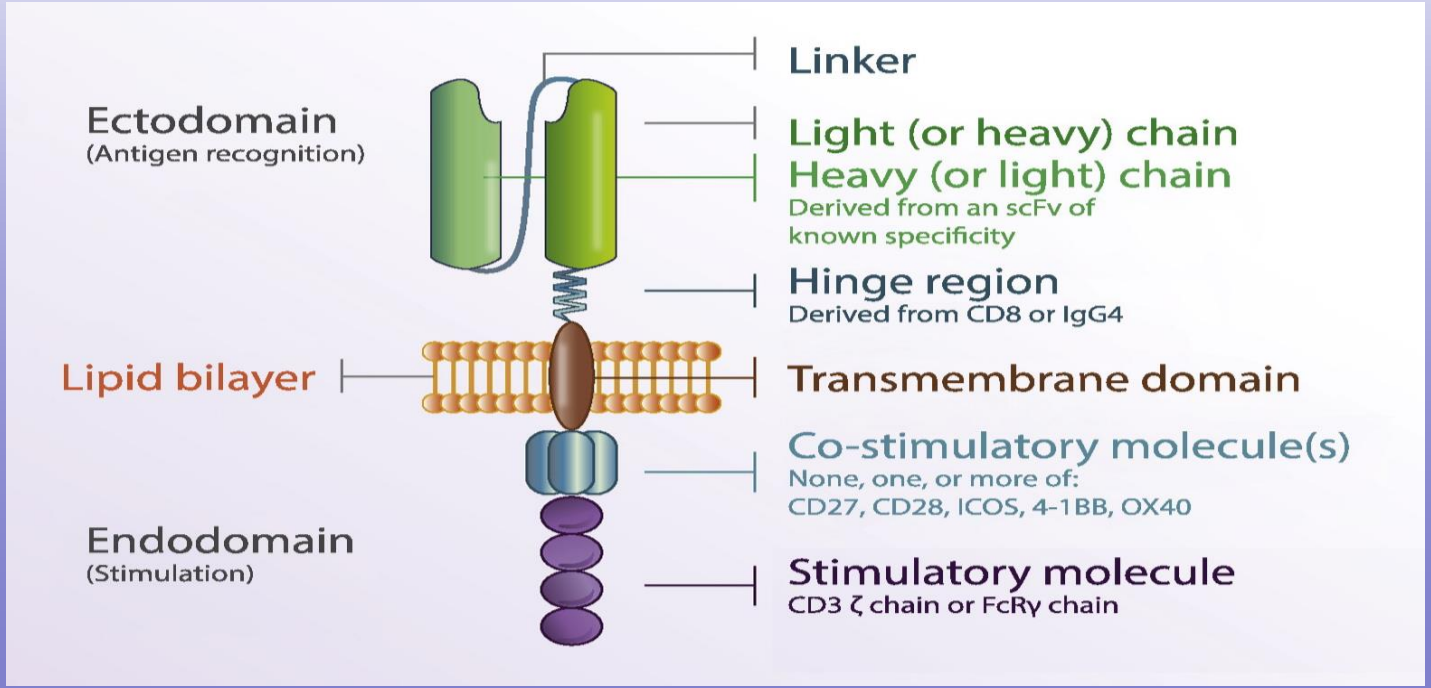

1 Leukapheresis
5 Modified T-cell infusion
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction*
Bead removal
3 Modified T-cell expansion*
* Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

CAR T cells: basic concepts



CAR19 toxicity

B-cell Depletion

- Targeting of normal B-cells
- Duration correlates with persistence
- IVIg can be given to pts with persistent hypo-gammaglobulinaemia
- No serious infectious complications arising following this in trials reported to date

Neuro-toxicity

- Obtundation, cranial nerve palsy, aphasia, seizures
- Not related to presence of CNS disease
- CSF pleocytosis – CAR+ and CAR- T cells
- Self-resolves within weeks

Immune Syndromes

---->

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Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia Shannon L. Maude et al NEJM . 2014 ; 371(16): 1507–151

- Sustained remission was achieved with a 6-month EFS of 67% and an overall survival rate of 78%.
- At 6 months,
  - probability of persistence of CTL019 was 68%
  - probability that a patient would have relapse-free B-cell aplasia was 73%.

- All the patients had the cytokine-release syndrome, Severe cytokine-release syndrome developed in 27% of the patients, (associated with a higher disease burden before infusion and was effectively treated with the anti–interleukin-6 receptor antibody tocilizumab.)

- Chimeric antigen receptor–modified T-cell therapy against CD19 was effective in treating relapsed and refractory ALL. CTL019 was associated with a high remission rate, even among patients for whom stem-cell transplantation had failed, and durable remissions up to 24 months were observed

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Immune Activation Syndrome

- Fever/myalgia→ MOF with hypoxia/hypotension. Resembles HLH
- Associates with ↑ IL-6, IFN-γ, IL-10
- Severity may correlate with tumour burden
- ↑CRP + fever > 3 days predictive of those requiring Rx
- Proposed diagnostic criteria for severe Immune activation syndrome:

Fever for over 3 days
Maximal elevation of serum cytokines
One of the following clinical manifestations:

- Hypotension requiring vasporessor therapy
- Hypoxia with sat O2 <90%
- Neurological disturbance including delirium, obtundation, seizures

Treatment

- short course steroids – may compromise persistence of CAR T cells
- IL-6R antagonism via tocilizumab

Davila *et al* Science Transl Med 2014

CAR-T Cells in DLBCL

	JULIET (CTL019) (n=51)	TRANSCEND (JCAR017) (n=54)	ZUMA-1 (KITE-C19) (n=101)
Best ORR (%)	59	76	82
ORR at 3 months (%)	45	51	-
ORR at 6 months (%)	-	-	36
CR (%)	43	52	49
CR at 3 months (%)	37	39	-
CR at 6 months (%)	-	-	31
Grade 3/4 CRS/neurotoxicity (%)	26/13	2/16	13/28
Tocilizumab/steroids (%)	16/11	11/24	43/27

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CAR19: challenges

- **Bespoke individualised therapies – complex logistics**
  - Automated manufacture
  - Expensive
  - Allogeneic CAR-T
- **Antigen escape relapses**
  - Targeting multiple antigens – single CAR construct, multiple CAR constructs, multiple cellular products
- **Clinical challenges**
  - Durability of responses?
  - Defining cell dose, optimal lymphodepletion
  - Positioning in overall treatment pathway
  - Optimal approach to limit or manage toxicities

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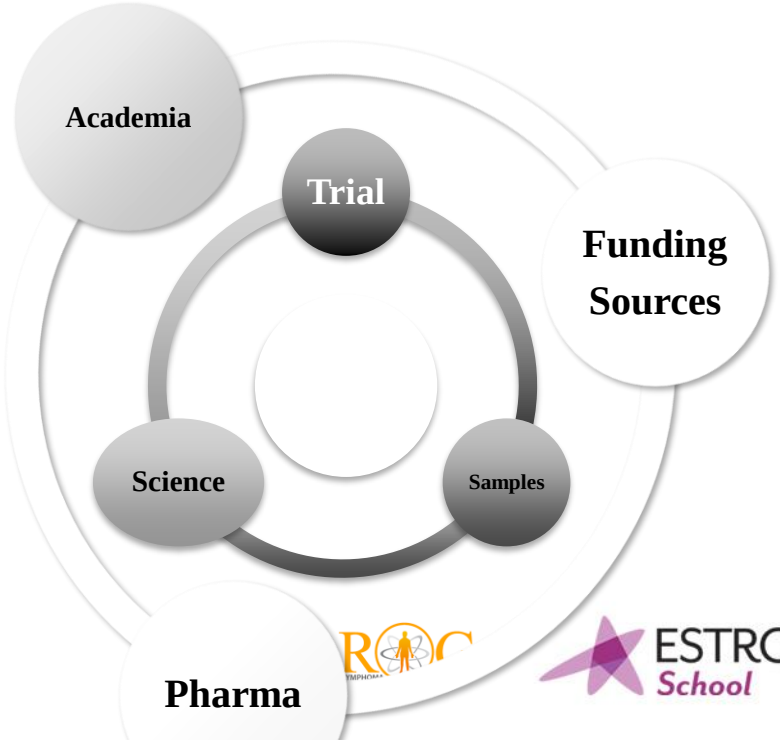
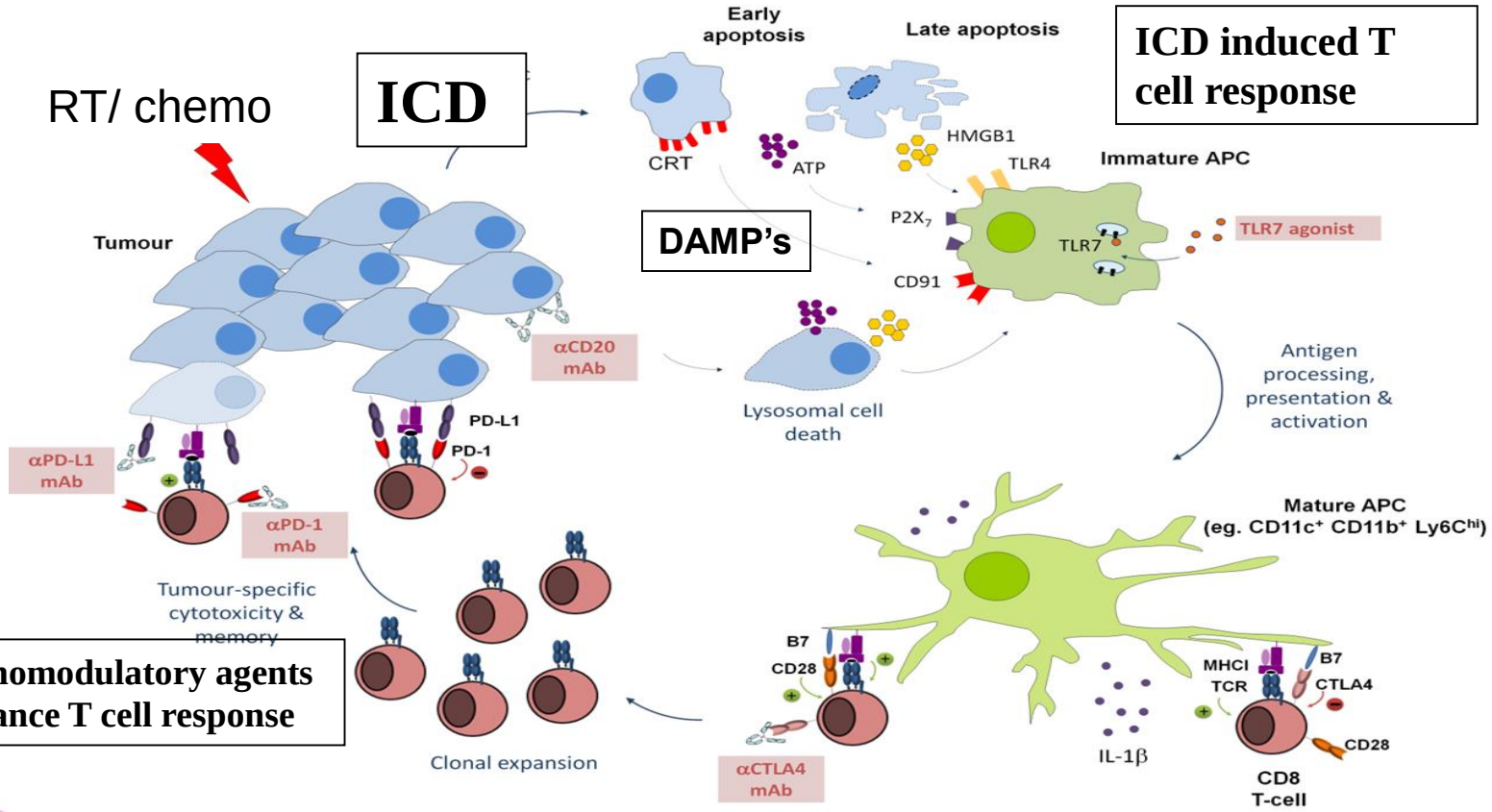
The future of immunoregulation in lymphoma

- The immune explosion in oncology – ICI, CAR-T cells
- Combinatorial immensity
- Too big to fail
- Too big (and costly) to succeed?
  - Study design
  - Collaboration
  - Biomarker driven
  - Further scientific discovery required

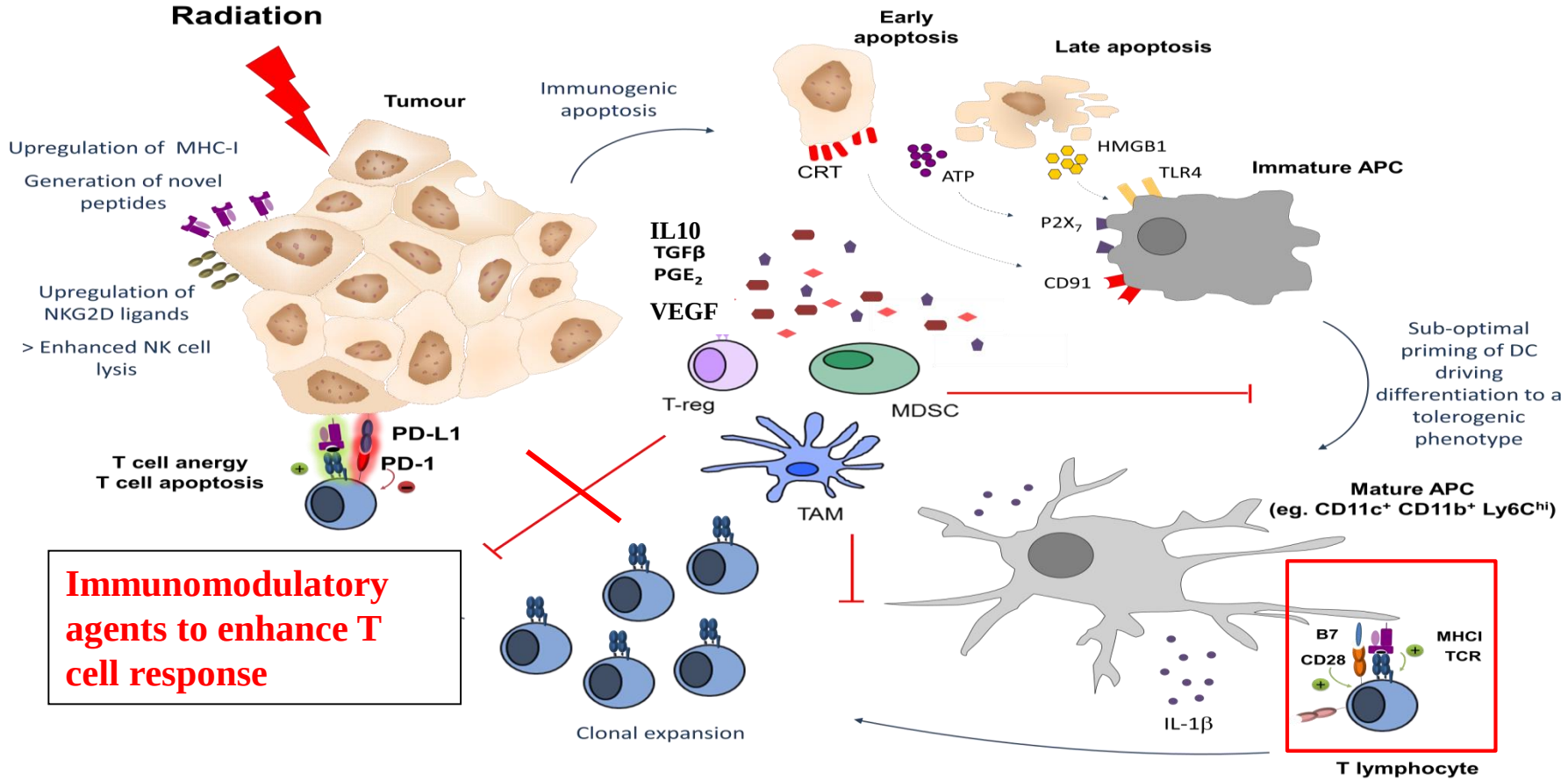


Slide courtesy of Phillip Armand

Potential Effects of Radiotherapy to stimulate the Immune System



Enhancing the immune response of Radiotherapy using immunomodulatory agents



Is it possible to overcome Immunosuppression in the tumour microenvironment with immunomodulatory agents ?

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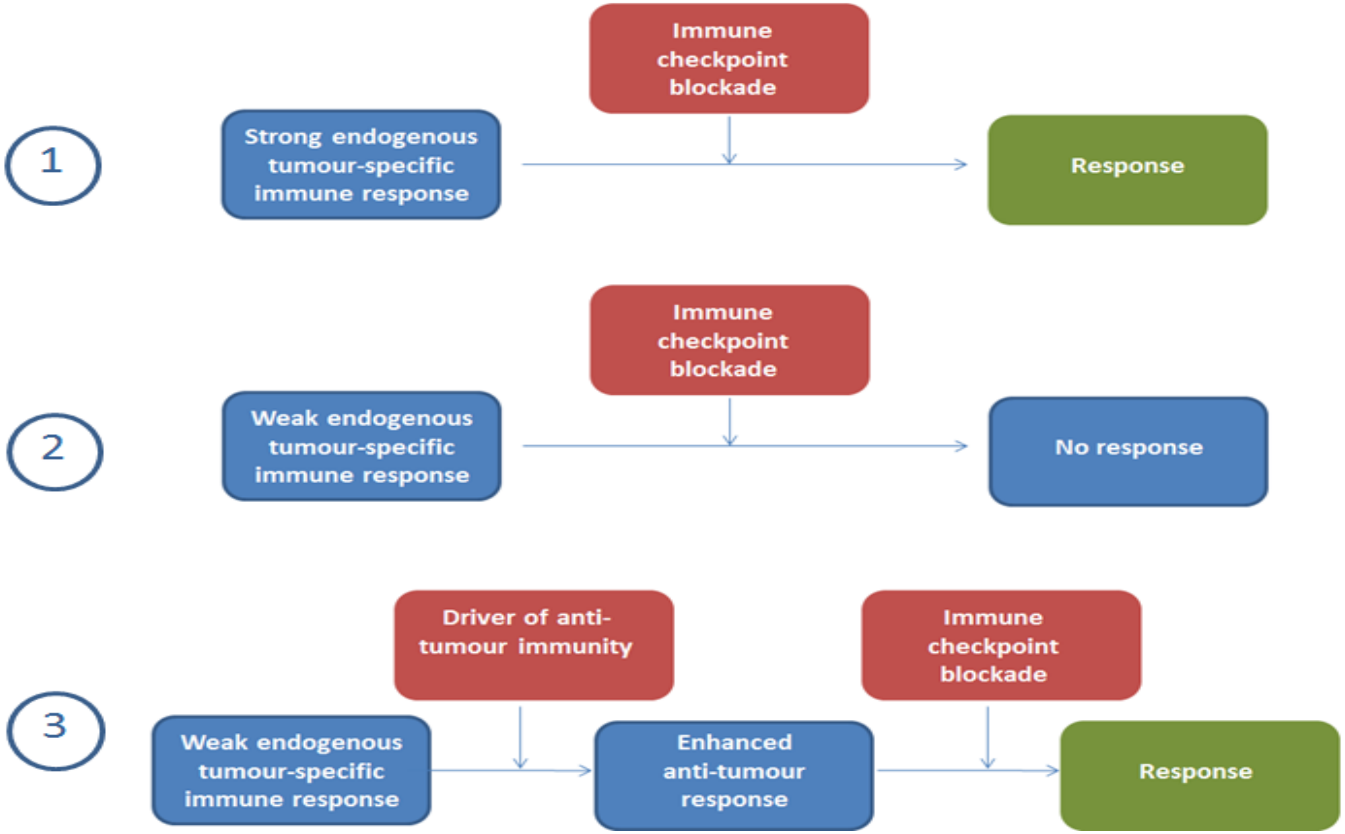
Rationale for RT and immunotherapy combination approaches



Optimal results will require combinations – RT an ideal partner ?

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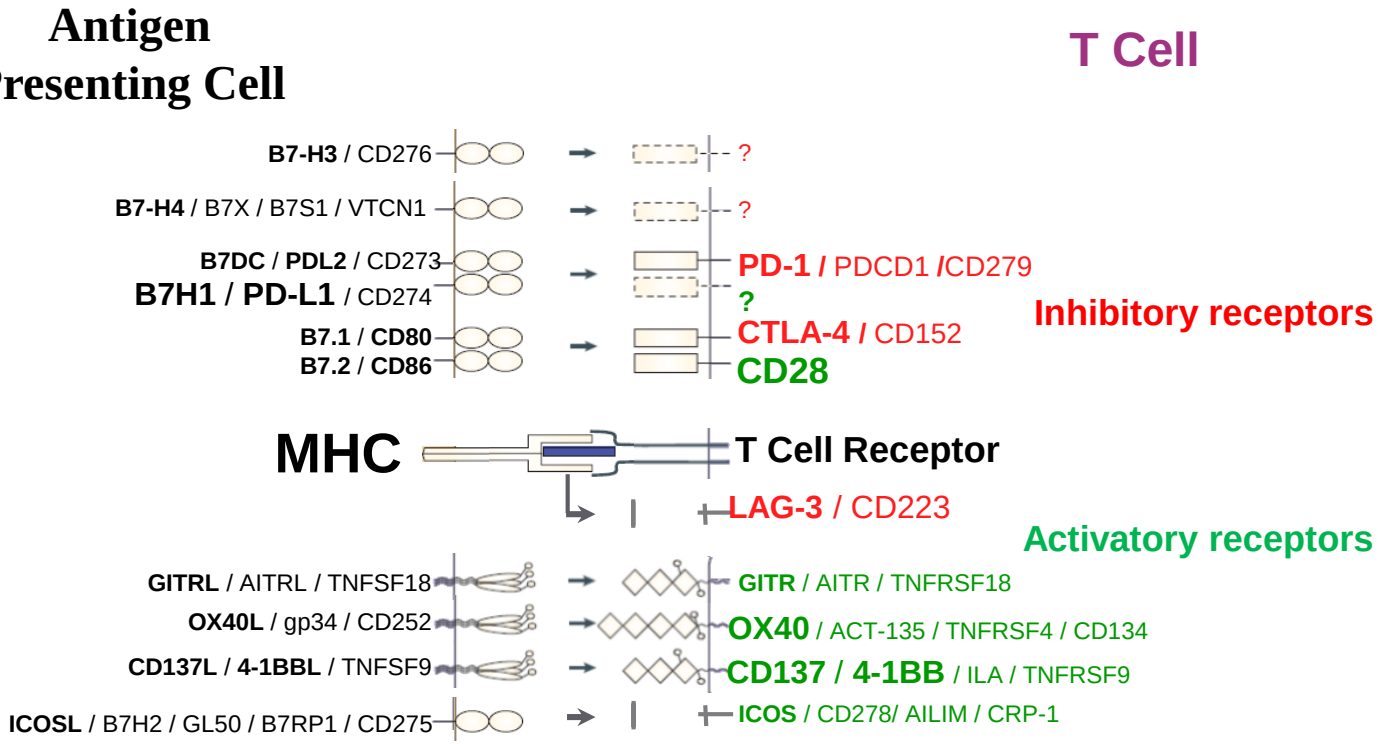
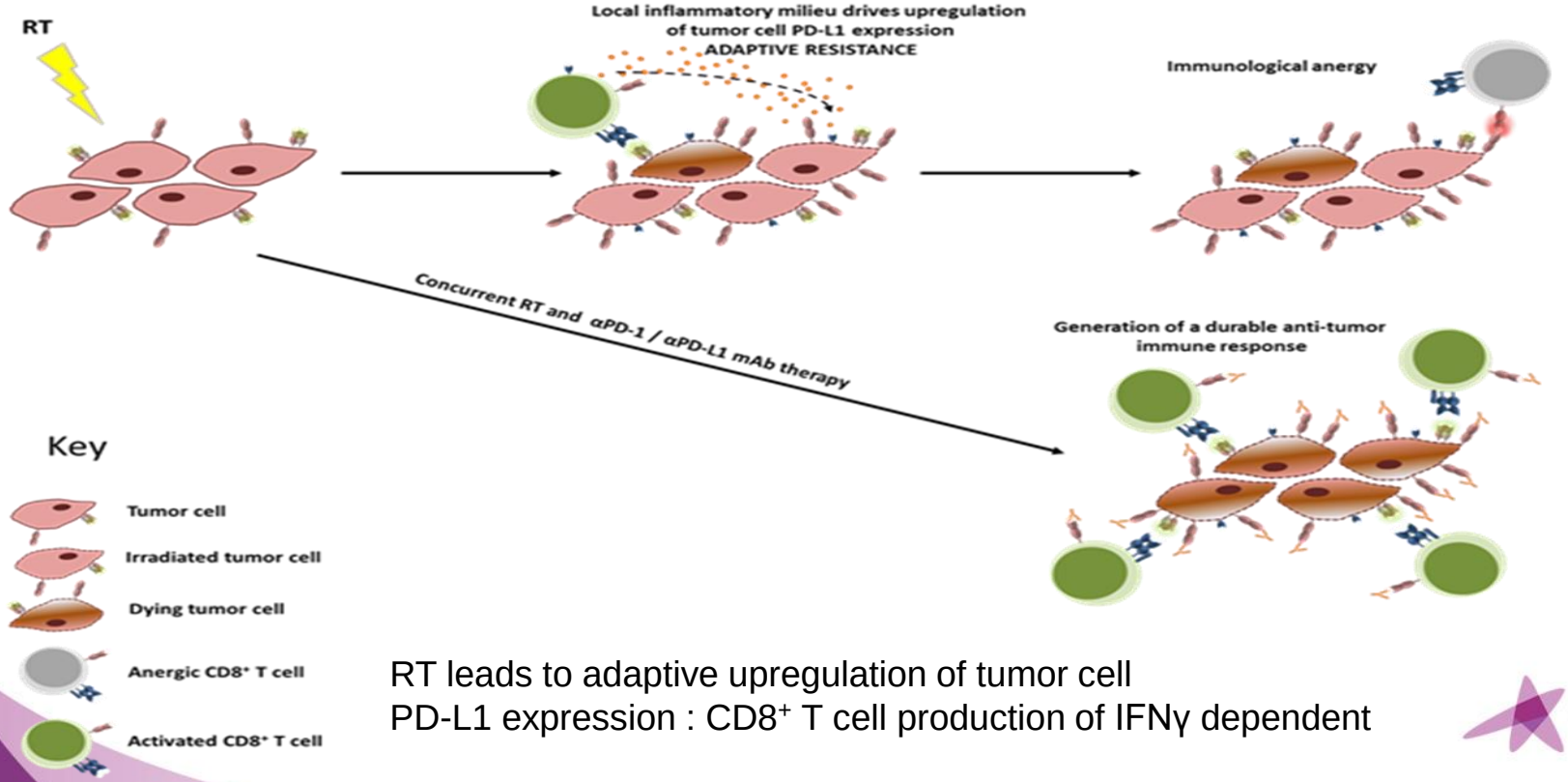
Understanding T- cell immune check-points in the tumour microenvironment and reversing immunosuppression



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



RT leads to adaptive upregulation of tumor cell
PD-L1 expression : $CD8^+$ T cell production of IFNγ dependent

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

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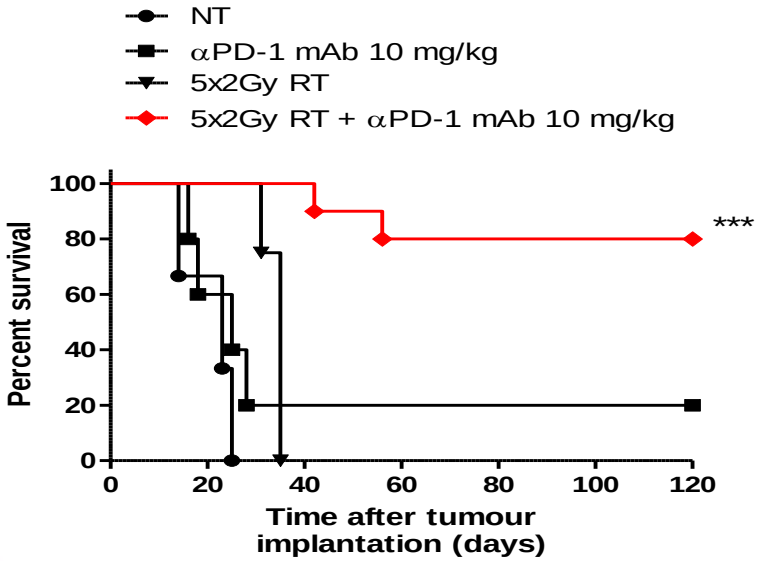
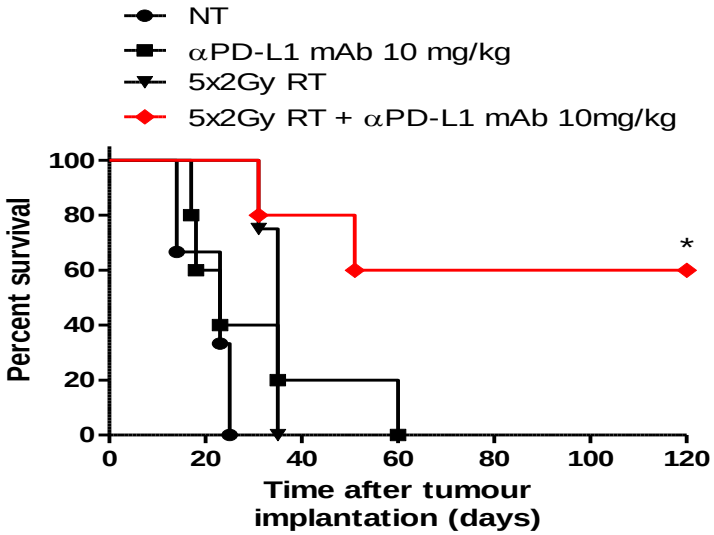
Cancer Research





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

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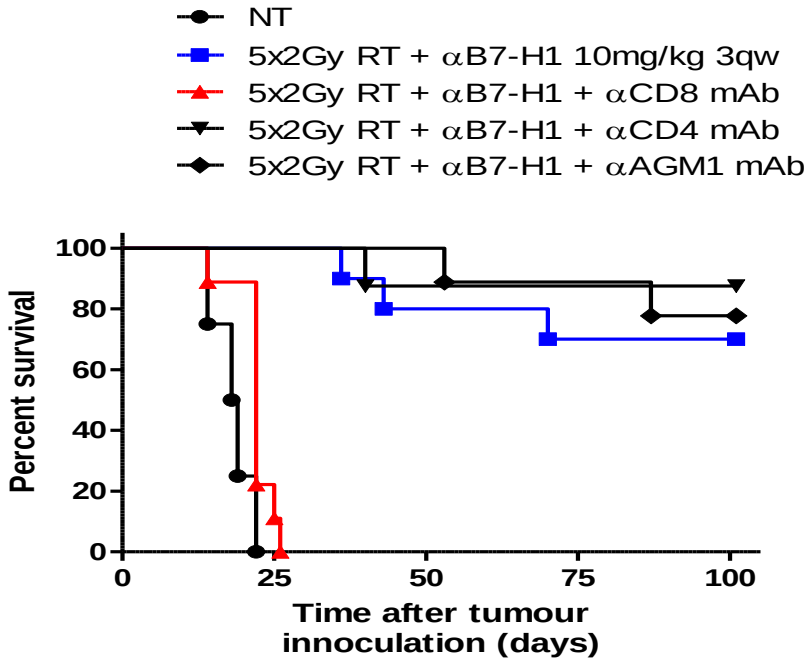
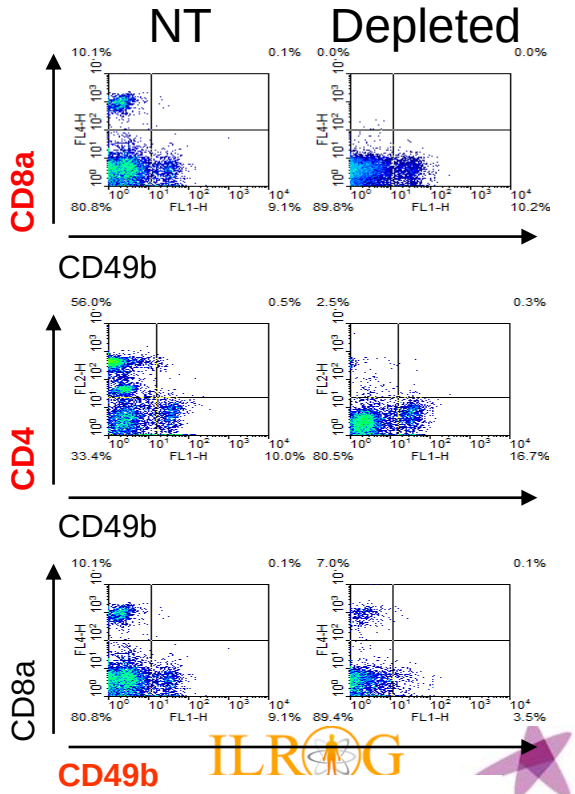
Cancer Research





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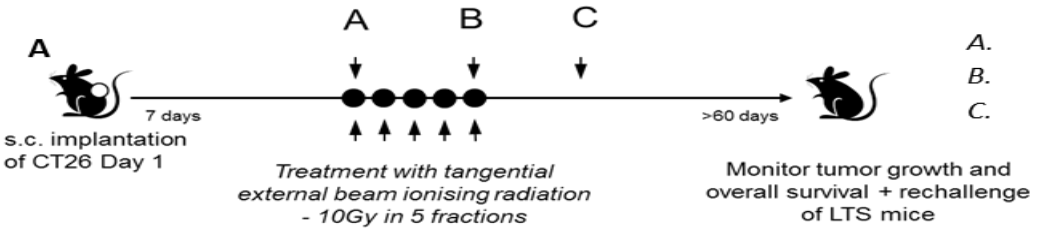
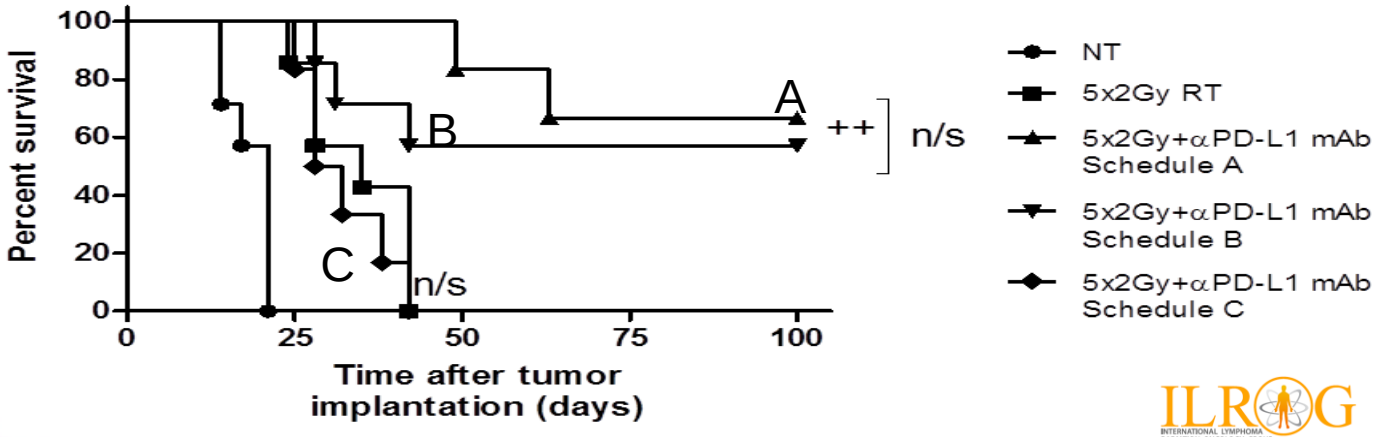
Efficacy of RT and anti-PD-L1 combination is CD8+ T cell dependent

Scheduling of RT and anti-PD-L1 combination determines outcome



A. αPD-L1 mAb starting on day 1 of RT
B. αPD-L1 mAb starting on day 5 of RT
C. αPD-L1 mAb starting 7 days after the last dose of RT

B



A Phase II Study of Pembrolizumab and Involved Site Radiation Therapy (ISRT) for Early Stage Relapsed or Primary Refractory Hodgkin Lymphoma

PI: Craig Moskowitz, MD , Co-PI: Joachim Yahalom, MD, Santosh Vardhana MD, PhD , Gunjan Shah MD, MS

Study hypothesis

- HDT/ASCT may be overtreating a subset of patients who have excellent outcomes in relapsed HL
- Radiation therapy alone can induce durable remissions, particularly in patients with early stage disease at relapse
- Radiation therapy induces a diverse repertoire of anti-tumor T cells, but progression is associated with upregulation of the immune checkpoint PD-L1
- Combination of ISRT with anti-PD1 will lead to durable remissions

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Aims

1. Evaluate the **complete remission rate** of pembrolizumab combined with ISRT as an alternative to HDT/ASCT in early stage rel/ref HL patients
2. Determine the **single agent response rate** of pembrolizumab in this population
3. Determine the **toxicity and 2-year EFS** with this strategy
4. Evaluate **biological markers of response and resistance:**
    1. Tumor and TME immune evasion markers
    2. Development of anti-tumor T-cell clonal expansion
    3. T-effector:T-reg ratio
    4. Serum TARC

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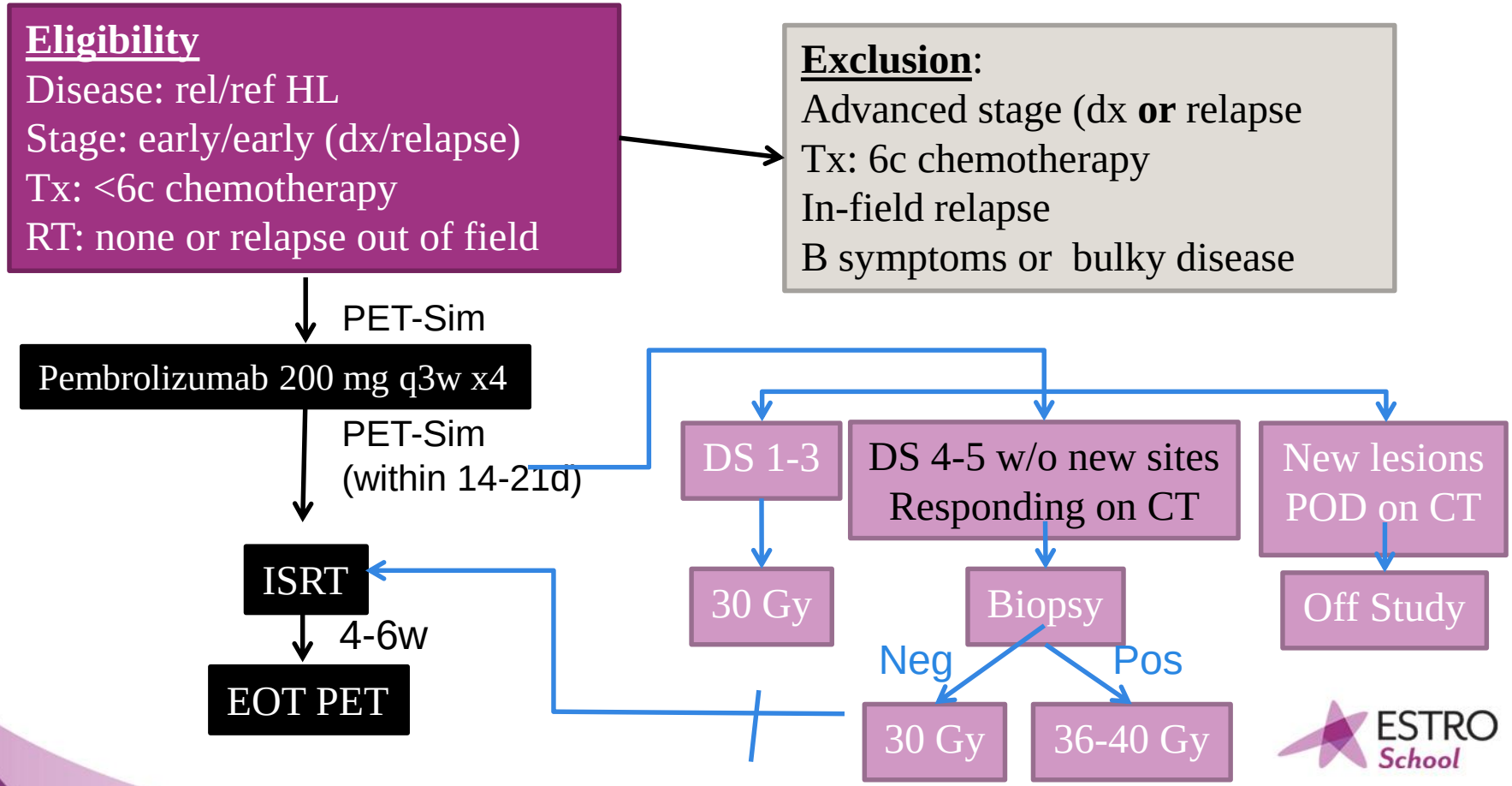
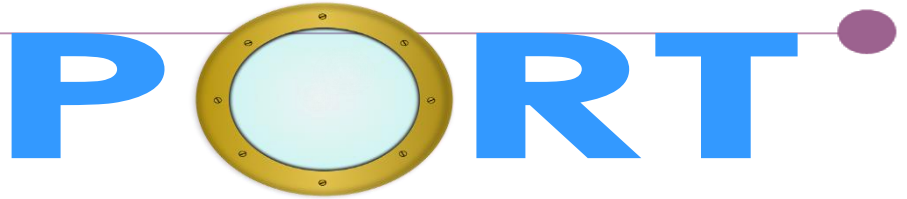
Eligibility and treatment schema



Phase II Trial of Pembrolizumab and Radiotherapy in Cutaneous T cell lymphoma



Chief investigator Professor Tim Illidge

Trial Sponsor:	University College London
Trial Sponsor reference:	UCL/17/0053
Trial funder(s):	Merck Sharp & Dohme Limited
Funder(s) reference:	MISP# 52167
Clinicaltrials.gov no:	NCT03385226
EUDRACT no:	2017-000433-30
CTA no:	TBC

PORT Trial design

- All registered patients will receive 4 infusions of pembrolizumab given at 3 weekly intervals at a dose of 200mg.
- At 12 weeks, patients will start radiotherapy ：12Gy in 3 fractions.
- Patients who progress on pembrolizumab before week 12 will start radiotherapy as soon as possible after progression.
- Following completion of radiotherapy patients will continue pembrolizumab until disease progression or unacceptable toxicity.

Week	0	3	6	9	12	15	18	21	24
Pembrolizumab 200mg i.v.	x	x	x	x	x	x	x	x	x
Radiotherapy 12 Gy in 3 fractions					x				

Trial Endpoints

Primary

- Global assessment of overall response of the combination of pembrolizumab plus radiotherapy at 24 weeks

Secondary

- Response after 12 weeks of pembrolizumab
- Change (improvement) in response with combinational RT
- Duration of response for the combination treatment/time to next treatment
- Abscopal effect (measured by ‘shrinking’ of 5 pre-defined lesions which have not been irradiated using a 5 point score).
- Safety
- Progression-Free & Overall survival

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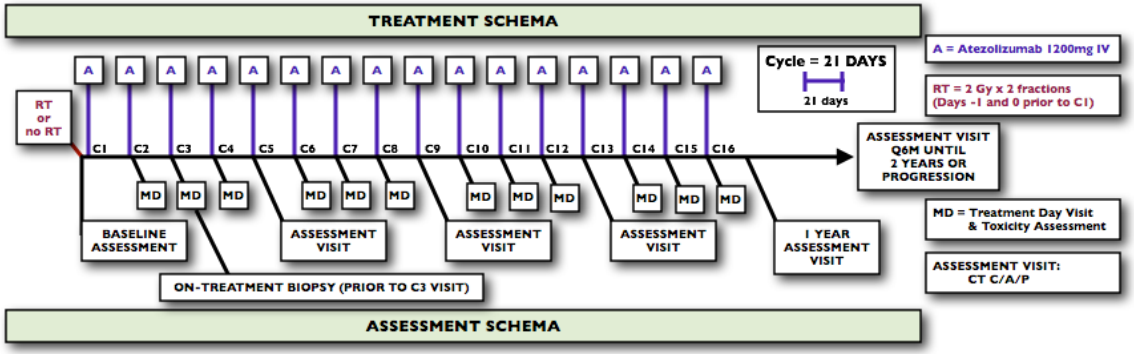
Designing a clinical trial of RT + checkpoint blockade for relapsed and refractory FL

Hypothesis

Low-dose RT plus anti-PD-L1 Ab (atezolizumab) is safe and able to improve systemic responses compared to atezolizumab alone

Two-Arm Parallel Phase 2 Clinical Trial of Atezolizumab with or without Low Dose Local Radiotherapy (2 x 2Gy) in Patients with Relapsed/Refractory Advanced Stage Follicular Lymphoma

PI: M. Lia Palomba



Primary Objective	ORR for atezolizumab vs atezolizumab + single site IRT (2x2Gy)
Secondary Objectives	PFS and OS for atezolizumab vs atezolizumab + single site IRT (2x2Gy), Safety
Exploratory objectives	Mandatory biopsies. Immune monitoring correlatives.

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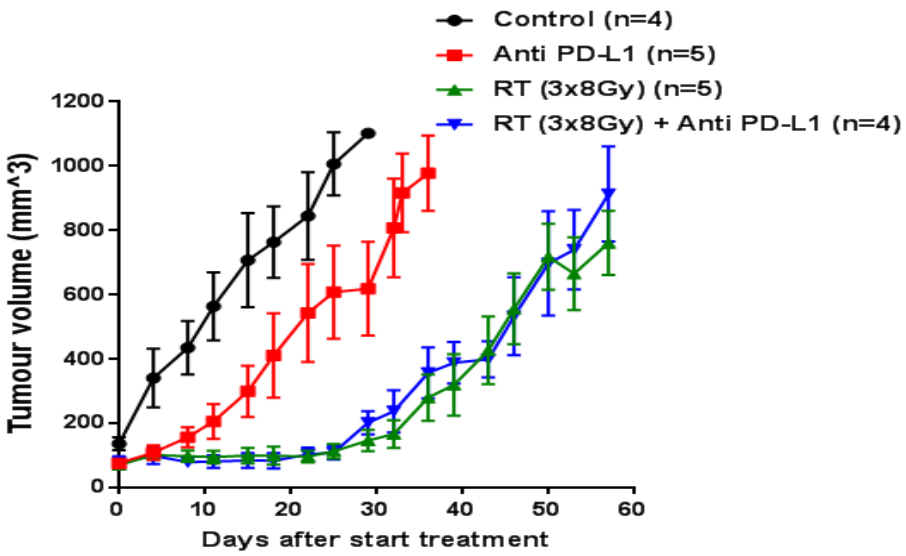
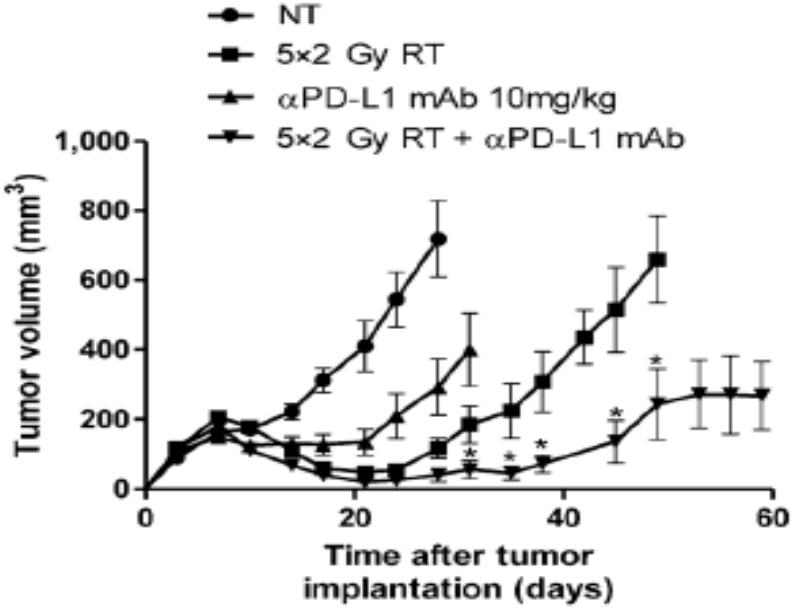
Beyond immune checkpoints inhibitors ?

RT and anti-PD1 combinations do not work with immunologically “cold” or T cell low tumours ?

Immune checkpoint blockade in combination with RT does not improve survival in murine prostate model





TRAMP-C1 Prostate

Melanoma

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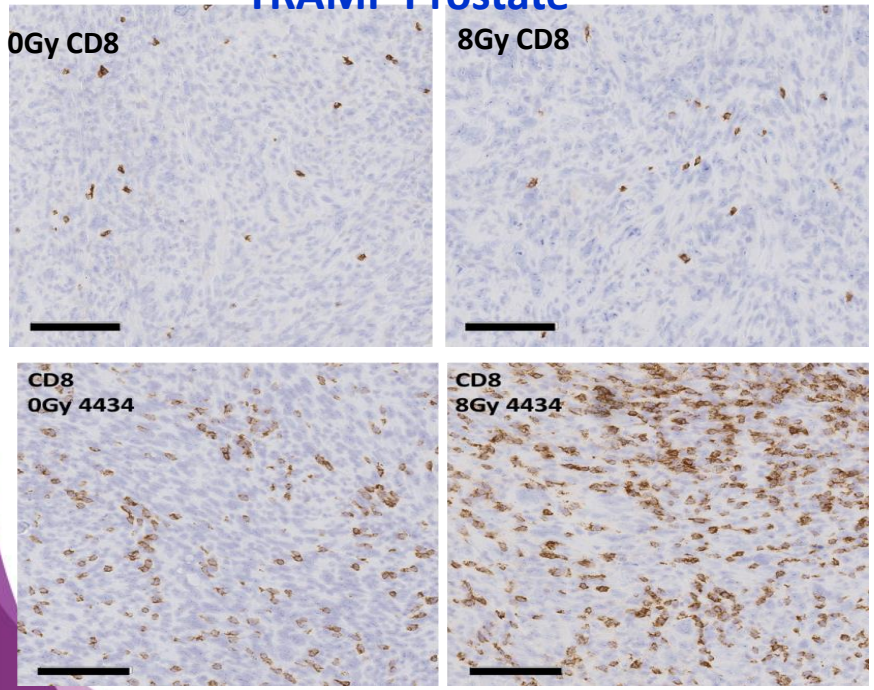
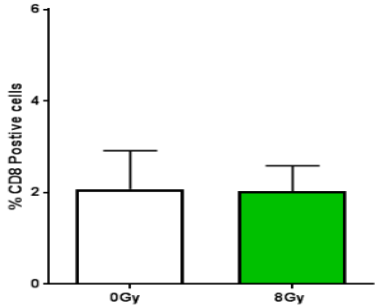
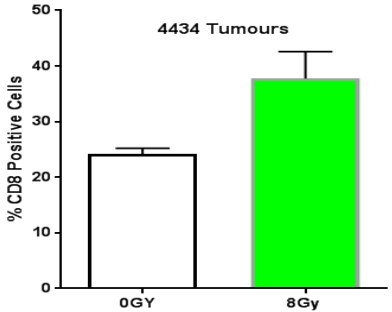
Prostate tumours have lesser proportion of CD8+ T-cells compared to melanoma

TRAMP Prostate



4434 Melanoma





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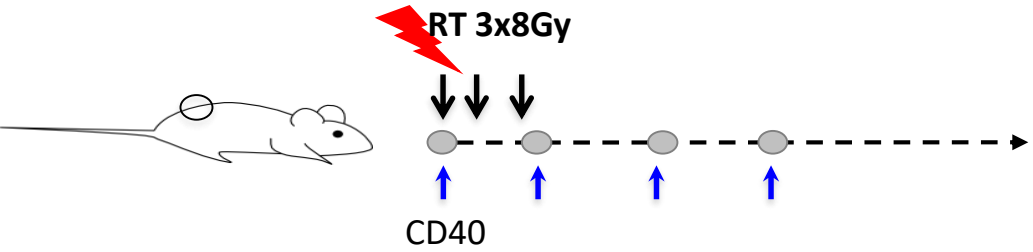
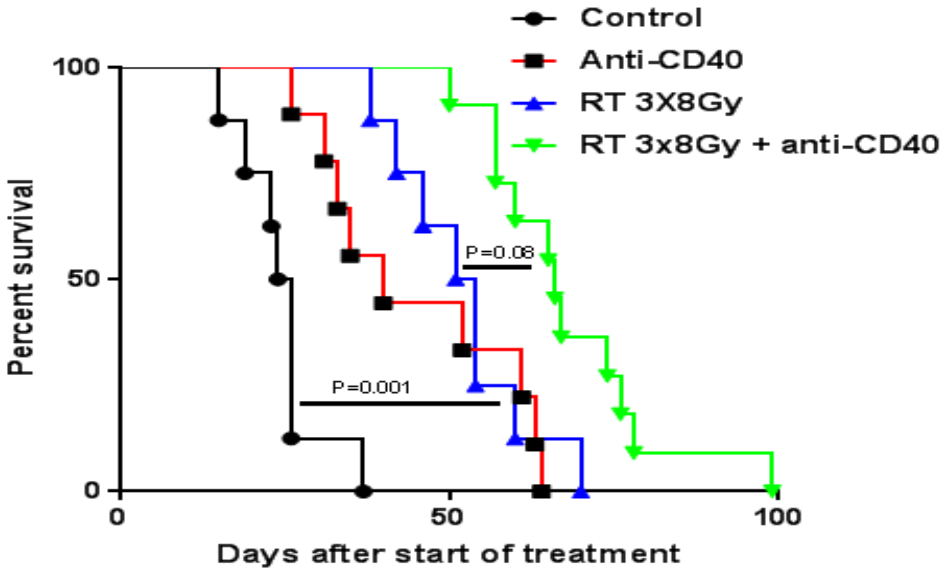
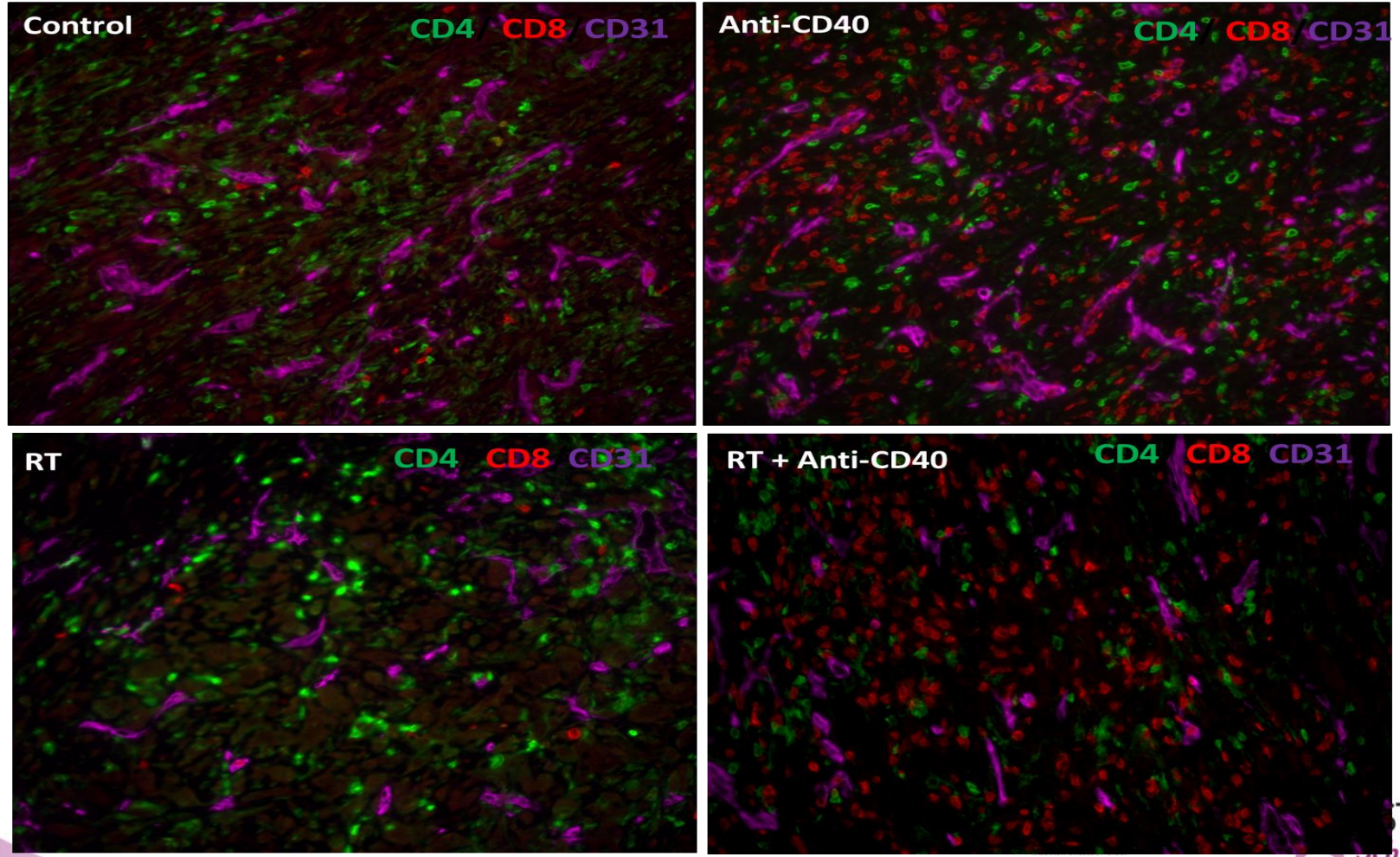
Therapeutic efficacy of administering anti-CD40 in combination with hypo-fractionated radiotherapy

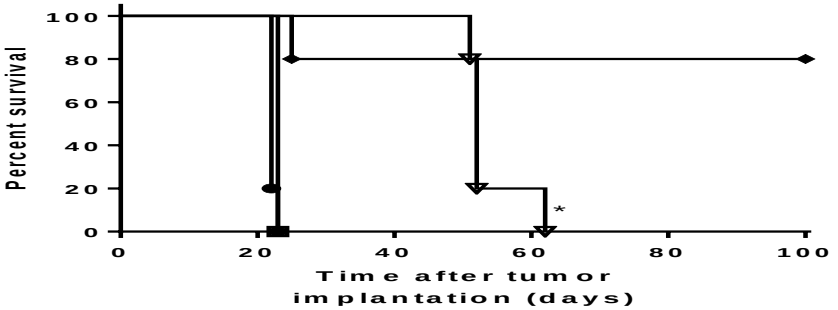


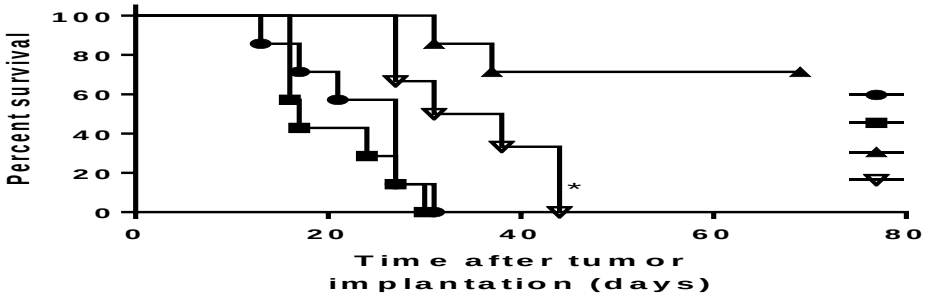


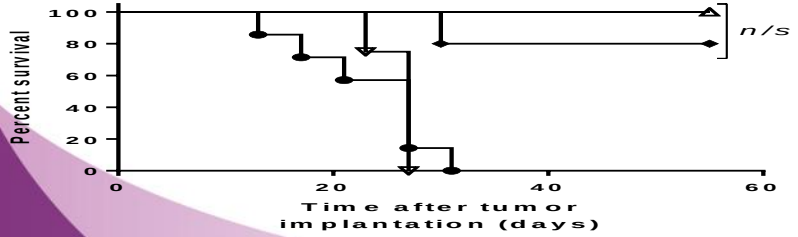

Control
CD4 CD8 CD31
Anti-CD40
CD4 CD8 CD31
RT
CD4 CD8 CD31
RT + Anti-CD40
CD4 CD8 CD31

Dendritic cell depletion abrogates the therapeutic effect of RT and anti-CD40 combinations

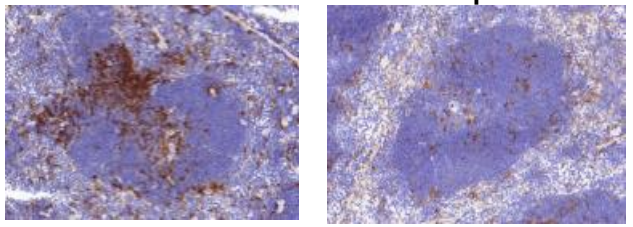
S. J. Dovedi, G.L. Bhalla, S.A. Beers, E. J. Cheadle, L Mu, M.J. Glennie, T.M. Illidge, J. Honeychurch.
(Cancer Immunol Res. 2016 Jul;4(7):621-30)

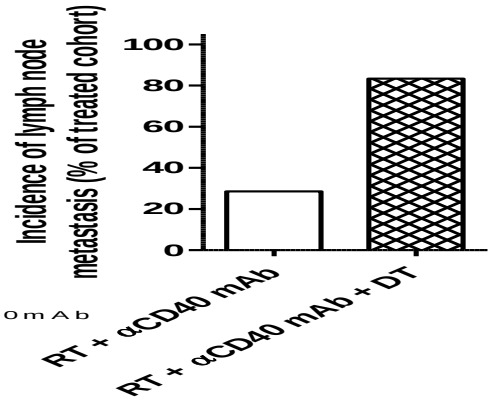




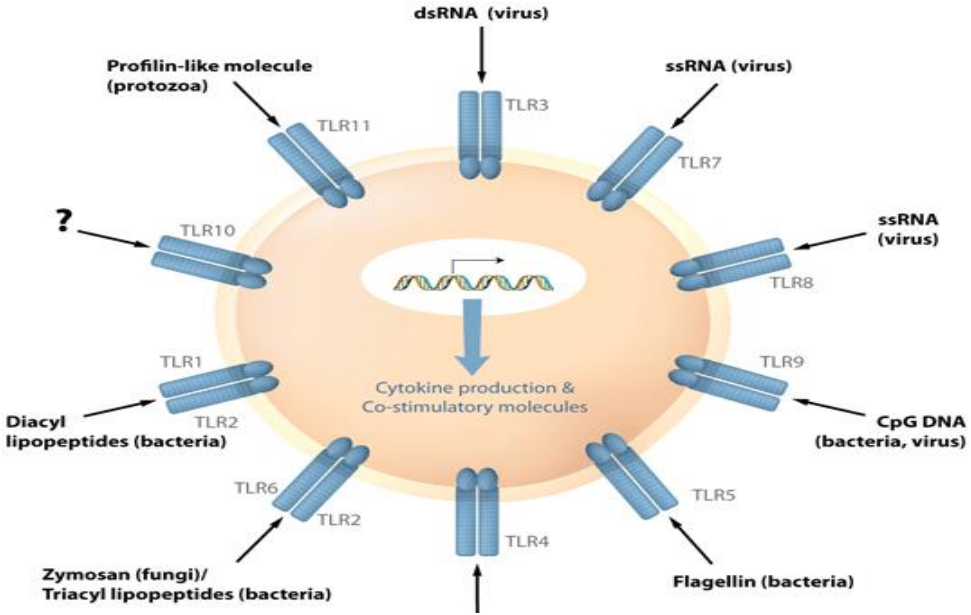


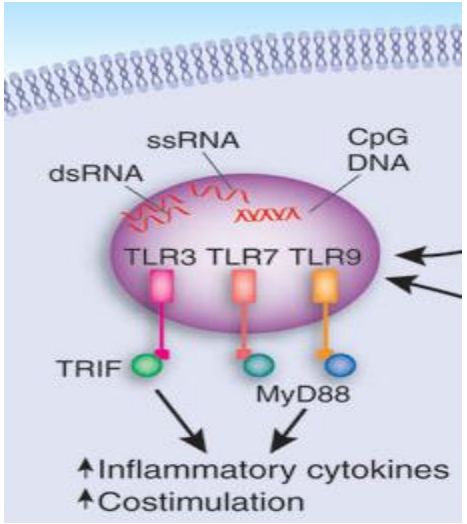
- DT + DT
CD11c depletion





TOLL-like receptors in cancer





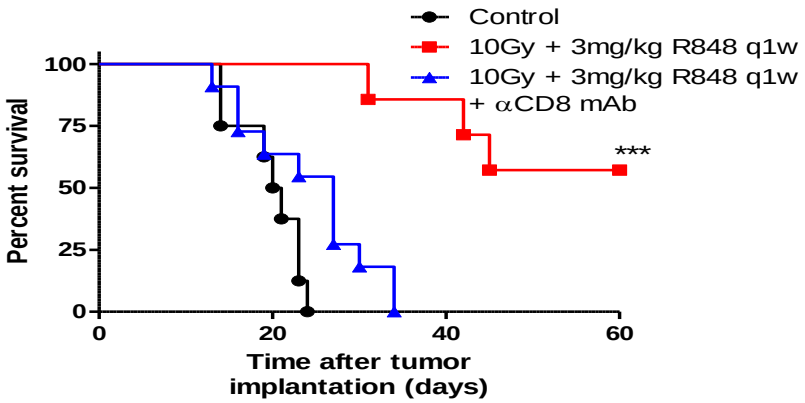
- TLR's class of proteins play a key role in the innate immune system
- 32 open clinical trials of TLRs in cancer
- Selective TLR7/8 agonist Imiquimod approved for topical treatment of BCC (topical)

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

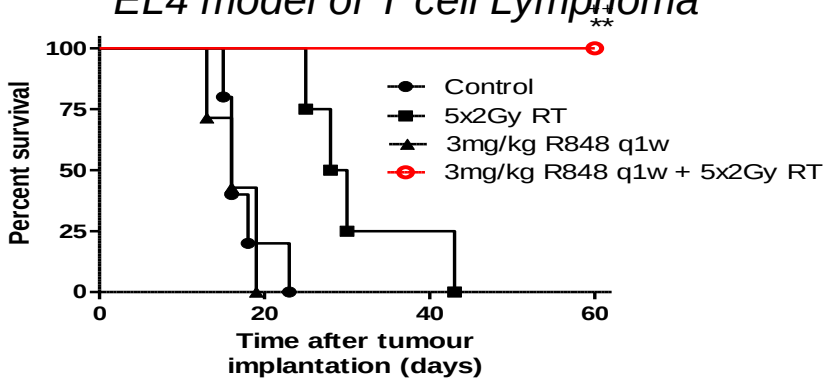
Simon J. Dovedi,[1] Monique H. M. Melis,[1] Robert W. Wilkinson,[2] Amy L. Adlard,[3] Ian J. Stratford,[3] *Jamie Honeychurch,[1] and *Timothy M. Illidge[1]

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

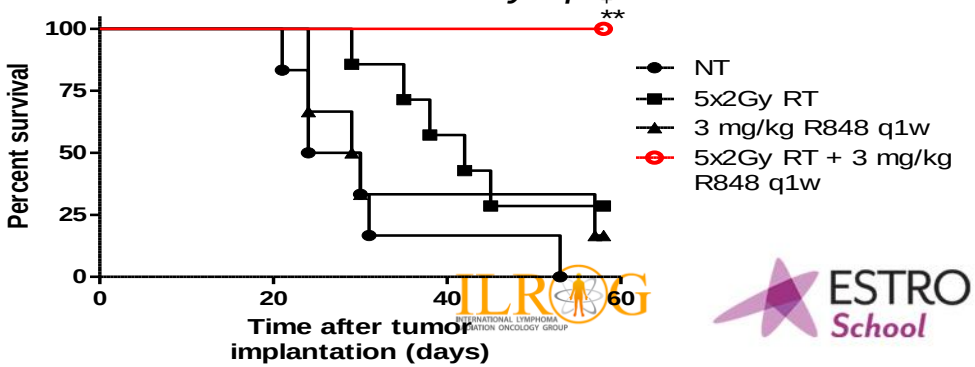
EG7 model of T cell Lymphoma



EL4 model of T cell Lymphoma

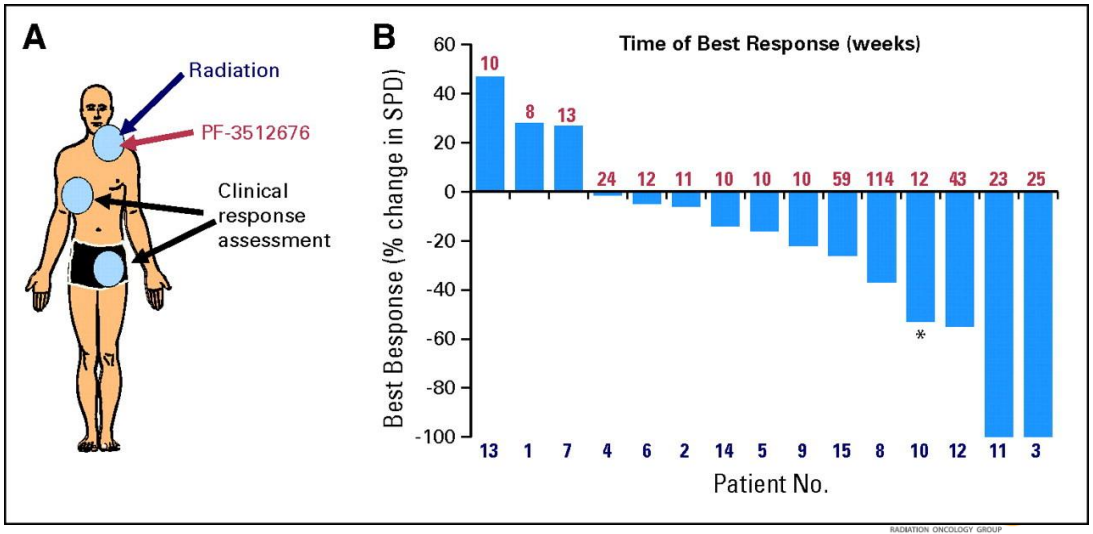


A20 model of B cell Lymphoma



In situ vaccination with a TLR9 agonist induces systemic lymphoma response

- 15 patients with r/r iNHL
- CpG + low-dose RT single site of disease
- Response assessment at distant sites
- Treatment induced CD8+ memory T cells and Treg expansion in some patients
- Best response in Tregs non inducers



JD Brody, *J Clin Oncol 2010;28(28):4324-4332*

Conclusions (1)

- Anti -PD-1-pathway-blocking agents highly active in HL but more limited efficacy in other lymphomas. Mechanistic insights are emerging in HL
- Currently very large number of combination therapies involving anti-PD-1/PD-L1 agents and conventional chemotherapies, targeted therapies, or other immunotherapies are being studied
- CAR-T cells look promising in relapsed and refractory DLBCL and other lymphoid malignancies. Efficacy and validity of delivery require on-going further international studies
- Clinical trials outrunning new immunological scientific insights.

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Conclusions (2)

- Evidence of synergy between RT and checkpoint inhibition is strong in preclinical lymphoma models with “high” T cell infiltrates or immunologically “hot” tumours
- Studies in HL of RT and anti-PD1 mAb underway
- Studies in NHL of RT and other immunoregulatory agents ongoing
- Currently there are opportunities to exploit the potential of RT and immunoregulatory agents in other lymphomas
- Need well planned studies with high quality RTQA and carefully record efficacy and toxicity

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What is the impact of RT on the local tumour microenvironment ?

Why does local RT rarely result in systemic anti-tumour immunity and an "abscopal" effect ?

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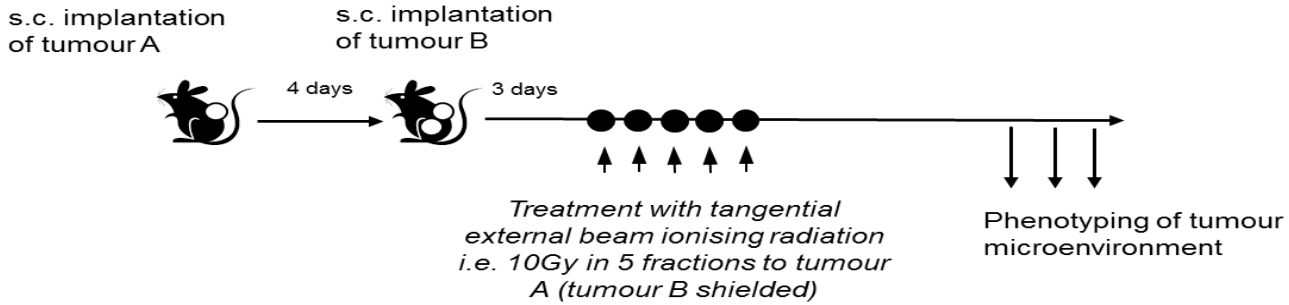
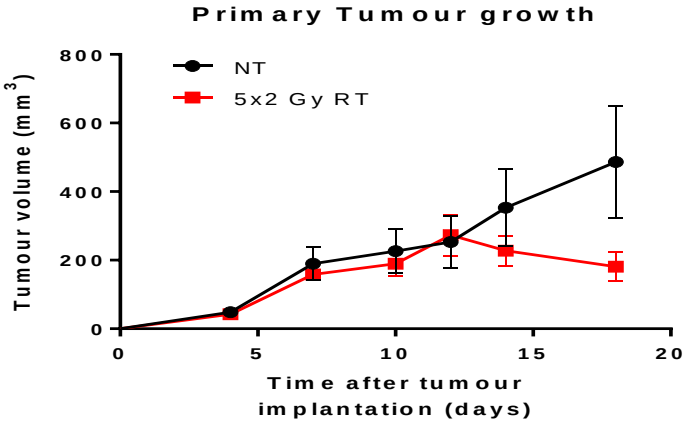
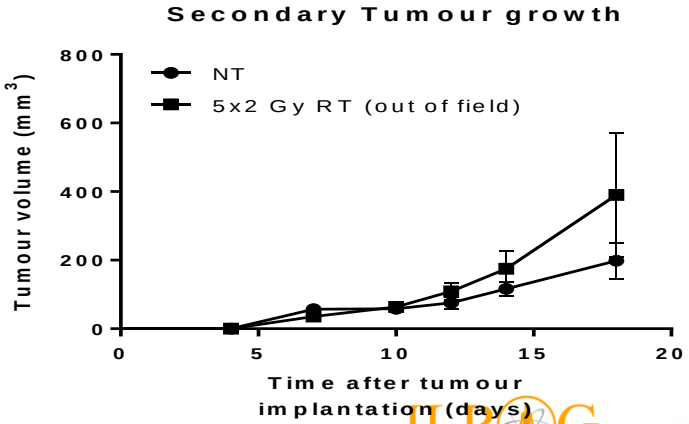
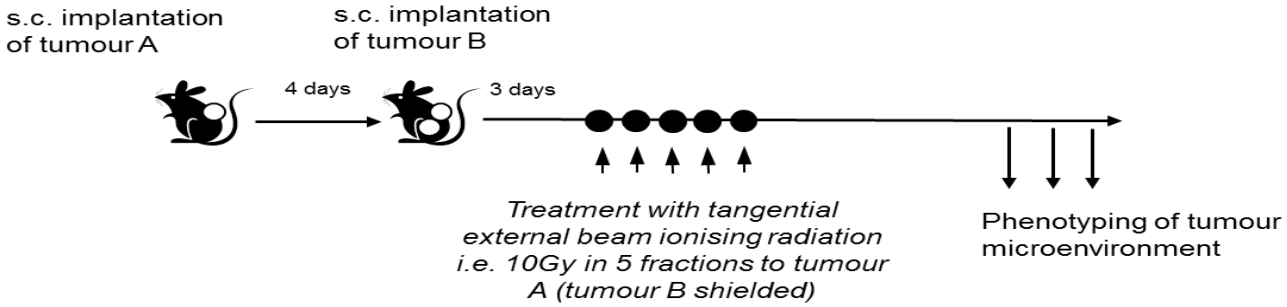
Impact of RT on the generation of local and systemic anti-tumour immune responses

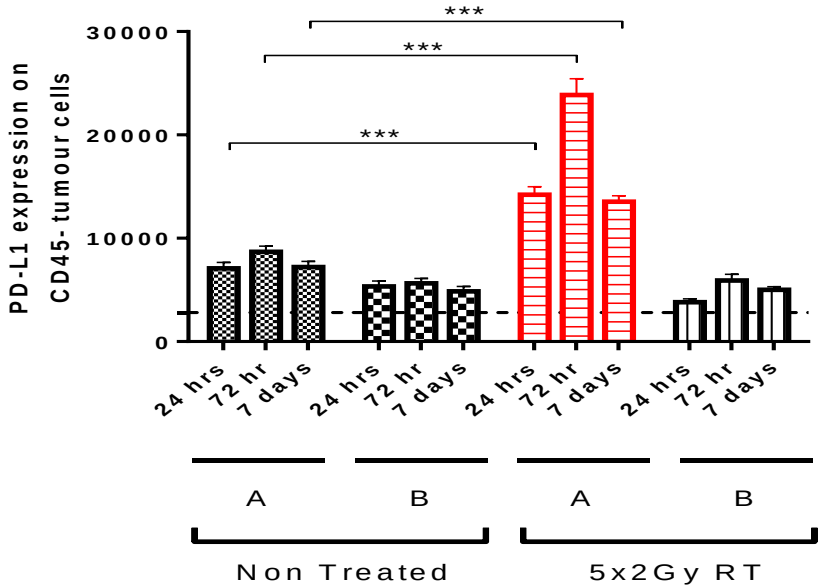






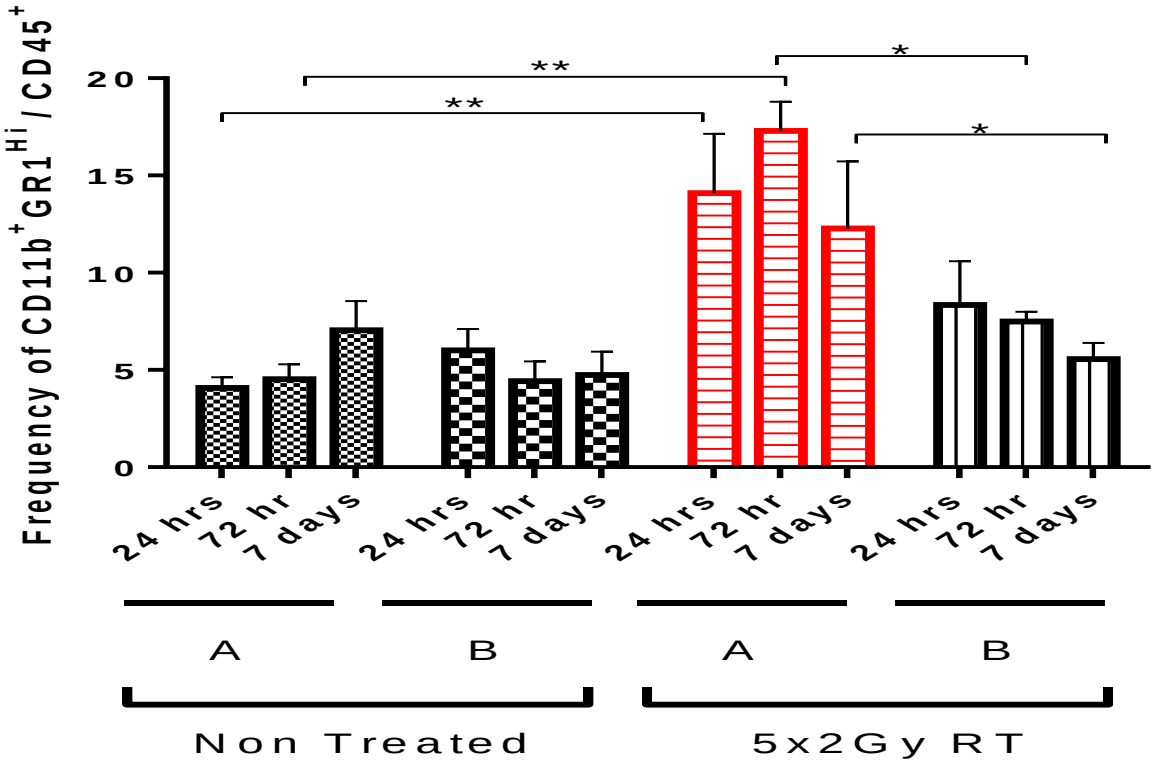
Local RT increases PD-L1 tumour expression in RT field but has no effect out of RT field





Dovedi et Clin Cancer Res 2017

Local fractionated RT leads to increases in MDSC only in RT field



Tumour A=irradiated, B=shielded

Dovedi et Clin Cancer Res 2017

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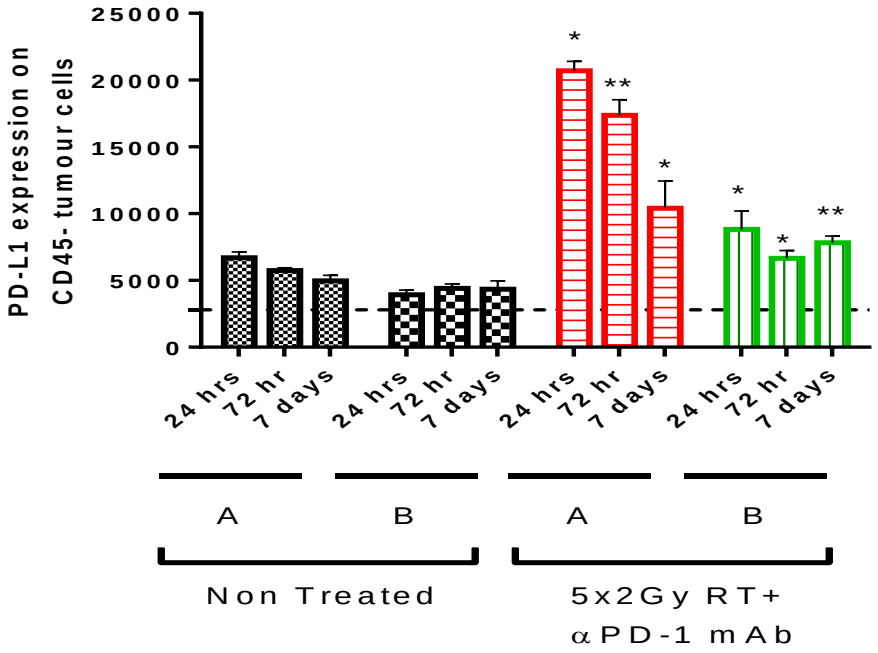
Does RT and anti-PD1 leads to generation of systemic anti-tumour immune responses ?

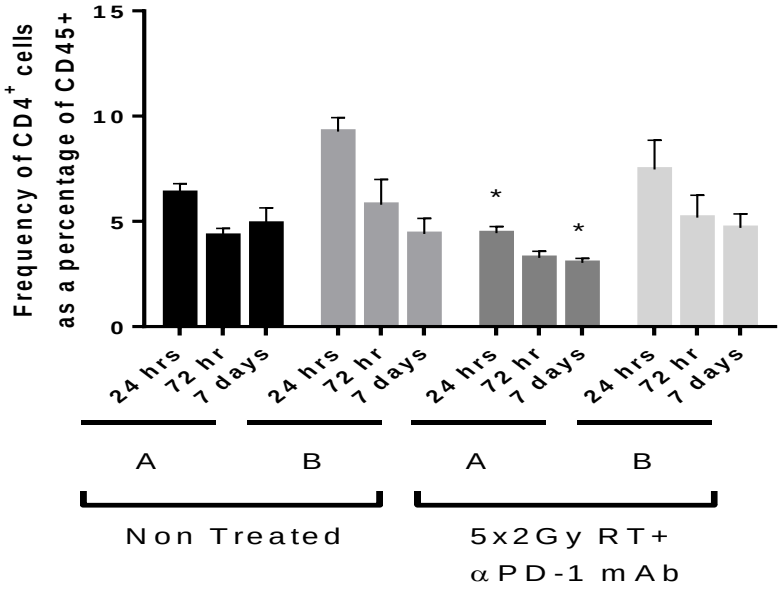


Dovedi et Clin Cancer Res 2017

Tumour A=irradiated, B=shielded

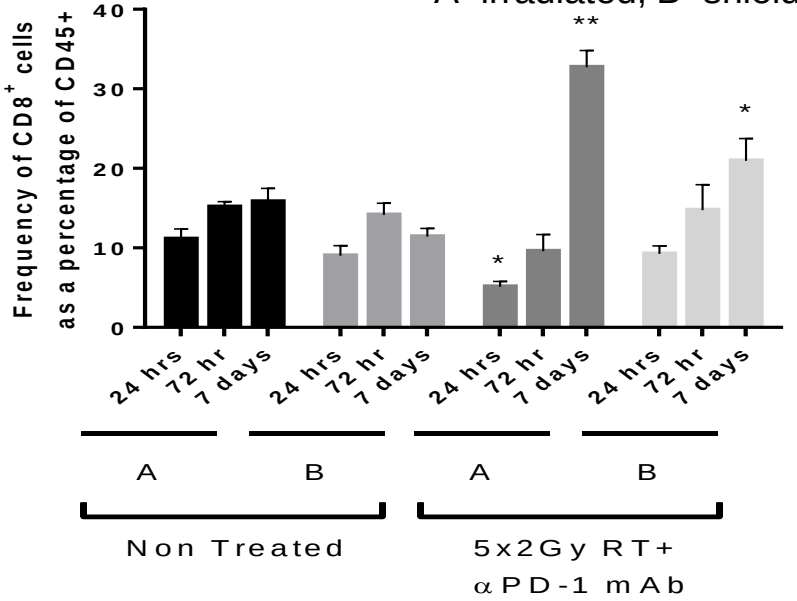
RT and anti-PD1 therapy results in changes in TIL population with increase in CD8 T cells

CD4



CD8

A=irradiated, B=shielded



- RT and αPD-1 mAb leads to reduction in CD8⁺ T-cells (but not CD4⁺ T-cells) infiltrating the tumor (when compared to out-of field lesions at 24 hours).
- Reduction in CD8⁺ T-cells acute, by day 7 both the irradiated and out-of-field tumors had significantly greater numbers of CD8⁺ T-cells

Dovedi et Clin Cancer Res 2017

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Long term toxicity

Late effects after Hodgkin lymphoma: incidence and clinical implications

Berthe Aleman

Radiation oncologist

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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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

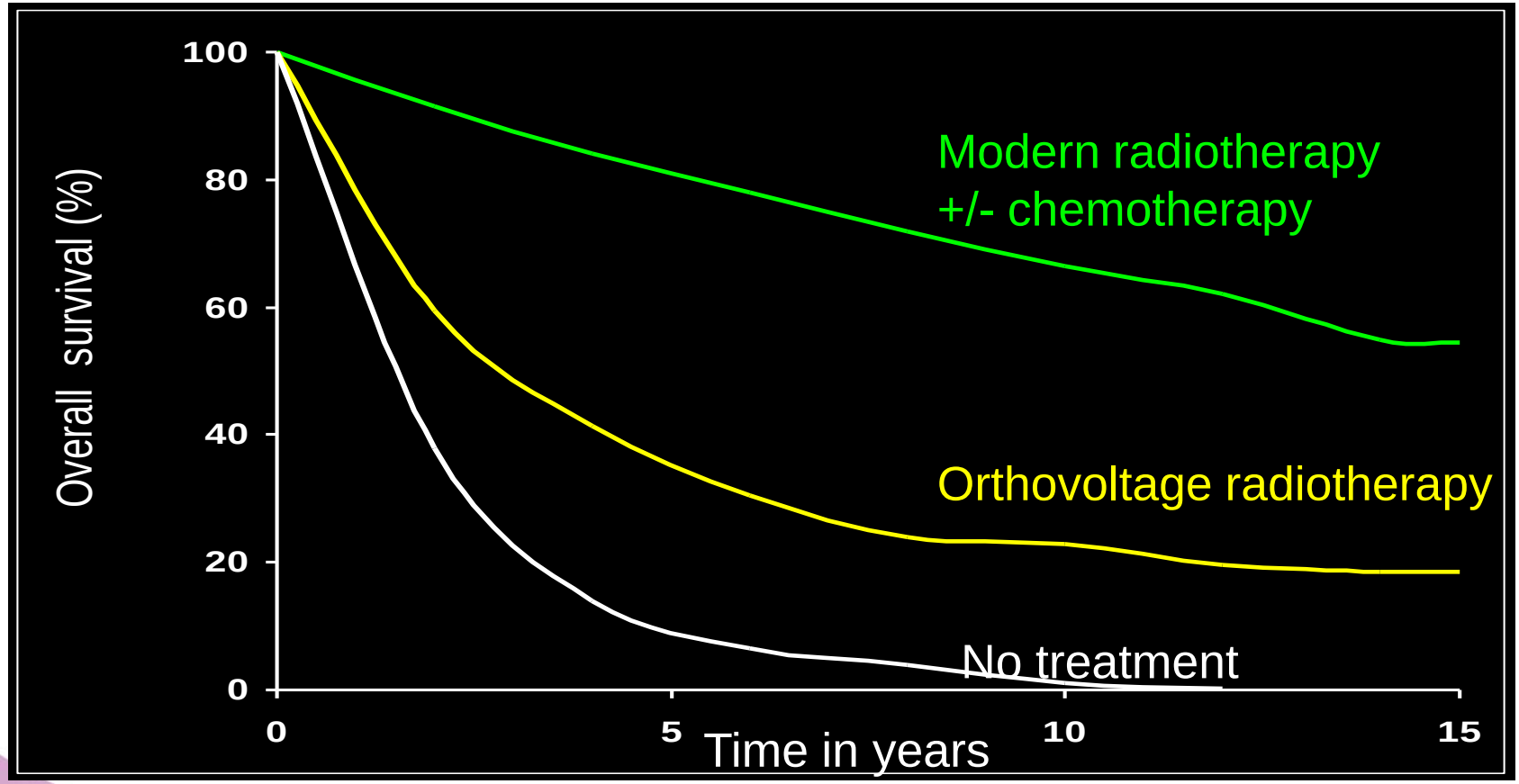
Hodgkin’s disease

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

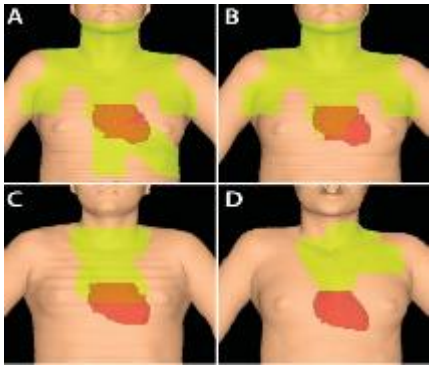


Kaplan 1978

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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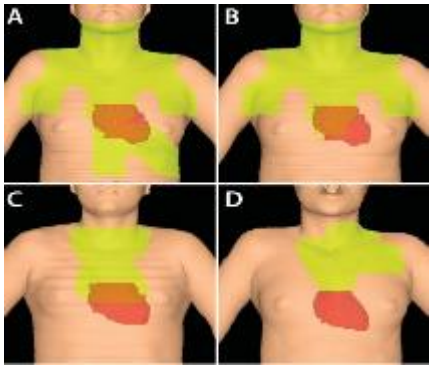


Hodgson, ASH educational 2011

Successes of HL treatment

⬇

Long-term survival

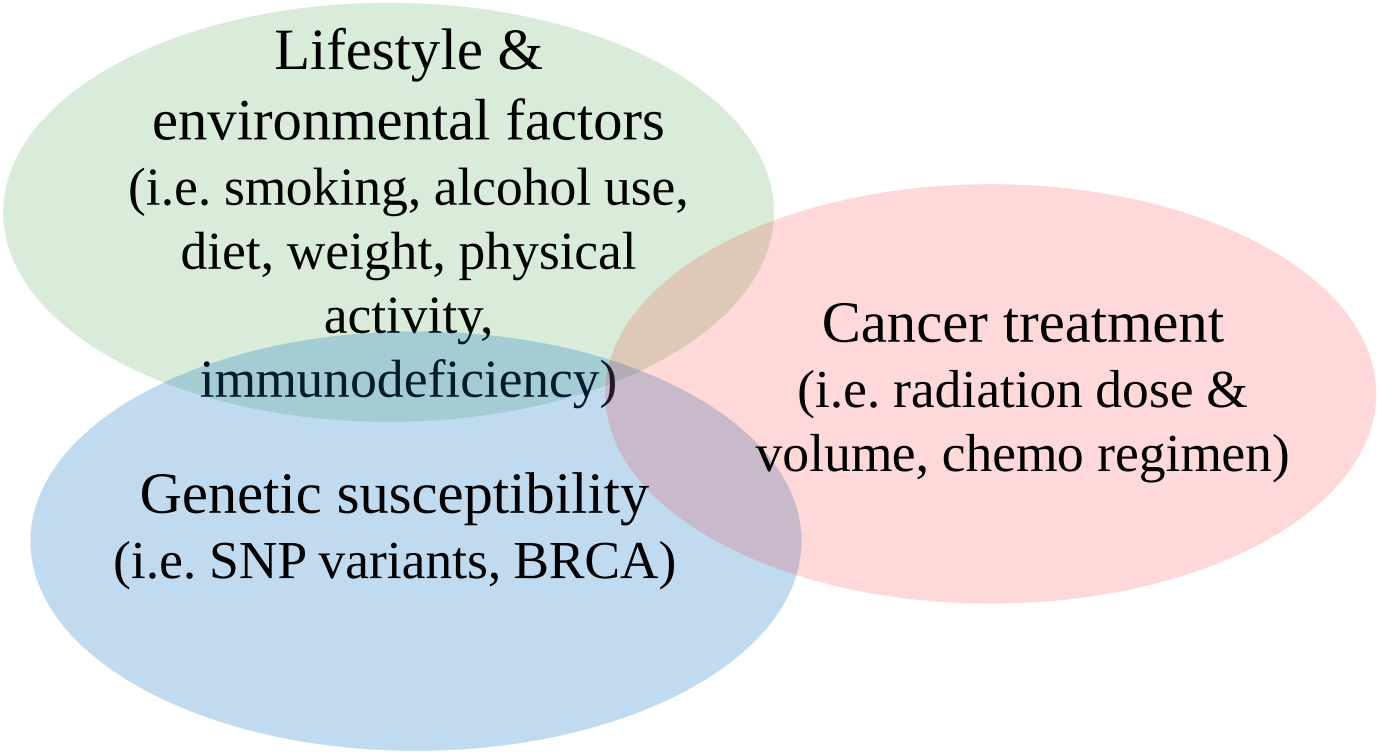
⬇

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



Risk measures in late effect research

- Standardized Incidence Ratio (SIR) =

  Observed / Expected numbers of events =

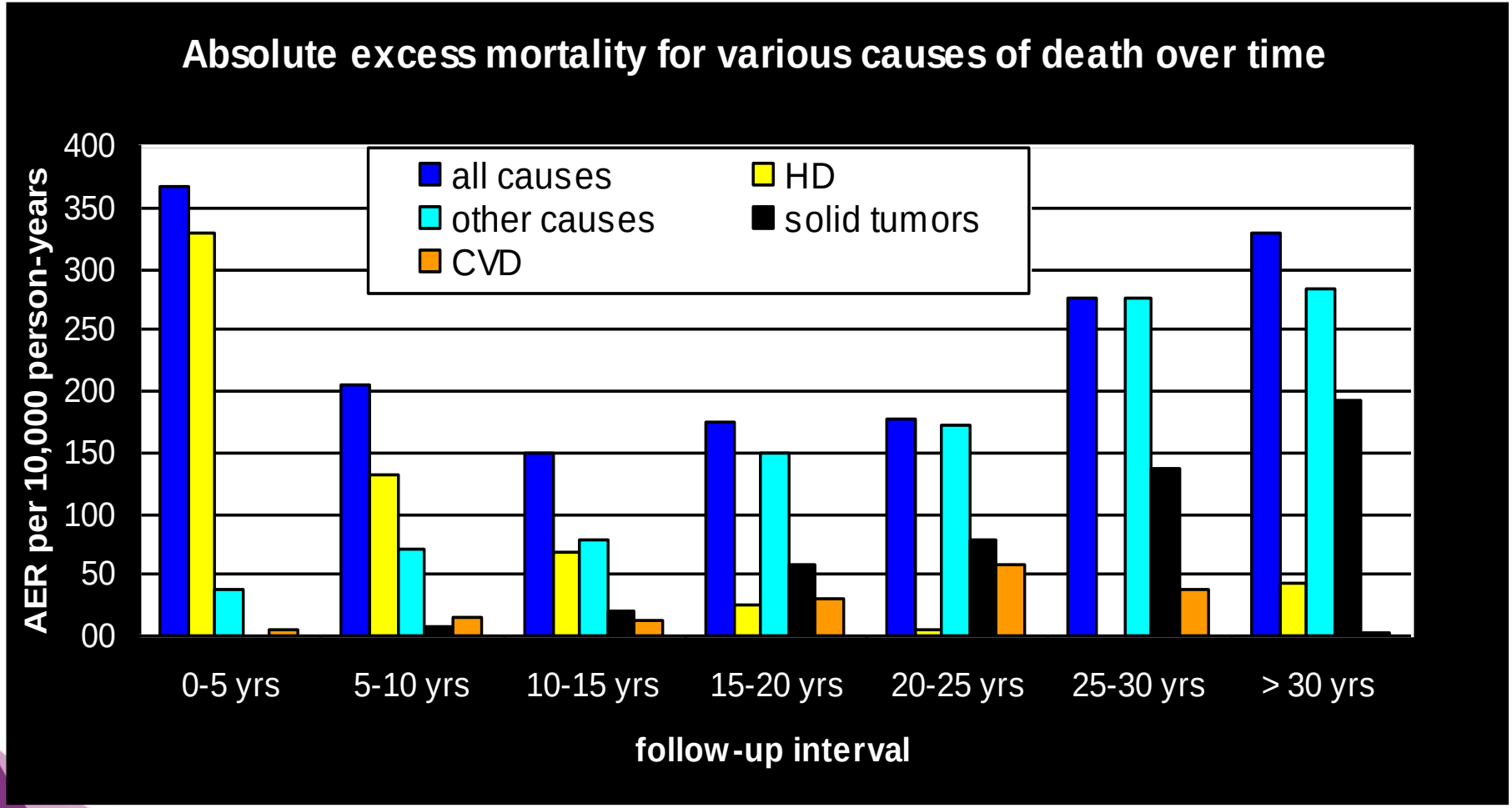
  Relative risk compared to general population
  - High SIR for rare event → low absolute risk

- 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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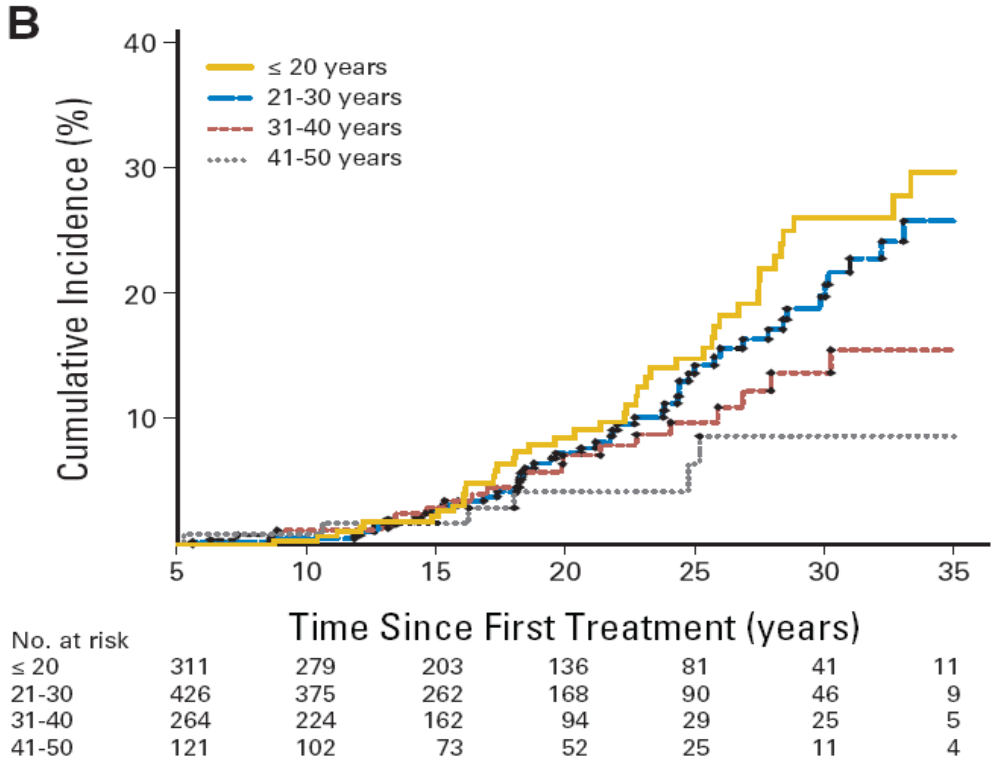
Ng et al., Blood 2002

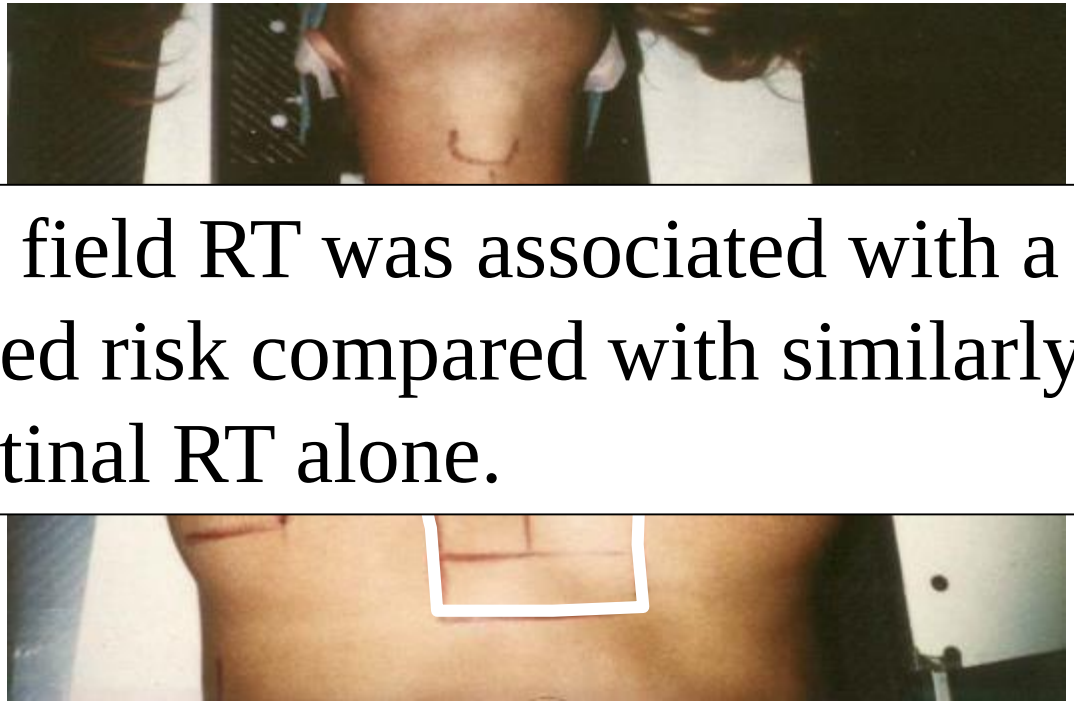
Cumulative incidence of breast cancer by age at HL

(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

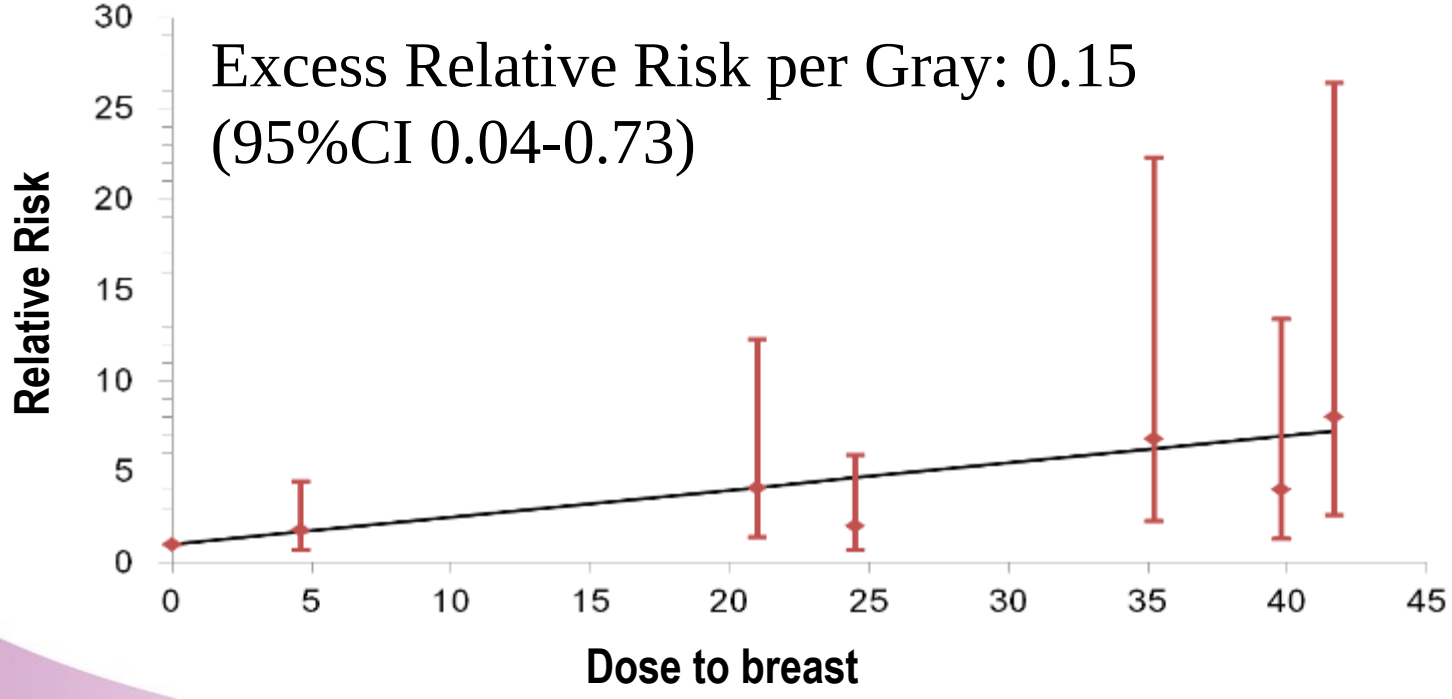


Mantle field RT was associated with a 2.7-fold increased risk compared with similarly dosed mediastinal RT alone.

De Bruin et al, JCO 2009

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.



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

Breast cancer following HL

a Dutch case-control study

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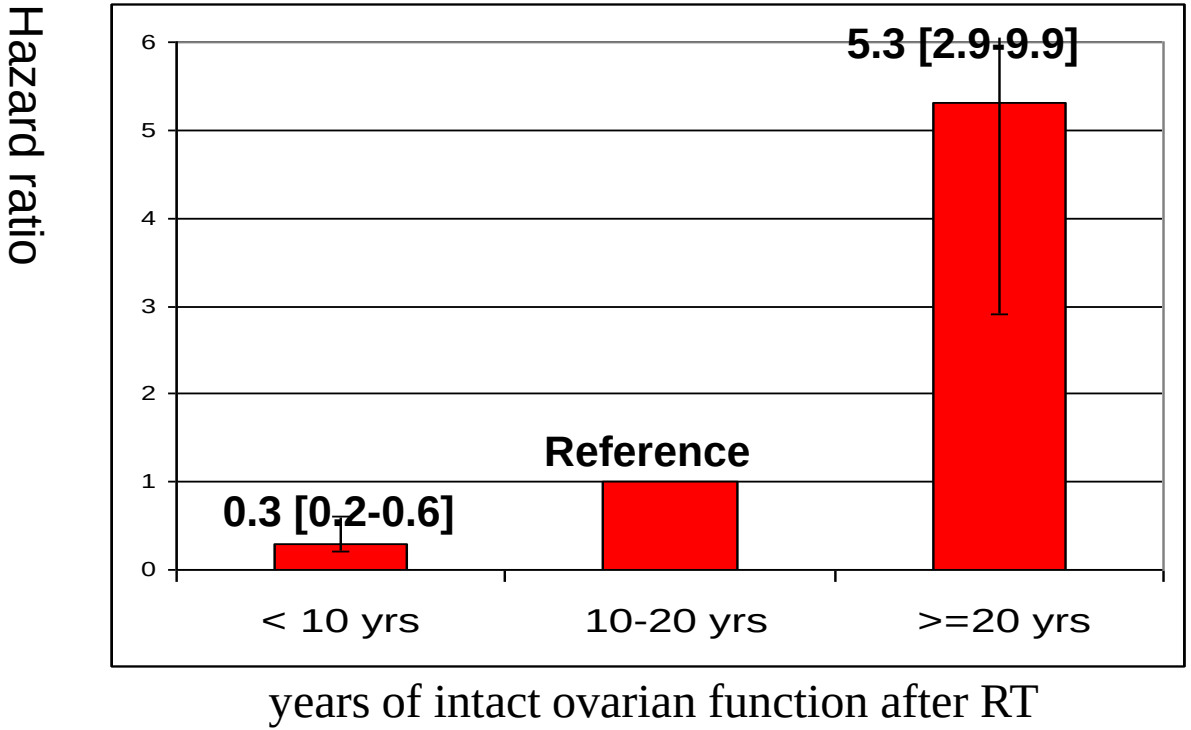
4-24 (15.5)	10	39	1.11	0.32-3.85
24-38.5 (30.2)	14	44	4.20	0.99-17.8
≥38.5 (40.7)	15	45	5.16	1.27-21.0
Overall treatment	**Cases**	**Controls**	**OR†**	**95%CI**
RT only	30	68	1.0	Ref
RT+CT	18	104	0.45	0.22-0.91

* 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

Cumulative incidence of breast cancer among female HL survivors by RT field, prescribed dose and duration of intact ovarian function

174 BC cases and 466 controls nested in cohort of 3905 5-yr HL survivors treated 1965-2000

Conclusion:

- Hormone replacement therapy does not appear to increase BC risk for HL survivors with therapy-induced early menopause.

Krul et al, IJROBP 2017

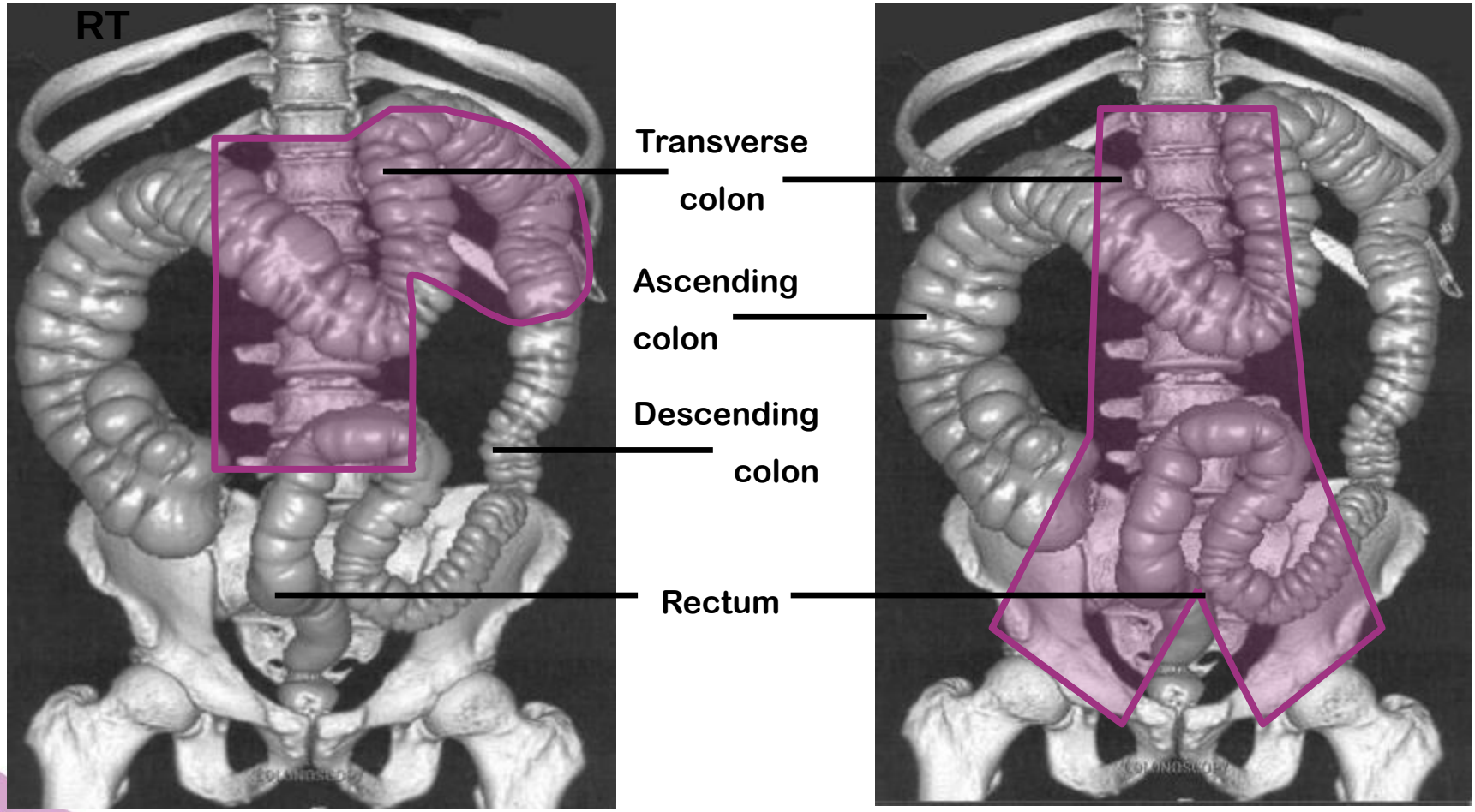
Literature on CRC risk after HL or childhood cancer and in A-bomb survivors

- 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



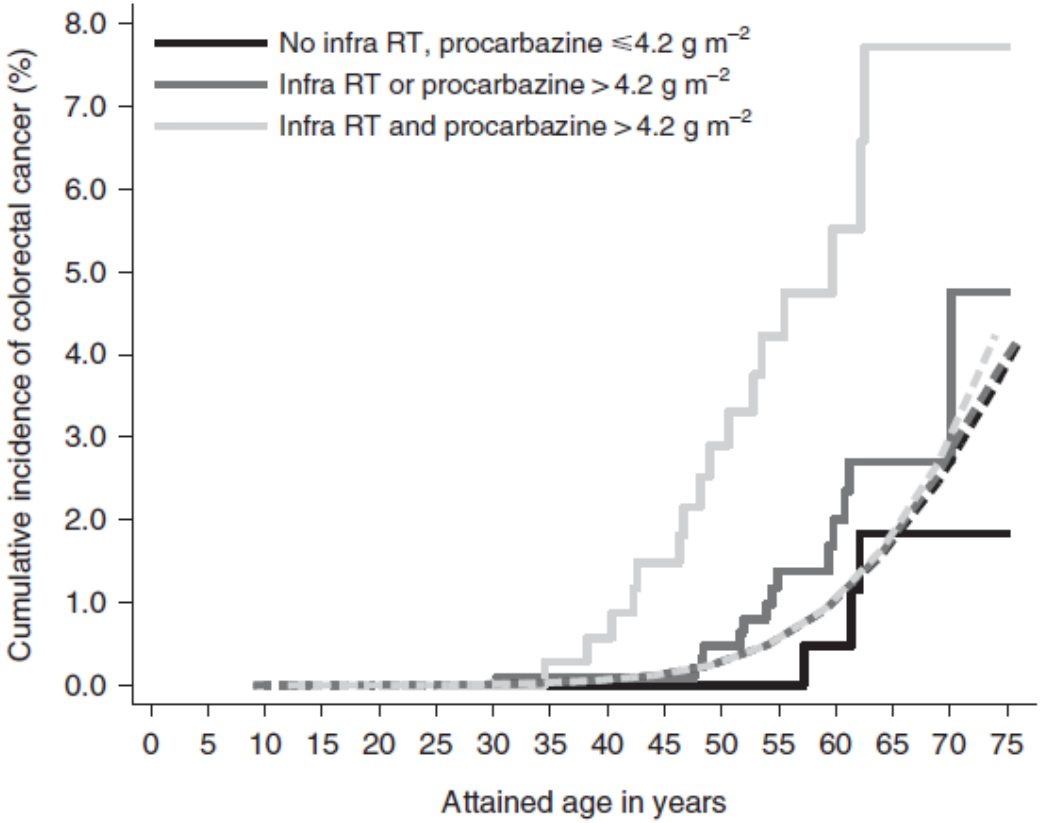
van Eggermond et al. BJC 2017

Colorectal cancer risk in Dutch HL survivors

- Study population
- 3121 5-year HL survivors
- Treated 1965 – 1995
- Seven Dutch hospitals and Eindhoven Cancer Registry
- Treated before age of 51 years
- Median follow-up 22.9 years
- 55 colorectal cancers

van Eggermond et al. BJC 2017

Cumulative incidence of CRC in patients treated < 35 yrs according to treatment

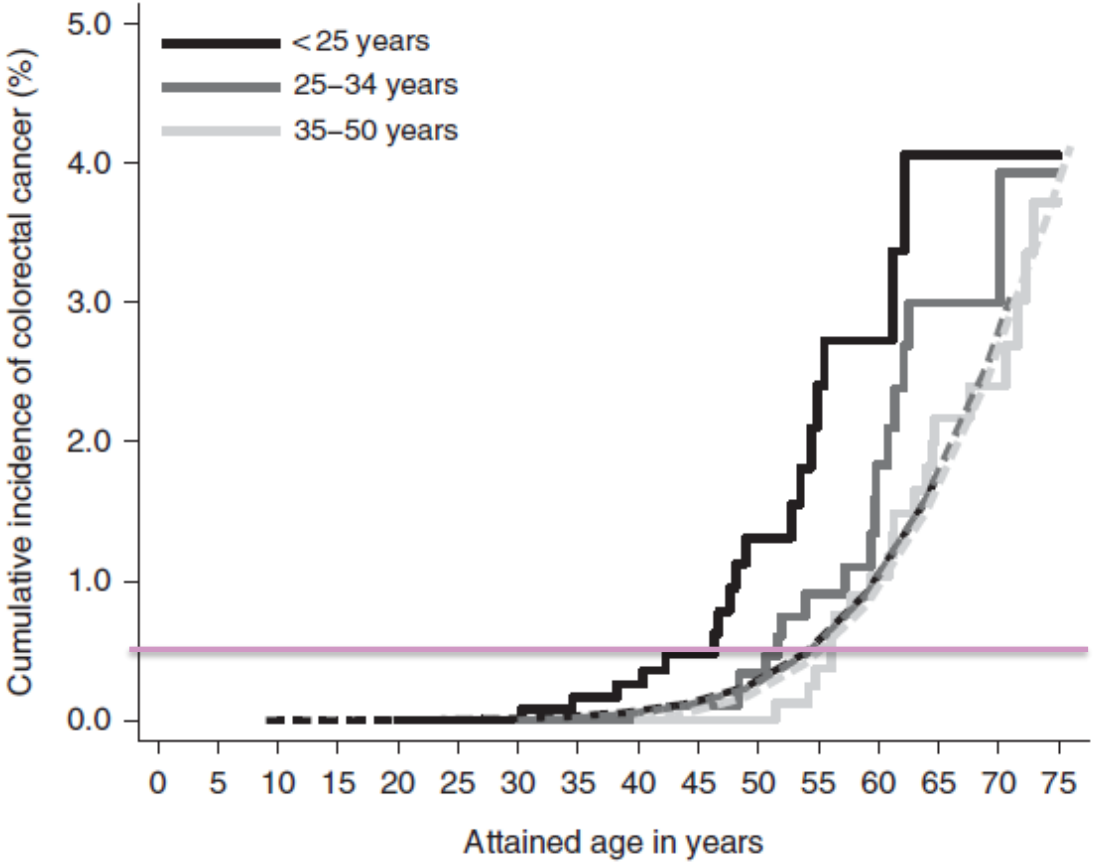


Multivariate analysis:

Most strongly increased risks for transverse colon

van Eggermond et al. BJC 2017

Cumulative incidence of CRC according to age at HL



47-year old HL survivor (treated < 25 yr) same CRC risk as 55-60 year old person from general population (0.5%)

van Eggermond et al. BJC 2017

Clinical consequences

Prevention of CRC in HL survivors

- Population screening?
- Surveillance programs?

Courtesy: L. Rigter

Dutch CRC prevention programs

	Lifetime CRC risk	Starting at	Colonoscopy
Screening			
General population	5%	55-75 years	FIT+

FIT sensitivity

CRC 80% (56-100%)

High-risk precursor lesions

- Adenoma 27% (6-56%)
- Serrated lesion 5-10%

Courtesy: L. Rigter

Lee et al 2014 Ann of Internal Med, Anderson 2016 Clin Gastroenterol Hepatol, Robertson et al. 2016 Gastroenterology

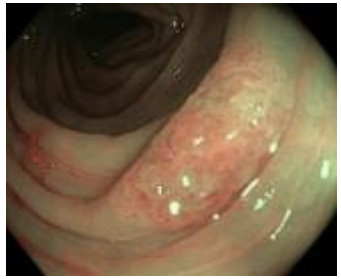
Dutch CRC prevention programs

	Lifetime CRC risk	Starting at	Colonoscopy
Screening			
General population	5%	55-75 years	FIT+
Surveillance			
High-risk populations	≥ 10%	45 years	every 5 years

Courtesy: L. Rigter

Robertson et al. 2016 Gastroenterology

Conclusions



Colorectal neoplasia in HL survivors vs. general population

- higher frequency
- right-sided location
- more serrated lesions

Prior HL therapy may be a predisposing factor for serrated polyposis syndrome

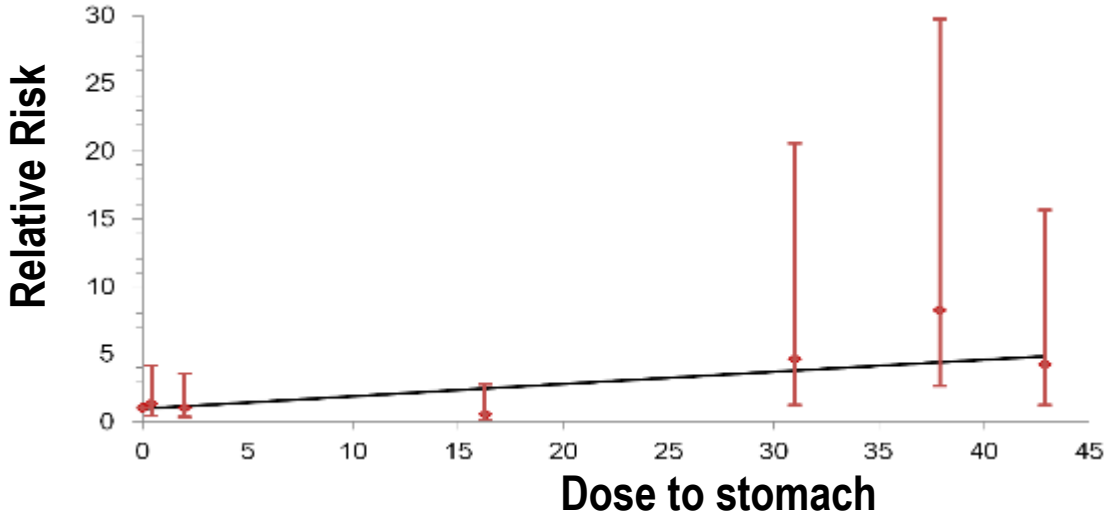
- development screening guideline

Courtesy: L. Rigter

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

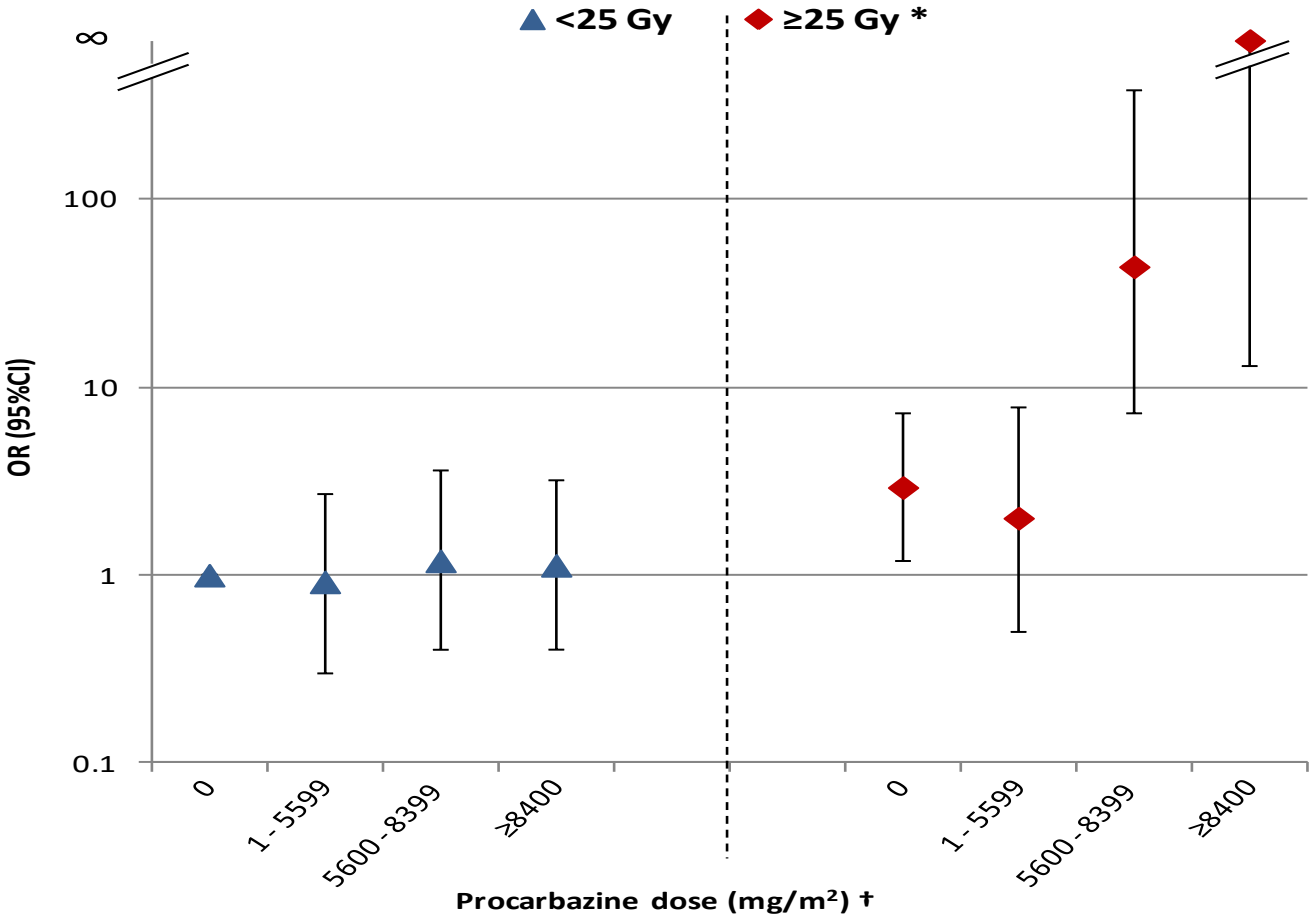
Morton et al. JCO 2013



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)

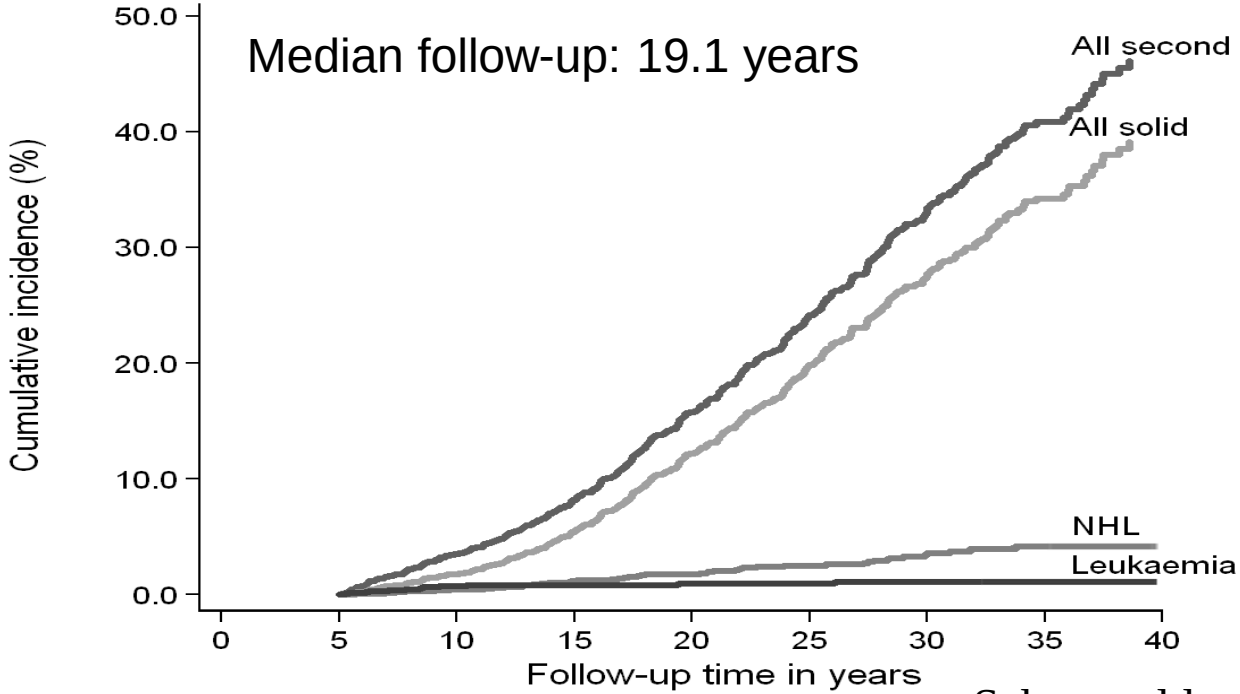
	RR non/light smokers	RR smokers
No RT (< 5 Gy), no CT	1.0 (ref)	6.0 (1.9-20.4)
RT (≥ 5 Gy), no CT	7.2 (2.9-21.2)	20.2 (6.8-68)
No RT (< 5 Gy), CT	4.3 (1.8-11.7)	16.8 (6.2-53)
RT (≥ 5 Gy), CT	7.2 (2.8-21.6)	49.1 (15.1-187)

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

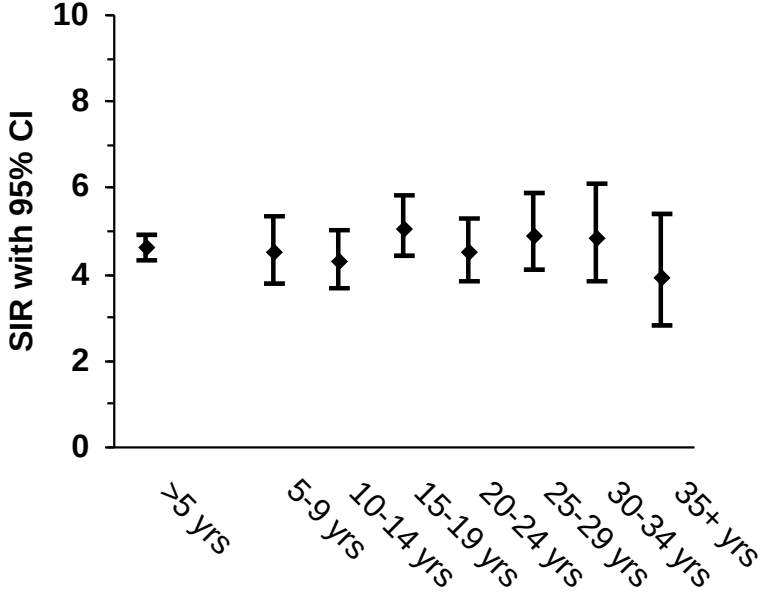
Dutch 5 year HL survivors treated 1965-2000 at age 15-51 years (n=3,905)

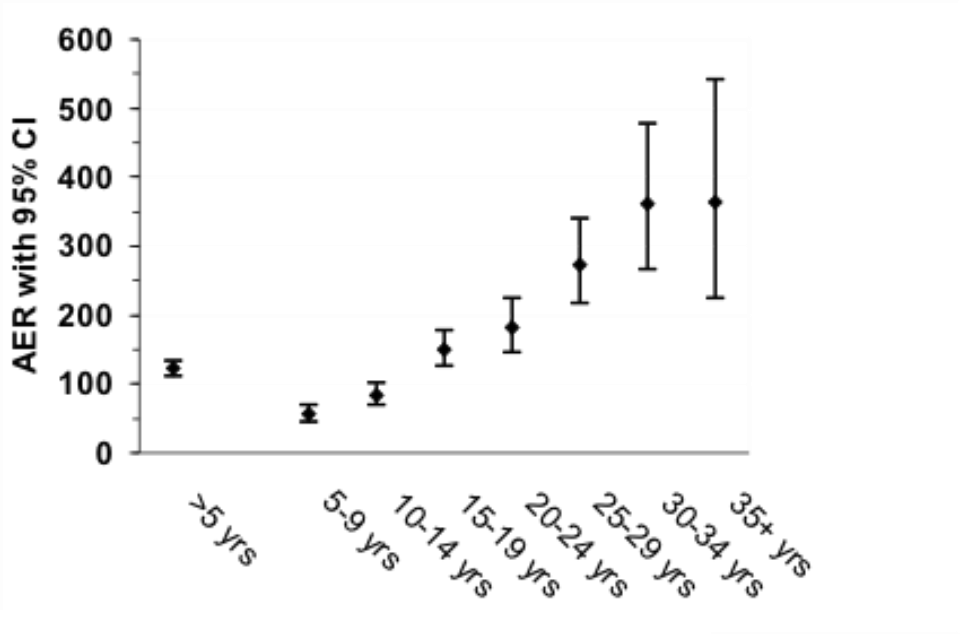


Schaapveld et al , NEJM 2015

Solid tumor risk by follow up interval

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

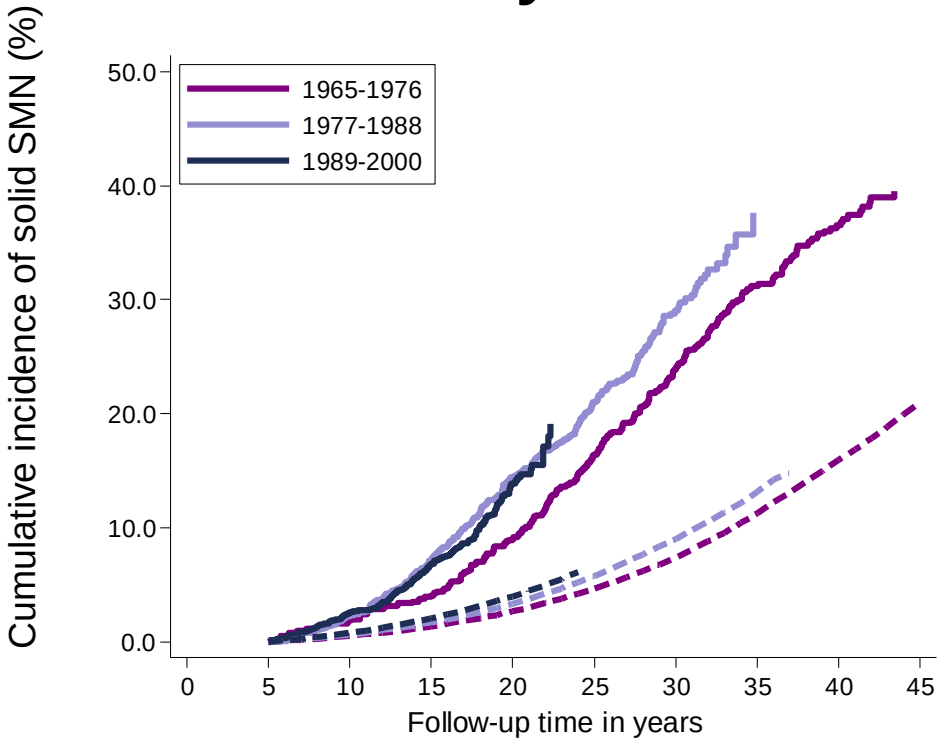




AER per 10,000 patients/yrs

Schaapveld et al , NEJM 2015

Cumulative incidence of solid tumors by treatment period

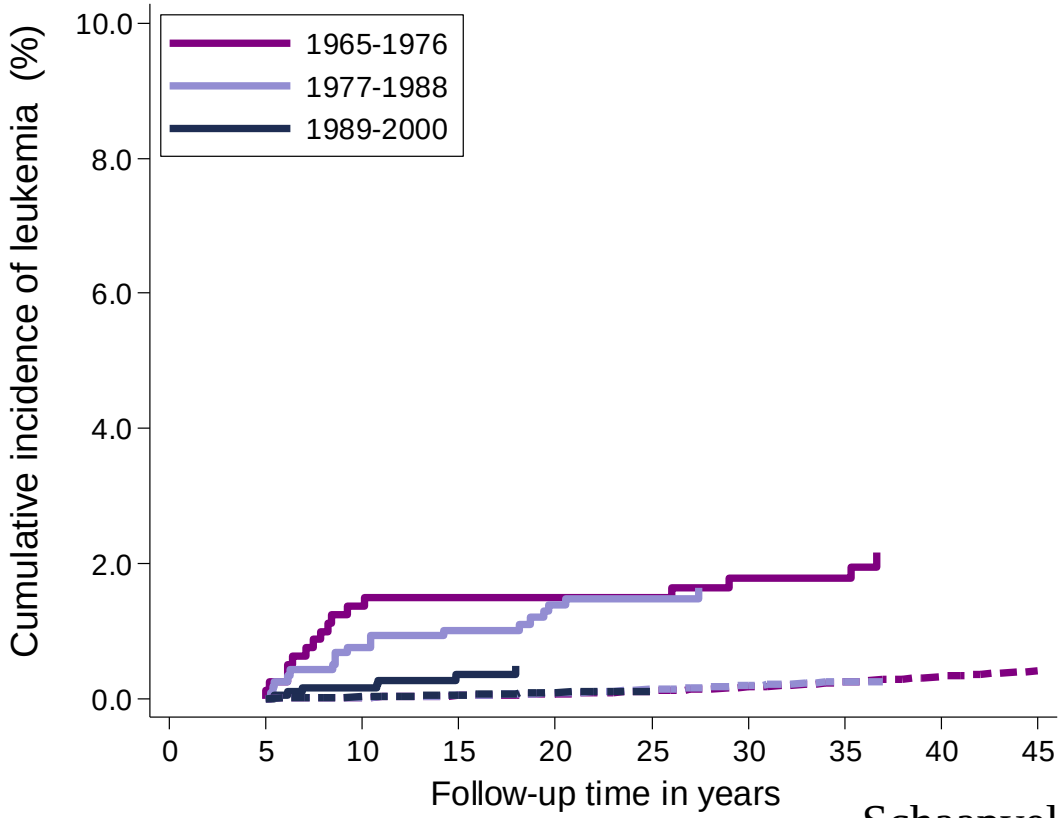


sHR 0.94 (95%CI 0.77-1.15)

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

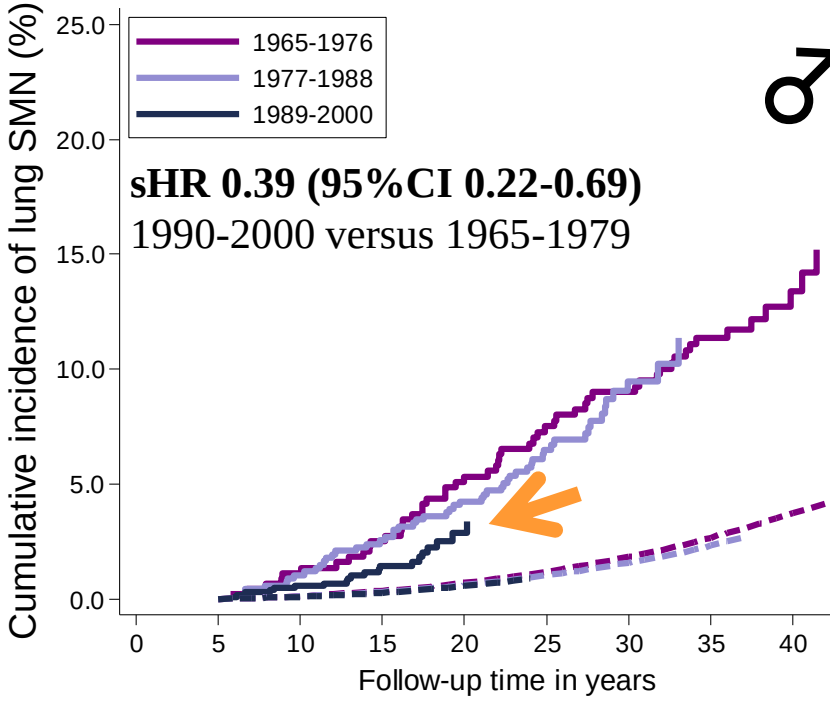
Schaapveld et al , NEJM 2015

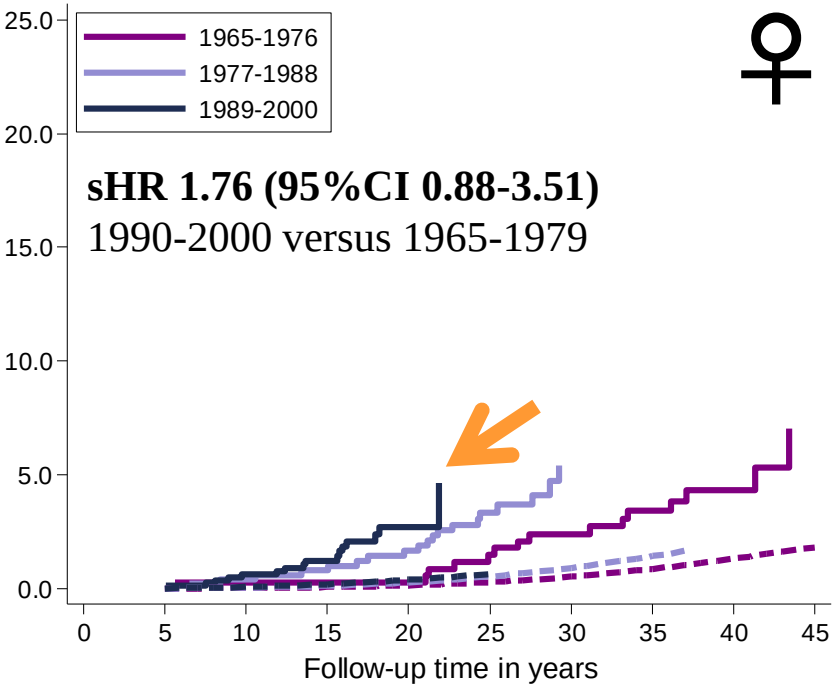
Cumulative incidence of leukemia (excluding MDS)



Schaapveld et al , NEJM 2015

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 et al , NEJM 2015

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.

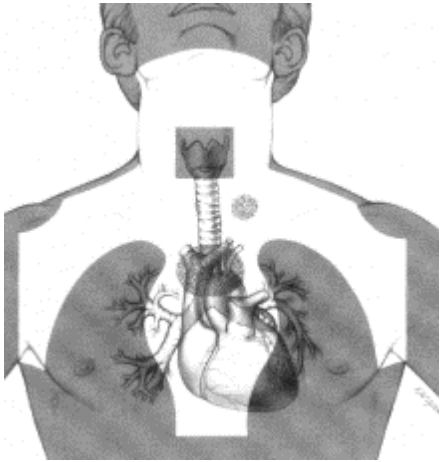
Schaapveld et al , NEJM 2015

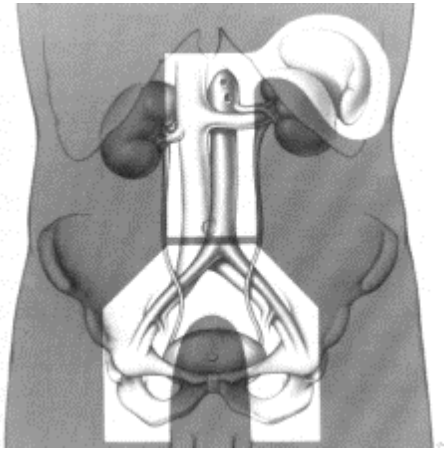
Summary SMN

- 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

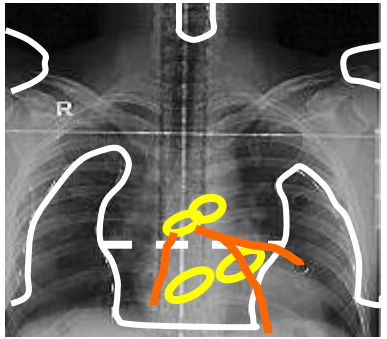
- Chemotherapy (anthracyclines)
- Radiotherapy





RT-associated heart diseases

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

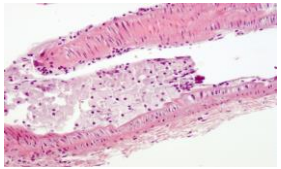


Cardiovascular toxicity

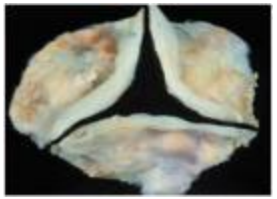
Differences in mechanisms

Radiation

Damage to vasculature (vulnerable plaques*)



Damage to valves

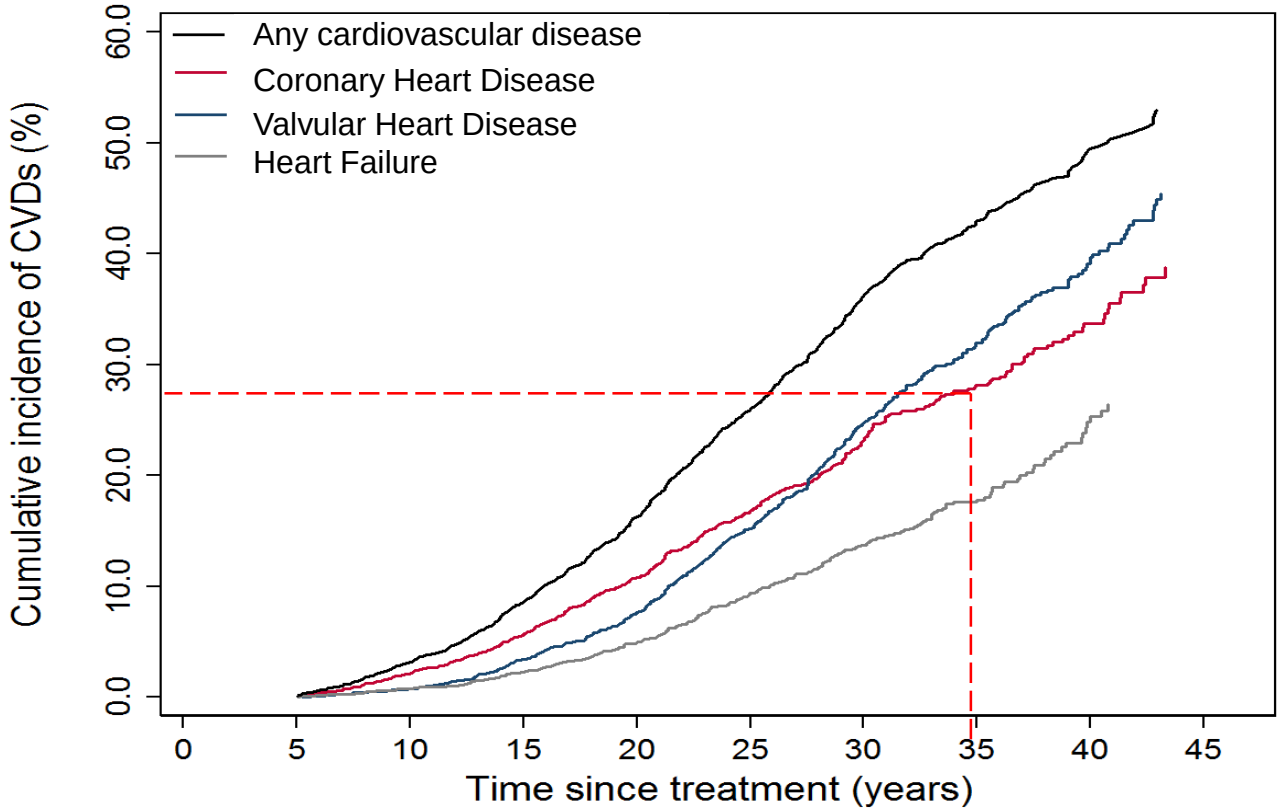


Damage to myocytes

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

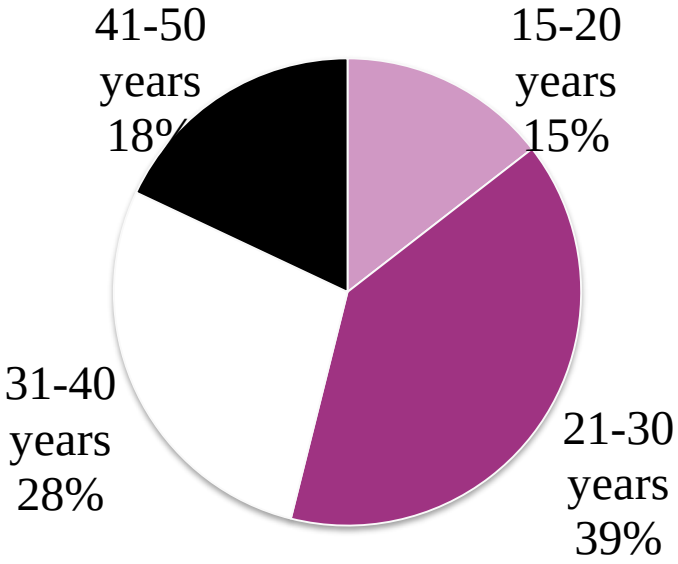
Morbidity of cardiovascular disease

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

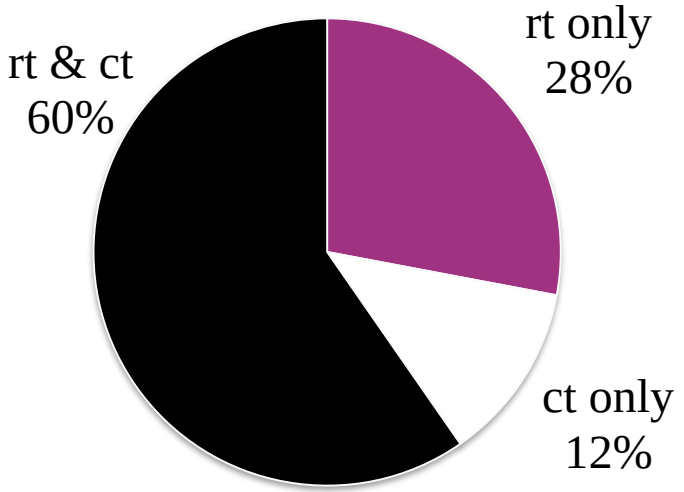


Van Nimwegen et al., JAMA int med 2015

HL age distribution



HL treatment



41% anthracycline-containing chemotherapy

Over time ↓ use mantle field and abdominal RT

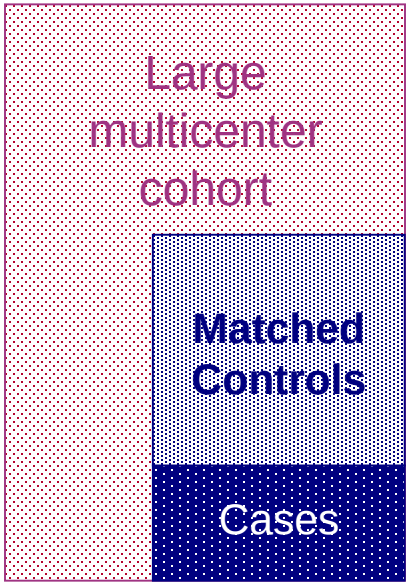
Schaapveld, NEJM 2015

Nested case-control studies

Endpoints:

- Valvular heart disease
- Ischemic heart disease
- Heart failure

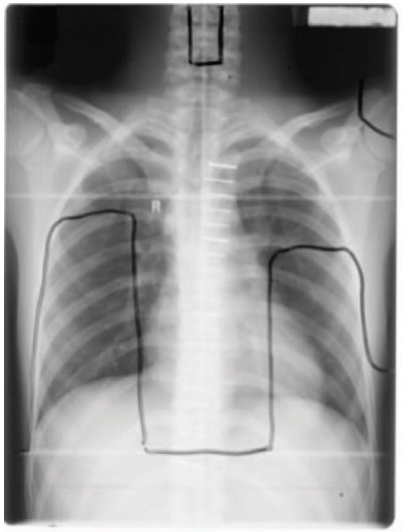
First events!

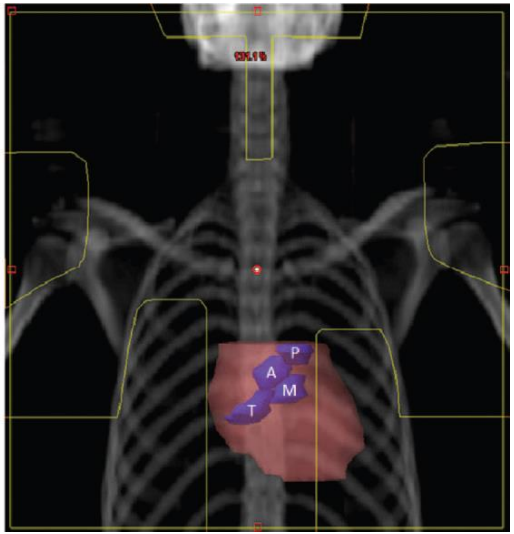


Nested case-control studies

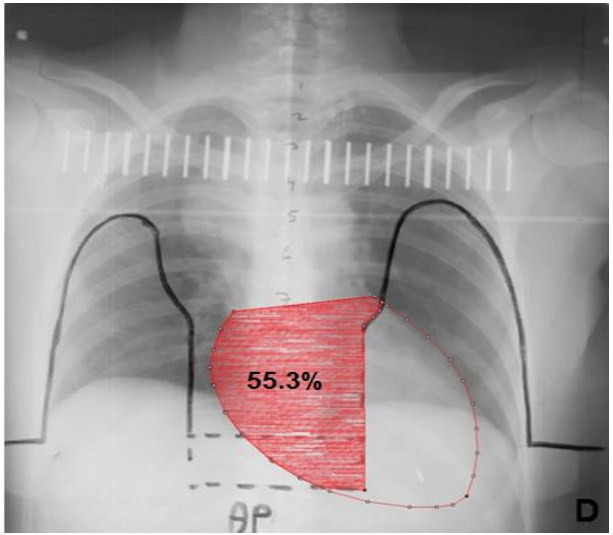
Dosimetry:

CT-based





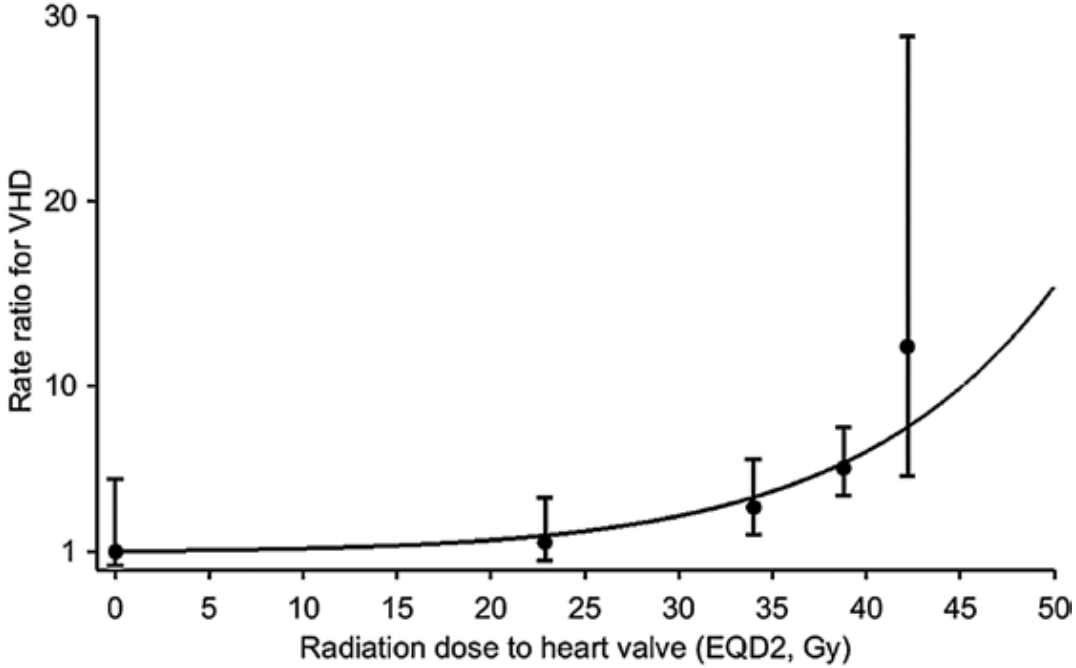
Simplified 2D method



Cutter, Schaapveld et al. JNCI 2015
van Nimwegen et al, IJROBP 2015

Valvular heart disease after HL

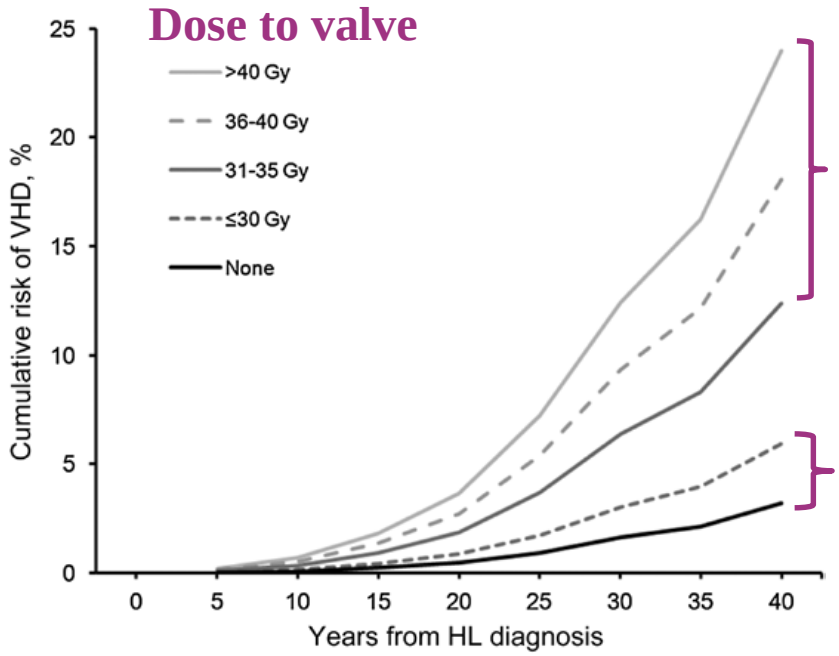
89 cases and 200 controls nested in cohort of 1852 Dutch five-year survivors of HL treated between 1965 and 1995



Cutter, Schaapveld et al. JNCI 2015

Cumulative incidence VHD (1st event) after HL

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

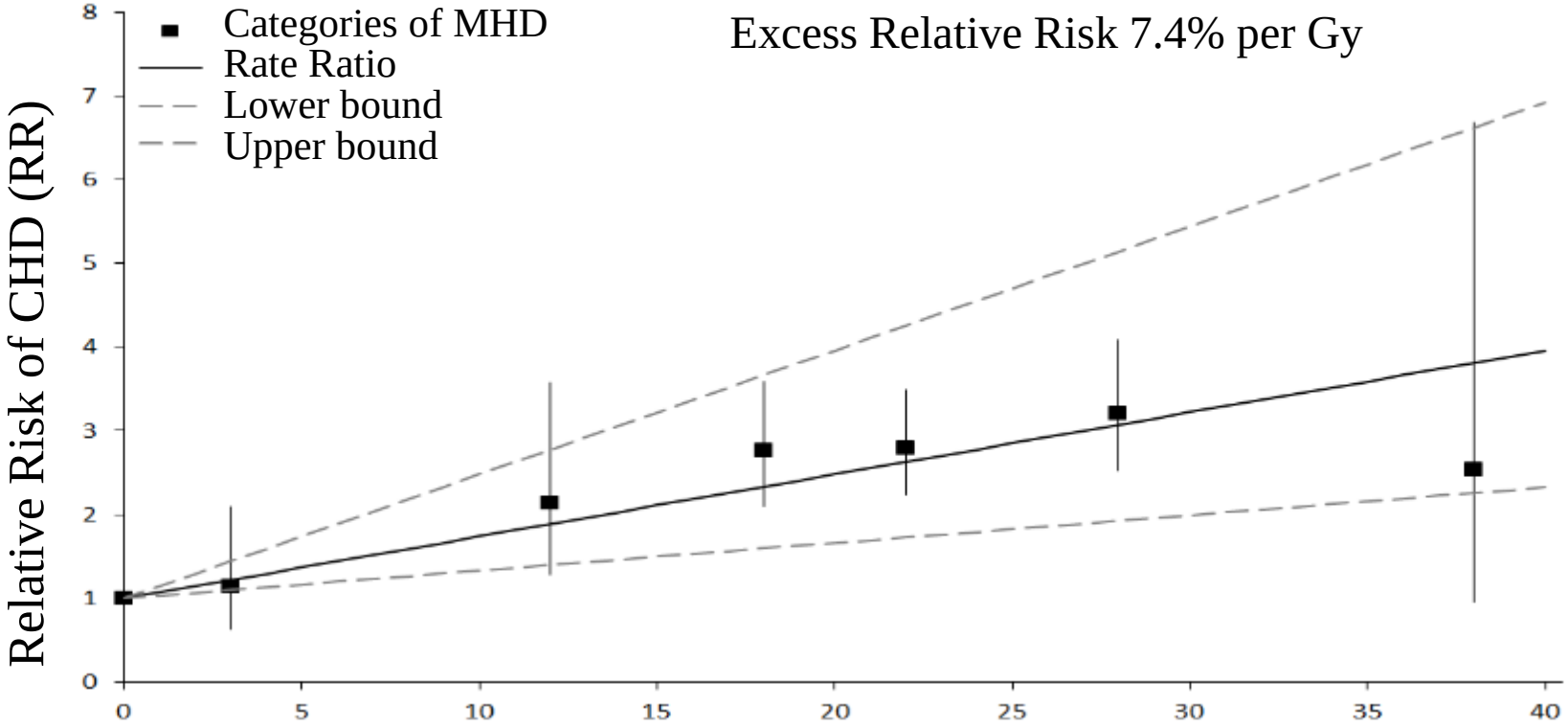


Exposure from: Mantle/mediastinal field 36-40 Gy/18-20 fractions

INRT/ISRT: 20-30 Gy/10-15 fr

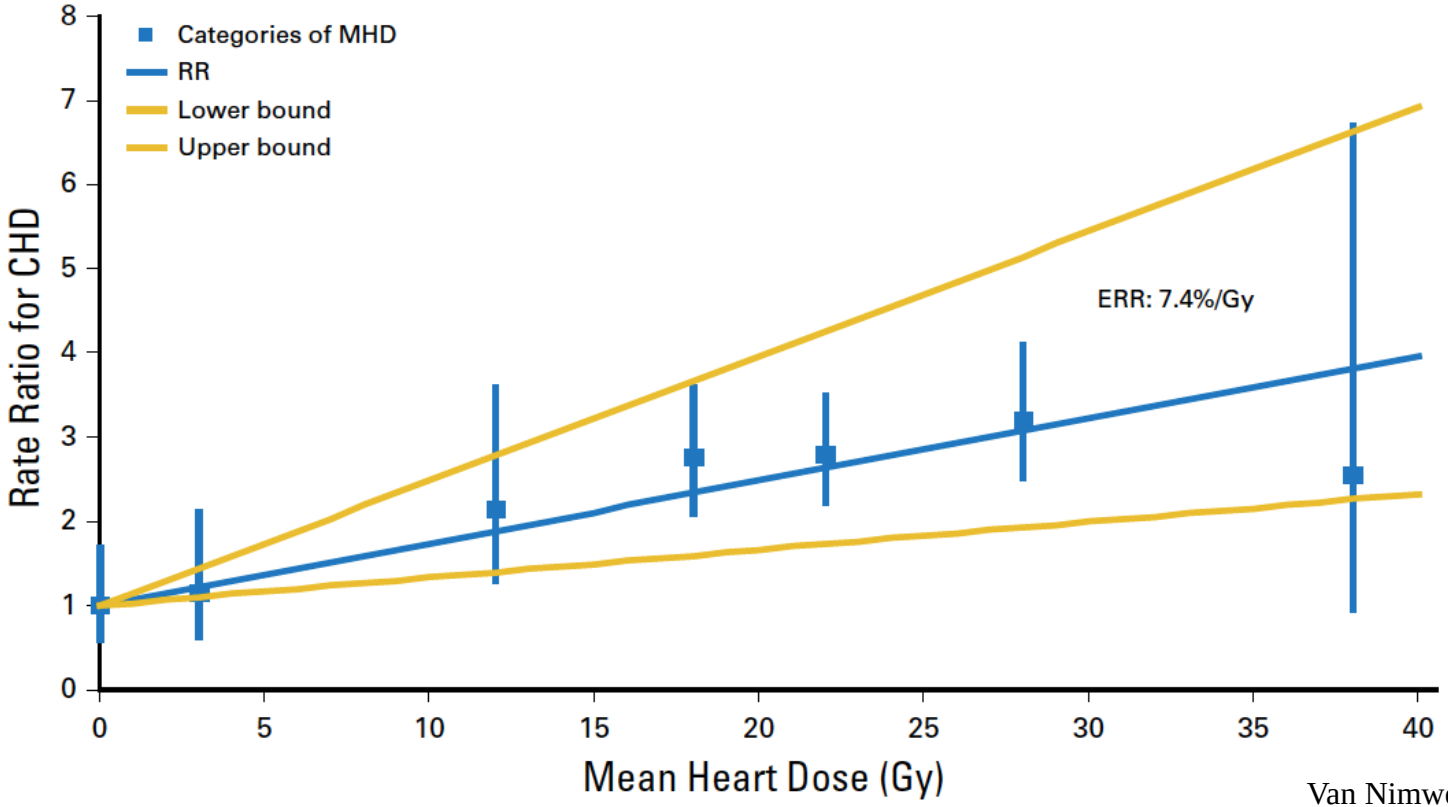
Cutter, Schaapveld et al. JNCI 2015

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



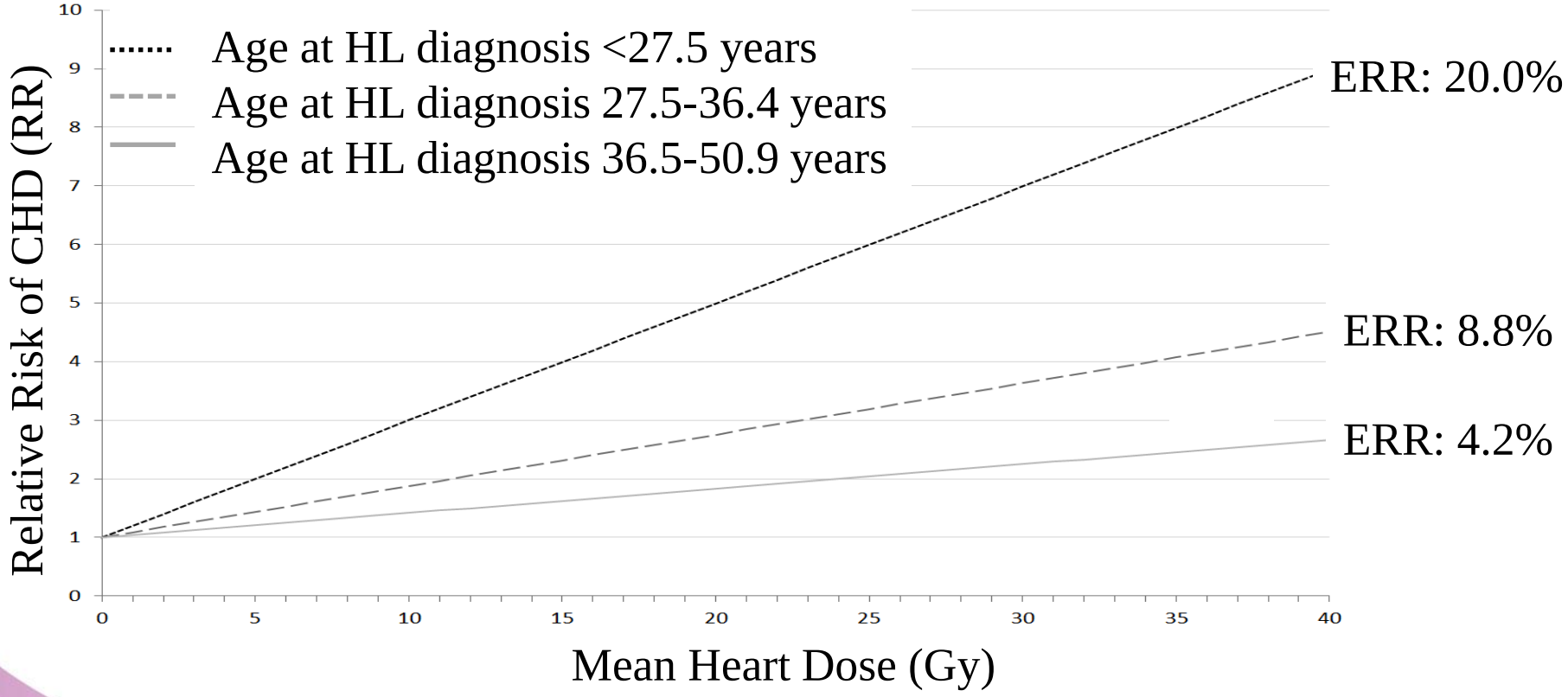
Van Nimwegen et al., JCO 2015

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., JCO 2015

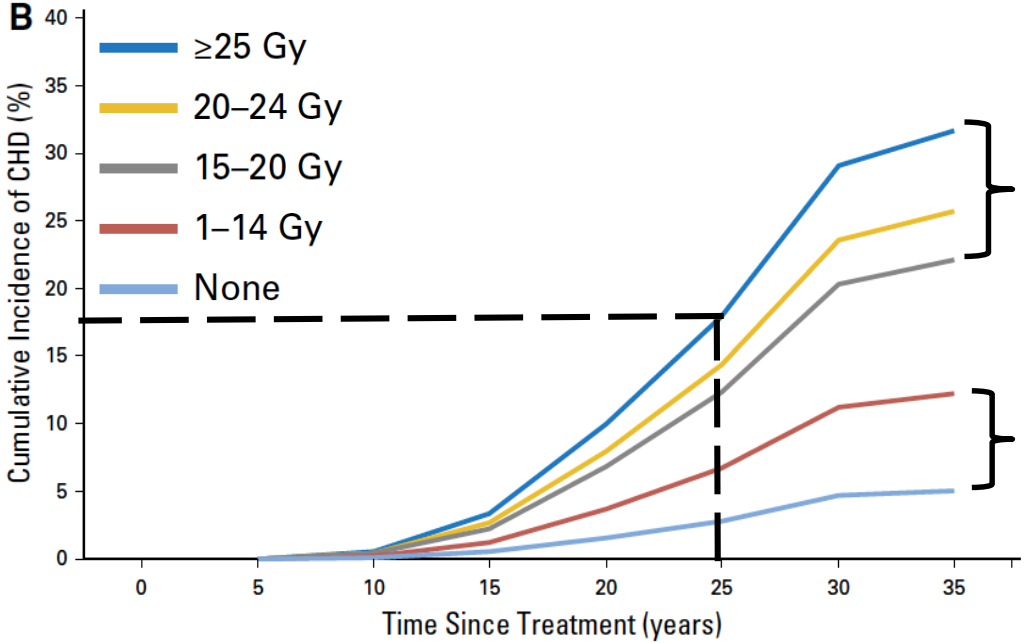
Dose-response by tertiles of age at HL treatment



Van Nimwegen et al., JCO 2015

Cumulative incidence of CHD (1st event) in HL survivors treated between ages 27.5 and 36.4 years

Mean heart dose



Exposure from:
mantle/mediastinal
field 36-40 Gy/18-20 fr

INRT/ISRT: 20-30 Gy/10-15 fr

Van Nimwegen et al., JCO 2015

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., JCO 2015

Established CVD Risk factors

Risk factor		p_{trend}
Physical acti		
Not active (<		
Moderately a		
Very active (		0.136

*p<0.05

¥ adjusted for n

¤ analyzed in s naire (84 cases and 158

Van Nimwegen et al., JCO 2015

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., JCO 2015

Heart failure after HL (1st event)

91 cases and 278 controls nested in cohort of 2,617 Dutch five-year survivors of HL treated between 1965 and 1995

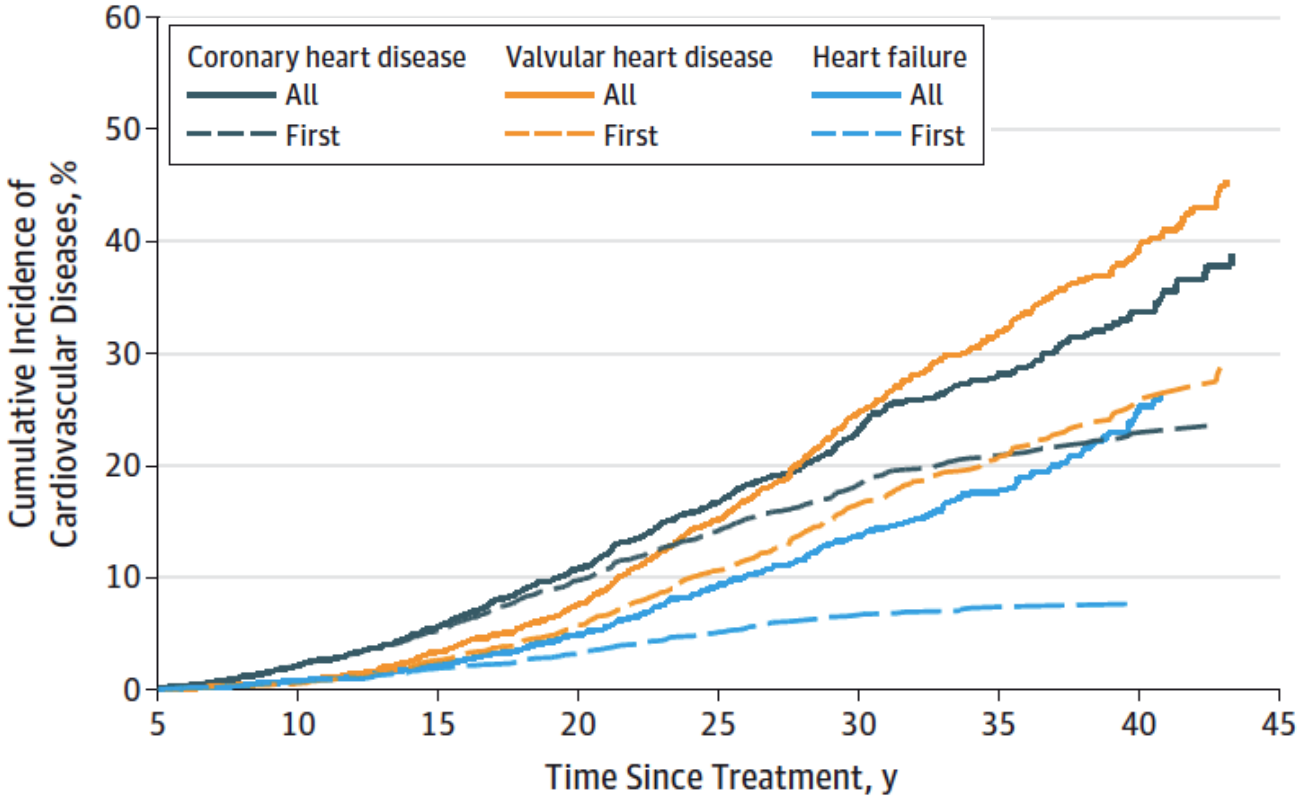
Dosimetry: CT-based

van Nimwegen et al, Blood 2017

Courtesy: G. Ntentas

Cumulative incidence of all and first cardiovascular disease

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



Van Nimwegen et al., JAMA int med 2015

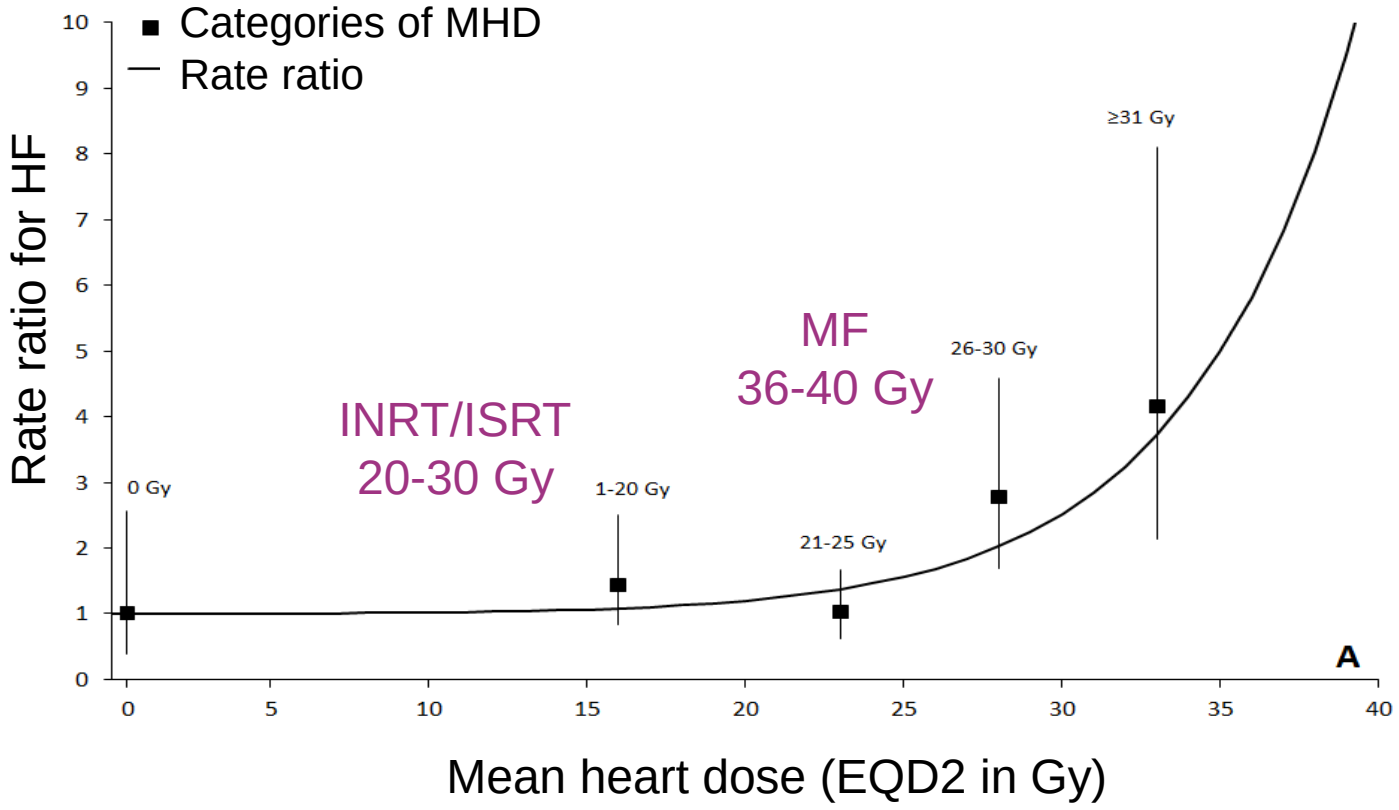
Heart failure after HL (1st event)

91 cases and 278 controls nested in cohort of 2,617 Dutch five-year survivors of HL treated between 1965 and 1995

- 44% grade 2 and 43% grade 3 heart failure (HF)
- Median interval until HF: 20.6 years (IQR: 13.7-25.2)
- Median age at HL diagnosis: 28.3 years (IQR: 21.9-37.7).
- 57% of the HF cases had died by the end of follow-up, with median time from HF to death of 3.6 years (IQR: 0.2-5.6).

Van Nimwegen et al., Blood 2017

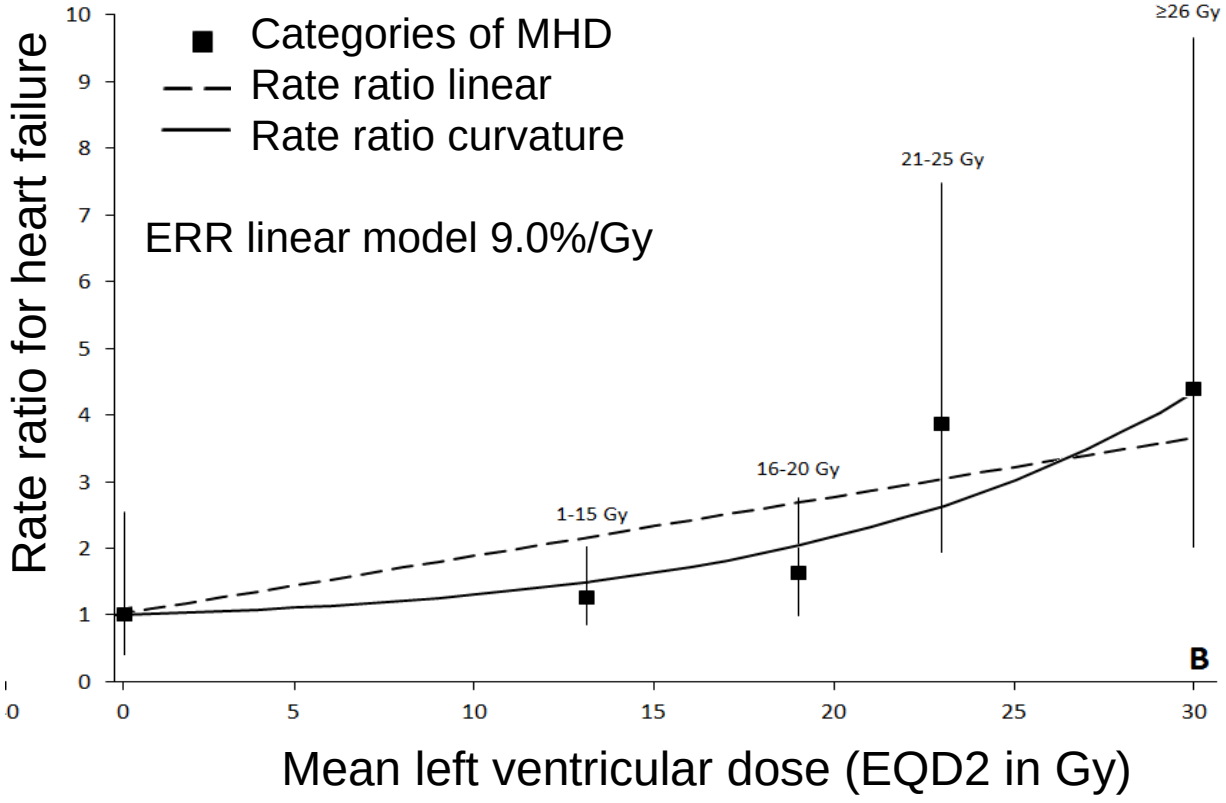
Relationship between heart failure rate and mean heart dose



Van Nimwegen et al., Blood 2017

Van Nimwegen et al., Blood 2017

Relationship between heart failure rate and mean left ventricular dose



Van Nimwegen et al., Blood 2017

Heart failure after HL (1st event)

91 cases and 278 controls nested in cohort of 2,617 Dutch five-year survivors of HL treated between 1965 and 1995

- Anthracycline-containing chemotherapy increased HF rate by a factor of 2.83 (95%CI: 1.43-5.59) with no significant interaction with mean left ventricular dose (p=0.09).
- No dose-effect relationship for anthracycline dose
- No interaction with general risk factors CVD

Van Nimwegen et al., Blood 2017

Conclusions HF ca-co study

- **Quantitative estimates** of HF risk in 5-year HL survivors following RT:
  - Little increase in HF risk for doses up to 25 Gy MHD or up to 15 Gy MLVD, but HF rates increase rapidly at higher doses.
- Anthracyclines: 3-fold increased HF rate, irrespective of the dose of anthracycline or of cardiac radiation.
- Our findings can be used to **predict HF risk**

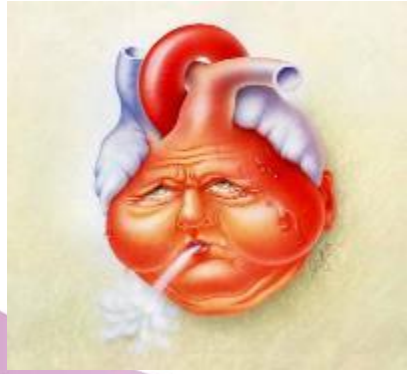
➢ Patients who received both anthracyclines + mediastinal RT need to be followed carefully.

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

Anthracyclines

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

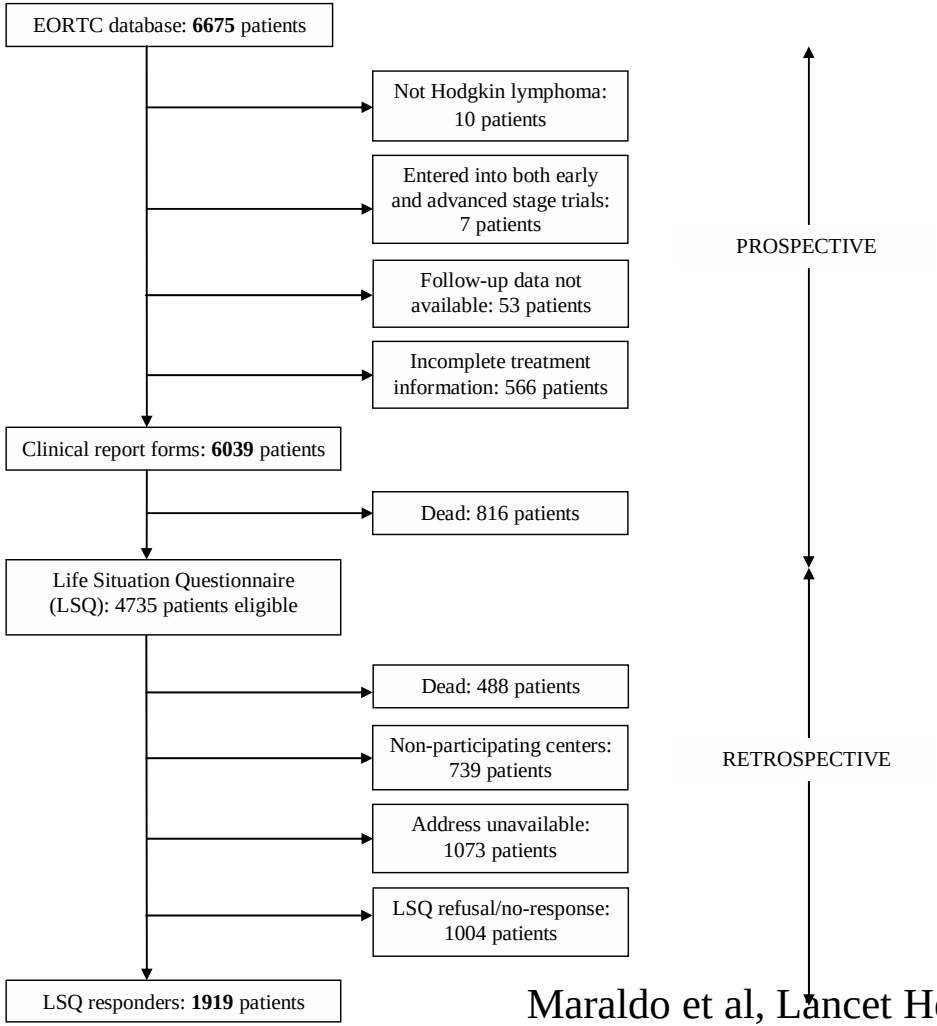


Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

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

Maraldo et al, Lancet Hemat 2015

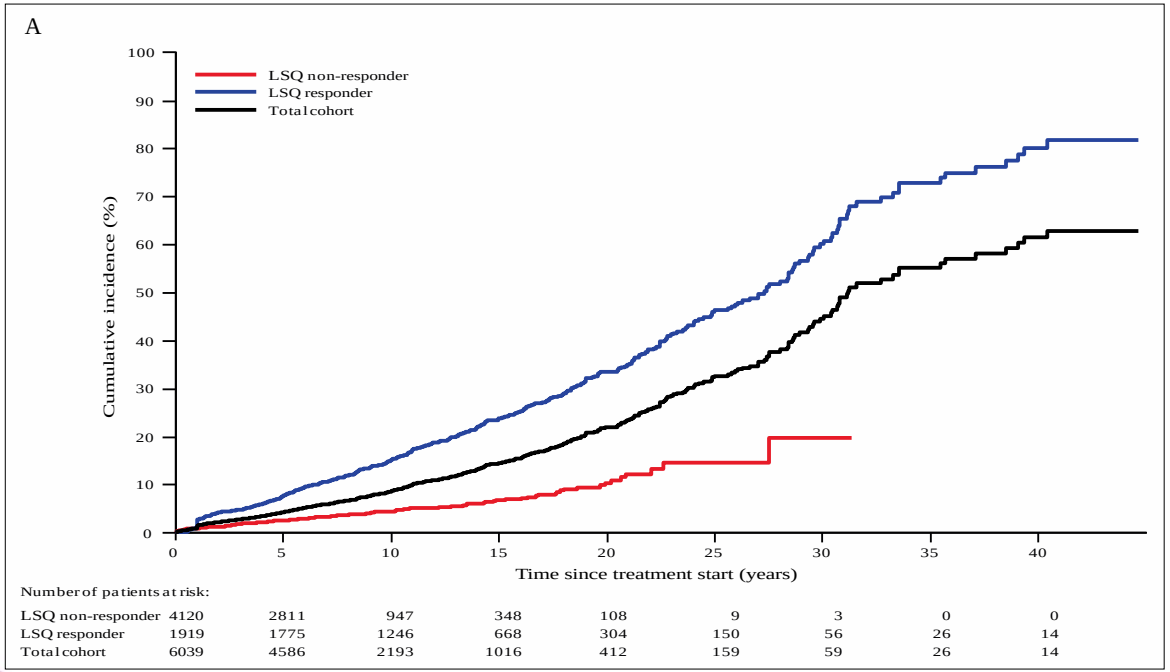
CVD after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials



Maraldo et al, Lancet Hemat 2015

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)



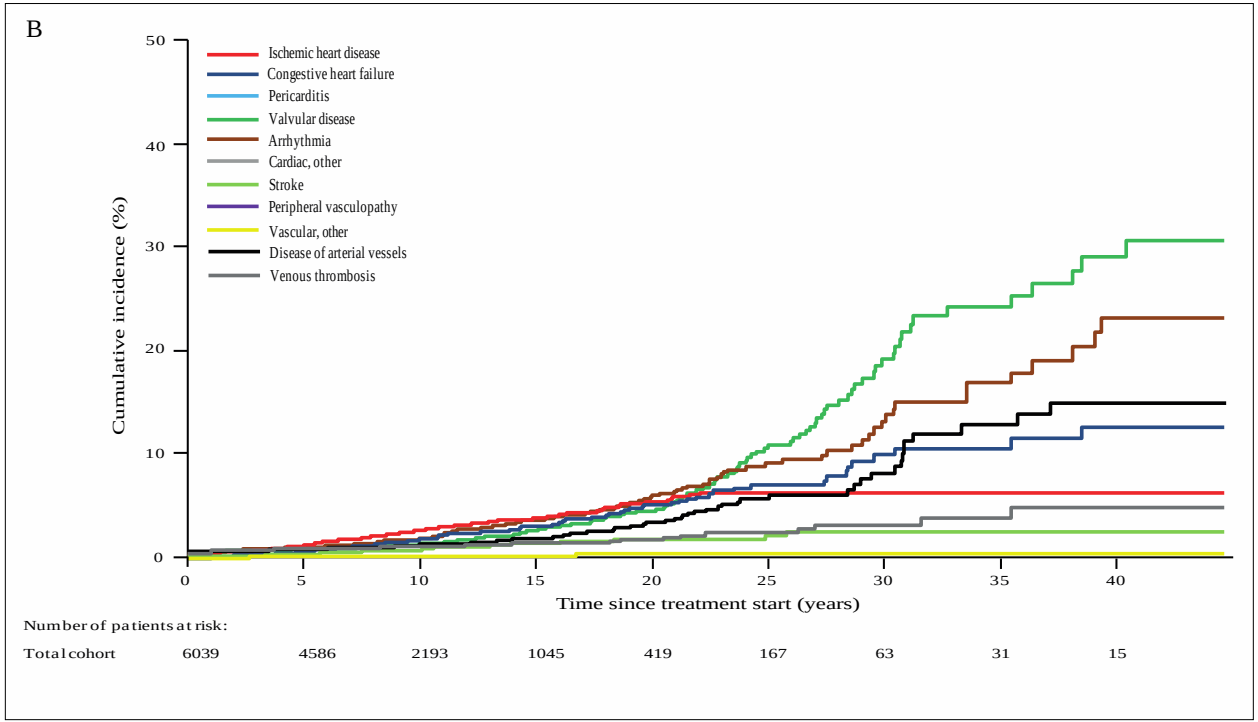
LSQ responder

Total cohort

LSQ non responder

Maraldo et al, Lancet Hemat in 2015

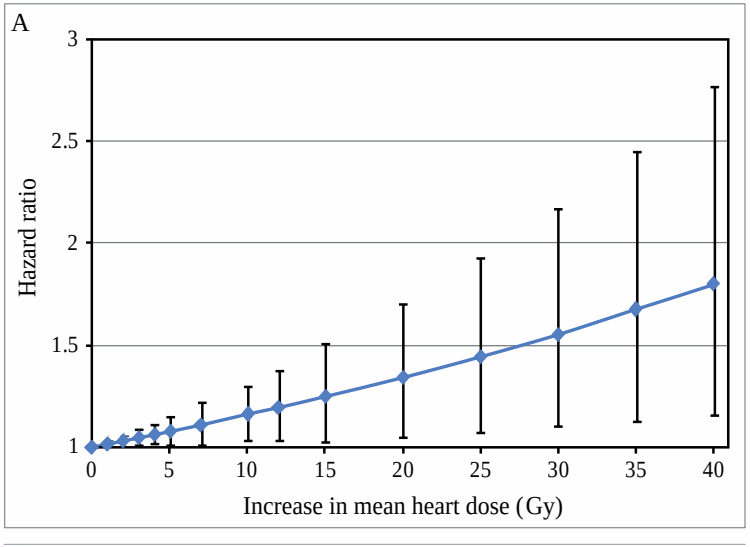
Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

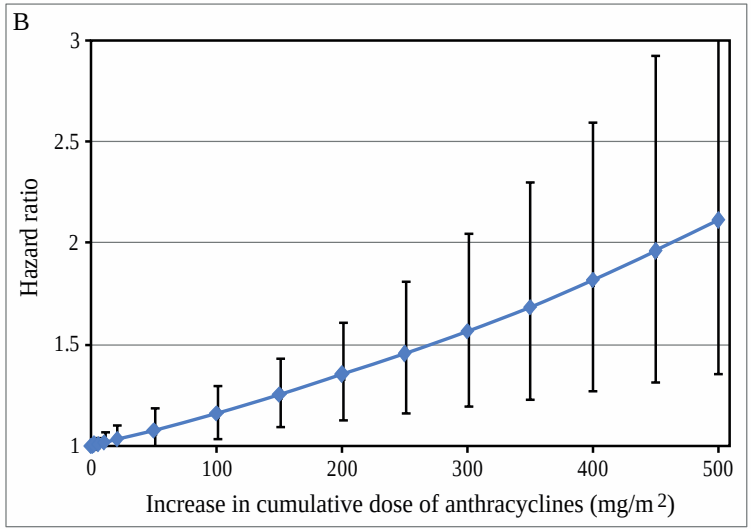


Maraldo et al, Lancet Hemat 2015

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 2015

Optimize treatment ?

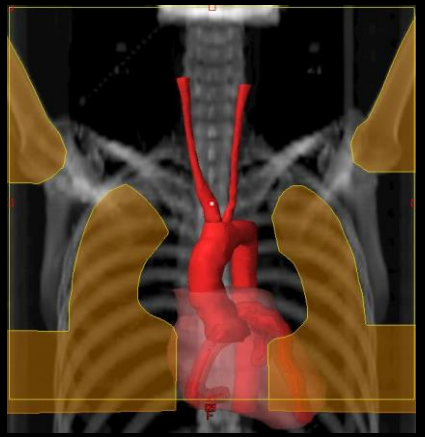
Disease control

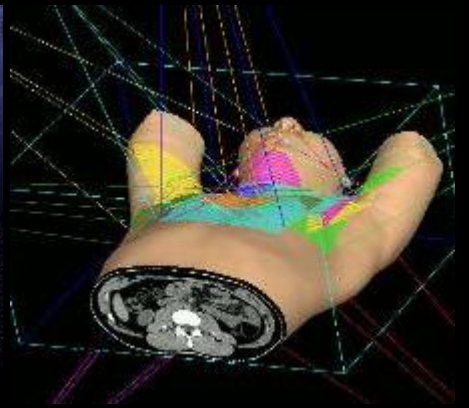
Chance early and late side effects

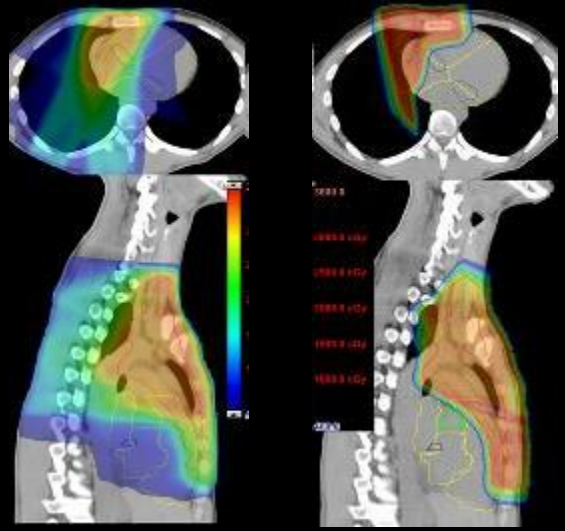
Treatment optimization:

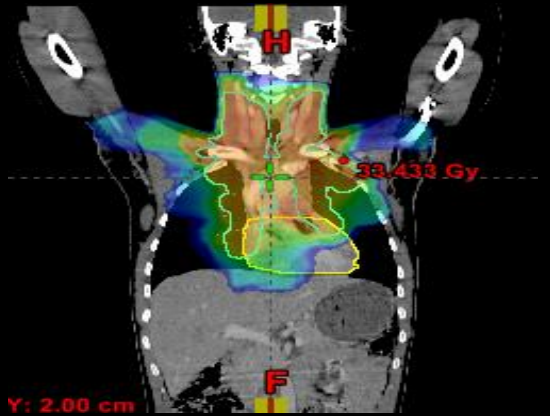
Extensively discussed during course:

- 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
38.398 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

- Refine dose effect relationships (”a lot to a little or a little to a lot”?)
- 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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University of Oxford
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Hodgkin lymphoma survivors

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


ESTRO
School

Chemotherapy and combined modality treatment, with a focus on 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

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/m²	iv bolus	1 + 8
(O)ncovin	1.4 mg/m² (max 2)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m²	po qd	1 - 14
(P)rednisone	40 mg/m²	po qd	1 - 14

COPP

Combination chemotherapy

Drug	Dose	Mode	Days
(C)yclophosphamide	600 mg/m²	iv infusion	1 + 8
(O)ncovin	1.4 mg/m² (max. 2 mg)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m²	PO qd	1 - 10
(P)rednisone	40 mg/m²	PO qd	1 - 14

ABVD

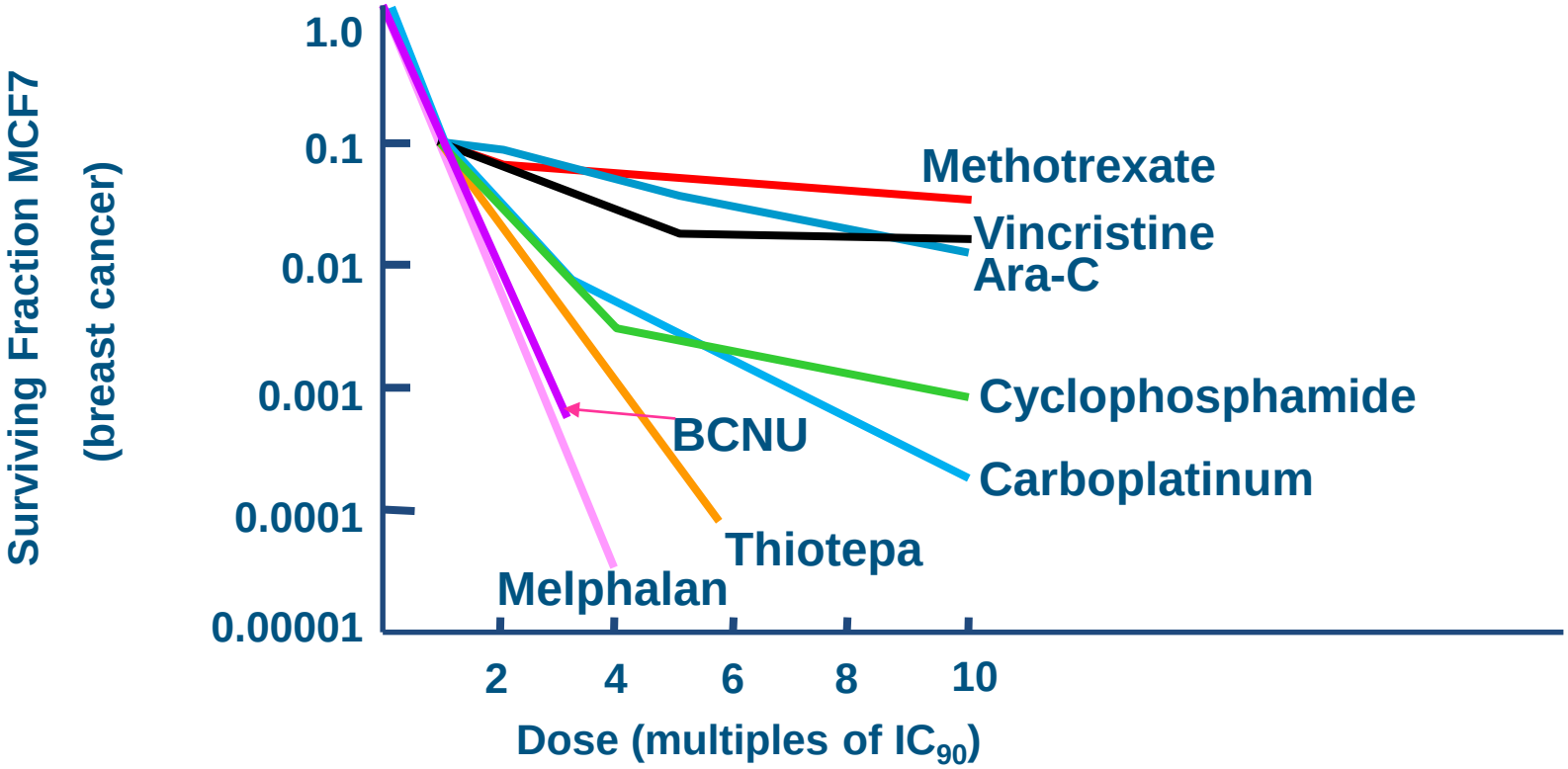
Combination chemotherapy

(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

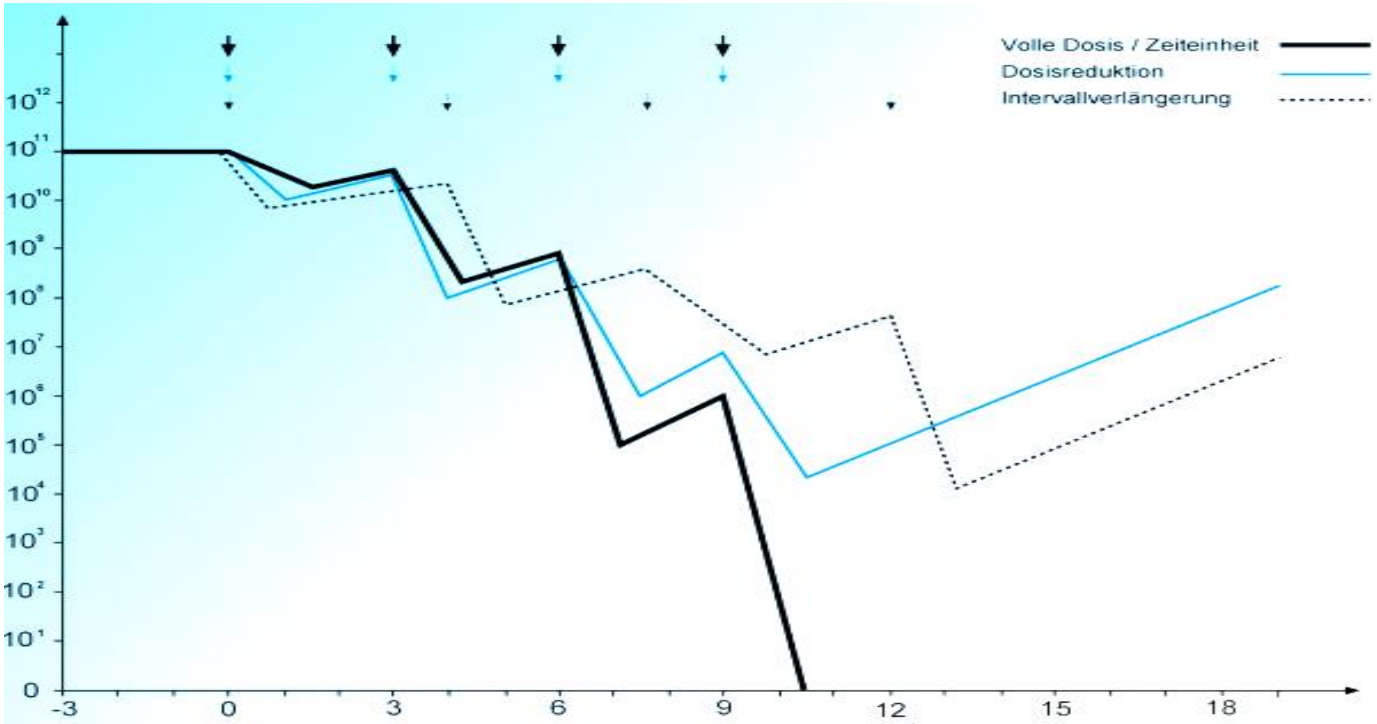
Correlation of dose and efficacy

Cytostatic drugs *in vitro*



Correlation of dose density and response

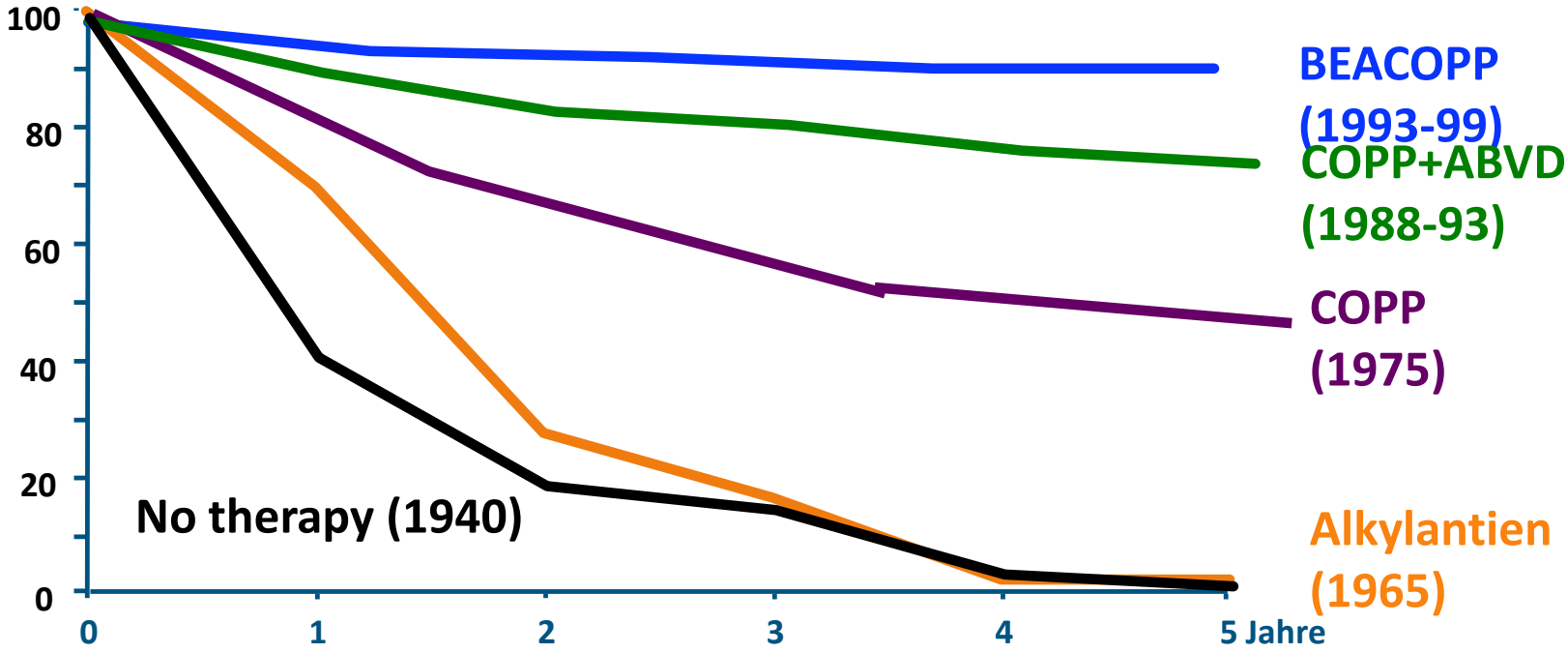
Chemosensitive malignancies



C. Jackisch

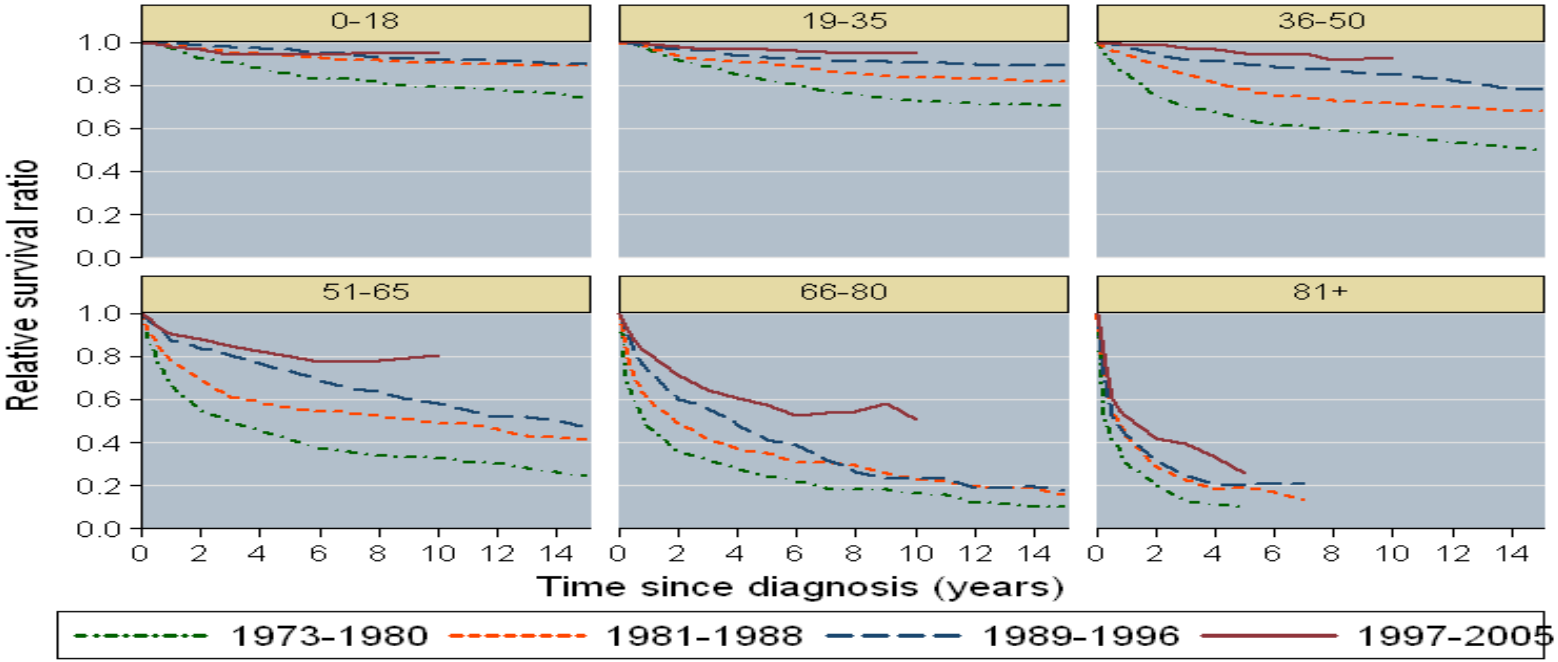
Hodgkin Lymphom

Progress in advanced stages



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**

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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%)

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

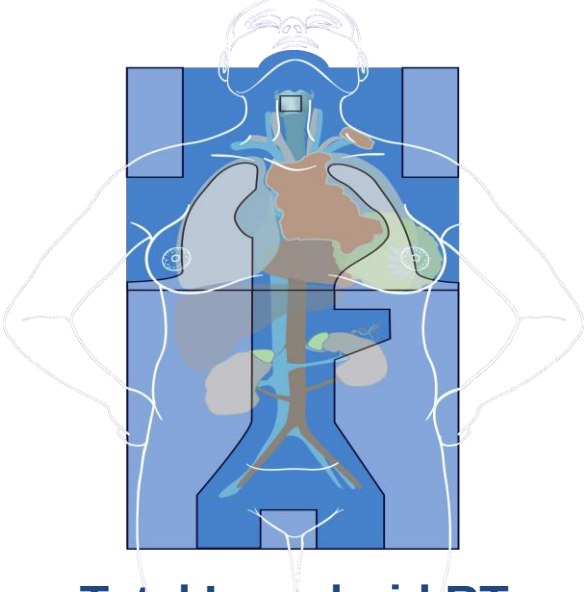
GHSG Clinical Trials

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 - 09	HD13-15	5171
2010 - 16	HD16-18	5279
Total		19804

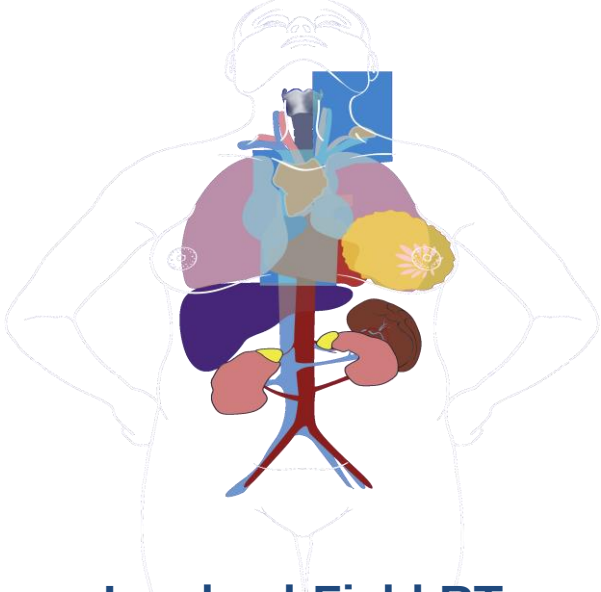
Hodgkin Lymphoma
Evolution of Radiotherapy

1970



Total Lymphoid RT
44 Gy

1995



Involved-Field RT
36 Gy

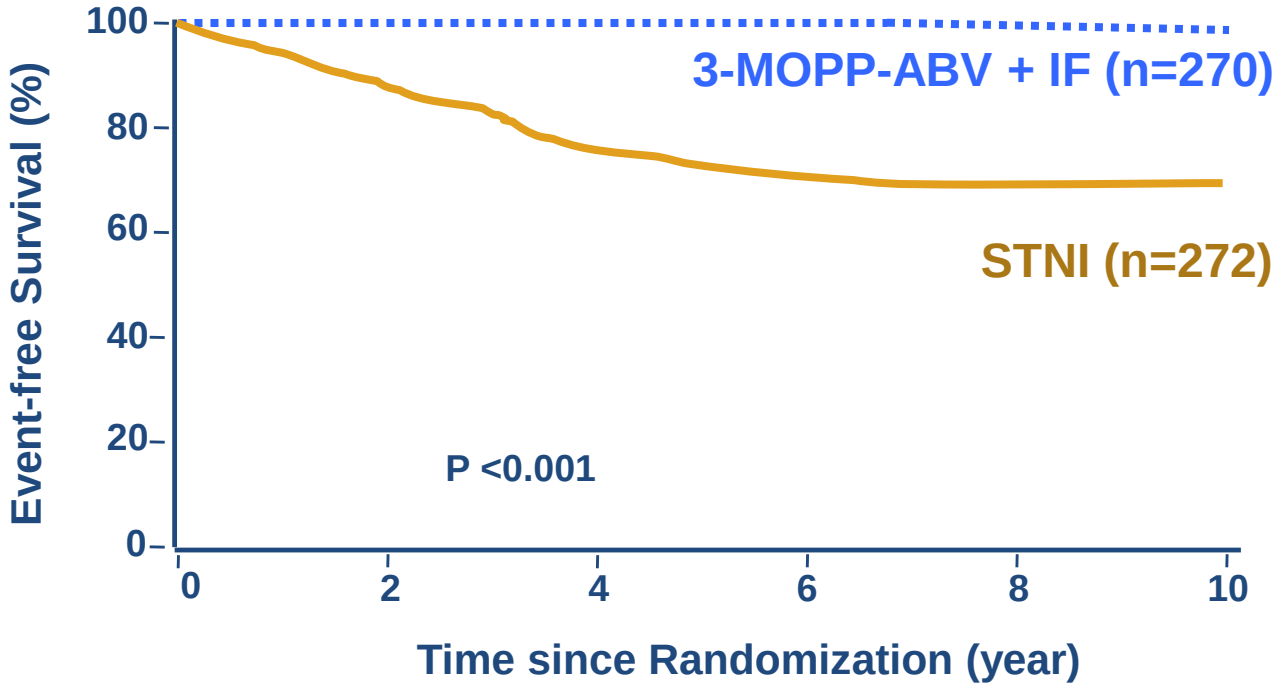
2008

Involved Node RT
20-30 Gy

Adapted from Yahalom, Lugano 2008

EORTC H8F Clinical Trial

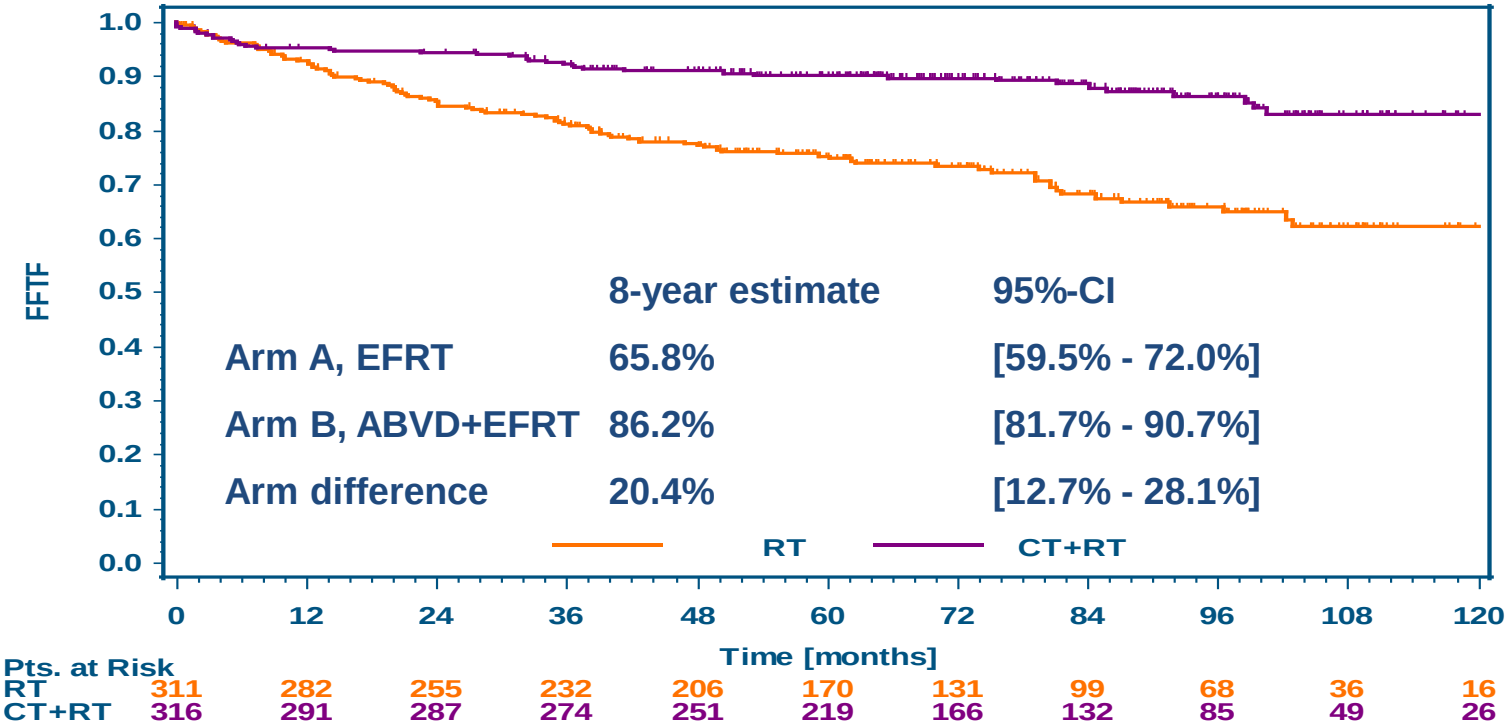
FFTF for pts with early favorable



Ferme et al; NEJM 2007

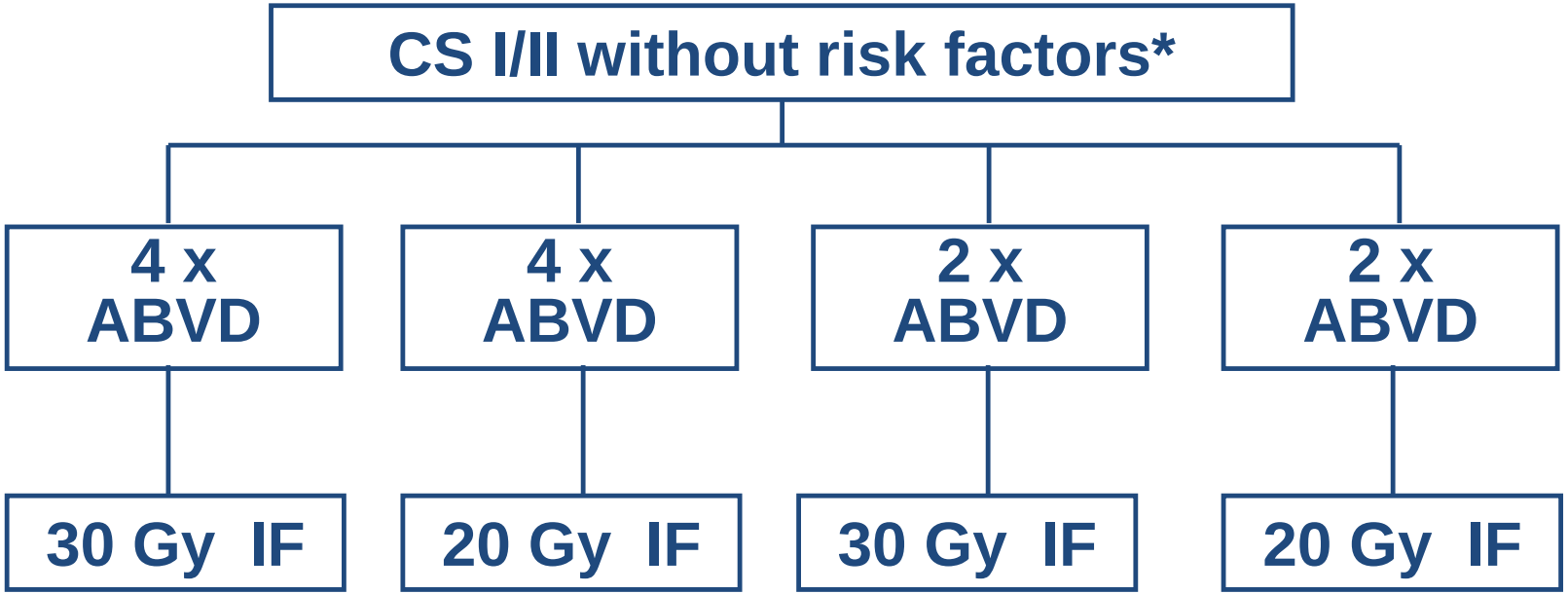
HD7 Clinical Trial

For early favorable HL (FFTF)



Engert et al; JCO 2007

GHSG HD10 Trial in early favorable HL

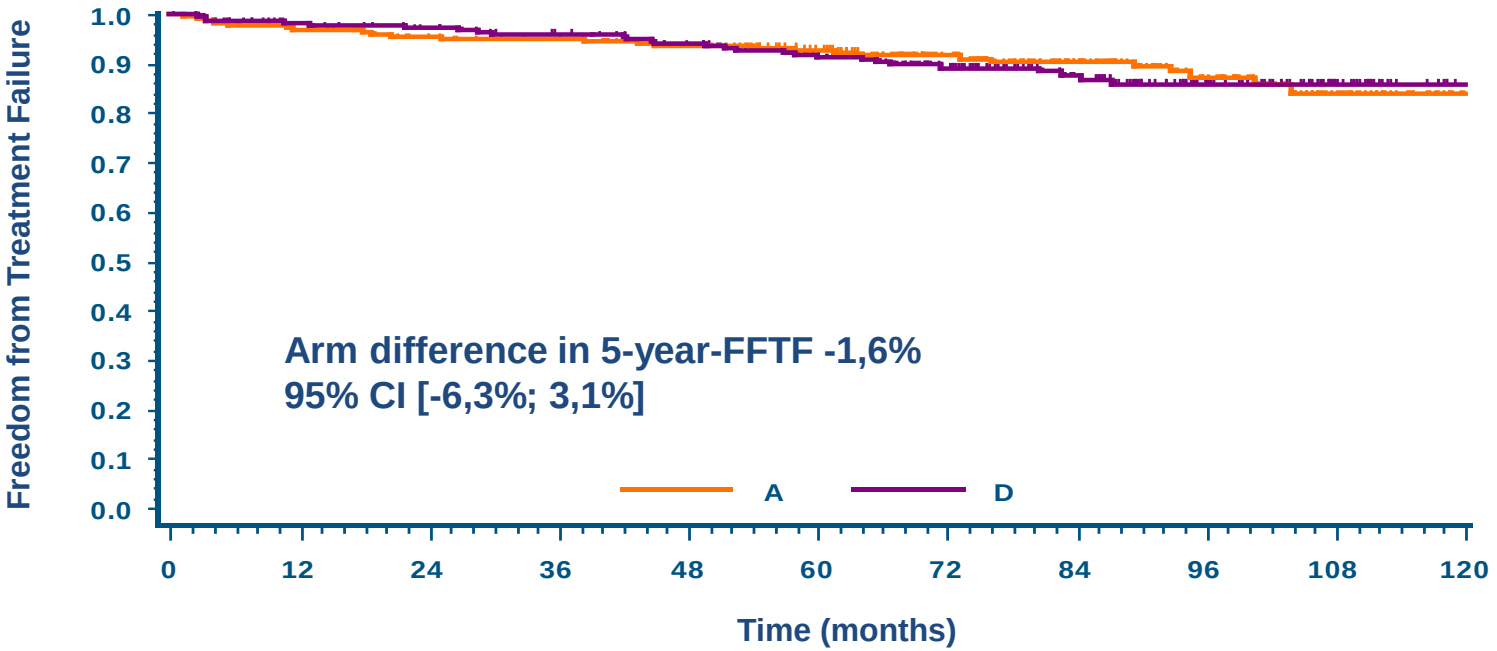


*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

GHSG 2010

GHSG HD10 Clinical Trial

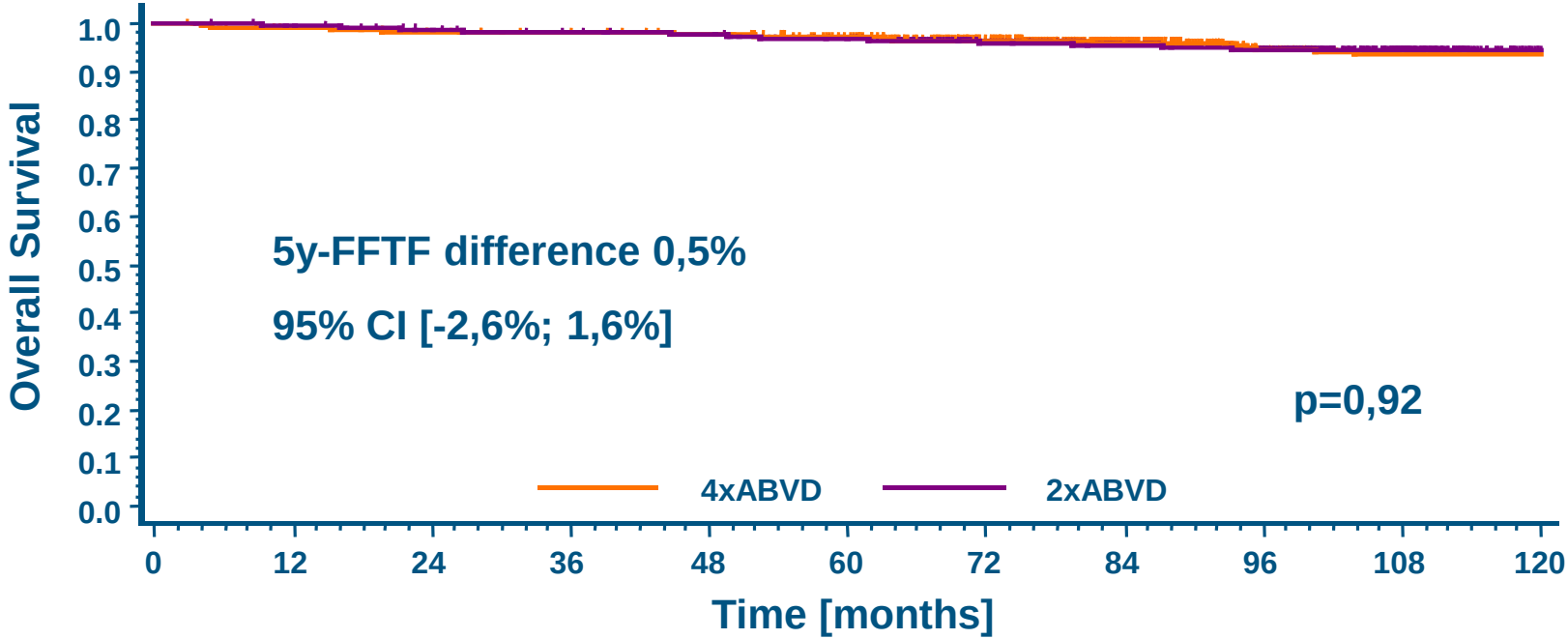
Weakest vs strongest arm (FFTF)



Engert A et al; NEJM 2010

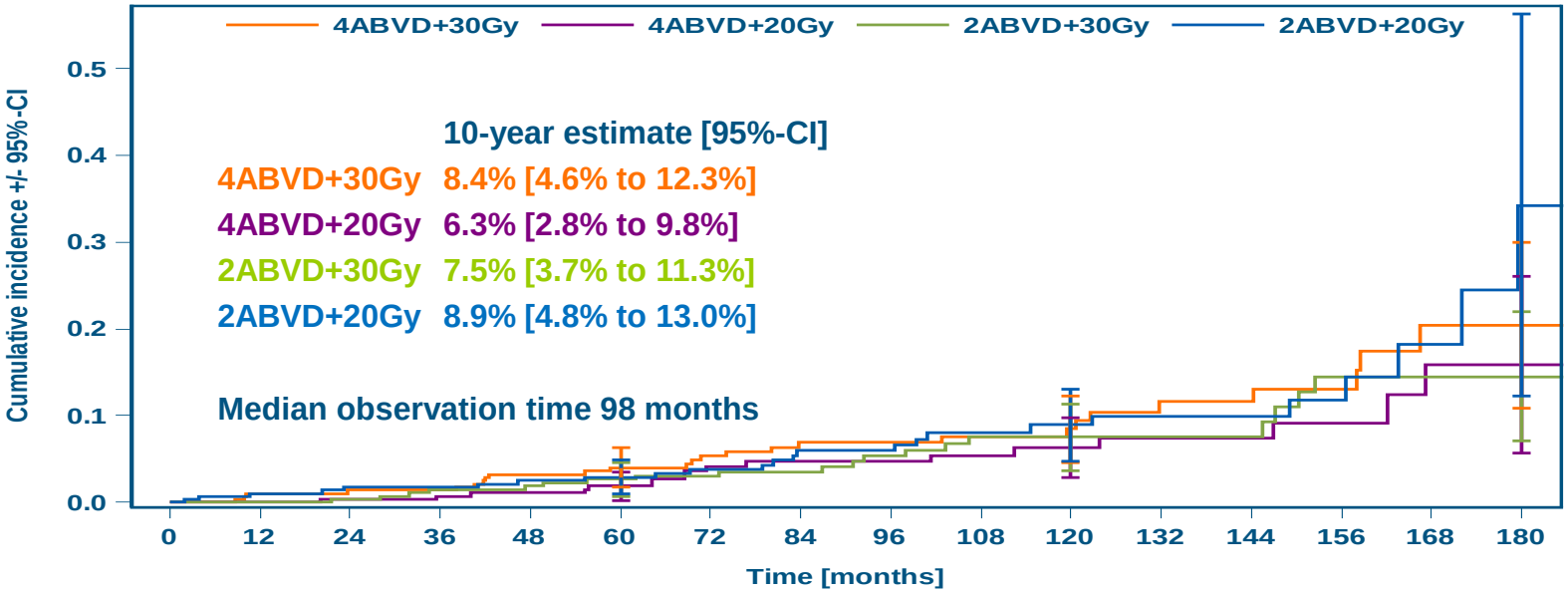
GHSG HD10 Clinical Trial

Overall Survival



Engert et al; NEJM 2010

HD10:
Second Neoplasia

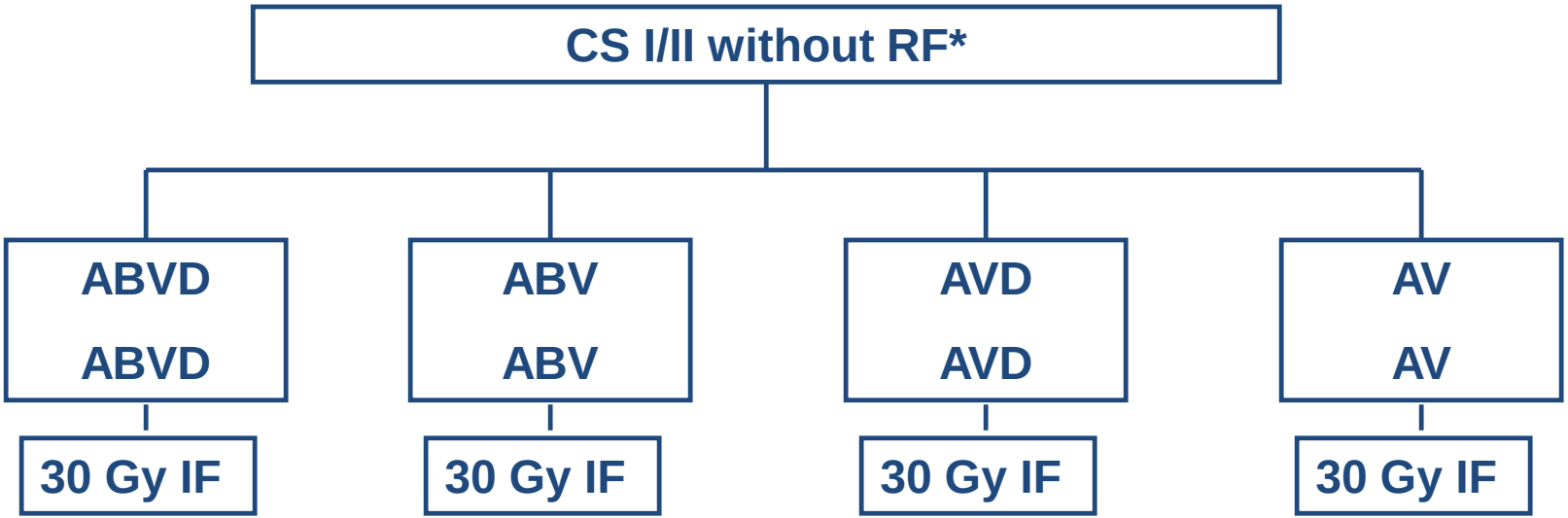


→ **No difference in SIR for any SN: A= 2.1, B= 1.5, C= 1.6, D= 2.1**
compared to the age- and sex-specific incidence in the German general population

Bröckelmann et al; EHA 2016

GHSG HD13 Clinical Trial

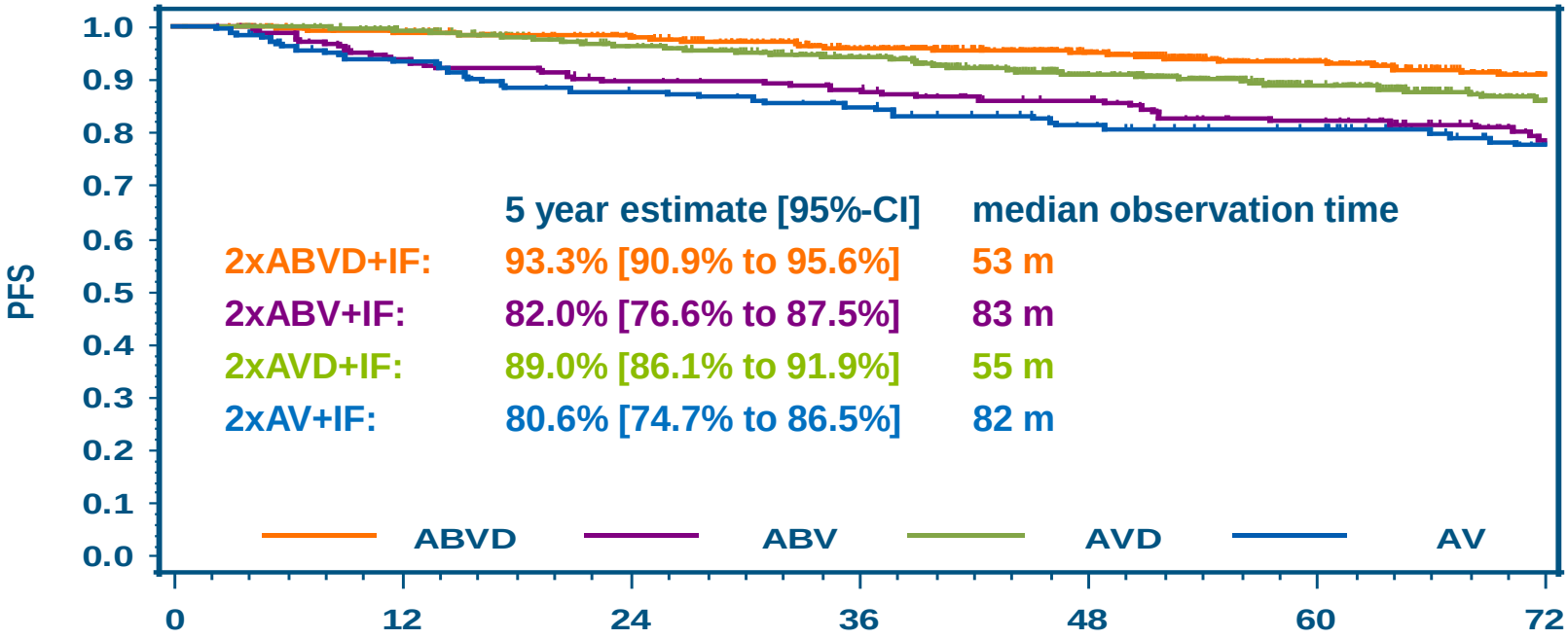
Early favorable HL



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

HD13: Progression-free survival

All patients (ITT)

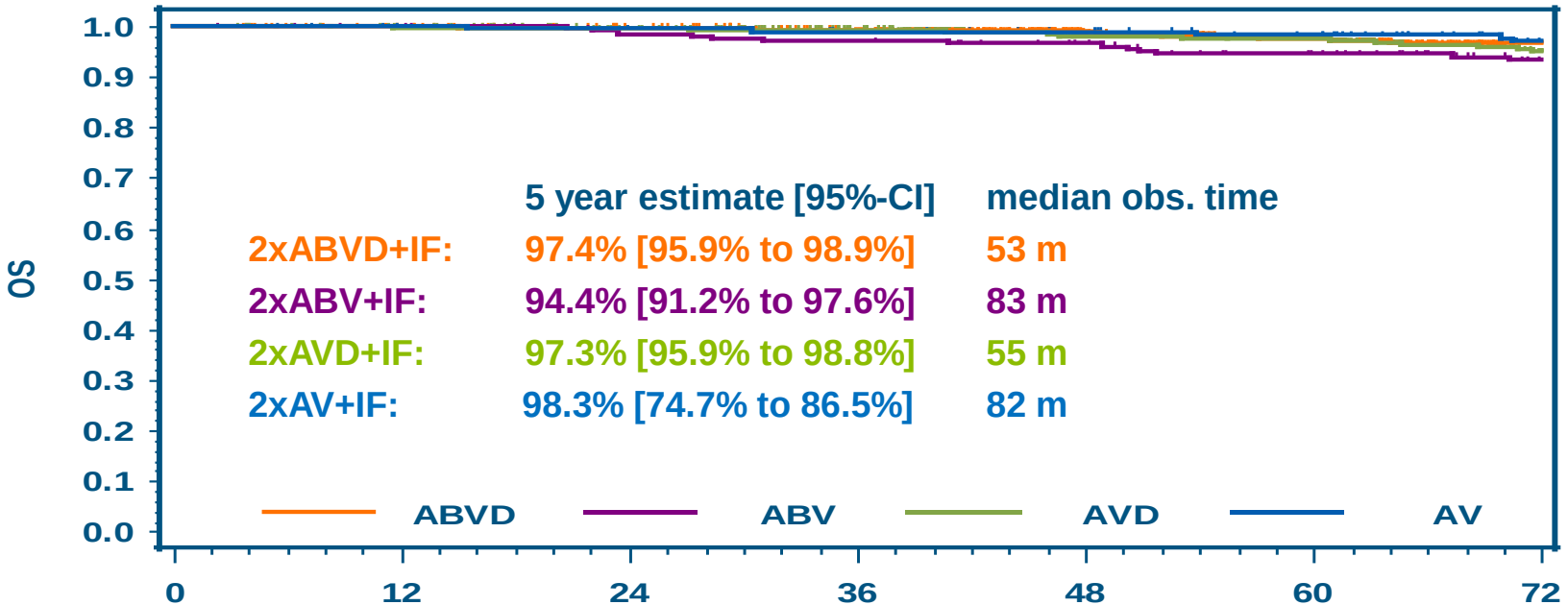


Pts. at Risk							
ABVD	623	593	556	490	362	228	130
ABV	209	189	178	170	156	139	109
AVD	620	592	540	477	344	230	126
AV	186	166	153	144	128	118	93

Behringer et al, Lancet 2014

HD13: Overall survival

All patients (ITT)



Pts. at Risk							
ABVD	623	609	590	551	431	298	183
ABV	209	206	198	195	187	173	154
AVD	620	608	587	550	424	306	191
AV	186	182	180	177	173	164	142

Behringer et al, Lancet 2014

GHSG Risk Allocation for HL patients

<table>
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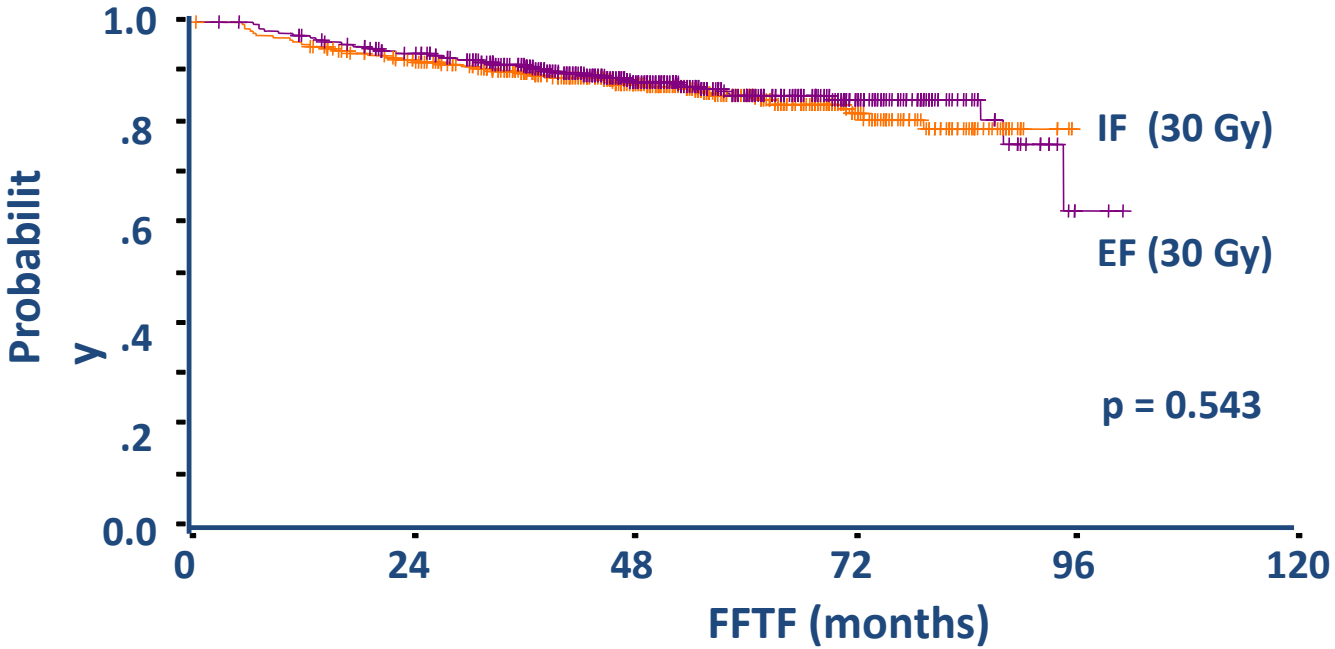
</table>

GHSG 2000

HD8 Trial comparing EF vs IF after 4 x chemo

Early unfavorable HL (FFTF)



FFTF @ 5years

EF-RT: 85.0%

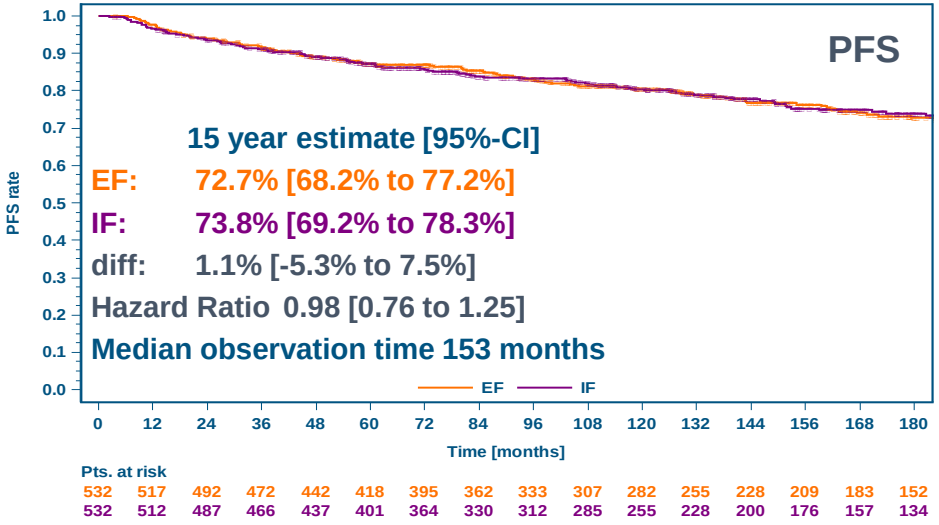
IF-RT: 85.9%

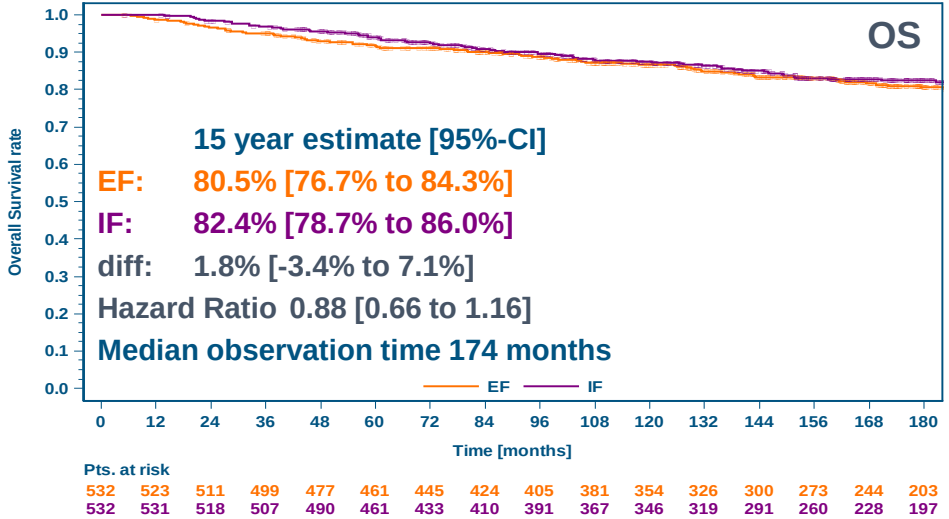
No difference in 15-year PFS and OS between EF and IF-RT after 2x COPP/ABVD in early-stage unfavorable HL

Engert et al JCO 2003

HD8 in early unfavorable HL

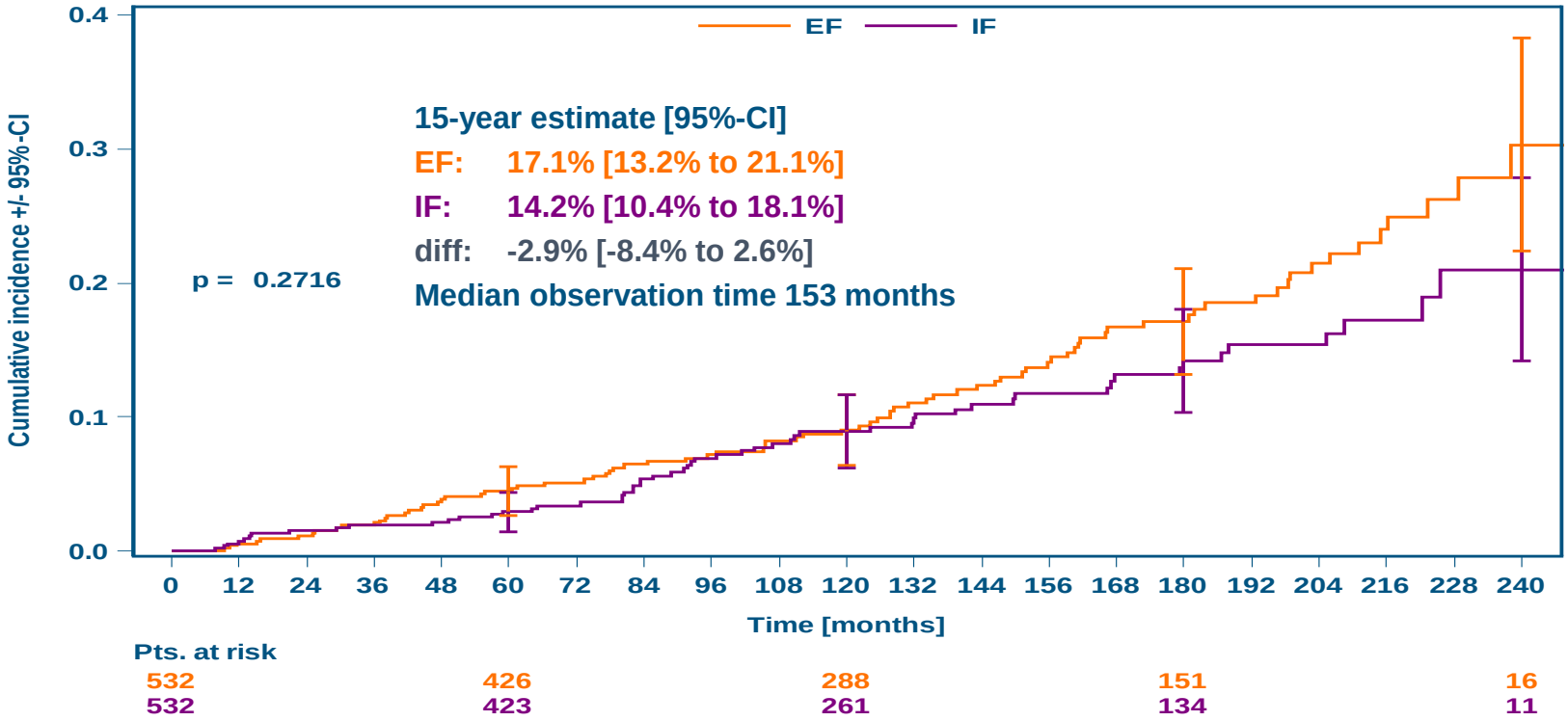
Long-term outcome





Bröckelmann et al; EHA 2016

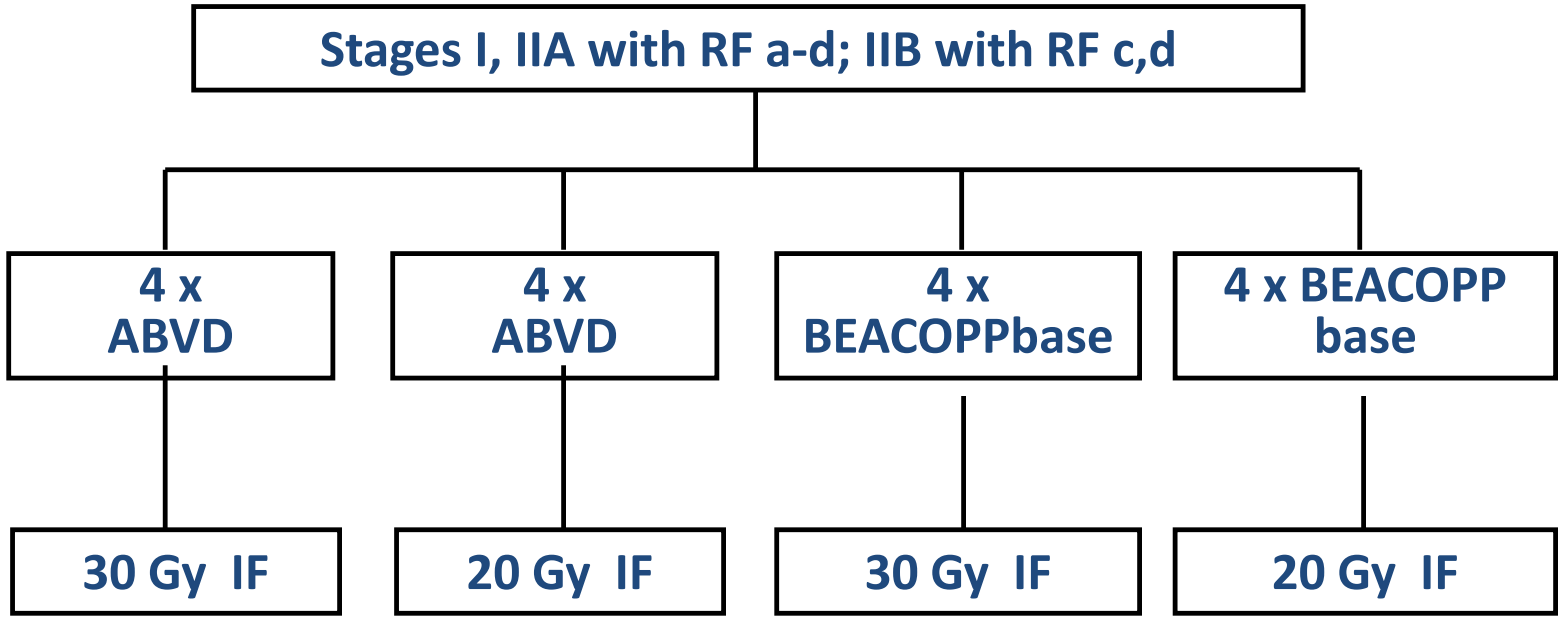
HD8: Second Neoplasia



→ **Trend towards increased SIR with EF: 3.6 (2.9-4.0) vs. 2.6 (2.0-3.3) compared to the age- and sex-specific incidence in the German general population**

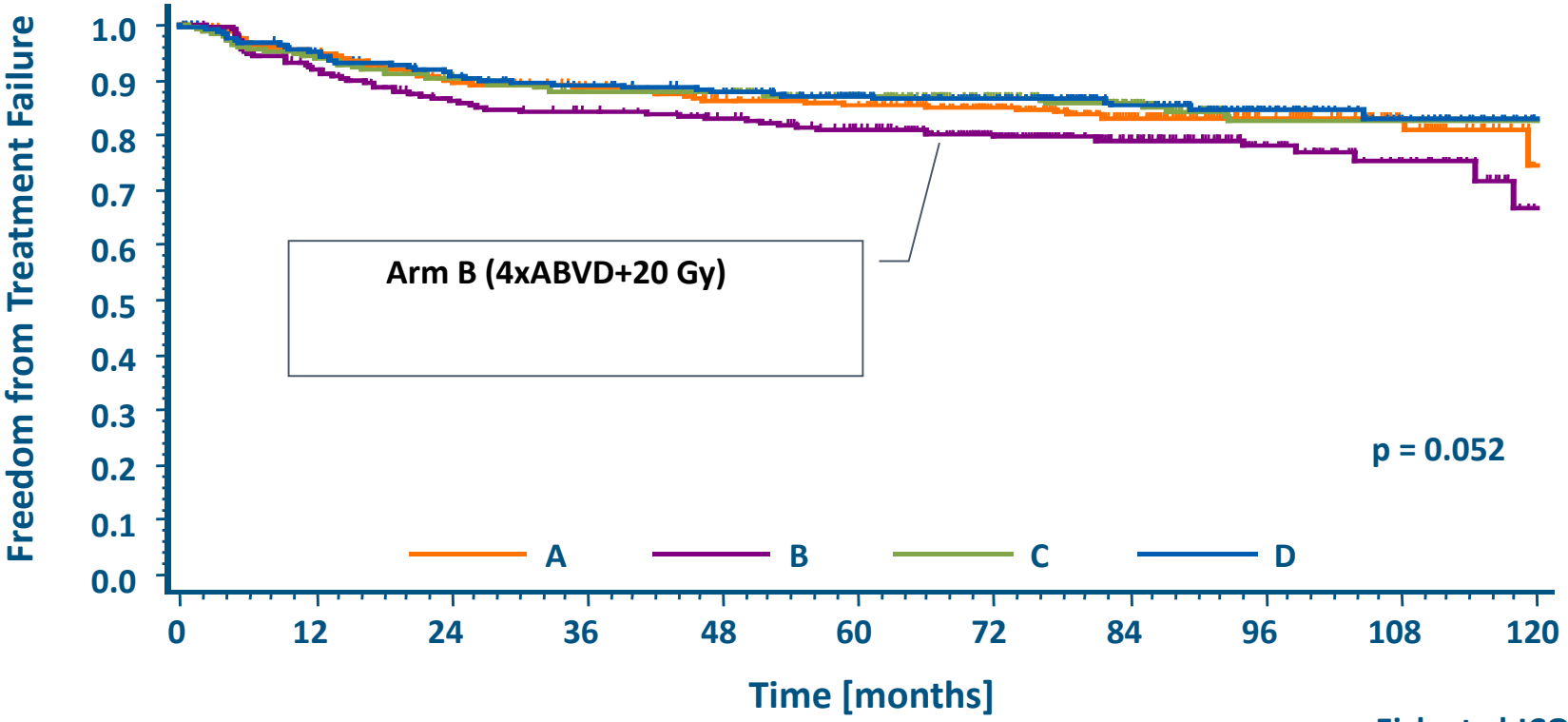
Bröckelmann et al; EHA 2016

HD11 trial for early unfavorable HL



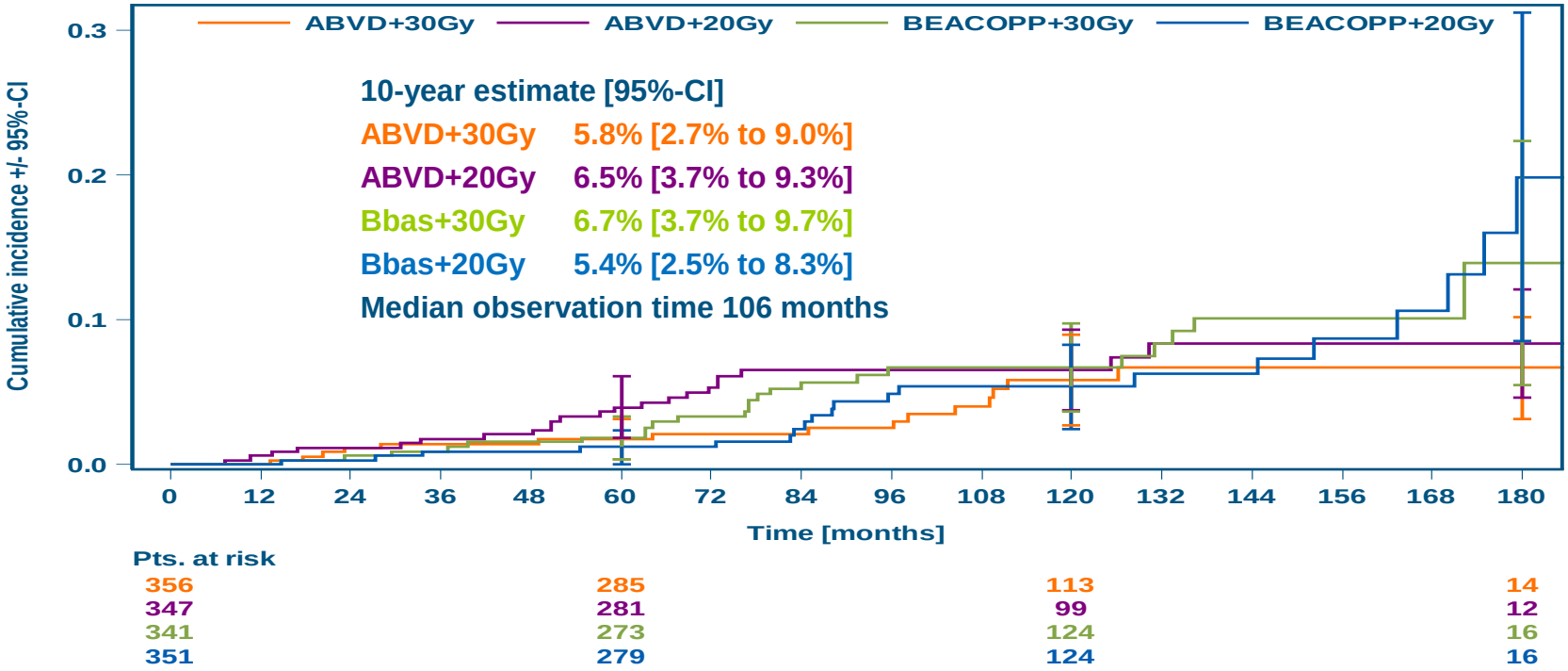
*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas

HD11 trial: FFTF – all 4 arms



Eich et al JCO 2010

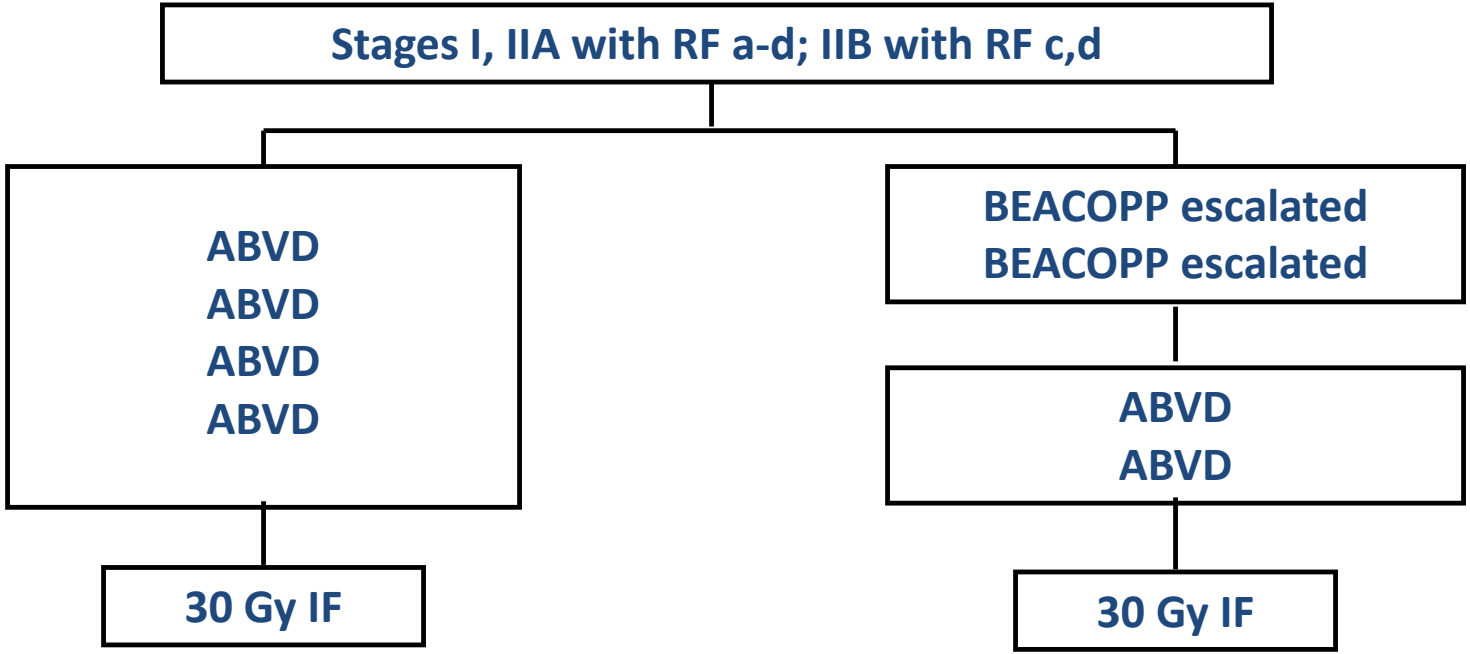
HD11: Second neoplasias



→ **No difference in the SIR: A= 1.4, B= 2.4, C= 2.2, D= 1.7**
compared to the age- and sex-specific incidence in the German general population

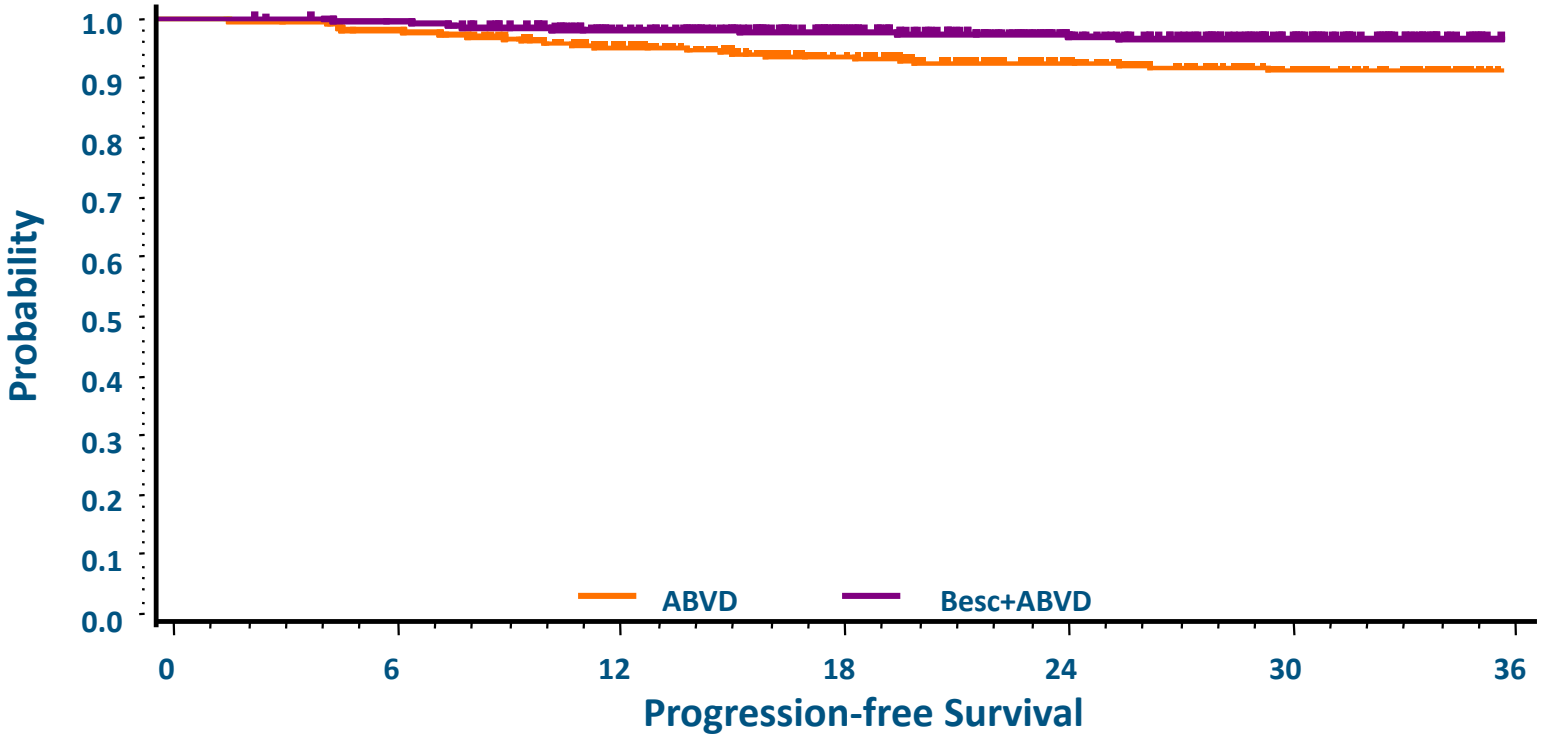
Bröckelmann et al; EHA 2016

HD14 study (GHSG) for early unfavorable HL



*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas

HD14 trial for early unfavorable HL (PFS)



von Treskow et al JCO 2012

Combined Modality Treatment of HL

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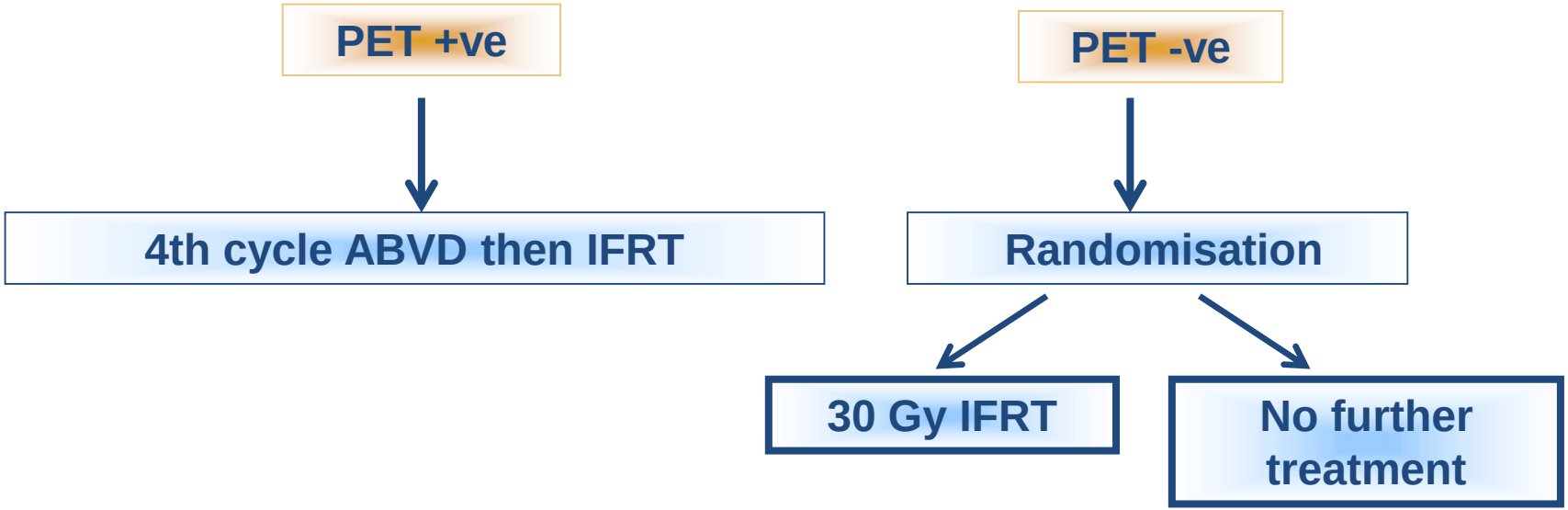
UK NCRI RAPID trial

In early stage HL

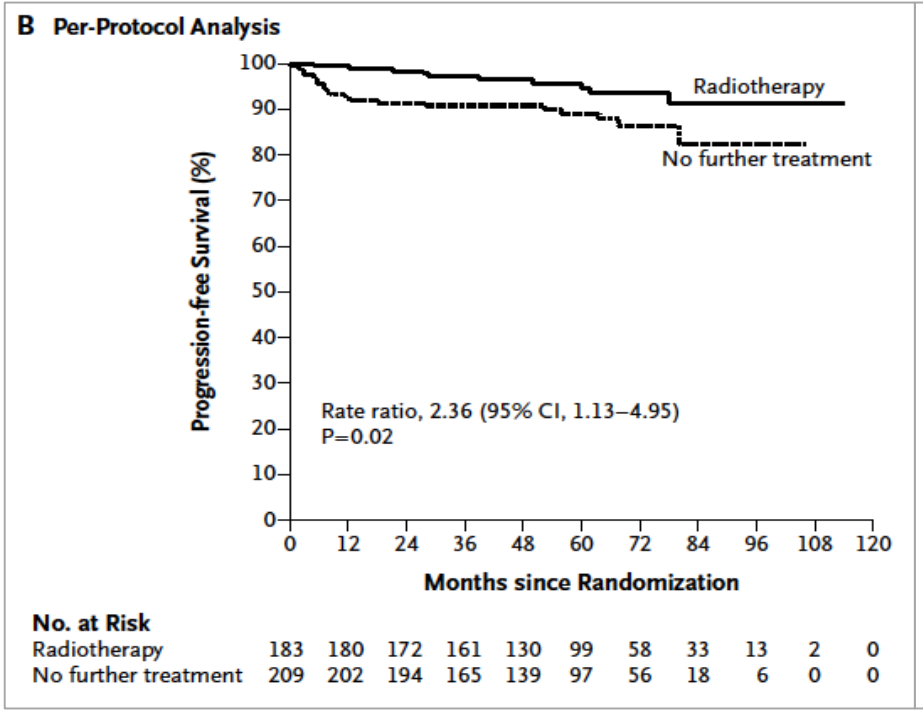
Initial treatment: 3xABVD

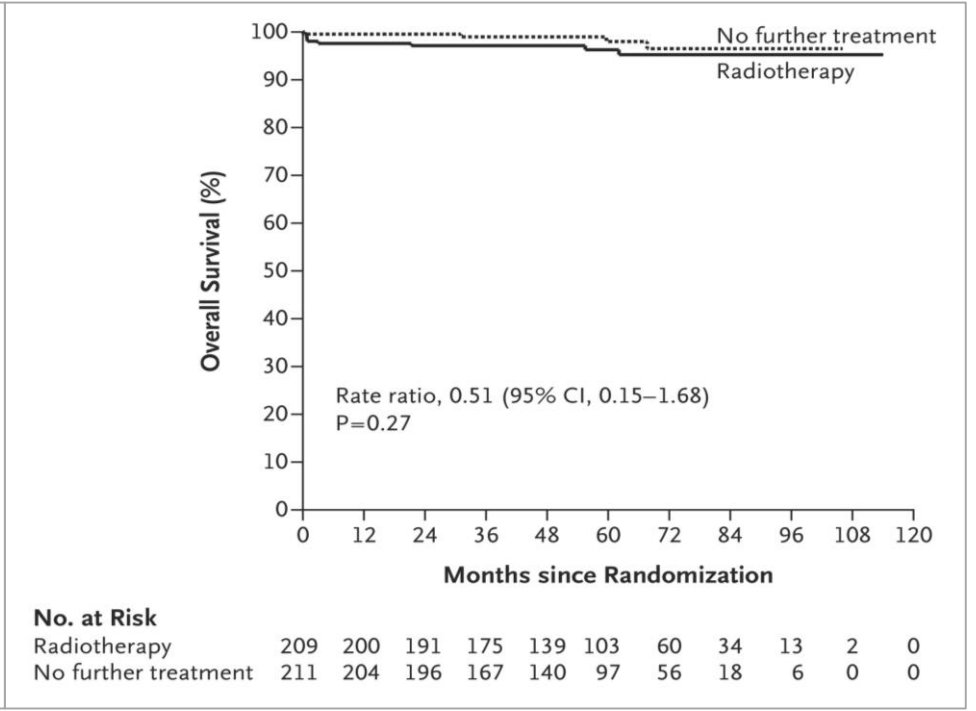
Re-assessment: if response, PET scan performed



UK NCRI RAPID trial

Early stage HL



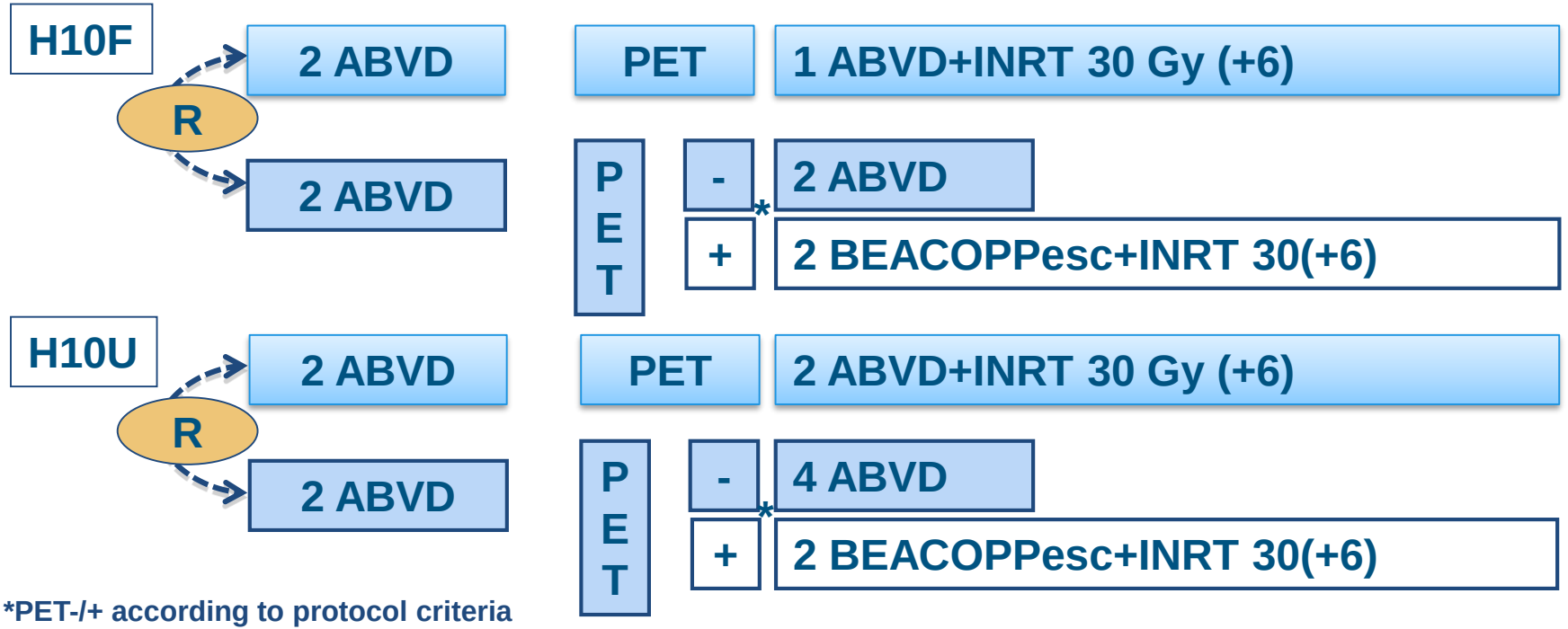


Radford J et al; NEJM (2015) 372;17:1598-1605

EORTC/GELA/IIL H10 Study

For early favorable and unfavorable

H10 (#20051): study design



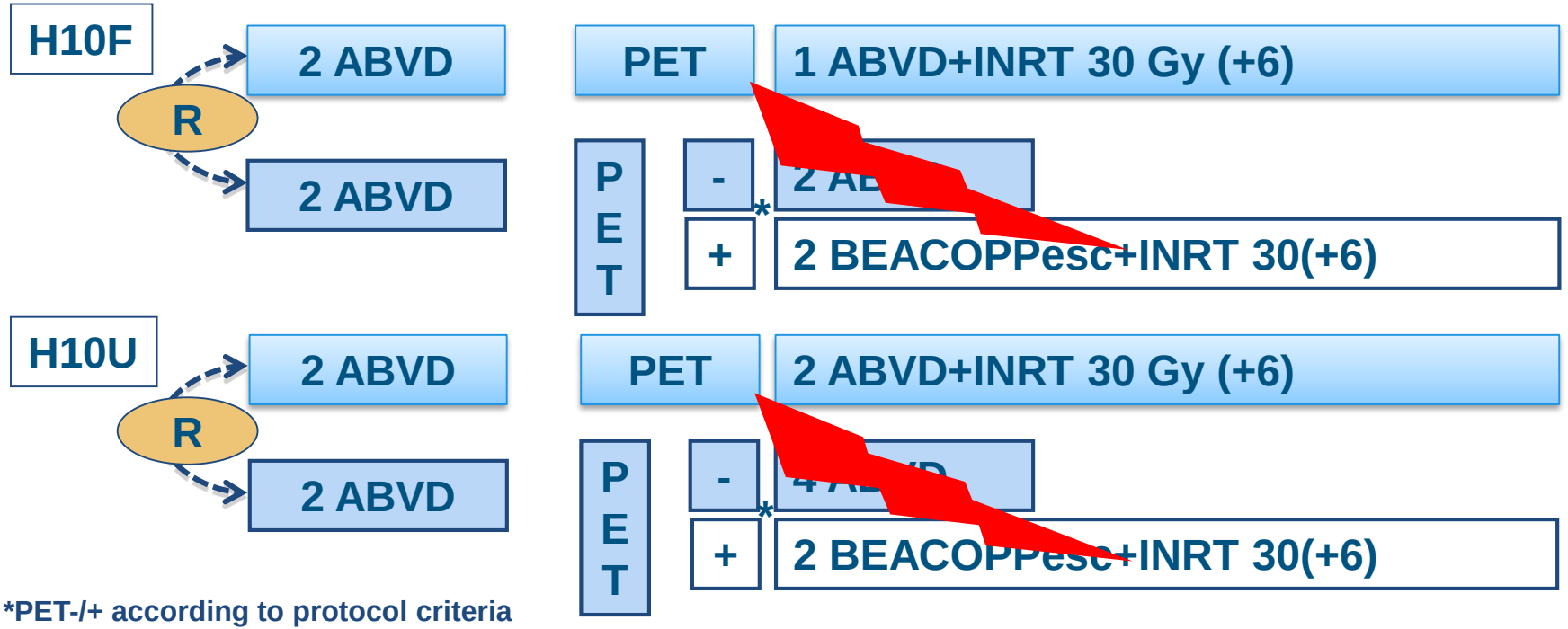
*PET-/+ according to protocol criteria

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

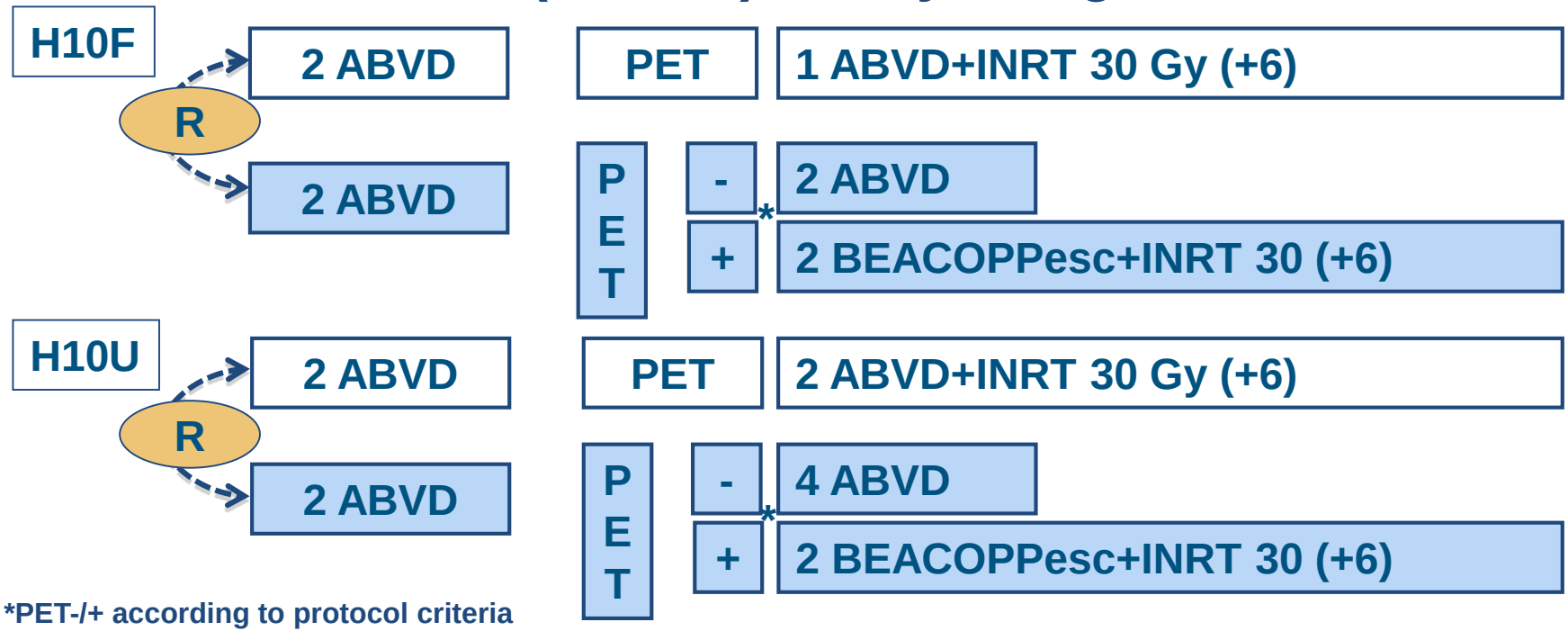
- Central PET review necessary
- More events in PET- patients with chemo only
- Similar findings but opposite conclusions (8 vs 20 and 8 vs 25 events) between RAPID[1] and H10[2]
- Rapid failed to demonstrate non-inferiority (HR 1.57; p=0.27) with PFS differences of up to 8.8% (ITT) and 11.0% (per protocol)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

[1]Radford et al; NEJM 2015
[2]Raemakers et al; JCO 2015

EORTC/GELA/IIL H10 Study

Results of PET+ patients

H10 (#20051): study design

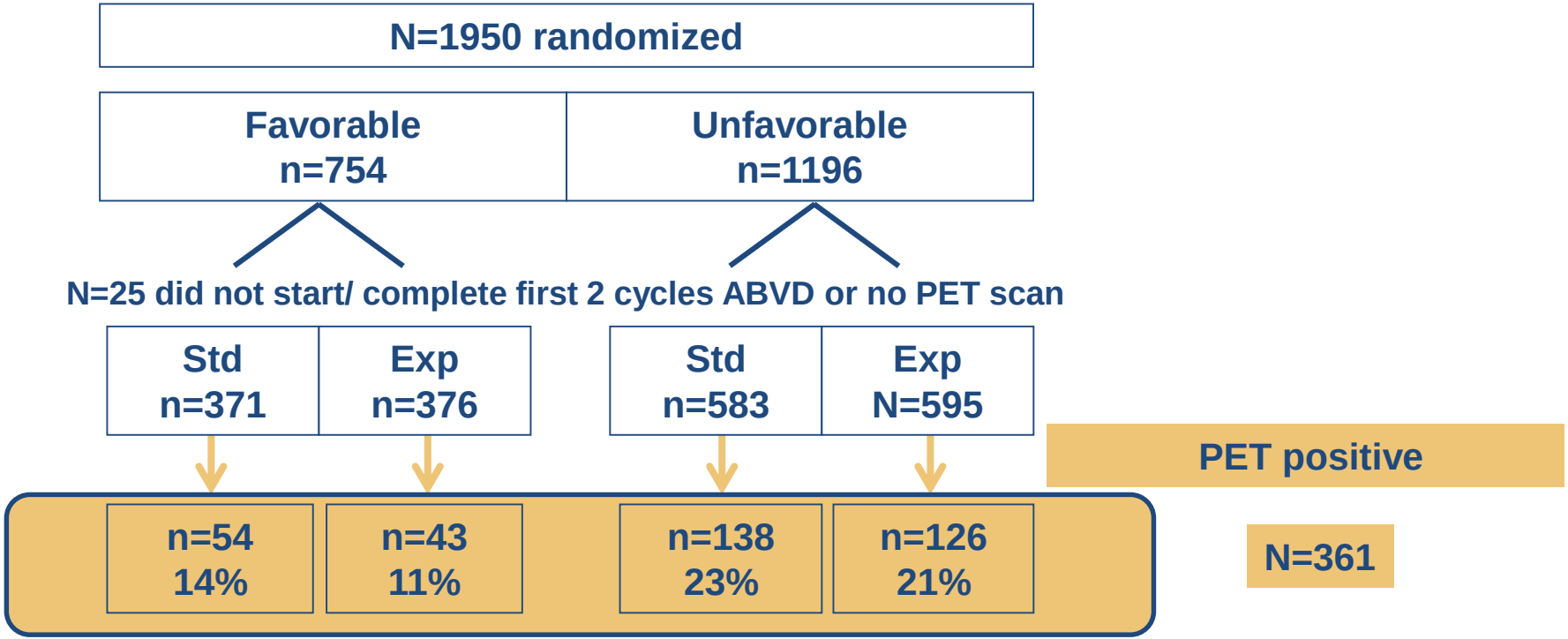


*PET-/+ according to protocol criteria

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

EORTC/GELA/IIL H10 Study

Accrual 2006 - 2011

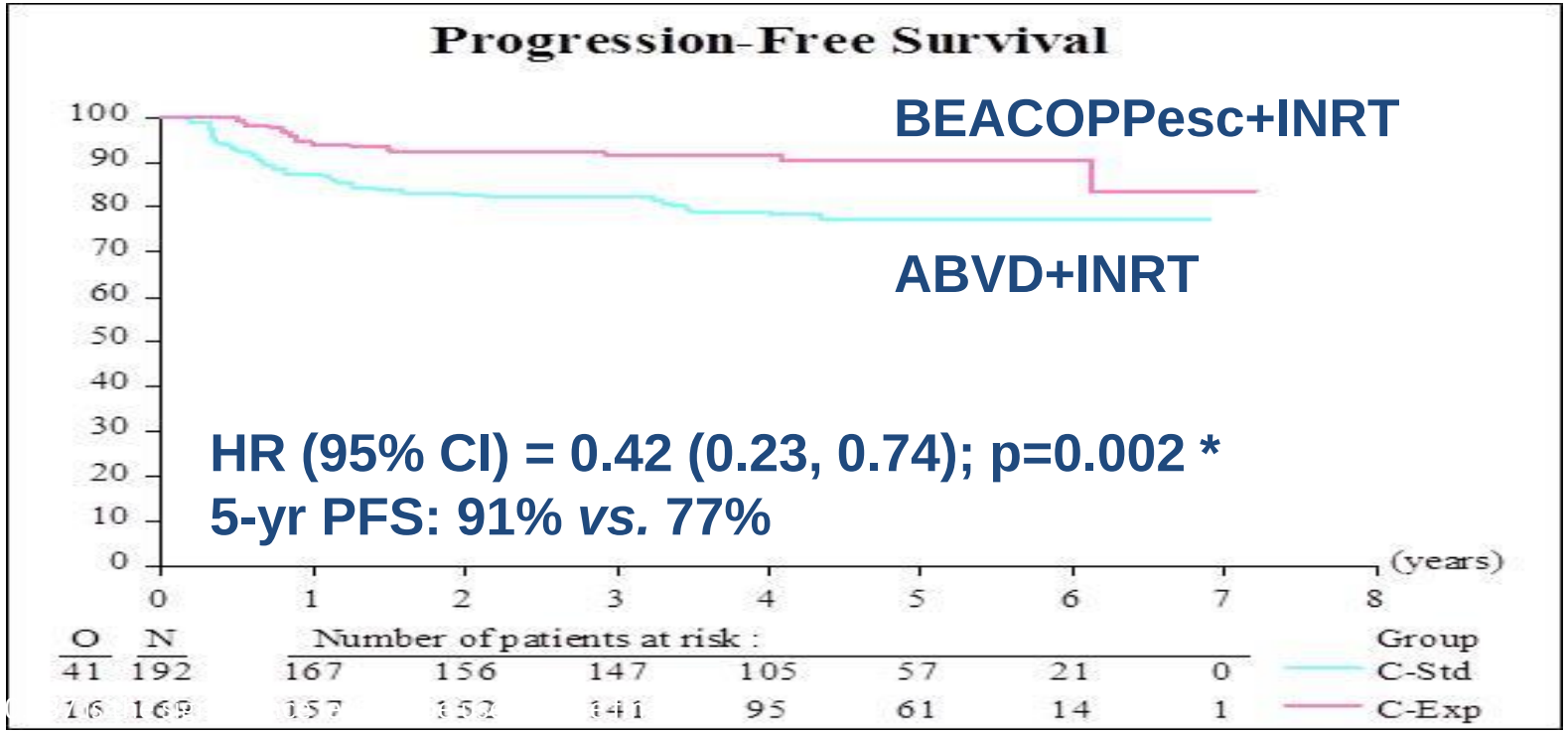


Median FU 4.5 yrs

Raemaekers et al; ICML 2015

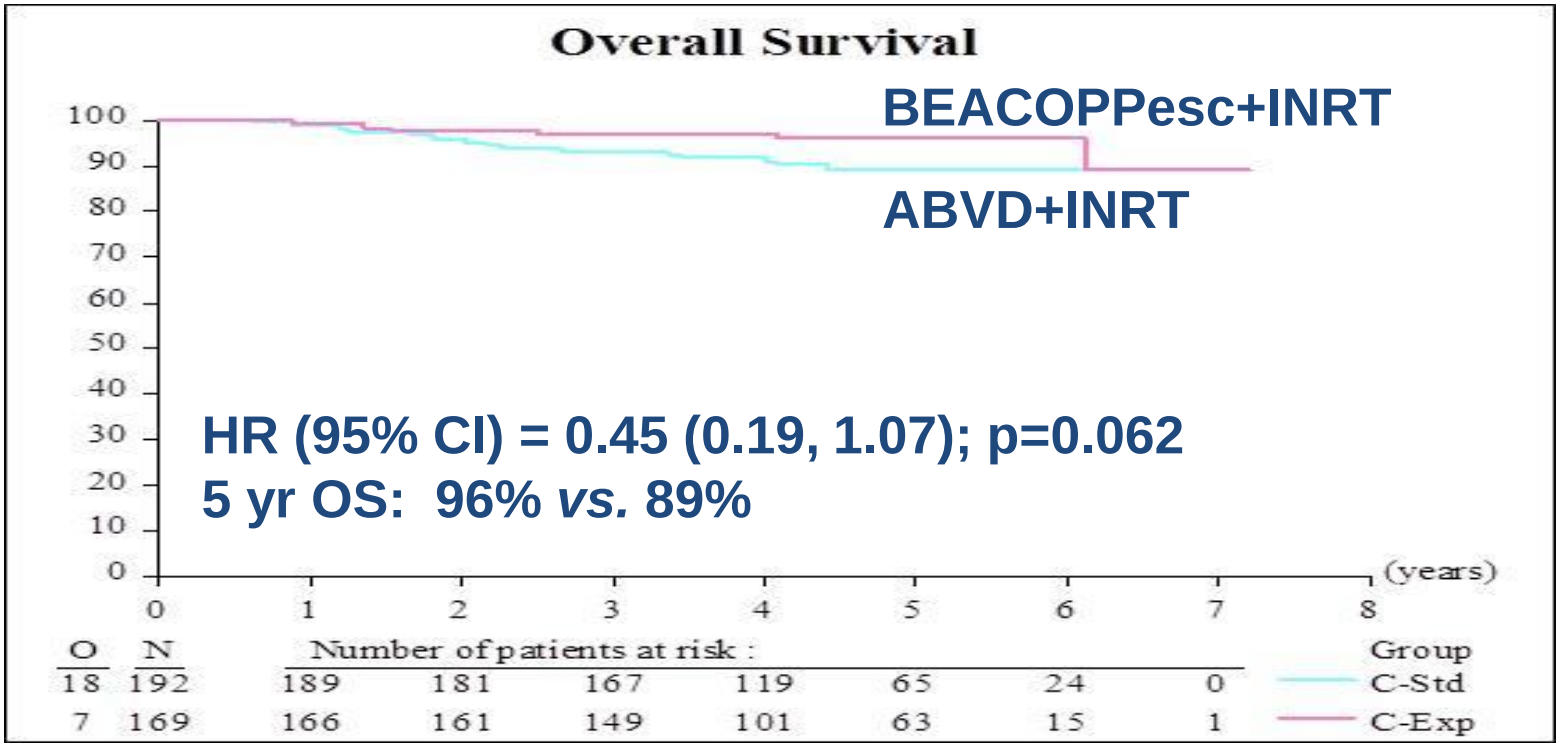
PET+ after 2xABVD: B.esc *vs.* ABVD

Progression-free survival (PFS)



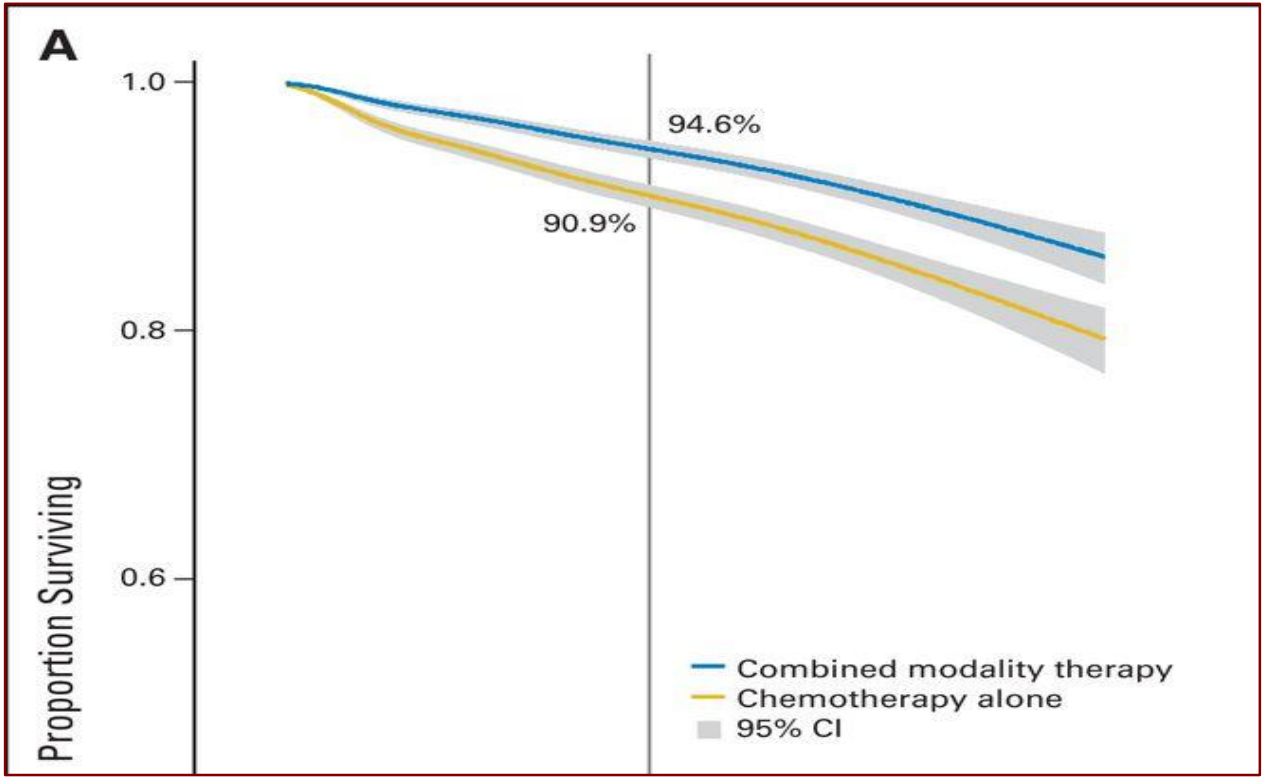
Raemaekers et al; ICML 2015

PET+ group: BEACOPPesc *vs.* ABVD
Overall Survival (OS)



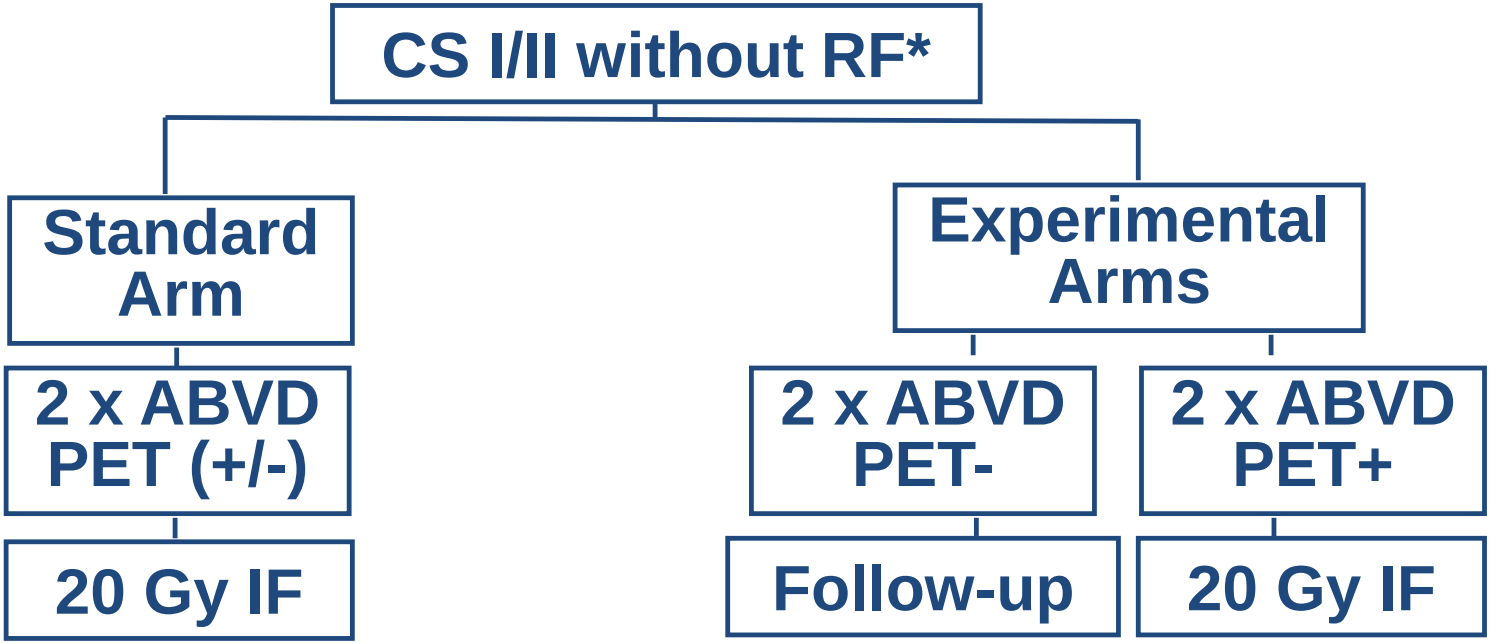
Raemaekers et al; ICML 2015

CMT or chemo alone in early cHL



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

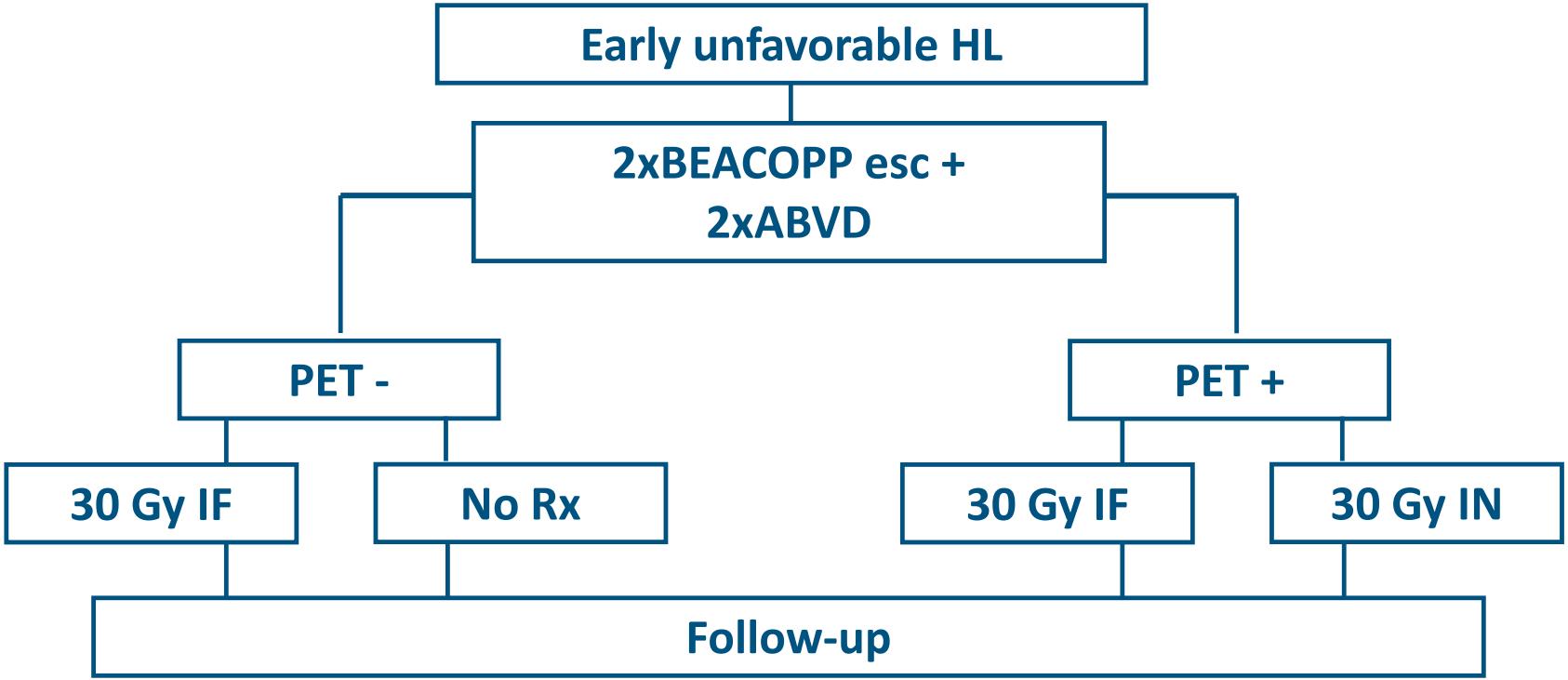
GHSG HD16 trial for early favorable HL



*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas

GHSG 2010

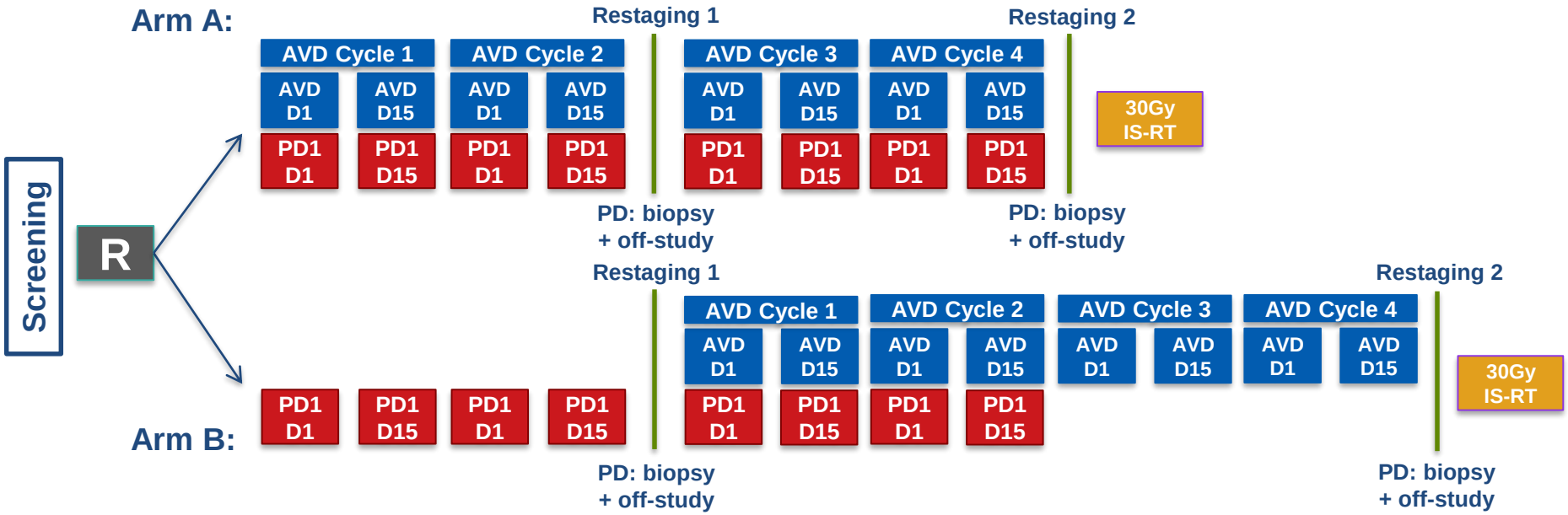
GHSG trial on early unfavorable (HD17)



GHSG 2011

HD20 Pilot

Randomized trial in early unfavorable HL



AVD: Adriamycin, Vinblastin, Dacarbazine; PD1: anti-PD1-antibody

Combined Modality Treatment of HL

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


GÜRZENICH, COLOGNE
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Nodular Lymphocyte Predominant HL
Role of Radiotherapy

Prof George Mikhaeel

Professor of Radiation Oncology, King's College London

Consultant Clinical Oncologist, Guy's & St Thomas' Hospital
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

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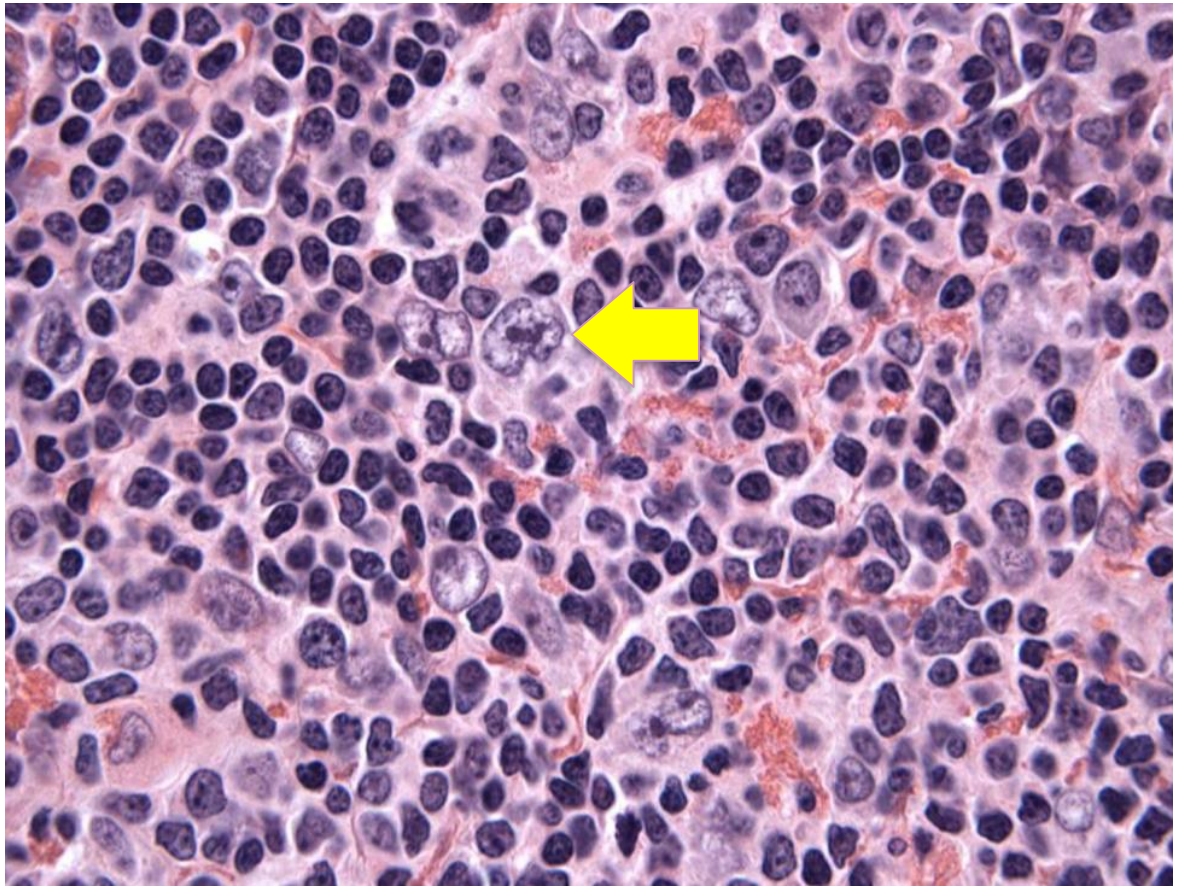
Characteristics

- 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.

	Entities Phenotype		
Antibody	*NLPHL*	*cHL*	*THRLBCL*
CD45	+	–	+
CD30	–	+	– (rarely +)
CD15	–	+	–
CD20	+	–	+
CD79a	+	– (rare + cases)	+
CD19	–/+	–	–/+
J-chain	+	–	n.a.
PAX-5	+	+ (weak) to –	+
OCT-2	+	– to + (weak)	+
BOB-1	+	– (few cases weak +)	+
BCL6	+	–	–/+
PU-1	+	–	–/+
IRF-4/MUM1	Variable	+	+
CD10	–	–	–/+
BTK	+	–	+
EMA	+	–	–/+

Popcorn cell



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Review Series

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]

Blood Volume 127(20):2375-2390
May 19, 2016

Hodgkin Lymphoma

Nodular lymphocyte–predominant Hodgkin lymphoma	• Variant growth patterns (e.g. diffuse areas, numerous T-cells), if present, should be noted in diagnostic report • Advanced stage and higher relapse risk. • Cases associated with • synchronous or subsequent sites that are • indistinguishable from T-cell histiocyte-rich large B-cell lymphoma (THRLBCL) • without a nodular component should be designated THRLBCL-like transformation.

Characteristics (2)

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

Characteristics (3)

- Prognosis:
  - Early stage: highly curable
  - Advanced stage: can be multiply relapsing

  - Transformation to HG-NHL particularly TCR-DLBCL
  - Importance of Bx of every relapse + long FU

  - Death due to NLP is uncommon

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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

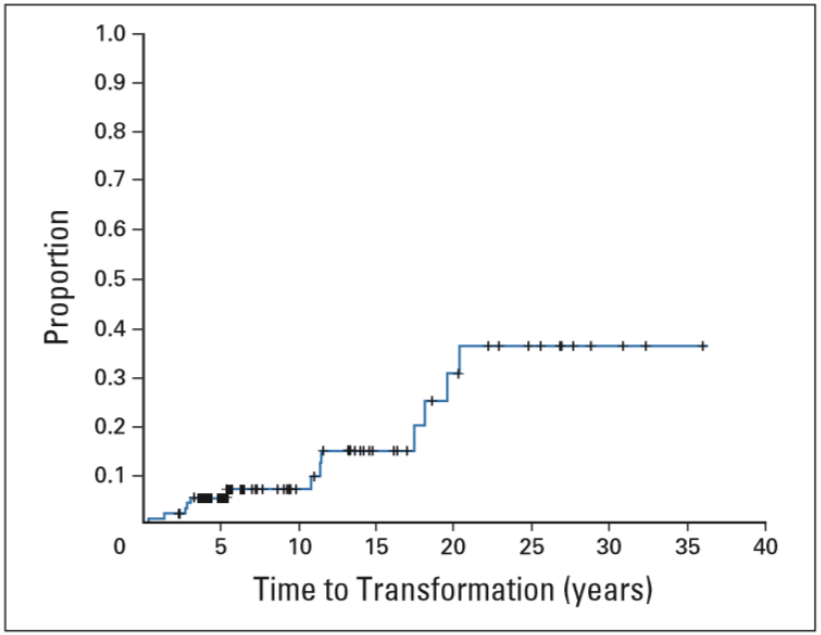

Fig 1. Time to transformation in patients with nodular lymphocyte-predominant Hodgkin's lymphoma.

- 95 pts, mFU 6.5ys
- Transf = 14%
- 10 y actuarial risk 7%
- 20 y actuarial risk 30%
- Risk fs:
  - advanced stage
  - spleen / abdominal presentation

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CME Article

Large B-cell transformation in nodular lymphocyte-predominant Hodgkin lymphoma: 40-year experience from a single institution

Saad Sirop Kenderian,[1] Thomas M. Habermann,[1] William R. Macon,[2] Kay M. Ristow,[1] Stephen M. Ansell,[1] Joseph P. Colgan,[1] Patrick B. Johnston,[1] David J. Inwards,[1] Svetomir N. Markovic,[1] Ivana N. Micallef,[1] Carrie A. Thompson,[1] Luis F. Porrata,[1] James A. Martenson,[3] Thomas E. Witzig,[1] and Grzegorz S. Nowakowski[1]

[1]Division of Hematology, Department of Internal Medicine, [2]Department of Laboratory Medicine and Pathology, and [3]Department of Radiation Oncology, Mayo Clinic, Rochester, MN

BLOOD, 21 APRIL 2016 • VOLUME 127, NUMBER 16

- 222 pts
- mFU 16 ys
- Transf = 7.6%
- RF:
  - Spleen
  - Chemo

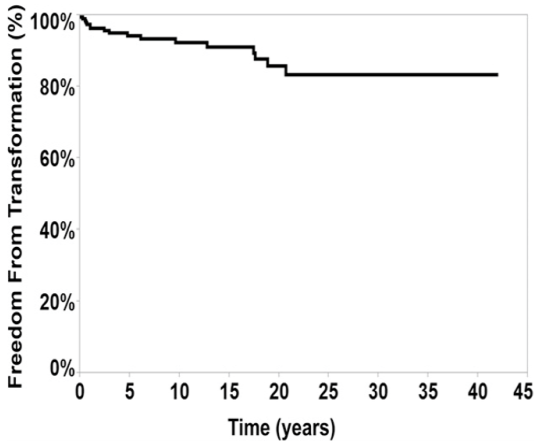

Figure 2. Freedom from transformation into DLBCL in 222 patients with NLPHL.

Key Points

- The risk of transformation of NLPHL to DLBCL is 0.74 per 100 patient-years of follow-up.
- Risk factors for transformation include prior exposure to chemotherapy and splenic involvement at time of diagnosis.

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Prognostic score

Prognostic scoring model for NLPHL patients
a. Features and assigned score

Feature		Scoring points
Histopathologic subtype	Typical pattern (A and/or B)	0
	Morphologic variant (C, D, E, and/or F)	1
Albumin	≥4 g/dL	0
	<4 g/dL	1
Gender	Female	0
	Male	2

b. Risk groups and corresponding outcomes

Risk group	Overall score	5-y PFS, %	5-y OS, %
Low risk	0-1	95.2	98.7
Intermediate risk	2	87.5	96.2
High risk	3-4	68.7	88.3

Adapted from Table 3 in Hartmann et al that begins on page 4246.

Hartmann Blood 2013

NLP versus cHL

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*

*Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York; and †Department of Epidemiology and Biostatistics, Health Outcomes Research Group, New York, New York

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 - - - - -

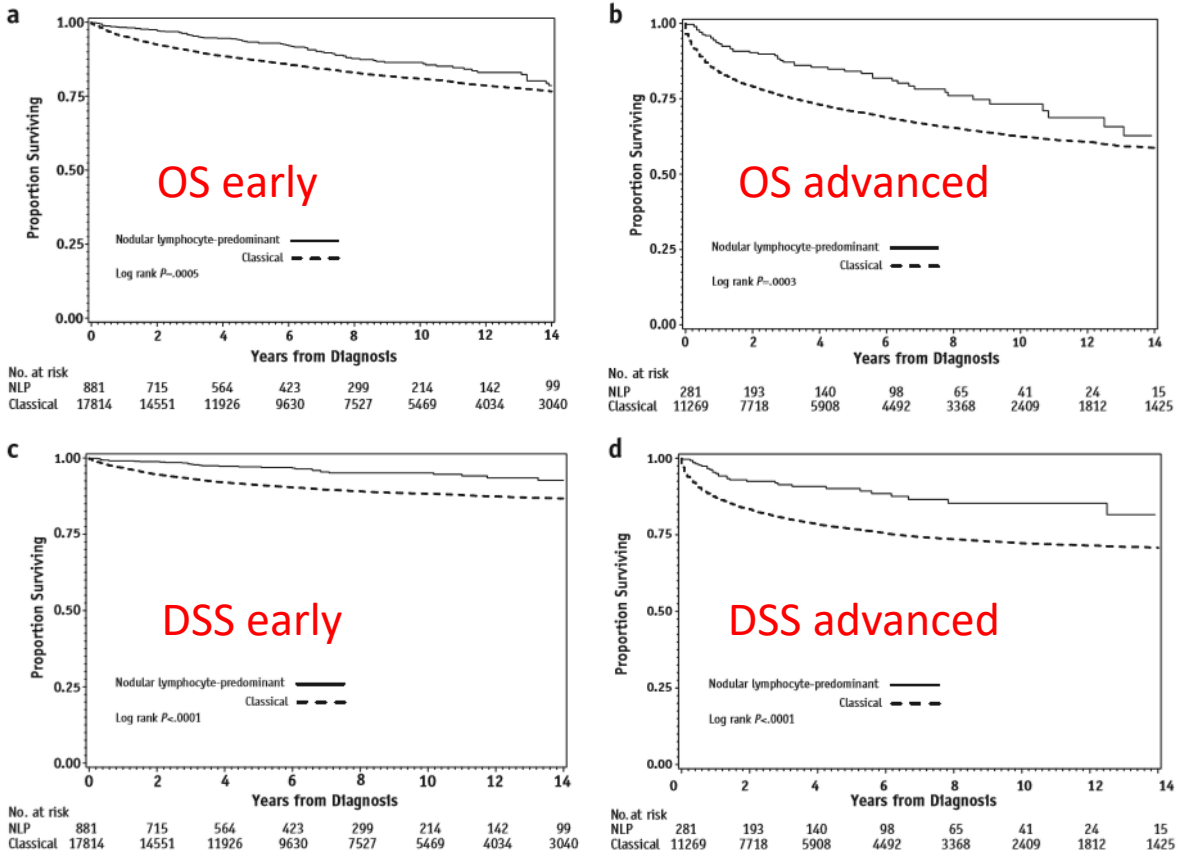

Fig. 1. (a) Overall survival for early stage patients by subtype. (b) Overall survival for advanced stage patients by subtype. (c) Disease-specific survival for early stage patients by subtype. (d) Disease-specific survival for advanced stage patients by subtype. NLP = nodular lymphocyte-predominant 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:
    - RT: outcome, volume & dose
    - Role of excision alone
    - Role of CMT
  - Advanced:
    - Which chemo
    - Role of Rituximab

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Outcome of RT in early stage

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OPEN ACCESS Freely available online PLOS ONE

Long-Term Outcomes in Patients with Early Stage Nodular Lymphocyte-Predominant Hodgkin's Lymphoma Treated with Radiotherapy

Abhishek A. Solanki[1], Melissa Horoschak LeMieux[1], Brian C.-H. Chiu[2], Usama Mahmood[3], Yasmin Hasan[1], Matthew Koshy[1,4]*

1 Department of Radiation and Cellular Oncology, University of Chicago, Chicago, Illinois, United States of America, **2** Department of Health Studies, University of Chicago, Chicago, Illinois, United States of America, **3** Division of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas, United States of America, **4** Department of Radiation Oncology, University of Illinois Hospital, Chicago, Illinois, United States of America

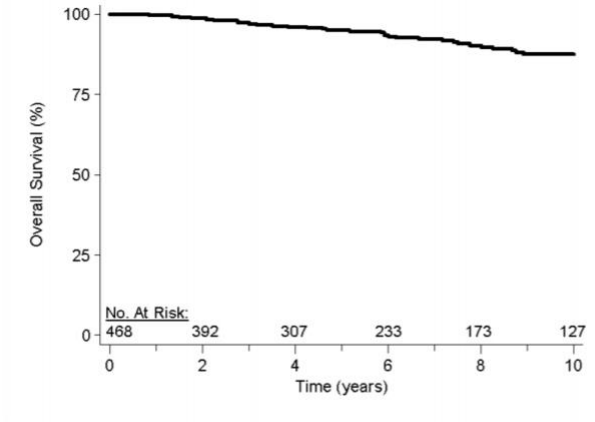

Figure 1. Overall survival. Overall Survival in patients with nodular lymphocyte-predominant Hodgkin's lymphoma treated with radiotherapy.

doi: 10.1371/journal.pone.0075336.g001

469 pts, median age 37

10y 99%

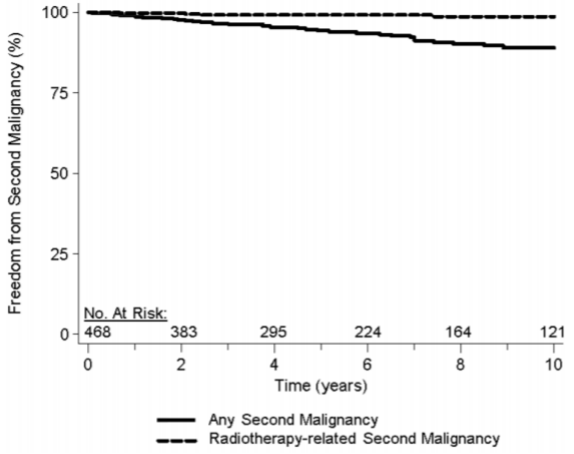

Figure 2. Freedom from any second malignancy and radiotherapy-related second malignancy. Freedom from any second malignancy (solid line) and freedom from radiotherapy-related second malignancy (dashed line) in patients with nodular lymphocyte-predominant Hodgkin's lymphoma treated with radiotherapy.

doi: 10.1371/journal.pone.0075336.g002

10 y OS 89%
10 y CSS 98%

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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

Dennis A. Eichenauer, Annette Plütschow, Michael Fuchs, Bastian von Tresckow, Boris Böll, Karolin Behringer, Volker Diehl, Hans Theodor Eich, Peter Borchmann, and Andreas Engert

All authors: University Hospital Cologne, Cologne; and Hans Theodor Eich, University Hospital Münster, Münster, Germany.

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/15/3399-1/$20.00

DOI: 10.1200/JCO.2014.60.4363

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.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

Variable	No. of Patients
Total	256
Treatment modality	
EF-RT	49
IF-RT	108
CMT	72
Rituximab	27

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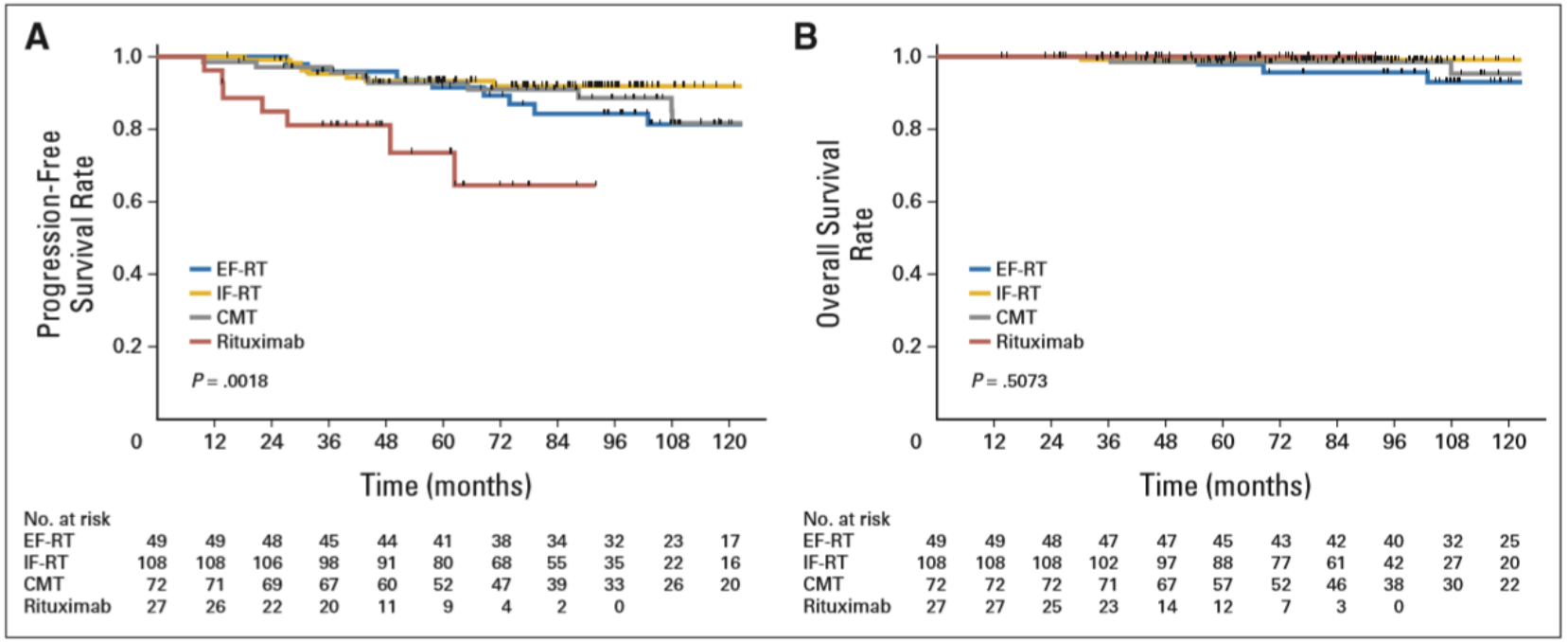

Fig 1. (A) Progression-free survival and (B) overall survival among patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma treated with combined-modality treatment (CMT), extended-field radiotherapy (EF-RT), involved-field radiotherapy (IF-RT), or rituximab.

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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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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.

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

Kerry J. Savage,[1] Brian Skinnider,[2] Mubarak Al-Mansour,[1] Laurie H. Sehn,[1] Randy D. Gascoyne,[2] and Joseph M. Connors[1]

[1]Centre for Lymphoid Cancer and Department of Medical Oncology, British Columbia Cancer Agency and the University of British Columbia, Vancouver, BC; and
[2]Centre for Lymphoid Cancer and Department of Pathology, British Columbia Cancer Agency, Vancouver, BC

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 – over 43 ys (1966 – 2009):
  - 121 pts, 33 revised histology = 88
  - 88: 78 confirmed, 10 missing histology
  - <1993: RT alone =32
  - >1993: ABVDx2 +RT =56 (14 ABVD alone)
- Results (CMT v RT):
  - 10y PFS: 91 v 65% (p=0.002)
  - 10y OS: 93 v 84% (p=0.07)
- Problems:
  - Effect of improvements in staging, RT, overall care??
  - FU length

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Surgical resection + Observation

- 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%

COG update
(Appel JCO 2016)
75% PFS for observation
> 90% PFS with chemo
100% OS.

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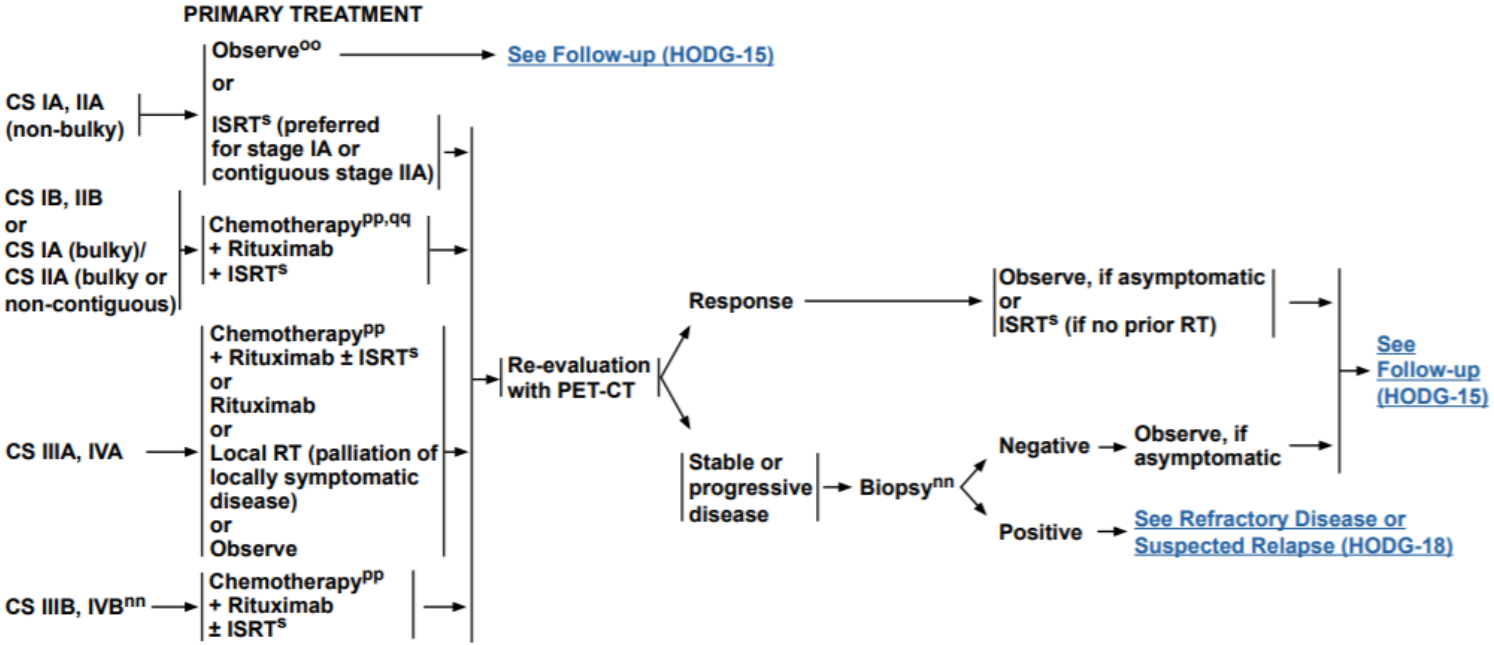
NCCN Guidelines Version 3.2018
Hodgkin Lymphoma (Age ≥18 years)

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL PRESENTATION:
Nodular Lymphocyte-Predominant Hodgkin Lymphoma[i]



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Summary of treatment of limited stage NLP

- Observation only:
  - Option in children + ? Adults (NCCN)
    - Single node
    - complete resection
- Radiotherapy:
  - Treatment of choice
  - Highly curative
- CMT:
  - B symptoms or Bulky disease ?

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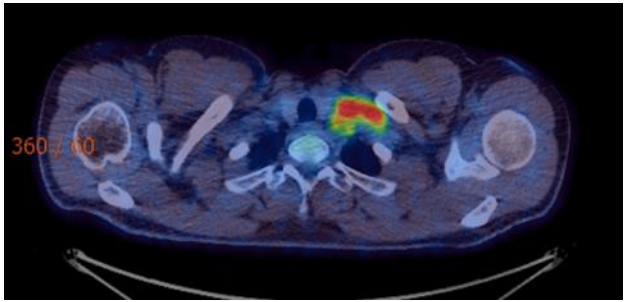
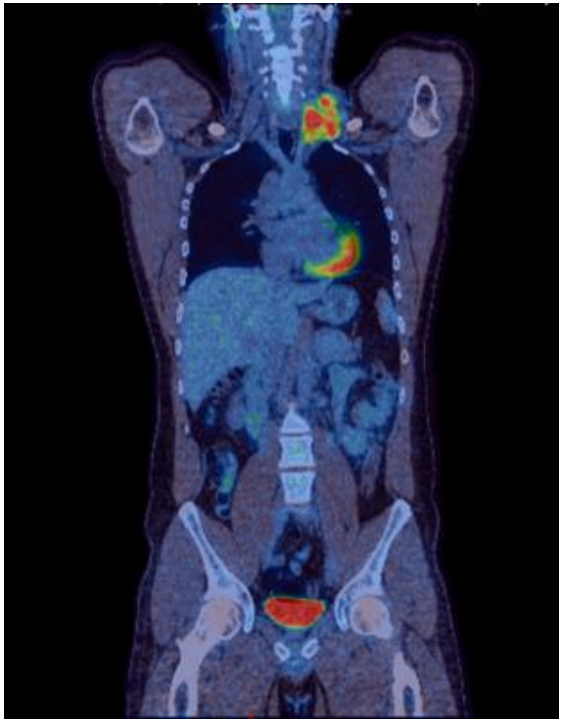
Radiotherapy

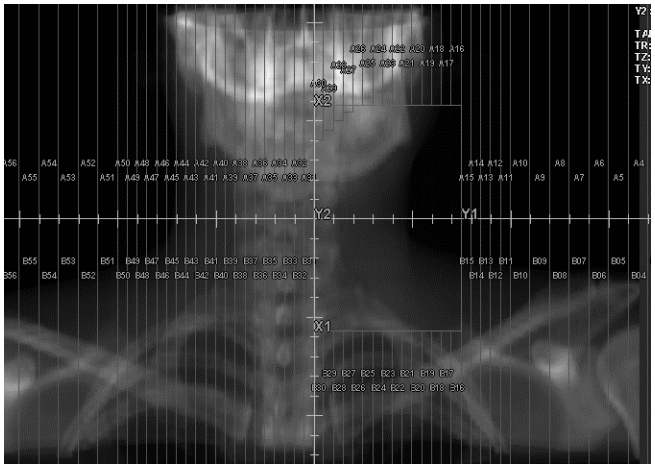
- ILROG guidelines: GTV, CTV, PTV
- PET / planning-CT image registration is ideal to outline GTV (as no prior chemo).
- Volume:
  - No chemo. RT needs to control *local microscopic* disease
  - No benefit to EF over IFRT *(Nogova 2005, Eichenaeur 2015)*

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

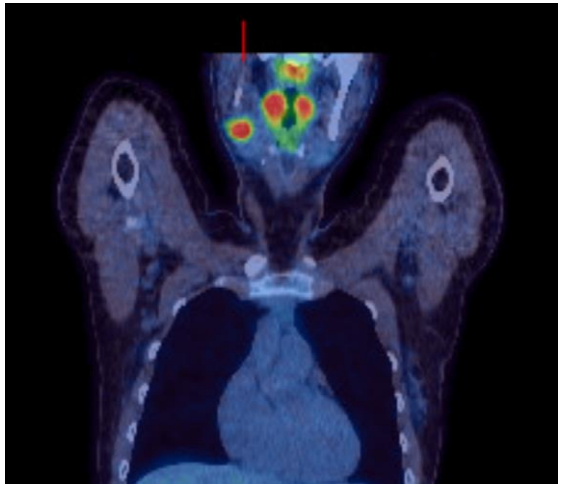
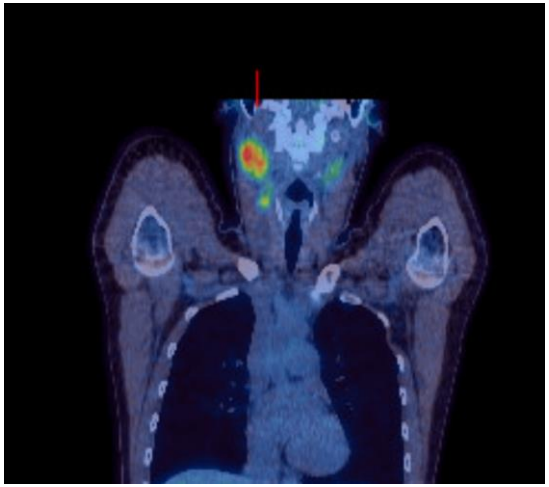
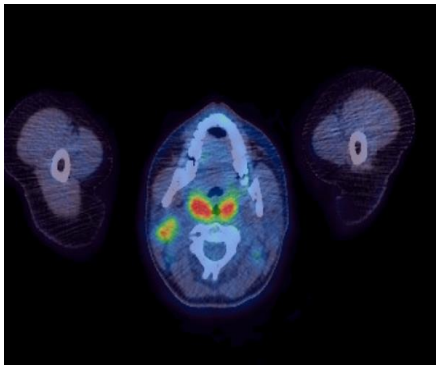
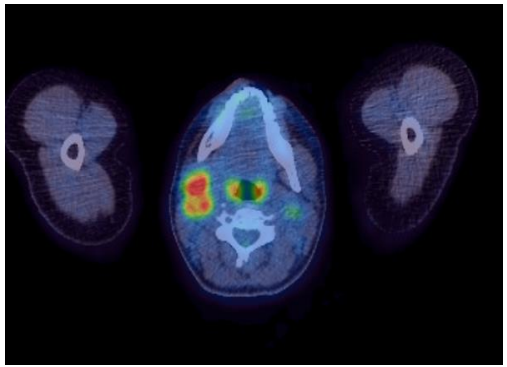
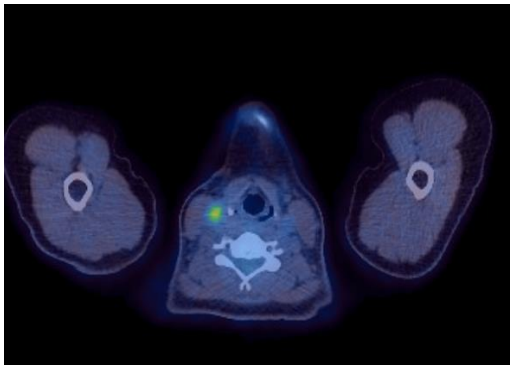


2014





2007

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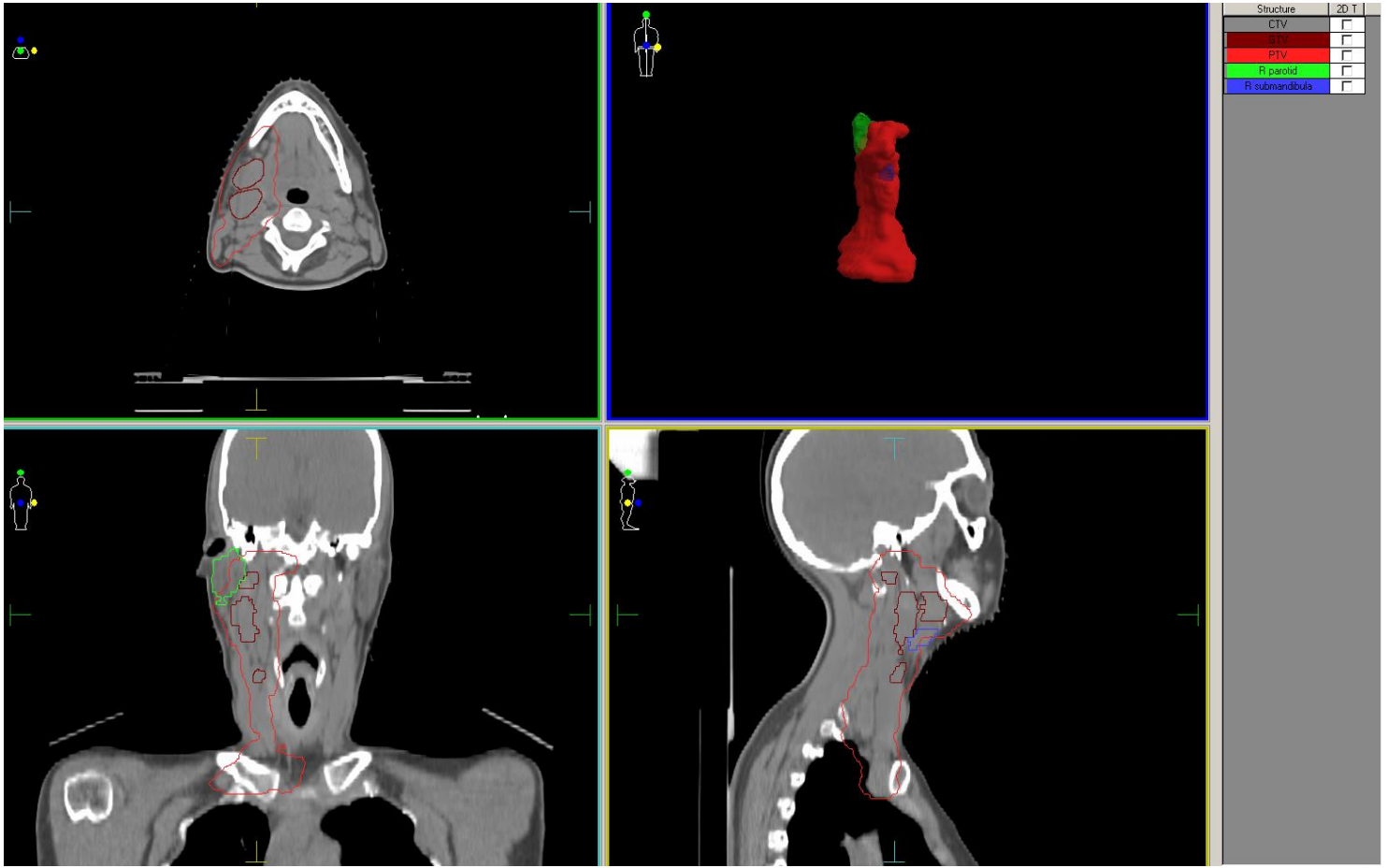

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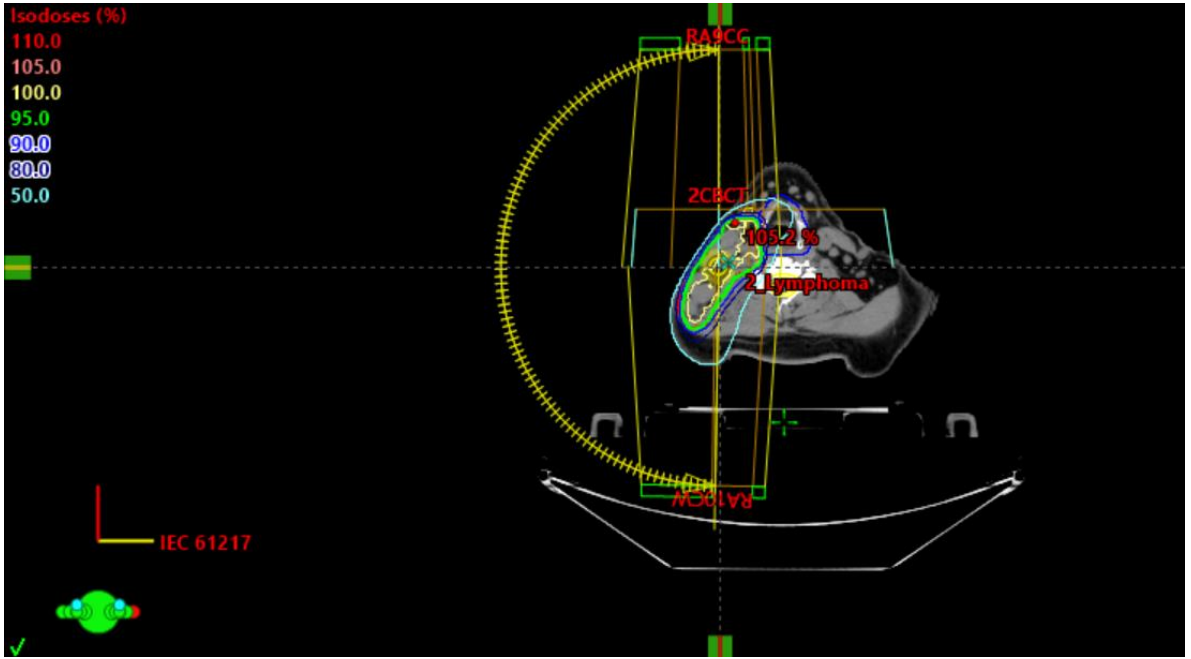
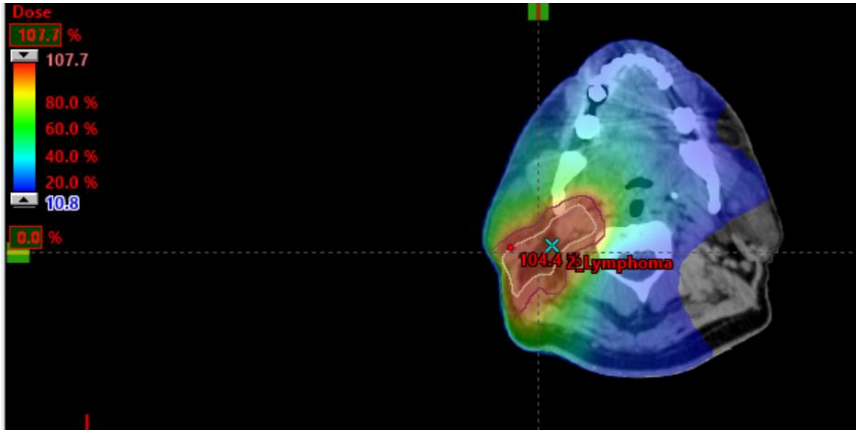
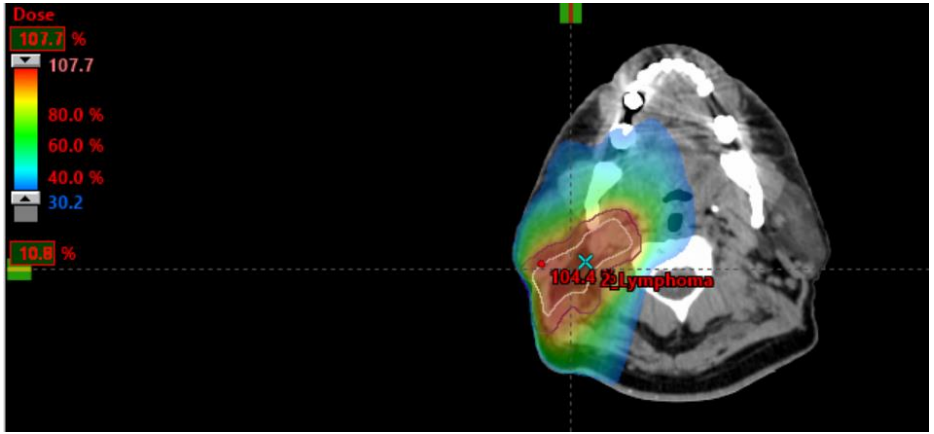
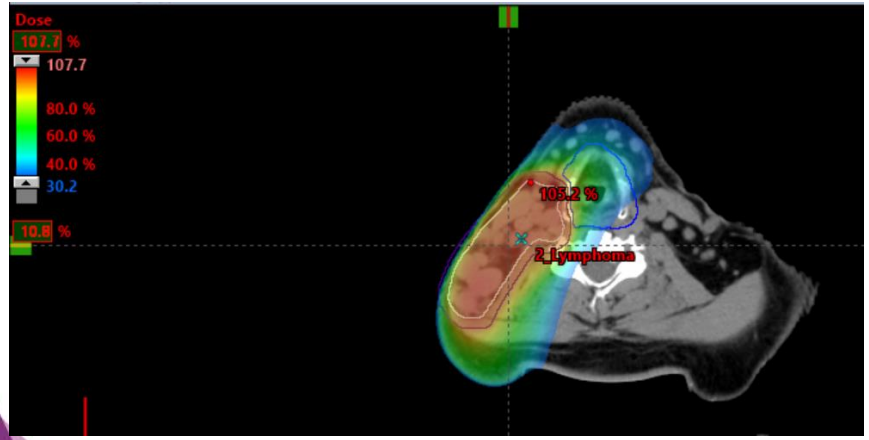
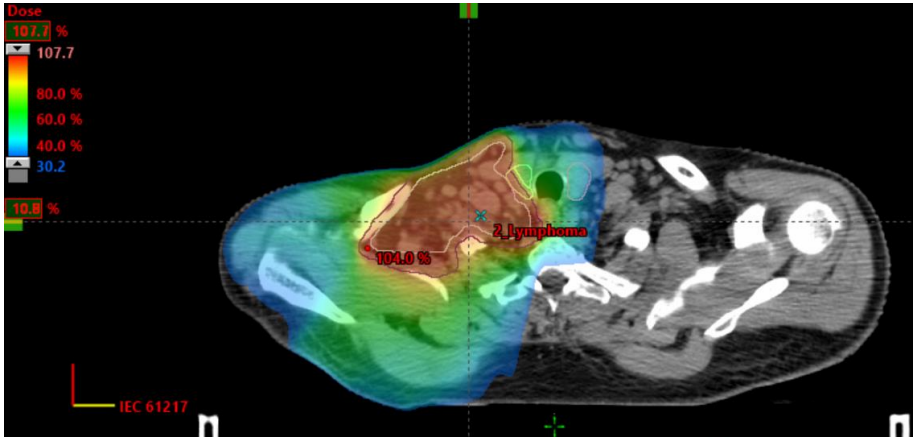

Isodoses (%)
110.0
105.0
100.0
95.0
90.0
80.0
50.0
RA9CG
2CBCT
105.2 %
2_Lymphoma
IEC 61217









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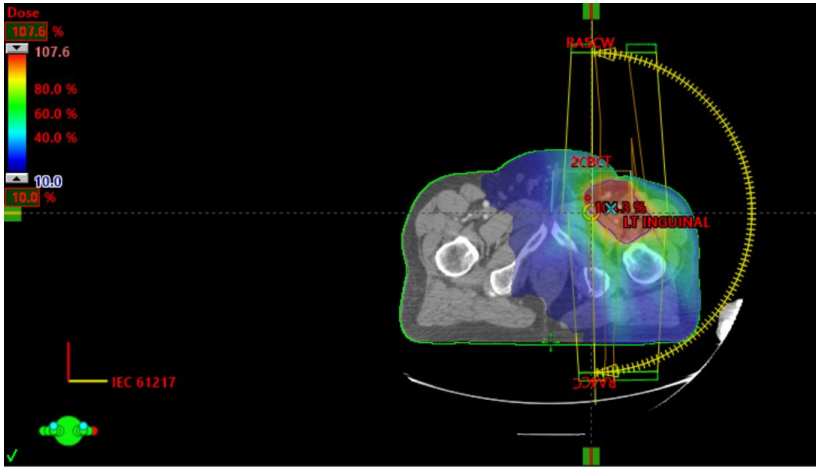
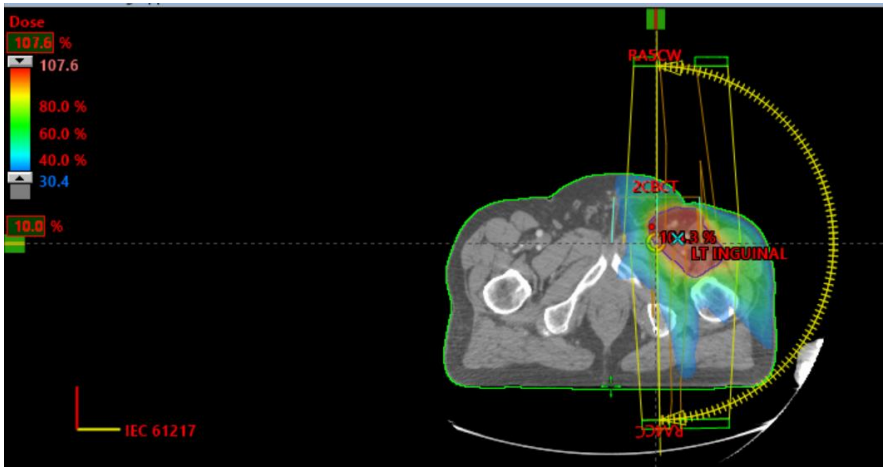

Dose
107.6 %
107.6
80.0 %
60.0 %
40.0 %
10.0
10.0 %
RASCW
2CBCT
110.3 %
LT INGUINAL
IEC 61217


Dose
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RASCW
2CBCT
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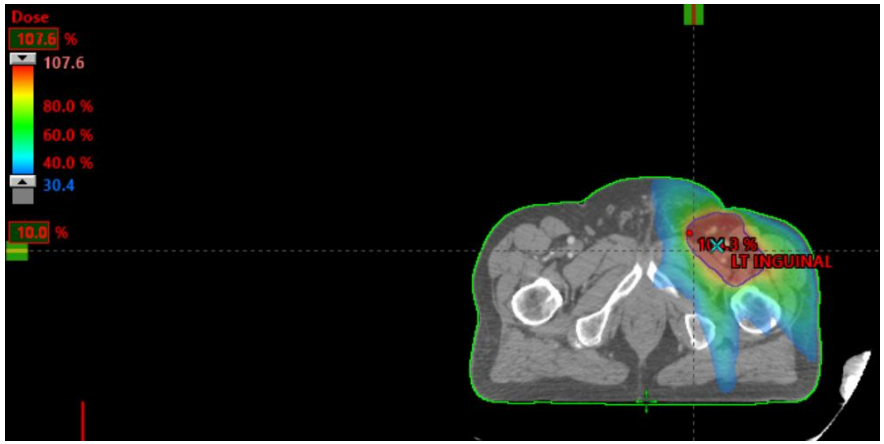
Dose
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107.6
80.0 %
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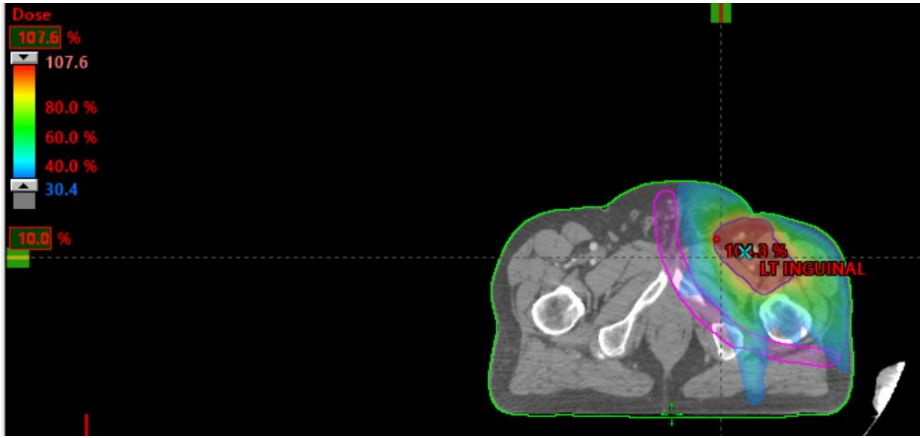
30.4
10.0 %
10X 3 %
LT INGUINAL


Dose
107.6 %
107.6
80.0 %
60.0 %
40.0 %
30.4
10.0 %
10X 3 %
LT INGUINAL

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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Tim Illidge

BSc PhD FRCR MCRP FRCPath

Classical Hodgkin lymphoma, the role of radiation therapy

Head of Cancer Sciences
University of Manchester
Manchester Cancer Research Centre
The Christie NHS Foundation Trust
Manchester, UK

Overview of talk

1. **Review of clinical data on management of early stage HL**
   - *Combined modality treatment*
   - *Progress and pitfalls with FDG-PET response adjusted therapy omitting RT*

2. **Moving towards personalised approaches to treatment of early stage HL**
   - Risk / benefit assessments

Overall results of therapy for early disease using combined modality treatment

- 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 late toxicity

Hypothesis : long term survival will be improved by decreasing long term toxicity and omitting RT

Considerations for personalised treatment in early stage HL

Highest cure rate with primary therapy

Fewest complications optimal survivorship

Second cancers

Cardiac toxicity

Pulmonary toxicity

Fertility

Quality of life

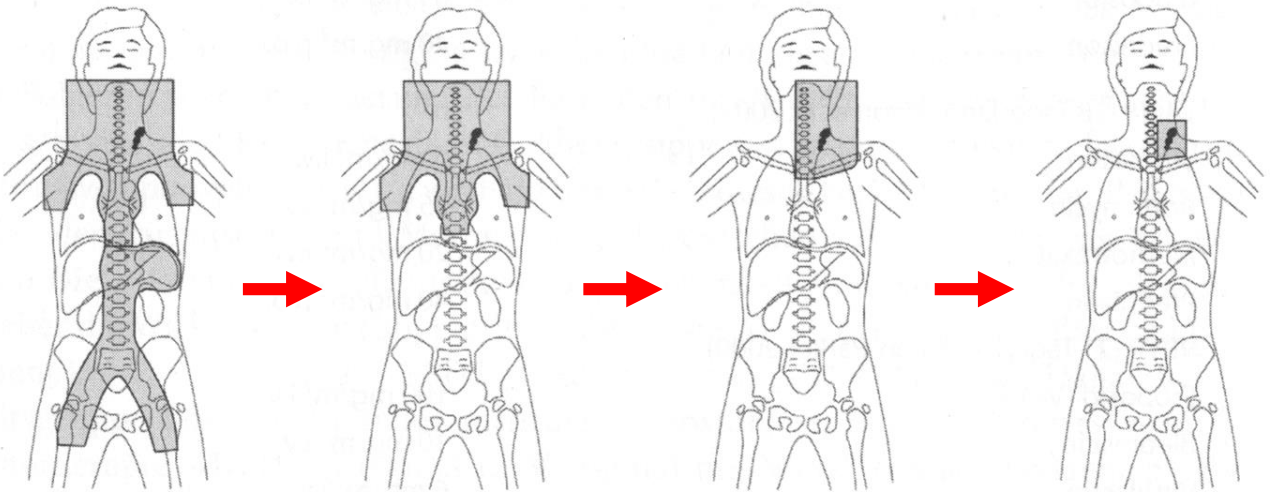
What is the risk of delivering RT (late toxicity) ?

What is the risk of omitting RT (loss of tumour control) ?

What is the optimal therapy for individual patients in balancing risks ?

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

From sole curative treatment to component in combined modality treatment



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

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

Schaapveld M et al , N Engl J Med. 2015 Dec 24;373(26):2499-511

- Risk of breast cancer was lower among patients who were treated with supradiaphragmatic-field radiotherapy not including the axilla than among those who were exposed to mantle-field irradiation (hazard ratio, 0.37; 95% CI, 0.19 to 0.72),
- Risk of breast cancer was not lower among patients treated in the 1989-2000 study period than among those treated in the two earlier periods.
- A cumulative procarbazine dose of 4.3 g or more per square meter of body-surface area (which has been associated with premature menopause) was associated with a significantly lower risk of breast cancer (hazard ratio for the comparison with no chemotherapy, 0.57; 95% CI, 0.39 to 0.84) but a higher risk of **gastrointestinal cancer** (hazard ratio, 2.70; 95% CI, 1.69 to 4.30).

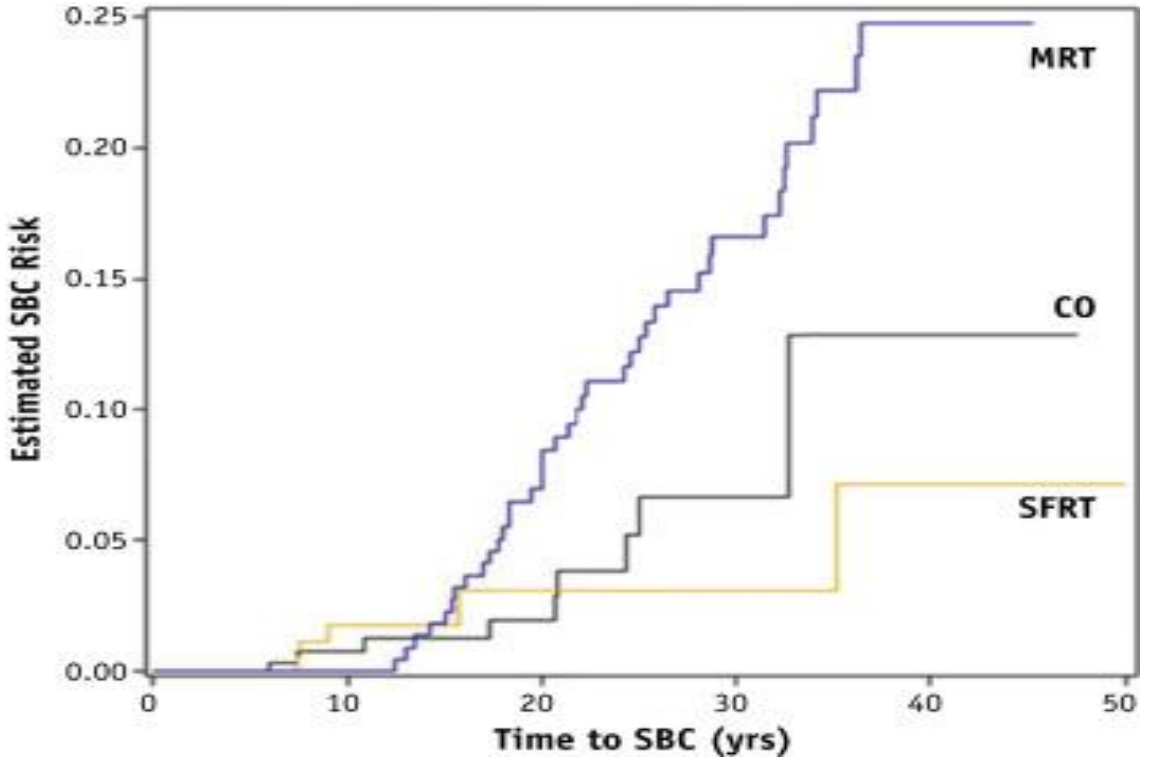
Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma.

Conway JL Int J Radiat Oncol Biol Phys. 2017 Jan 1;97(1):35-41.

- 734 eligible patients, 75% of the living patients have been followed up for more than 10 years, SBC has developed in 54, and 15 have died of breast cancer.
- The 20-year estimated risks (competing risk cumulative incidence) for SBC differed significantly: MRT 7.5% (95% confidence interval [CI] 4.4%-11.5%), SFRT 3.1% (95% CI 1.0%-7.7%), and chemotherapy-only 2.2% (95% CI 1.0%-4.8%) (P=.01).
- **Large-volume MRT is associated with a markedly increased risk of SBC; however, more modern small-volume RT is not associated with a greater risk of SBC than chemotherapy alone**

Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma.

Conway JL, et al Int J Radiat Oncol Biol Phys. 2017 Jan 1;97(1):35-41.



What is the risk of omitting RT – does it lead to decline in overall survival ?

Int J Radiat Oncol Biol Phys. 2010 November 1; 78(3): S65–S66. doi:10.1016/j.ijrobp.2010.10.069.

The Declining Utilization of Radiation Therapy in Stage I and II Hodgkin's Disease and its Impact on Survival and Secondary Malignancies

Matthew Koshy, MD[*,†], **Shayna E. Rich, PhD**[††], **Usama Mahmood, MD**[§], and **Young Kwok, MD**[§]

[*]Department of Radiation and Cellular Oncology, The University of Chicago, Chicago, IL

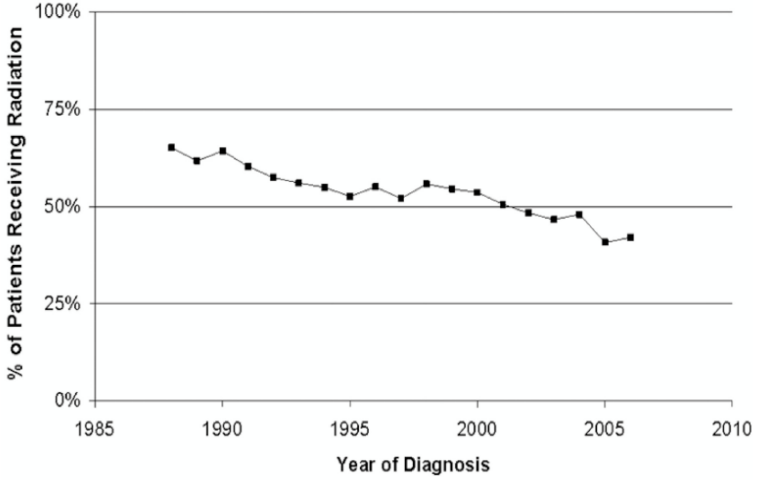


Figure 1.
Percentage of Hodgkin's Patients Receiving Radiation Between 1988–2006, by Year of Diagnosis

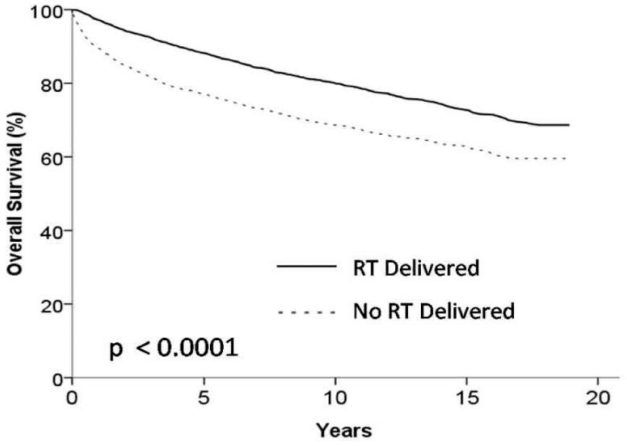


Figure 2.
Kaplan Meier Curve showing overall survival of patients receiving and not receiving radiation therapy (RT) ($p < 0.001$)

Early-Stage Classic Hodgkin Lymphoma: The Utilization of Radiation Therapy and Its Impact on Overall Survival.

Parikh RR et al Int J Radiat Oncol Biol Phys. 2015 Nov 1;93(3):684-93.

- Among 41,943 patients in National Cancer Database (1998-2011) with stage I/II HL, 29,752 patients were analyzed for this study. Over the study period, RT utilization for this cohort decreased from 55% to 44%, most commonly because it was not part of the planned initial treatment strategy

- **Radiation therapy use associated with younger age (≤40 years), favorable insured status, higher socioeconomic status (income, education), and treatment at comprehensive community cancer centers (all P<.05).**

- **Five-year OS for patients receiving RT was 94.5%, versus 88.9% for those not receiving RT (P<.01**). Radiation therapy use was a significant predictor of OS in the "As-Treated" cohort (hazard ratio 0.53, 95% confidence interval 0.49-0.58, P<.01) and intention-to-treat analysis (P<.01).

- **CONCLUSIONS:** Consolidation RT was associated with improved OS for patients with early-stage classic HL.

Clinical risk-adapted and PET response-adapted approaches

Clinical Risk adapted:

To what degree can we reduce treatment based on clinical prognostic data at presentation and can we improve this further with novel biomarkers ?

Clinical response adapted:

Is functional imaging response on FDG-PET a better indicator of prognosis and will response adopted approaches improve overall Survival)

Clinical risk stratification at presentation

	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	) Histology other than LP/NS) Age ≥40 years) ESR ≥50) ≥ 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	S 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)	S I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors (differentiating between bulky disease and other risk factors for treatment guidelines)

German HD 10 study: reducing therapy in early favourable HL

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

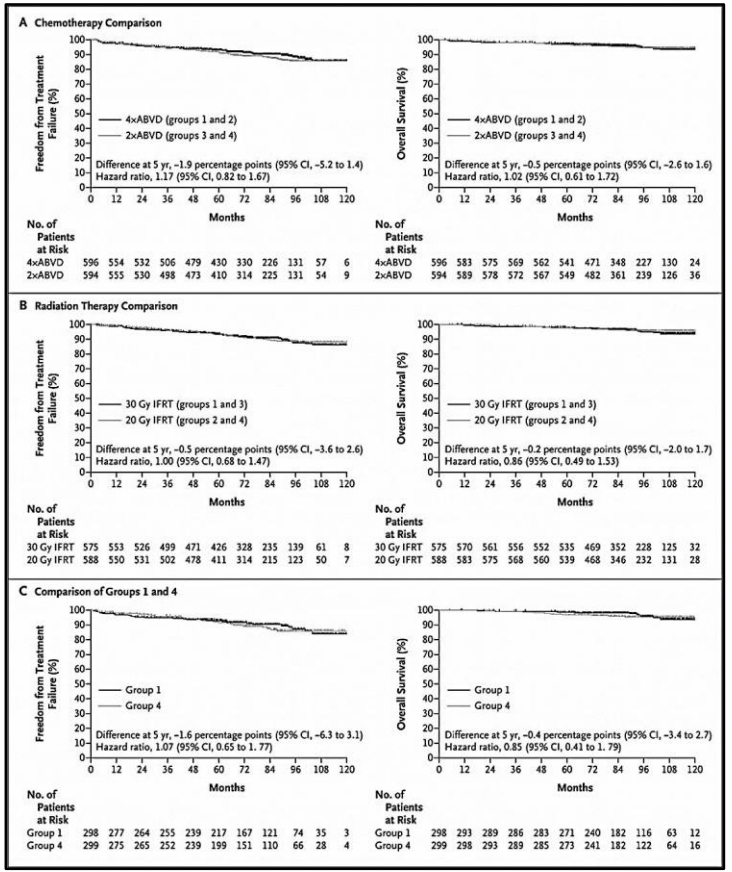
ABVD

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

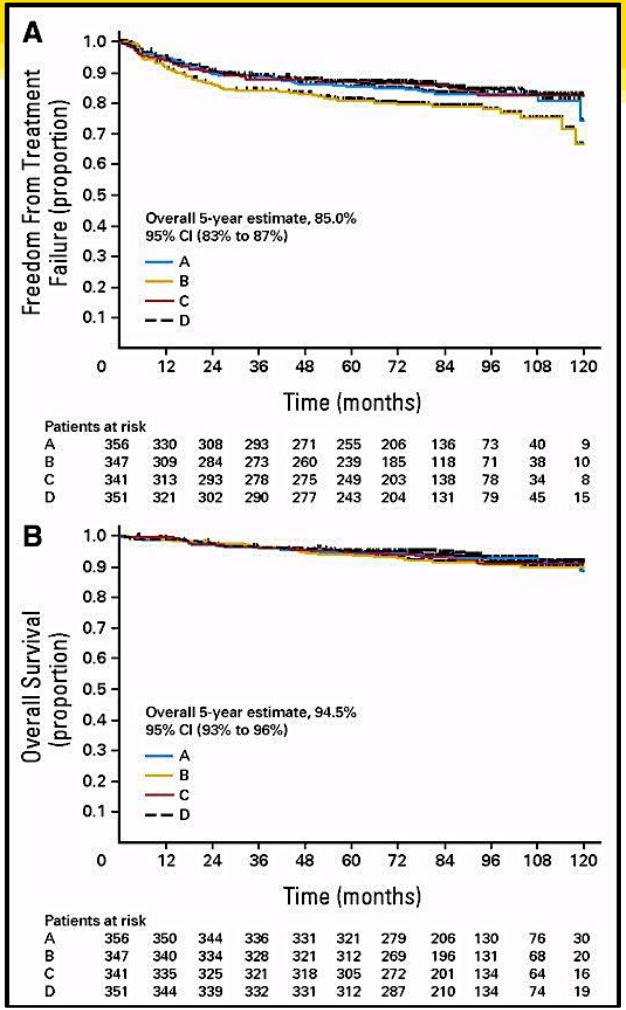
Chemotherapy

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

PET adjusted therapy in Early stage HL :

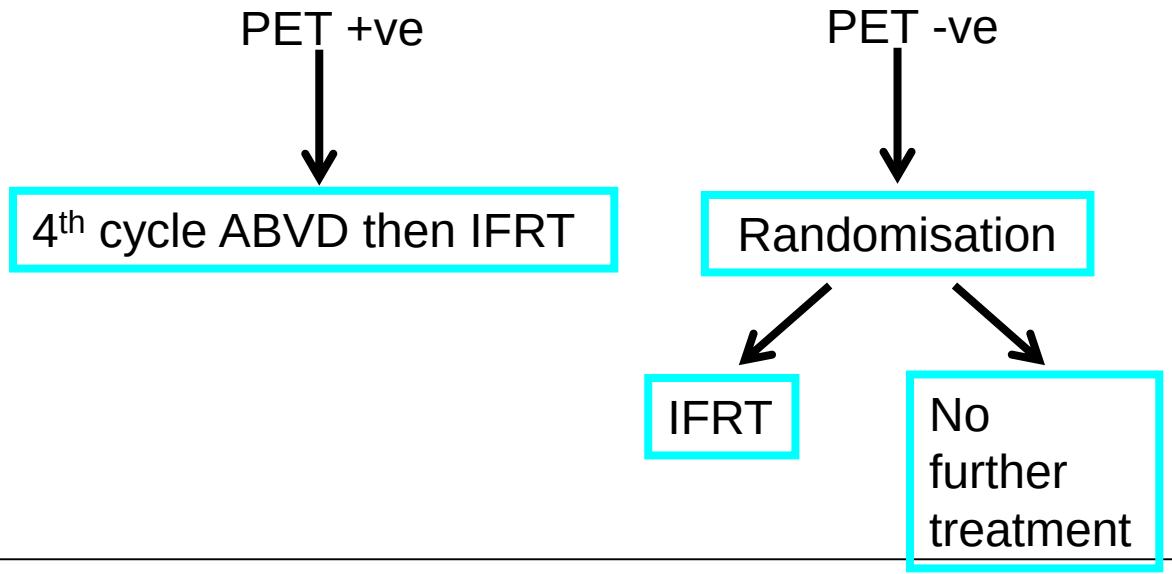
- **Can we use FDG-PET to select patients who can be cured with less chemotherapy and avoid RT ?**
- Primary objective UK NCRI RAPID and EORTC H10 trials
  - Is chemotherapy alone as effective - but less toxic to combined modality treatment in patients with CS I/II HL in terms of PFS in patients who are FDG-PET scan negative* after 3 cycles (UK NCRI) or two cycles (EORTC H10) of ABVD? *(non-inferiority)*

UK NCRI RAPID - trial design

Radford, Illidge *et al., NEJM 2015*

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**%**)
- Score 2 : 125 (22.0%)

74.7% PET NEGATIVE

- Score 3 : 90 (15.7%)
- Score 4 : 32 (5.6%)
- Score 5 : 23 (4.0%)

25.3% PET POSTIVE

- 420 of 426 PET –ve pts randomised to IFRT (209) or NFT (211)
- 6 not randomised; pt choice 3, clinician choice 2, error 1

UK NCRI RAPID Trial

	PET3	CT/RT	3-yr PFS (%)	3-yr OS (%)
ABVD x3	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*

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

Radford J *et al., NEJM 2015*

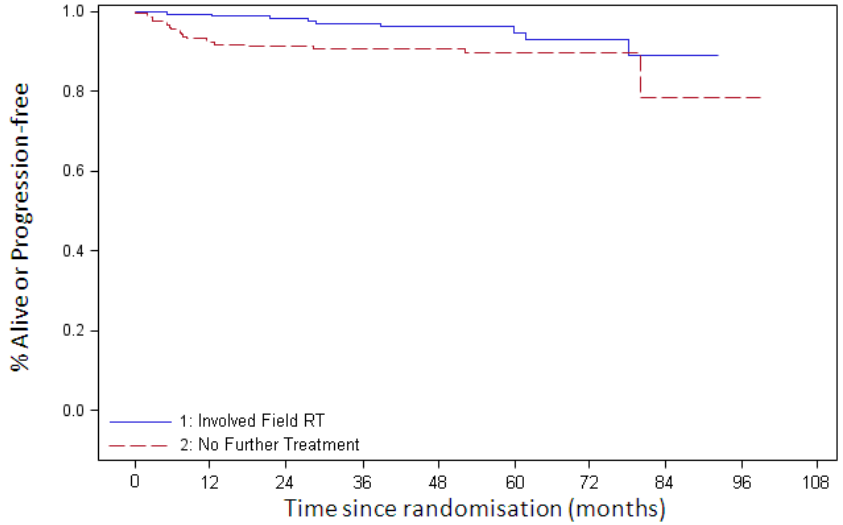
Results of a Trial of PET-Directed Therapy for Early Stage Hodgkin Lymphoma

Radford, Illidge et al NEJM 2015; 372:1598-607

Events	PET –ve IFRT (%)	PET –ve NFT (%)	PET +ve (%)
Alive without PD	193 (92.3)	190 (90.0)	127 (87.6)
PD only	8 (3.8)	20 (9.5)	10 (6.9)
Died with PD	3 (1.4%)	2 (0.9%)	5 (3.4%)
Died without PD	5 (2.4%)	2 (0.9%)	3 (2.1%)
Total	209	211	145

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

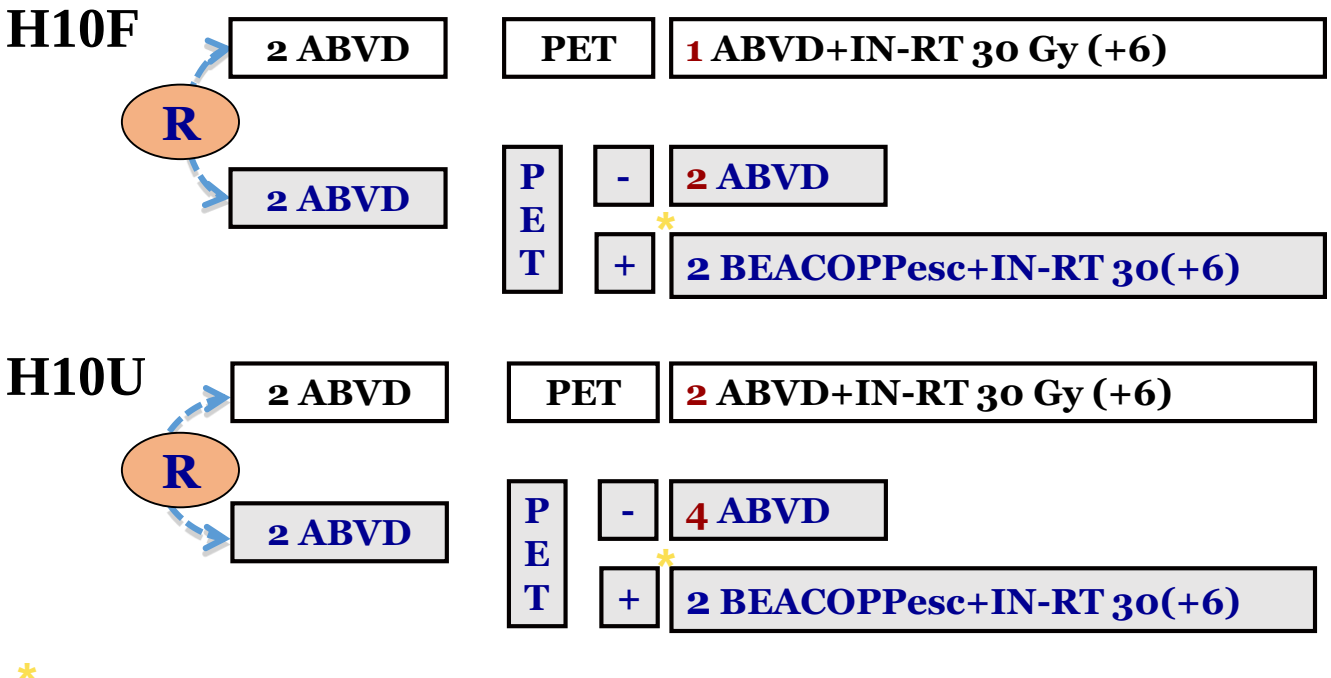
Per protocol analysis in 392 PET – ve patients

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
	ABVDx2 →	+/- →	INRT	1/188	100%
Experimental	ABVDx2 →	negative →	ABVDx2	9/193	94.9%
		positive	BEACOPPescx2 + INRT		**Standard**

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.

Early Positron Emission Tomography Response–Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial

Marc P.E. André et al J Clin Oncol. 2017 Jun 1;35(16):1786-1794.

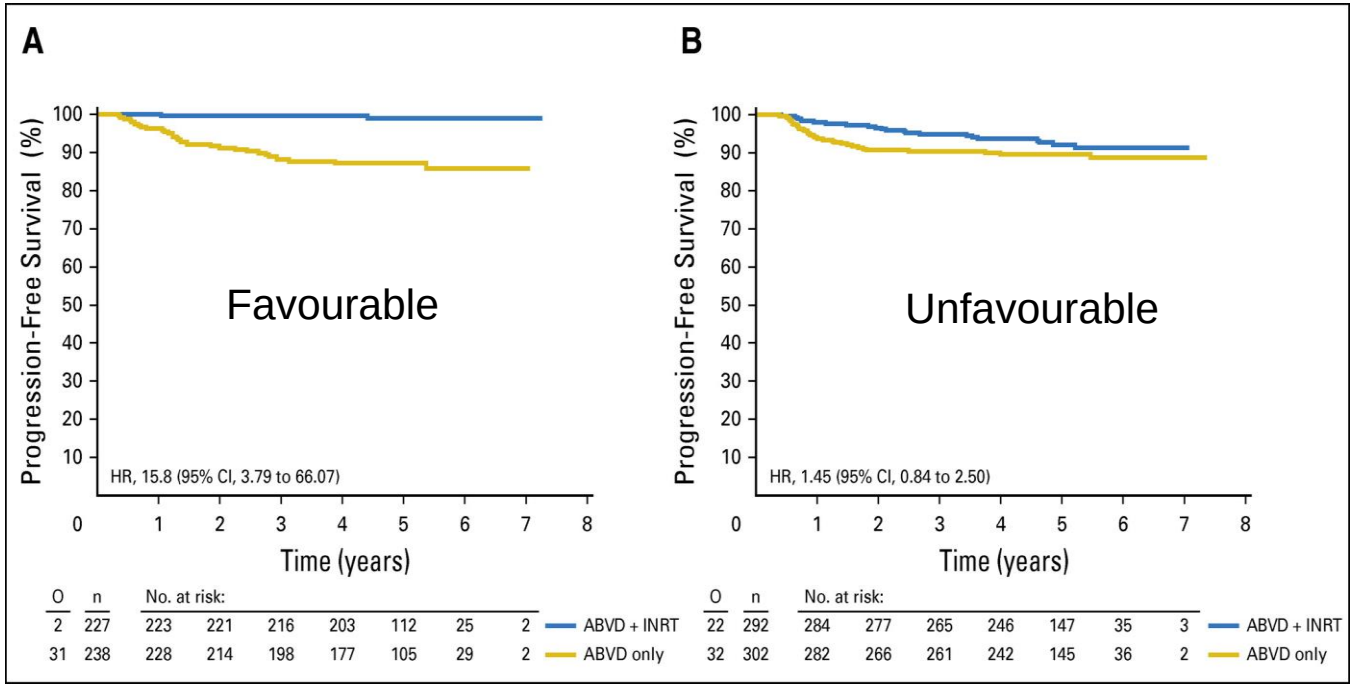
- Of 1,950 randomly assigned patients, 1,925 received an ePET- 361 patients (**18.8%**) + ve.

- In ePET-positive patients, 5-year PFS improved from 77.4% for standard ABVD + INRT to 90.6% for intensification to BEACOPPesc + INRT (hazard ratio [HR], 0.42; 95% CI, 0.23 to 0.74; P = .002).

- In ePET-negative patients, 5-year PFS rates in the
  - F group were 99.0% versus 87.1% (HR, 15.8; 95% CI, 3.8 to 66.1) in favor of ABVD + INRT;
  - U group, 92.1% versus 89.6% (HR, 1.45; 95% CI, 0.8 to 2.5) in favor of ABVD + INRT.

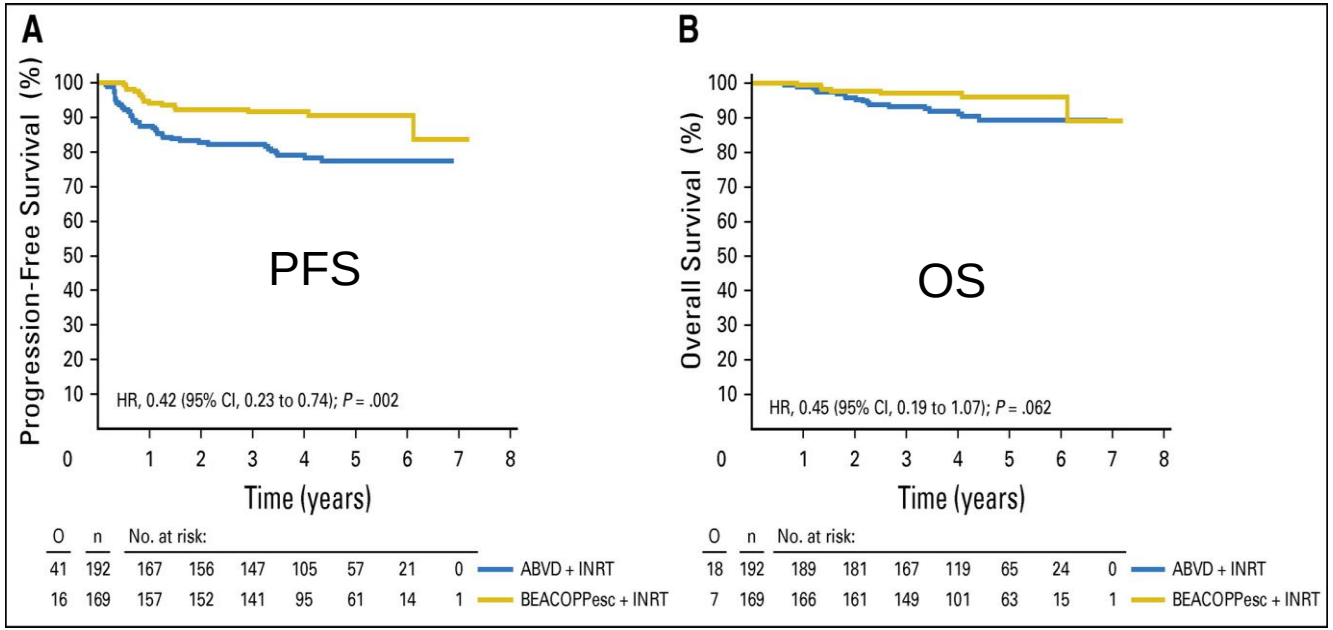
Progression-free survival of 1,059 early PET–negative patients who were treated per the initial protocol.

progression-free survival of the (A) favorable (F) groups of patients randomly assigned to ABVD + involved-node radiotherapy (INRT; n = 227) or ABVD only (n = 238) and of the (B) unfavorable (U) groups randomly assigned to ABVD + INRT (n = 292) or ABVD only (n = 302).



Published in: Marc P.E. André; et al ; *JCO* **2017,** 35, 1786-1794 .

Progression-free and overall survival of early positron emission tomography (PET)–positive patients. *(A) progression-free and (B) overall survival of early PET-positive patients who were randomly assigned to treatment with either standard ABVD + involved-node radiotherapy (INRT; n = 192) or experimental BEACOPPesc + INRT (n = 169).*



Published in: Marc P.E. André; et al ; *JCO* **2017,** 35, 1786-1794.

Early Positron Emission Tomography Response–Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial

Marc P.E. André et al J Clin Oncol. 2017 Jun 1;35(16):1786-1794.

- For both F and U groups, non-inferiority of ABVD only compared with combined modality treatment could not be demonstrated.
- Conclusion In stage I and II HL, PET response after two cycles of ABVD allows for early treatment adaptation.
- When ePET is positive after two cycles of ABVD, switching to BEACOPPesc + INRT significantly improved 5-year PFS.
- In ePET-negative patients, noninferiority of ABVD only could not be demonstrated: risk of relapse is increased when INRT is omitted, especially in patients in the F group.

Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial

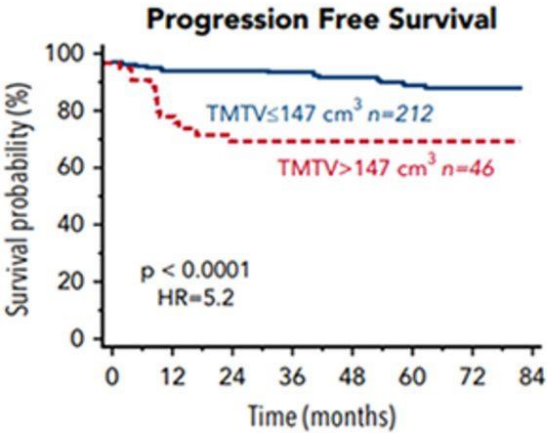
Cottereau et al. Blood 2018;131:1456-1463

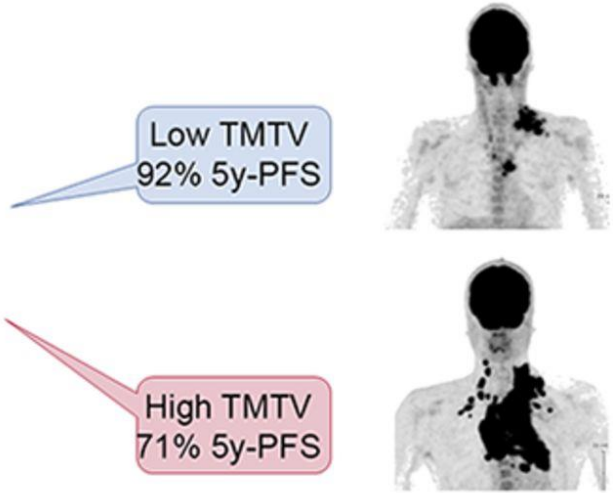
- Tested baseline PET / CT as a measure of total tumor burden to better identify high-risk patients with early-stage Hodgkin lymphoma (HL).
- Total metabolic tumor volume (TMTV) was measured on baseline PET. iPET2 findings were reported negative (DS1-3) or positive (DS4-5) with the Deauville scale (DS).
- The prognostic value of TMTV was evaluated and compared with baseline characteristics, staging classifications, and iPET2.
- A total of 258 patients were eligible: 101 favorable and 157 unfavorable. The median follow-up was 55 months, with 27 progression-free survival (PFS) and 12 overall survival (OS) events.
- TMTV was a prognosticator of PFS ($P < .0001$) and OS ($P = .0001$), with 86% and 84% specificity, respectively. Five-year PFS and OS were 71% and 83% in the high-TMTV (>147 cm3) group (n = 46), respectively, vs 92% and 98% in the low-TMTV group (≤147 cm3).

Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial

Cottereau et al. Blood 2018;131:1456-1463

Total Metabolic Tumor Volume measured on baseline PET :
a new prognosticator of PFS and OS in early stage HL
from the standard arm of the H10 trial





Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial

Cottereau et al. Blood 2018;131:1456-1463

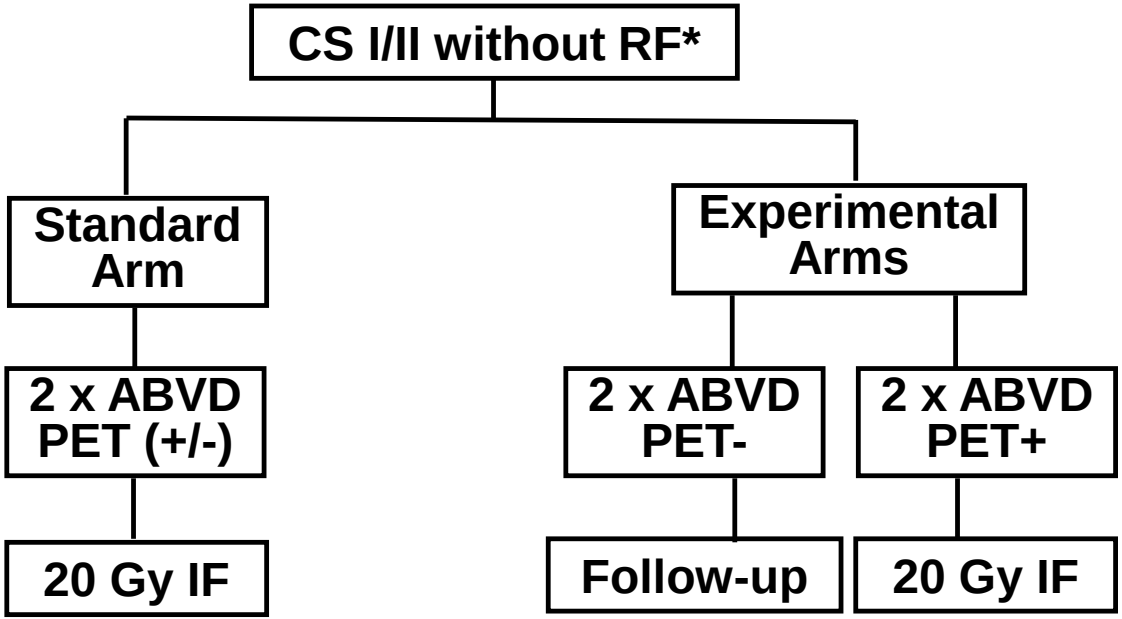
- In multivariable analysis including iPET2, TMTV was the only baseline prognosticator compared with the current staging systems proposed by the EORTC, GELA, GHSG, or National Comprehensive Cancer Network.

- TMTV and iPET2 were independently prognostic and, combined, identified 4 risk groups: low (TMTV≤147+DS1-3; 5-year PFS, 95%), low-intermediate (TMTV>147+DS1-3; 5-year PFS, 81.6%), high-intermediate (TMTV≤147+DS4-5; 5-year PFS, 50%), and high (TMTV>147+DS4-5; 5-year PFS, 25%).

- **TMTV improves baseline risk stratification of patients with early-stage HL compared with current staging systems and the predictive value of early PET response as well.**

GHSG trial (HD16) for early favorable HL

Further data awaited that will inform the discussion



a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas

Developing a balanced approach to risk in personalising care in early HL ?

- **What is the risk of delivering RT ?**
  - late toxicity, age of patient, site of disease)
- **What is the risk of not delivering RT ?**
  - reduced disease control, further treatment for relapse, patient choice)

What do we need to better understand risk in personalising care in early HL ?

- **Risks models for assessing potential consequences of radiation therapy delivery**
  - Age of patient (young vs older)
  - Sex of the patient (breast tissue in < 35 years))
  - Site of disease (groin, neck, axilla vs mediastinum)
  - Volume, field, dose, technique (IMRT, VMAT)
- **Risk models for assessing response to chemotherapy ?**
  - Internationally Reproducible Deauville scoring
  - Internationally reliable PET QA
  - Integration of clinical risk and /or other biomarkers
- **Risk models for assessing consequences of chemotherapy**
  - Bleomycin lung injury
  - Anthracycline induced cardiac damage
  - neuropathy

Conclusions

- Large numbers of well conducted RCT supporting CMT
- Recent FDG-PET data inform patient specific discussions about risk of relapse (increased over chemo alone) versus late toxicity (potentially increased with CMT but patient specific)
- Response adapted treatment using FDG PET - Ongoing challenges to implement in routine clinical practice with QA measures required to meet Deauville criteria
- Patient specific risk models are being developed alongside further biomarkers eg TMTV

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

- As a treatment option for patients with favorable disease, especially when **risk of late toxicity of RT considered lower than risk of relapse (Age, site of disease, sex)**
- Older patients – increased risks associated with ABVD
- Definitely for patients with a positive interim PET scan (in RAPID and EORTC +/- BEACOPP)
- Patients with large mediastinal adenopathy (younger female patients always a difficult individual discussion)

Role of additional radiotherapy in advanced stages of Hodgkin's disease.

Meerwaldt JH, Coleman CN, Fischer RI, Lister TA, Diehl V Ann Oncol.1992 Sep;3 Suppl 4:83-5

- Although radiotherapy is widely used as additional treatment following chemotherapy, its precise role has never been clearly proven.
- Relapses tend to occur in previously involved bulky sites.
- Non-randomized studies may suggest a positive effect of the addition of radiotherapy. This effect however, might also be caused by selection.
- Randomized studies have not resulted in a survival advantage for the patients treated with additional radiotherapy compared to no further treatment or additional chemotherapy.

Has anything changed in 25 years ?

SWOG 7808 “low dose involved field radiation after chemotherapy in advanced Hodgkin disease (1978-1988)

- 530 Stage III-IV patients enrolled.
  - 322 achieved CR after MOP-BAP
  - 278 pts randomized
- Randomized to low-dose RT (10-20 Gy) to all initially involved sites vs observation.
- Abstract:

  “Remission duration, relapse-free survival, and overall survival were similar for the two groups (P = 0.09, P>0.2, and P = 0.14, respectively).”

Fabian C et al Ann Intern Med. 1994 Jun 1;120(11):903-12

SWOG 7808 “low dose involved field radiation after chemotherapy in advanced Hodgkin disease (1978-1988)

- Among 278 CR patients 5-year “similar” RFS was 79% vs 68% in favour of RT.
  - P = 0.09 for the difference of 11%.
- RT improved relapse rate in
  - patients with **nodular sclerosis**
    - 5-year relapse free 82% vs 60% (P = 0.002)
    - Non-bulky NS: RFS 88% vs 68% favouring RT (P = 0.06)
  - patients with **bulky disease** (>6cm)
    - 5-year relapse free 75% vs 57% (P = 0.05).

Fabian C et al Ann Intern Med. 1994 Jun 1;120(11):903-12

Conclusion

- SWOG 7808 often cited asevidence against using RT but….
- Suggests a 20% benefit in remission duration for NS group, 18% benefit in bulk disease

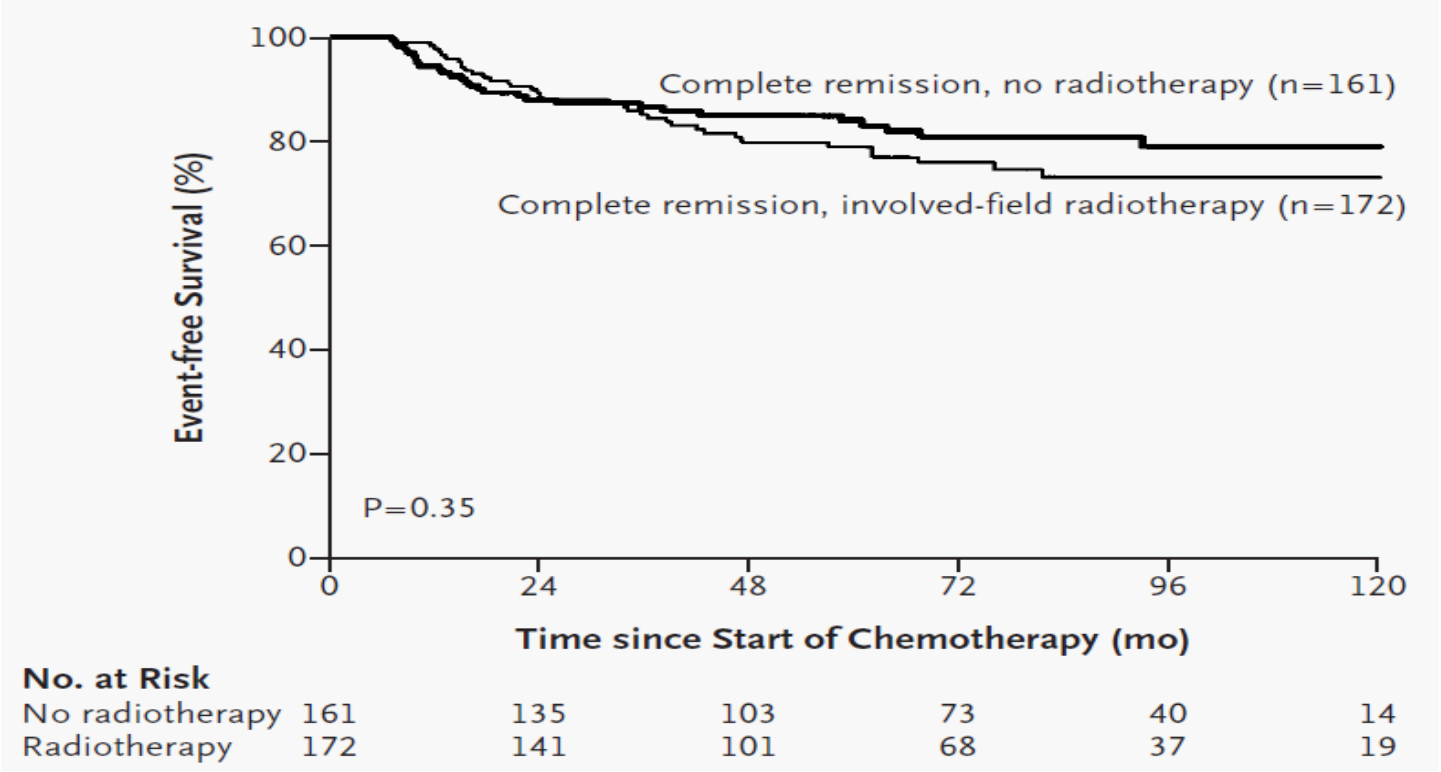
- Major limitations are outdated chemotherapy and RT, no functional imaging…….

EORTC 20884 “Involved-field radiotherapy for advanced Hodgkin Lymphoma

- 739 Stage III-IV patients enrolled.
- MOPP-ABV x 6-8 cycles depending on response.
  - If CR after 4 cycles (early CR), received 6 cycles total.
  - If CR at 6 cycles, received 8 cycles total.
- 20% progressed or were removed from protocol.
- 333 CR patients randomized to RT vs observation.
  - CR = “the disappearance of all disease-related symptoms and measurable lesions”
  - 45% of patients participated in the RT randomization.

Aleman B. et al N Engl J Med. 2003 Jun 12;348(24):2396-406

EORTC 20884 “Involved-field radiotherapy for advanced Hodgkin Lymphoma



No. at Risk

No radiotherapy	161	135	103	73	40	14
Radiotherapy	172	141	101	68	37	19

EORTC 20884 Conclusions

- No need for IFRT in patients who are in CR after MOPP-ABV, only patients in PR after chemo benefit
- 45% of advanced stage patients who achieve “the disappearance of all disease-related symptoms and measurable lesions” do not require RT.
- Approximately 35% should receive RT based on chemotherapy response (+ others who progress on chemotherapy).

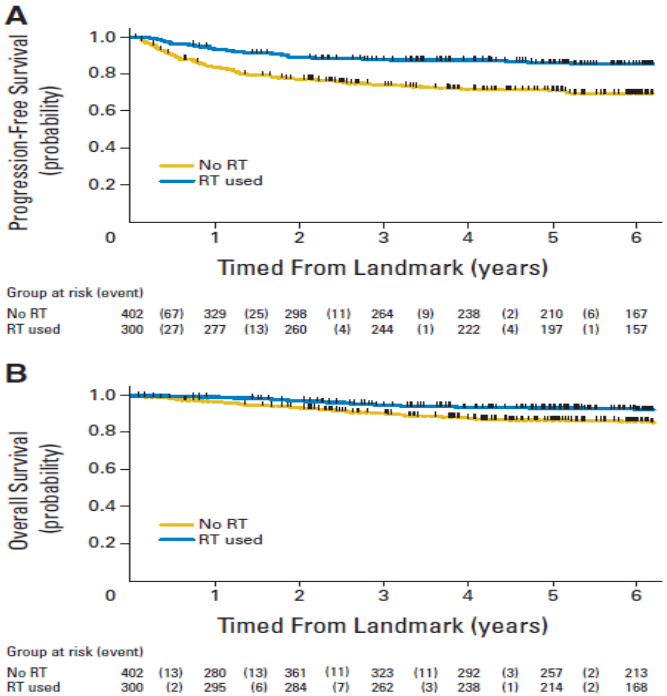
N Engl J Med. 2003 Jun 12;348(24):2396-406

Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial

- 807 patients with advanced stage HL
  - (II+bulk, III to IV)
- Randomized to either ABVD or one of two MDRs.
  - either alternating ChlVPP /PABlOE or hybrid ChlVPP/EVA
- RT was recommended (not randomized) for patients with bulk disease or incomplete response after 6-8 cycles of doxorubicin containing chemotherapy.

Johsnon P et al J Clin Oncol. 2010 Jul 10;28(20):3352-9

Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial



- With a median follow-up of 6.9 years, outcome superior for patients having RT
- 5-year PFS 86% vs 71%
  - (HR = 0.43; P<.0001)
- Similar advantage was seen for overall survival
  - HR = 0.47 (95%CI = 0.29 to 0.77; p = 0.0014).

Johnson P et al J Clin Oncol. 2010 Jul 10;28(20):3352-9

Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 RCT

Conclusions

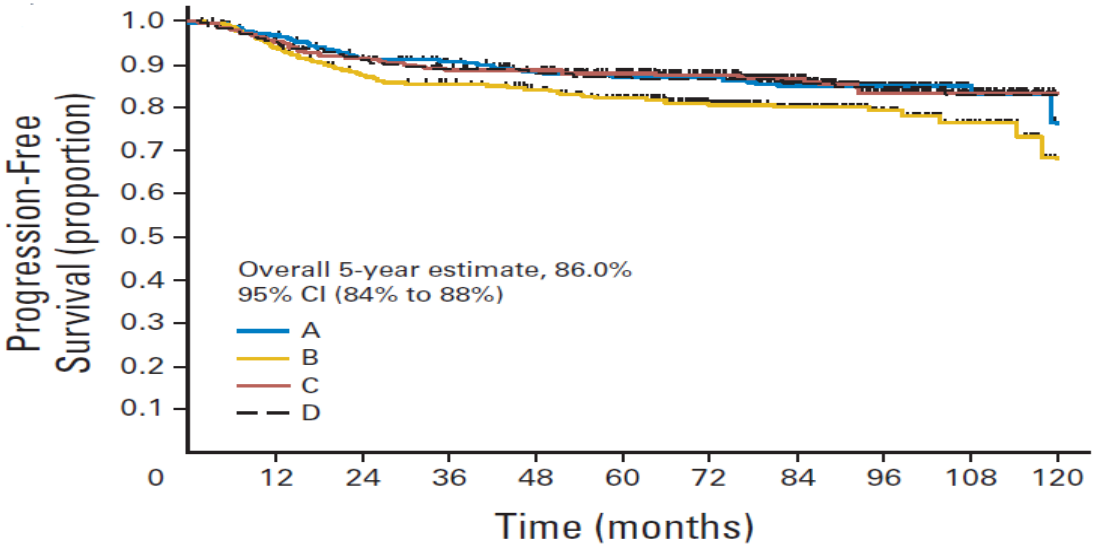
- Non-randomized prospective trial demonstrates significant improvement in EFS and OS when RT added to chemotherapy
- Improved EFS in patients all subsets
  - advanced stage disease,
  - +/- bulk,
  - ABVD other regimens
  - CR/Cru.

What About PET-adapted Selection of Patients for RT? GHSG HD15

- “The results from HD15 study also support a reduced role for radiation therapy in frontline therapy for advanced Hodgkin lymphoma…demonstrating that radiation therapy can be omitted in cases that have residual disease on CT imaging following BEACOPP-based chemotherapy but are FDG-PET-negative”
- “…..these results support the omission of radiotherapy in advanced-stage HL patients who achieve a PET-negative remission after 6 cycles of chemotherapy.”

Can We Restrict RT to PET +'ve Residual Masses?

- GHSG HD11 informs us more intensive chemotherapy BEACOPP$_{esc.}$ can lead to sparing of use of RT to PET +ve patients.
- Should not apply the same rules for RT after ABVD
  - Reducing RT consolidation after ABVD in advanced HL likely to increase relapse rate ?.



PET-Based Trials in Advanced Stage HL

- SWOG S0816: stage III/IV patients
  - PET scan after two cycles of ABVD; PET –ve no RT complete ABVD.
  - 2-year PFS in PET2 neg = 76%[1]
- GITIL/FIL HD0607: stage IIB, III, IV patients have same approach but PET2 negative patients randomized to +/-RT
  - 1-year PFS in PET2 neg = 97.3%[2]

1. Haematologica 98 (pp 36), 2013 .
2. ASH Abstract https://ash.confex.com/ash/2012/webprogram/Paper47545.html

Conclusion – PET Adapted RT Use in Advanced Stage HL

- GHSG does not provide any direct evidence that RT can be omitted in PET negative cases after ABVD.
  - Prior evidence illustrates that it is a mistake to extrapolate RT effect after BEACOPP to AVBD-treated patients.
- Trials in early unfavourable HL suggest that omitting RT based on PET will increase relapse rate.
  - The significance of the effect is debatable.
- The GITIL/FIL HD0607 results will shed light on the question.

Summary of Evidence

- Randomized trials in modern era lacking, older studies inconclusive for role of RT in advanced stage HL.
  - RT was given to 35% of patients on EORTC study, and improved EFS and OS for patients with bulk or incomplete response in SWOG and UK LY09 study
- Best PET-directed data to inform use HD15 is for BEACOPP – RT to PET +ve residual disease
- Early stage unfavourable GHSG data illustrate the benefit of RT is greater with ABVD (compensating for less intensive chemotherapy), making ongoing randomised PET directed studies with ABVD critical to decision making.

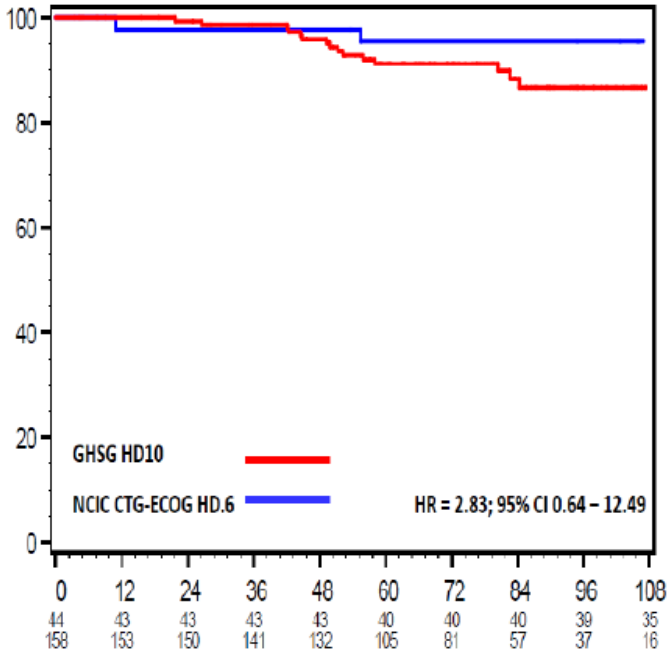
Conclusions

Does Radiation Have a Role in Advanced Stage Hodgkin's or Non-Hodgkin Lymphoma? Specht L et al. Curr Treat Options Oncol. 2016 Jan;17(1):4.

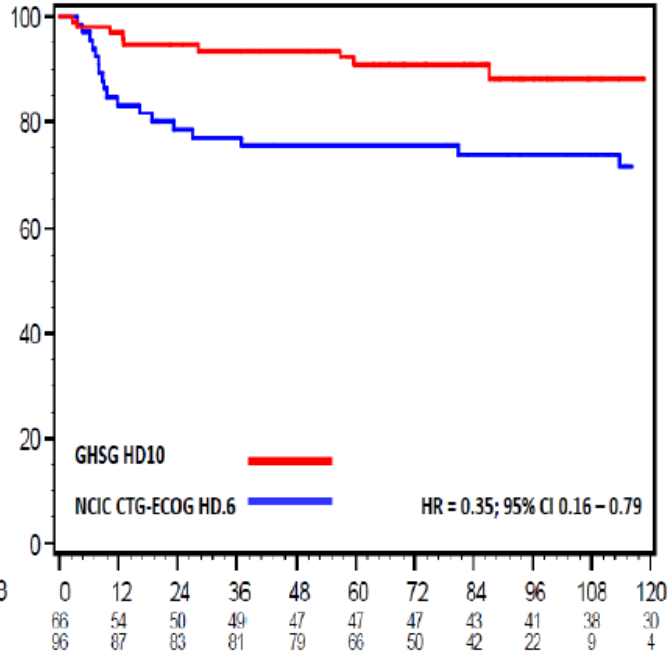
- For advanced stage lymphomas, the indications for the use of RT have been questioned and debated, and proper randomized evidence is sparse.
- The modern concept of involved site radiation therapy (ISRT) reduces late toxicity in advanced Hodgkin lymphoma.
- RT to residual disease and/or initial bulk benefits some patients, depending on the chemotherapy regimen used. The more intensive the chemotherapy regimen, the fewer patients benefit from RT

Combined Modality vs 4-6 x ABVD alone

Status after 2xABVD (HD10 eligible pts; PFS)



CR/CRu



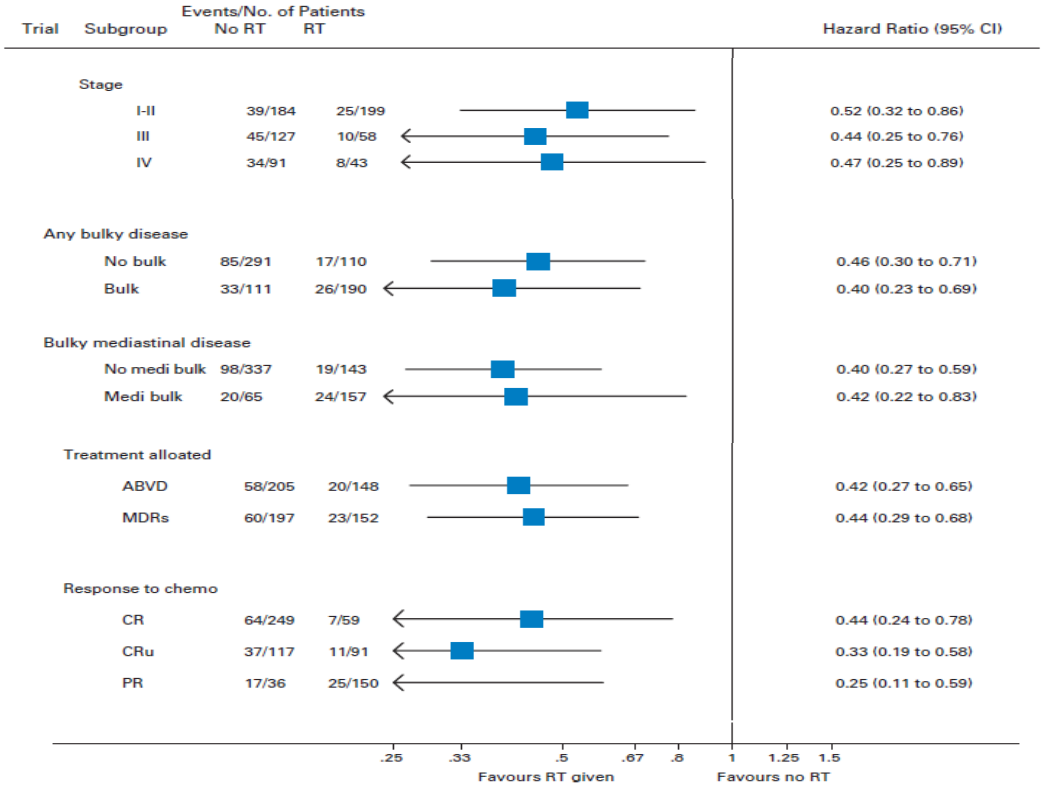
No CR/CRu

Hay et al Ann Oncol. 2013 Dec;24(12):3065-9

Summary of FDG PET in Early HL

- Using FDG PET it 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
  - High quality reproducible PET required to deliver such results
- Longer follow-up is required to establish the impact of a PET negative approach on 10 and 20 year survival and cause of death

UKLG LY09



- RT significantly improved EFS in subsets of
  - Advanced stage
  - ABVD or other
  - Bulk or not
  - LMA or not
  - CR to chemo or not

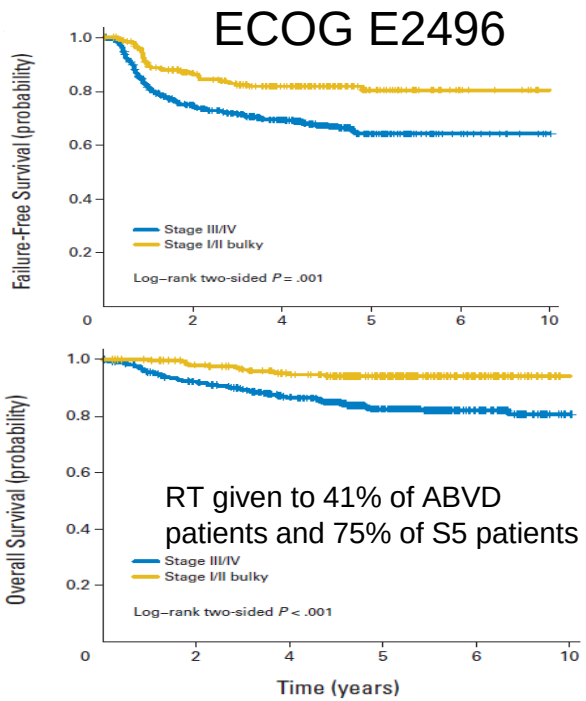
Johnson P et al J Clin Oncol. 2010 Jul 10;28(20):3352-9

Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 RCT

- 43% of patients received RT
- RT use by indication
  - indicated and used in 278 patients
  - indicated and not used in 212 patients
  - used but not indicated in 22 patients
  - neither indicated nor used in 190 patients.
- RT volumes
  - 114 had a single nodal site treated
  - 31 two nodal fields
  - 149 extending over <2 fields.

Johsnon P et al J Clin Oncol. 2010 Jul 10;28(20):3352-9

The Bigger Picture: ABVD-based Treatment Does not Cure Enough High Risk HL.

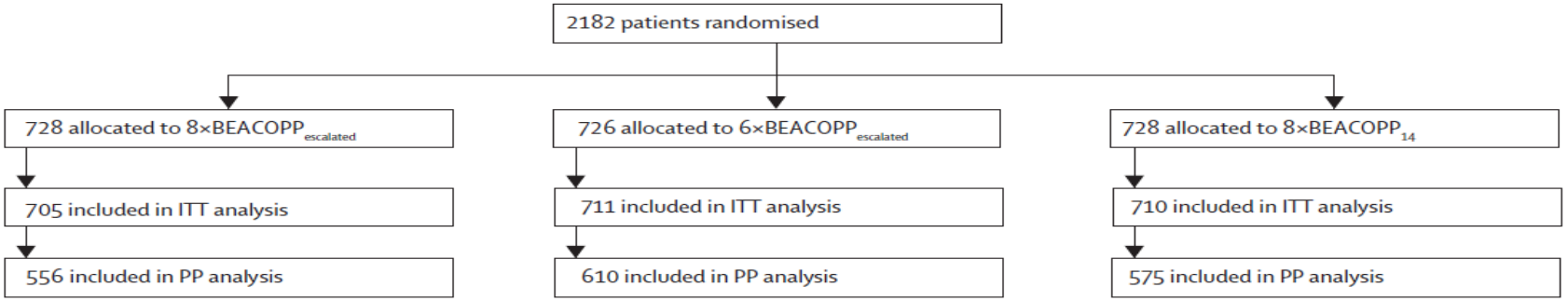


J Clin Oncol 31: 684-691; 2012

- 5 year survival in US for patients with advanced stage HL is comparable to node +'ve colorectal cancer and worse than node +'ve breast cancer.
- The 5-year risk of relapse is likely >2-3 fold higher than the 30-year risk of second cancer even if RT is given.
- Relapsed HL is by far the most common second cancer likely to be experienced by a patient with high-risk HL treated with ABVD.
- Conflating "readily curable" early favourable HL with the outcome of high risk HL risks under-treating the latter.

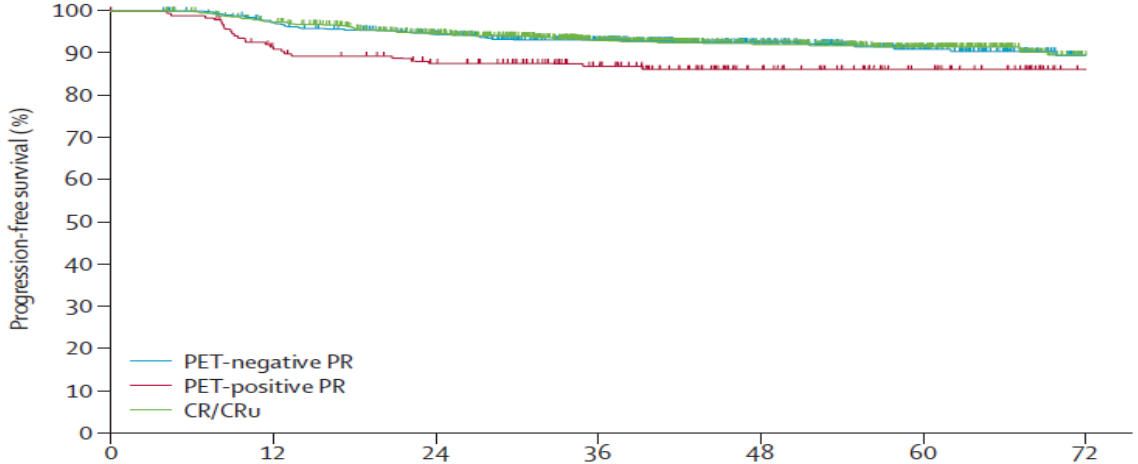
What About PET-adapted Selection of Patients for RT?
GHSG HD15

- Randomized 2182 patients with IIB+LMA, III,IV
- RT given only to PET +’ve residual masses >2.5cm.



GHSG HD15

- BEACOPP x 6 superior to BEACOPP x 8.
- Excellent PFS in those with PET +’ve PR after 30Gy



Number at risk							
PET-negative PR	548	522	485	393	280	177	84
PET-positive PR	191	167	153	123	81	54	23
CR/CRu	881	839	753	598	405	233	115


ESTRO
School

Advanced and relapsed Hodgkin Lymphoma

Andreas Engert, MD

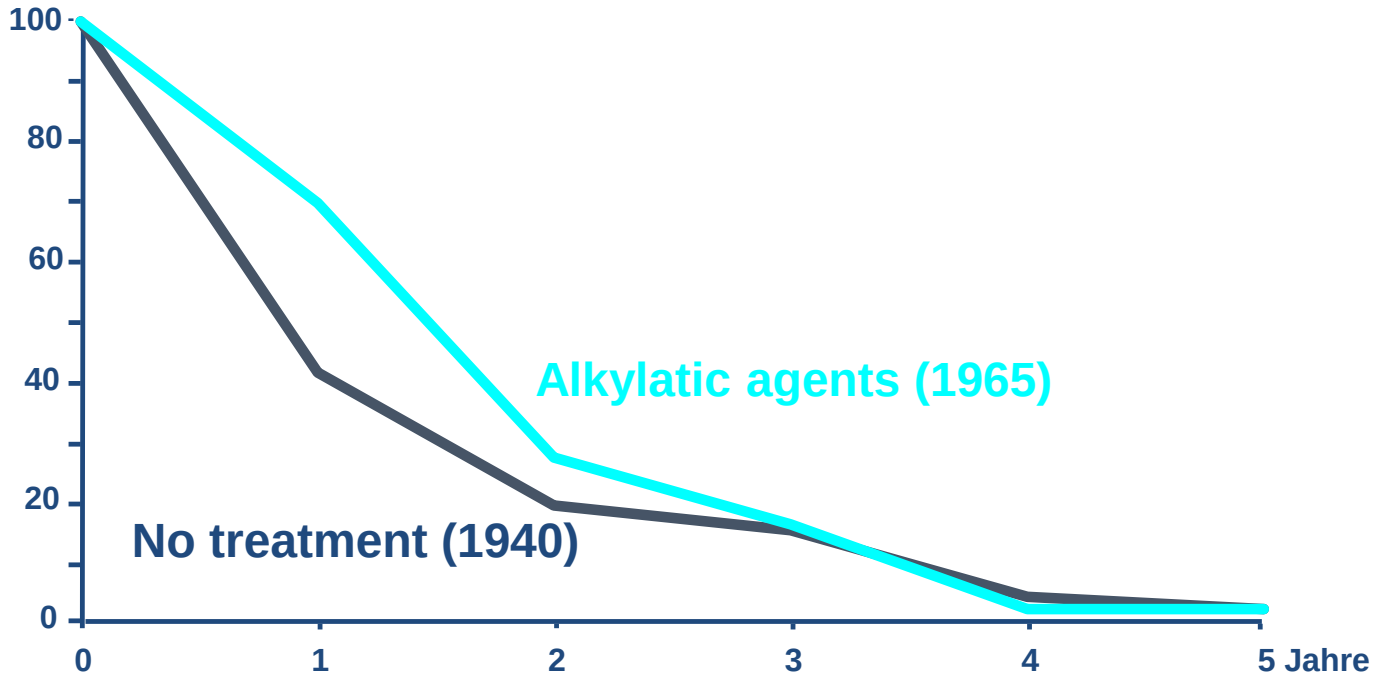
Chairman, German Hodgkin Study Group
University Hospital of Cologne

Advanced and relapsed Hodgkin lymphoma

- Introduction
- Advanced stage Hodgkin lymphoma
- relapsed & refractory Hodgkin lymphoma
- Immunotherapy
- Summary

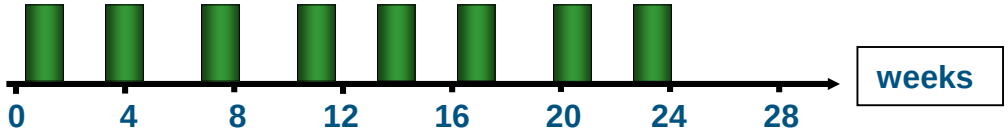
Hodgkin Lymphoma

Historical prognosis in advanced stages

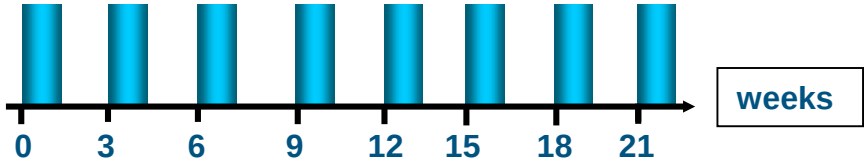


Dose-intensification strategies
for first-line Lymphoma treatment

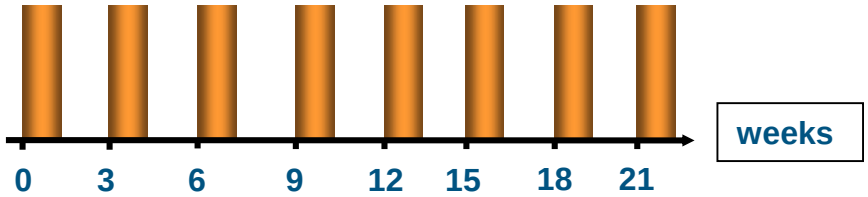
Conventional chemo



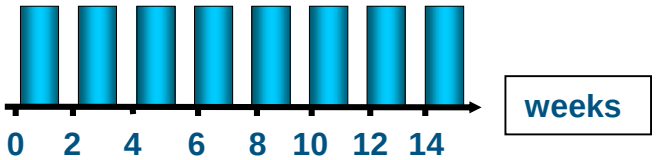
BEACOPP baseline



BEACOPP escalated

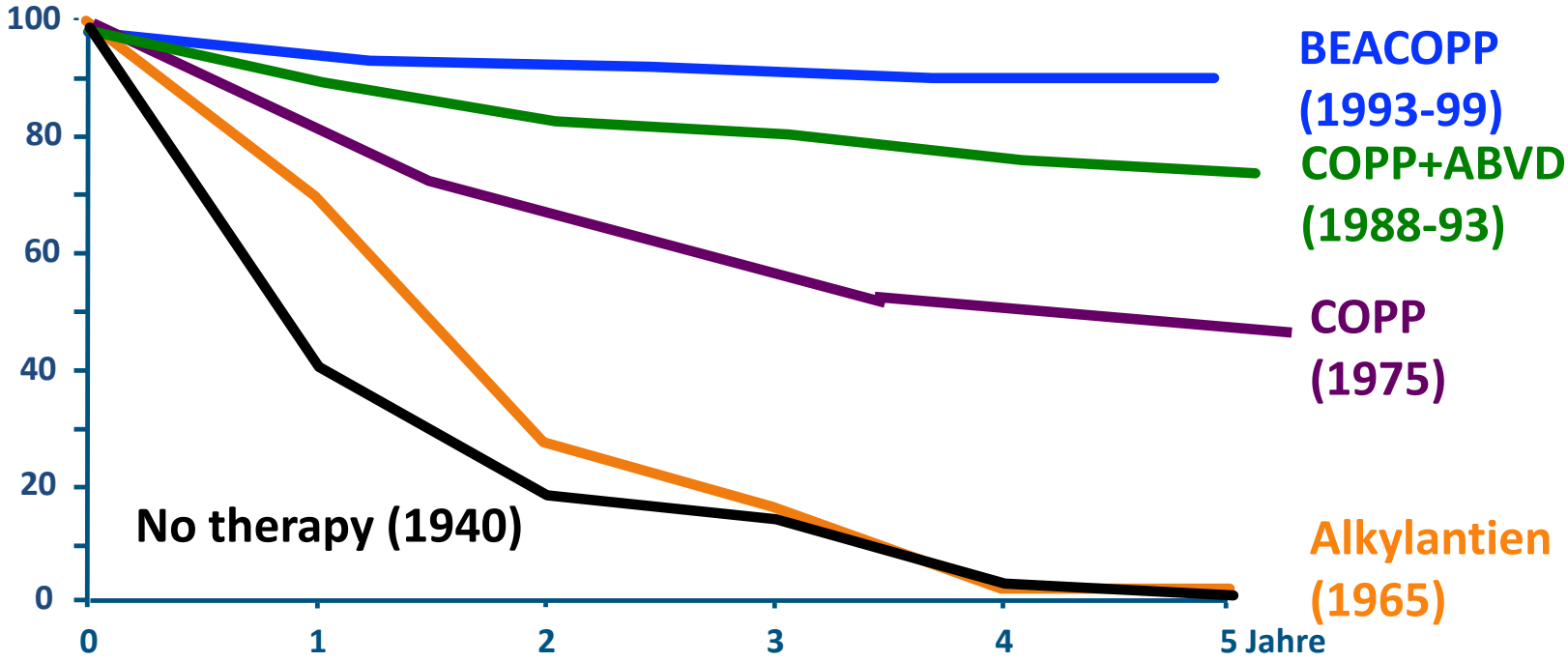


CHOP-14, BEACOPP-14



Hodgkin Lymphoma

Progress in advanced stages



Advanced and relapsed Hodgkin lymphoma

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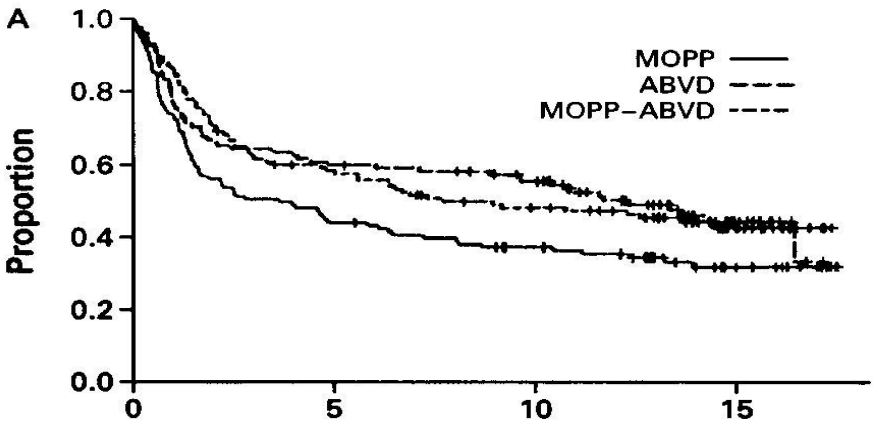
- Relapsed & refractory Hodgkin lymphoma
- Immunotherapy
- Summary

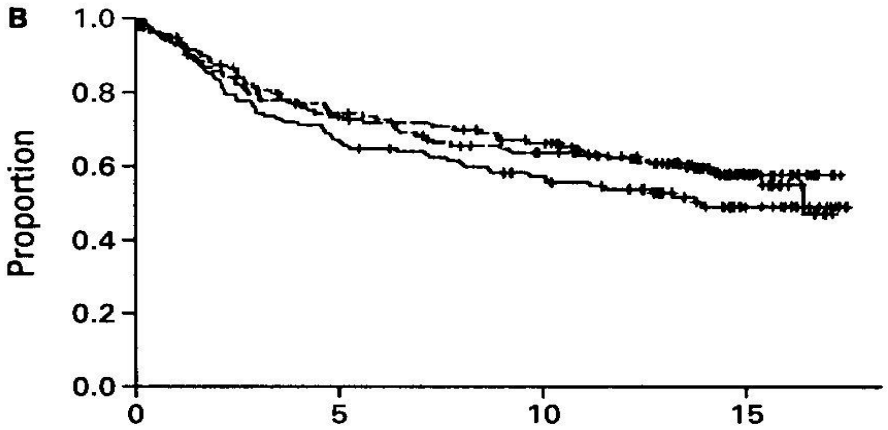
HL treated with MOPP and ABVD

Patients in advanced stages

FFTF



OS

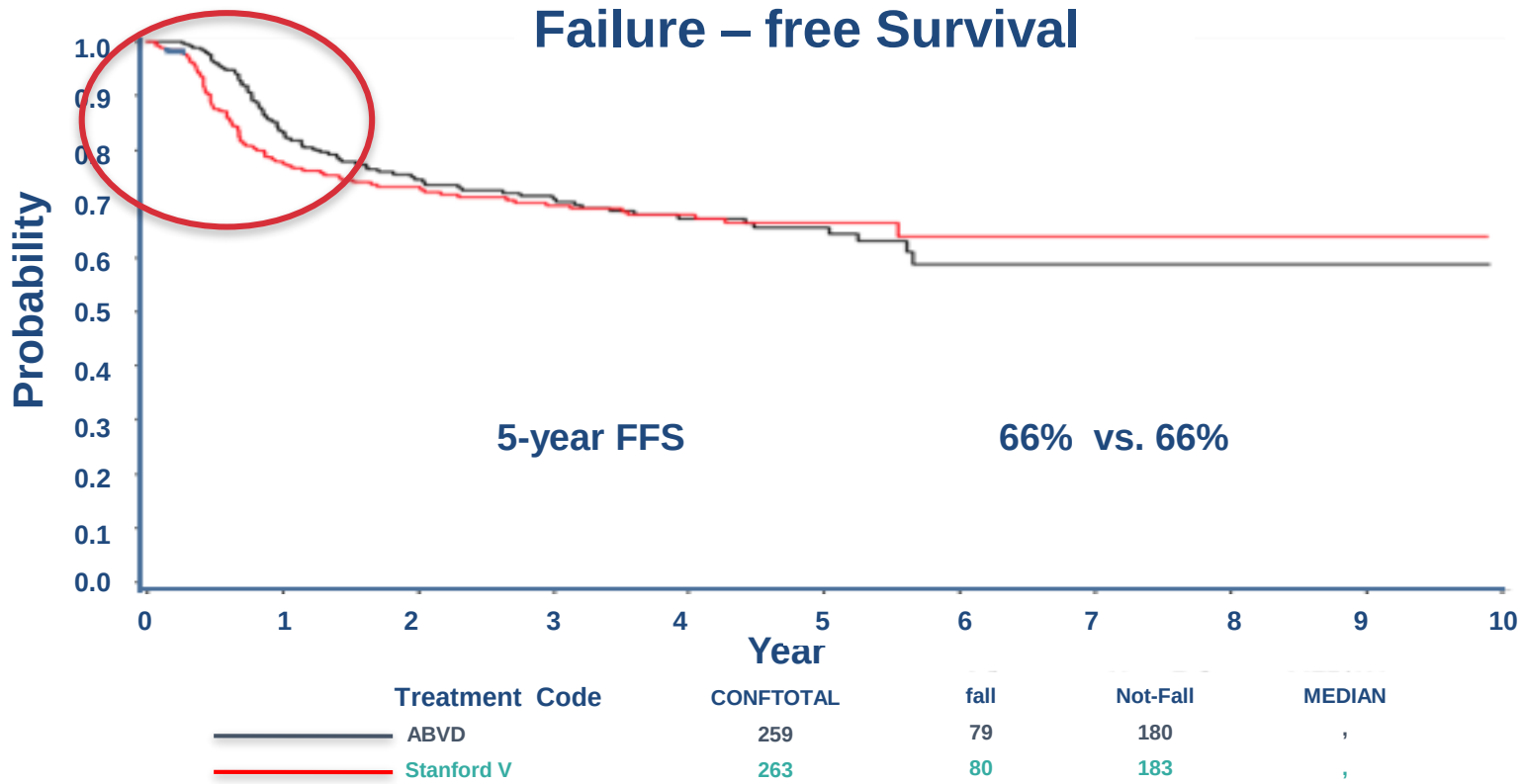


Years after study entry

Canellos G et al NEJM 2002

US Intergroup Trial E2496

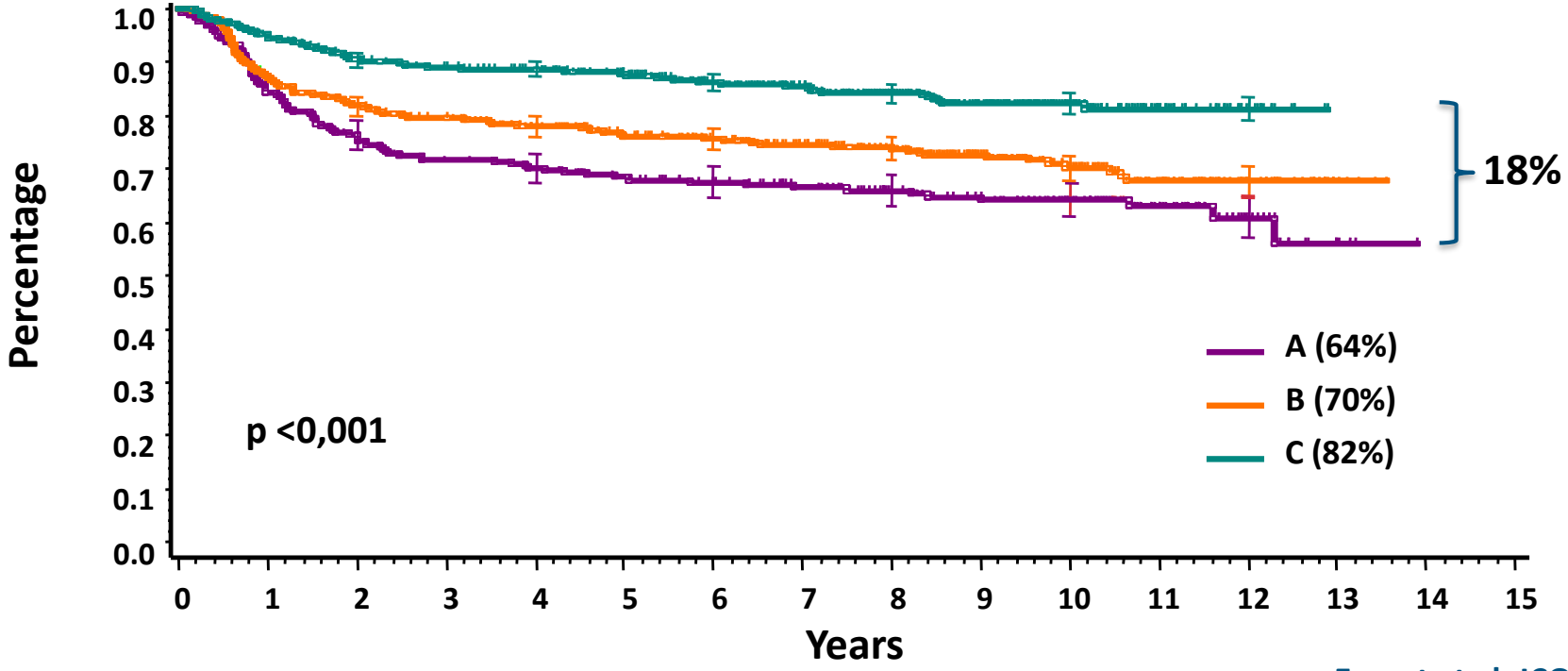
ABVD vs Stanford



Gordon et al; JCO 2013

GHSG HD9 Trial

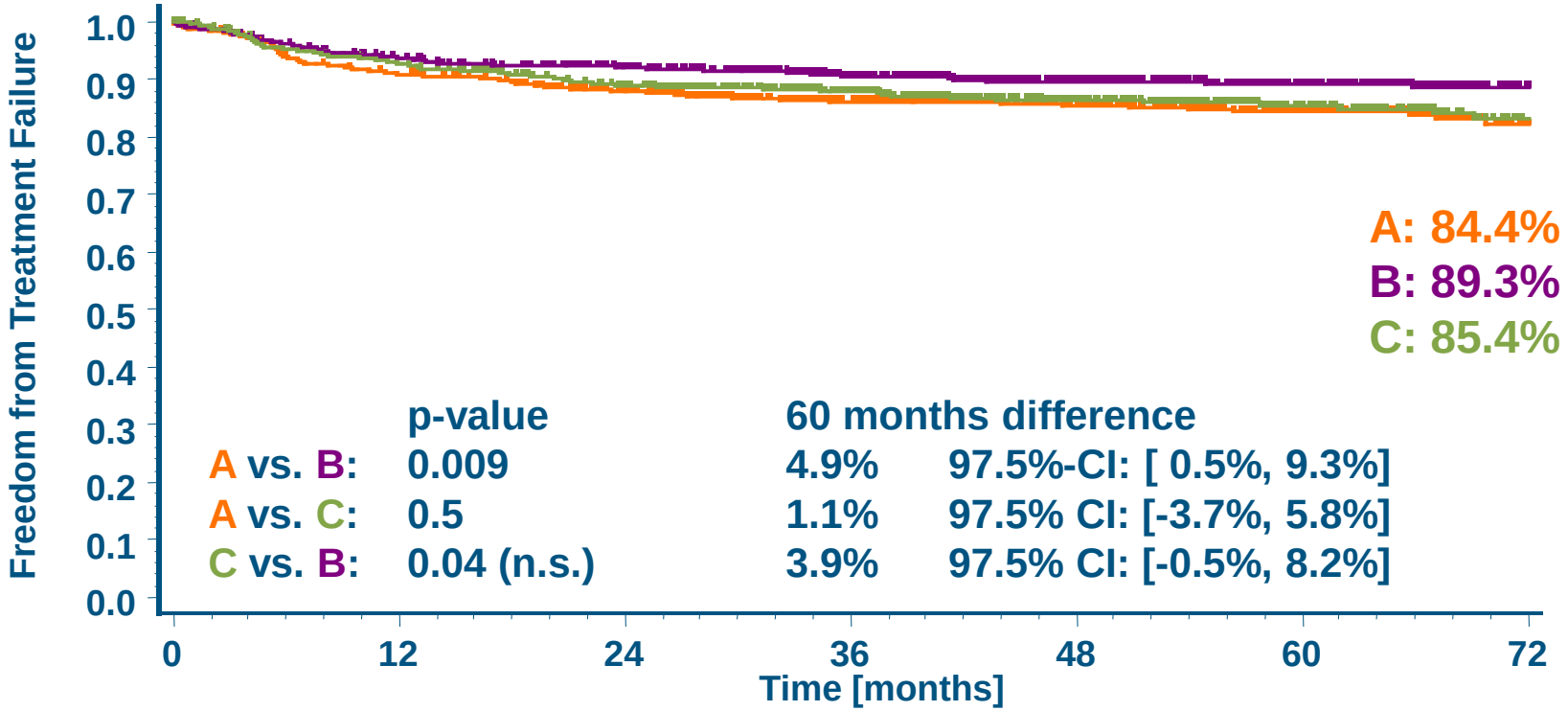
FFTF by treatment arm



Engert et al, JCO 2009

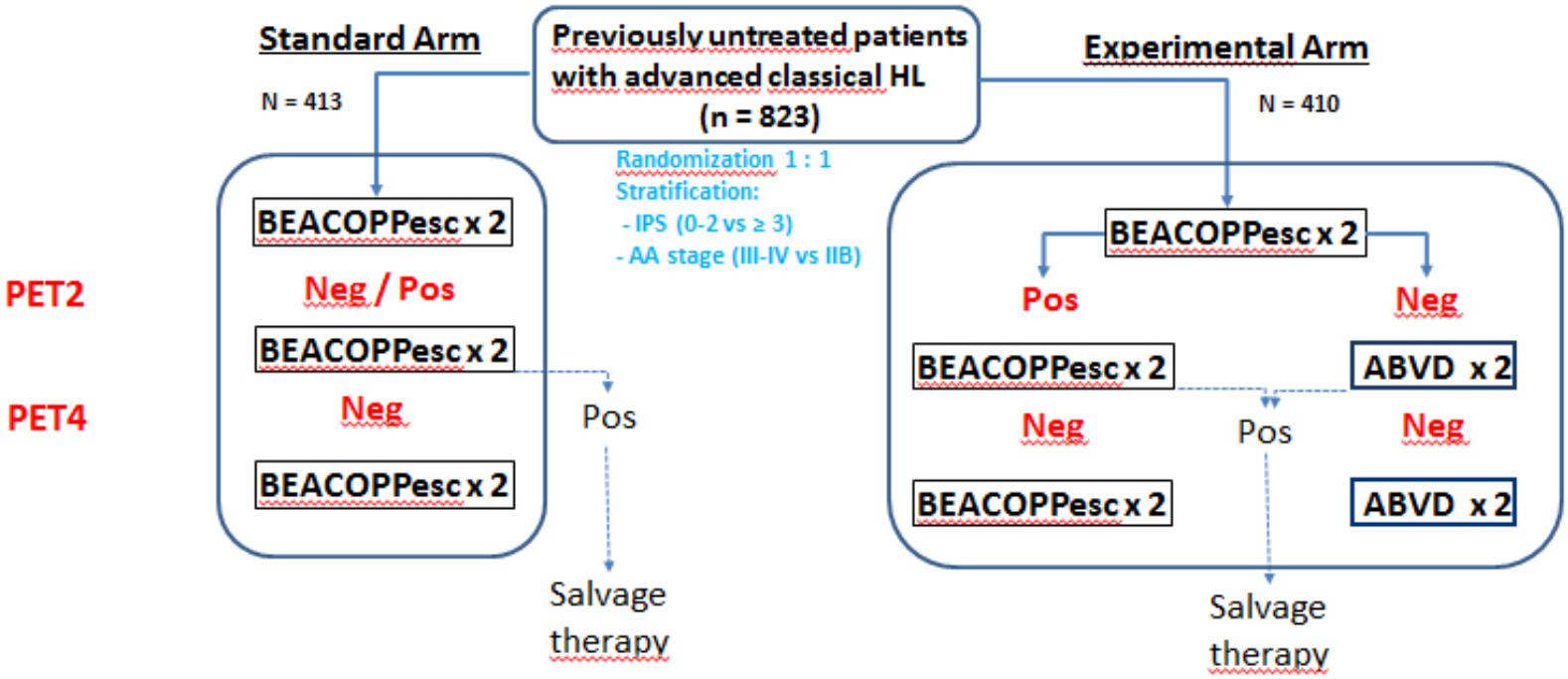
GHSG HD15 in advanced HL

Freedom from Treatment Failure (FFTF)



Engert A et al, Lancet 2012

AHL 2011:
Study design

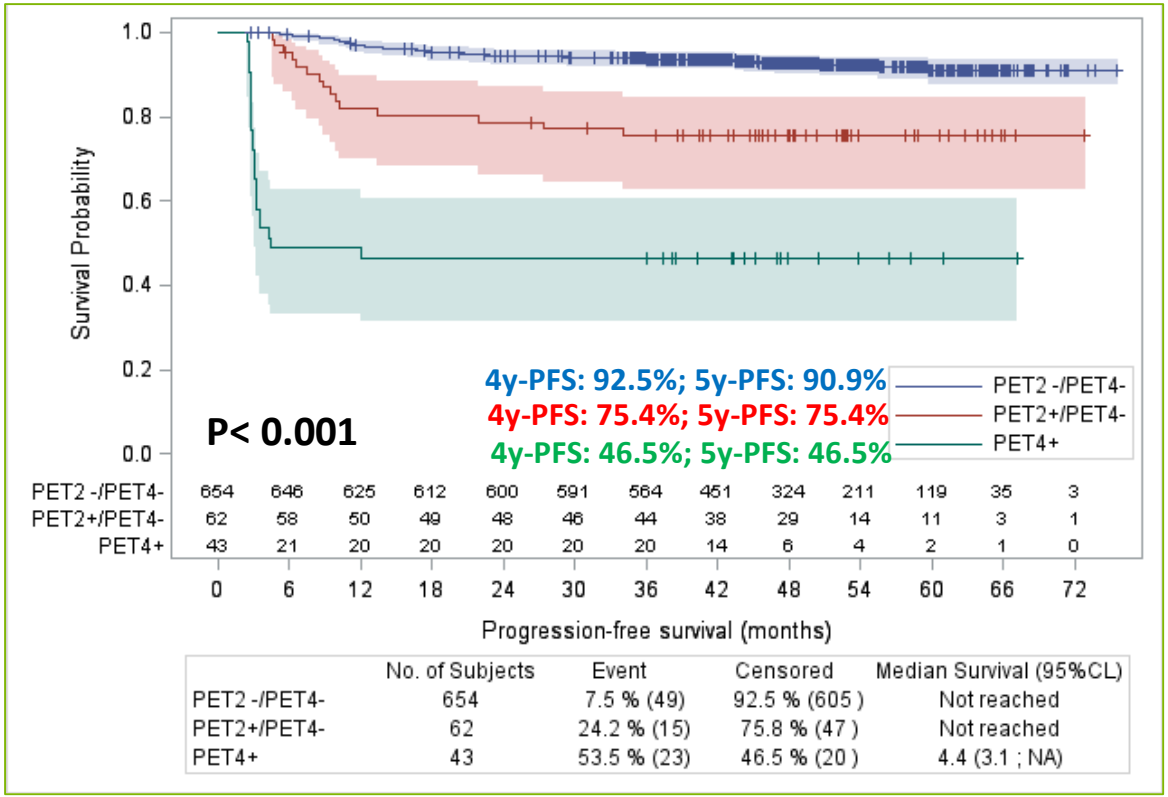


Non-inferiority 5y-PFS design: Standard arm: 85%; Experimental arm: >75% (HR=1.77)

AHL 2011:
Interim PET results (central review)

	Standard arm n = 413		Experimental arm n = 410		All n = 823	
PET2						
Evaluable	398	96%	397	97%	795	97%
Negative	**349**	**88%**	**346**	**87%**	**695**	**87%**
Positive	**49**	**12%**	**51**	**13%**	**100**	**13%**
PET4						
Evaluable	383	93%	376	92%	759	92%
Negative	**356**	**93%**	**360**	**96%**	**716**	**94%**
Positive	**27**	**7%**	**16**	**4%**	**43**	**6%**

AHL 2011:
PFS according to the PET-driven strategy



	No. of Subjects	Event	Censored	Median Survival (95%CL)
PET2 -/PET4-	654	7.5 % (49)	92.5 % (605)	Not reached
PET2+/PET4-	62	24.2 % (15)	75.8 % (47)	Not reached
PET4+	43	53.5 % (23)	46.5 % (20)	4.4 (3.1 ; NA)

n = 654 (86%)

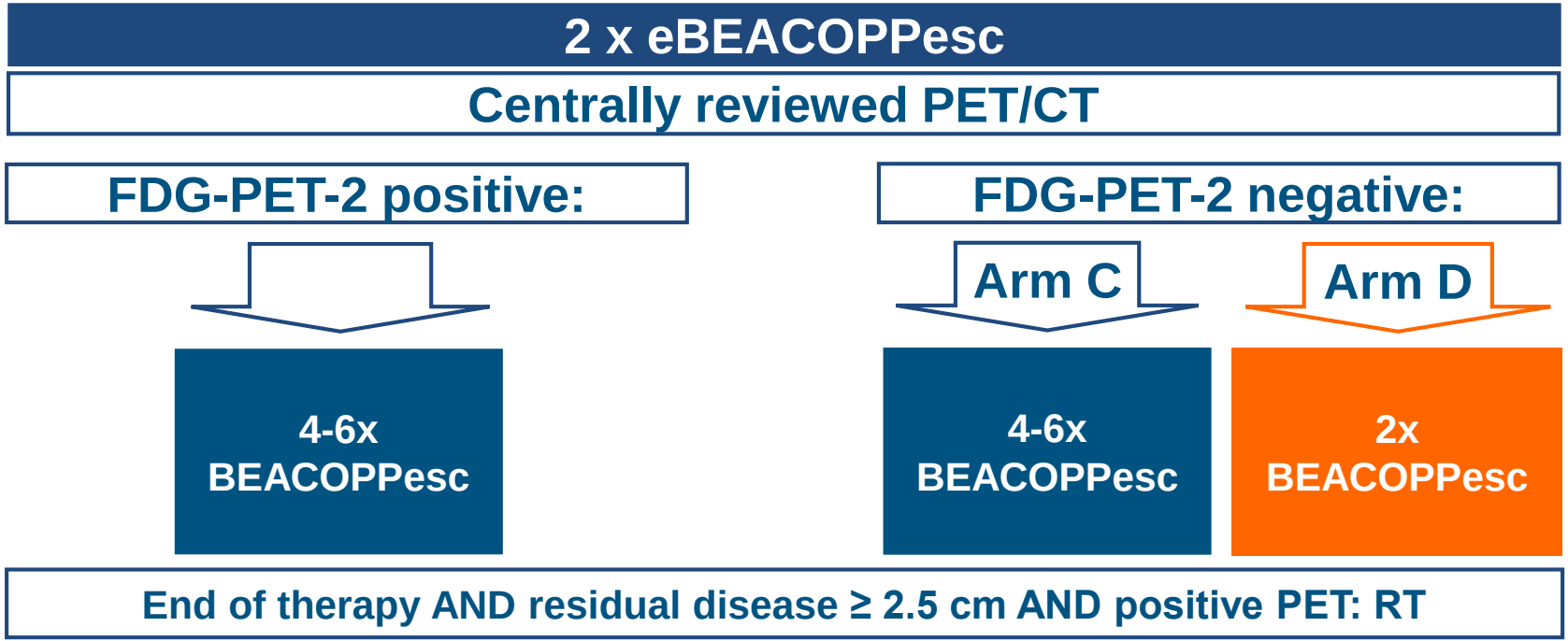
n = 64 (8%)

n = 43 (6%)

AHL 2011; EHA June 15, 2018

GHSG HD18 trial

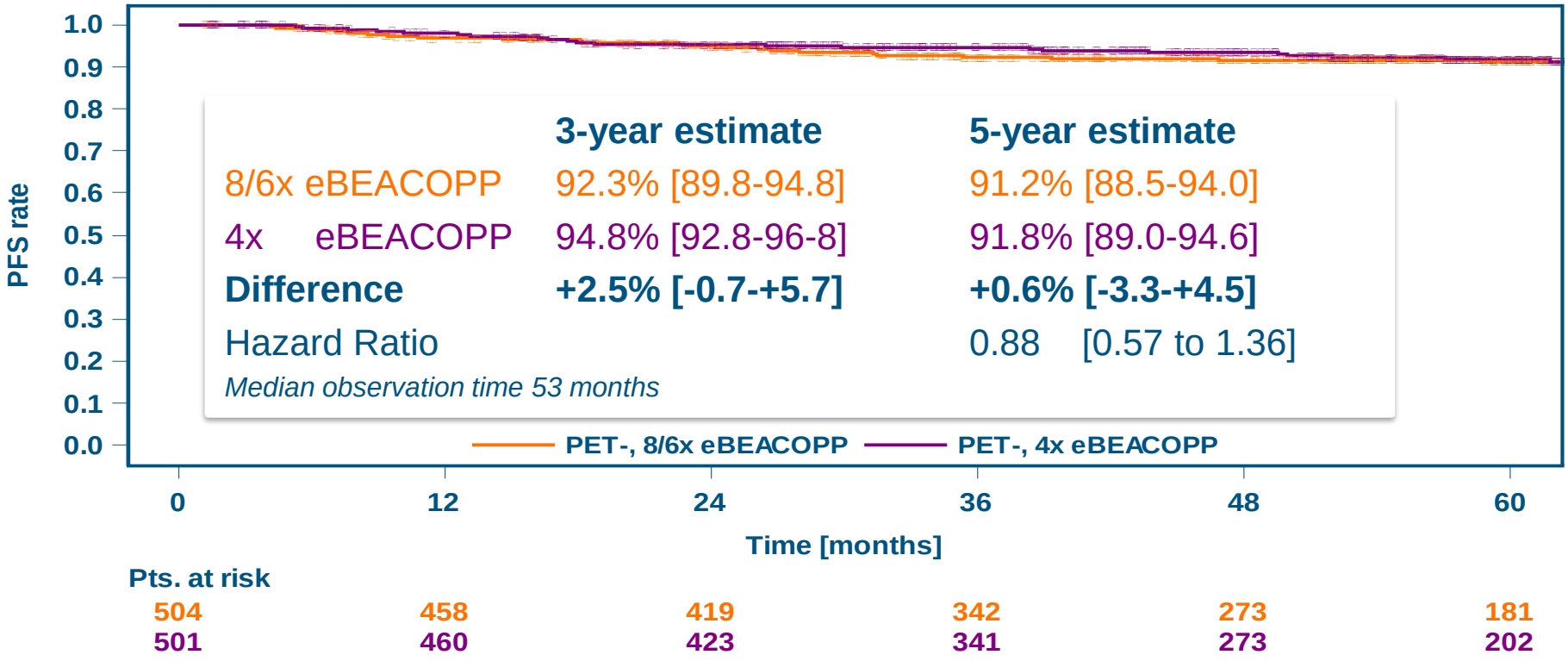
PET-guided therapy of advanced-stage HL



Final analysis of the GHSG HD18 trial

HD18 for PET-2 negative patients

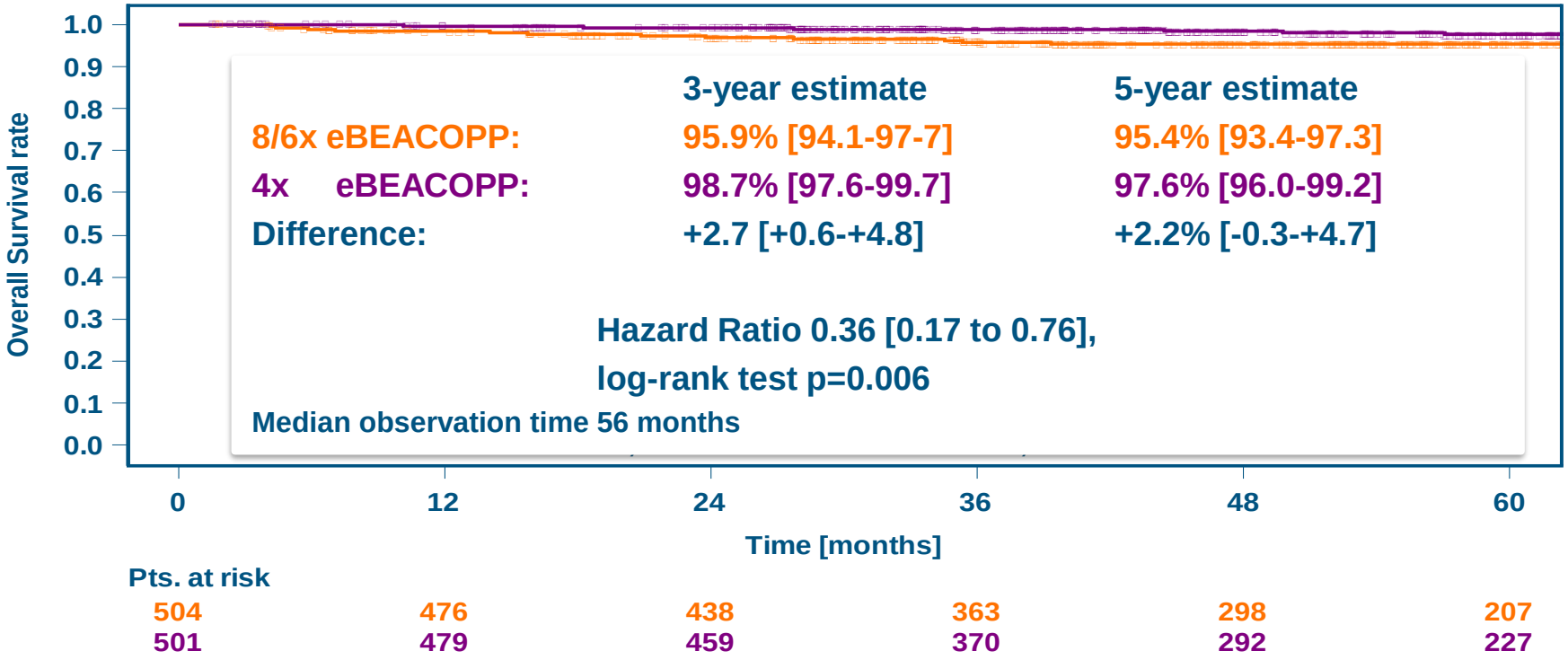
Progression-free survival



Final analysis of the GHSG HD18 trial

Borchmann et al, Lancet 2017

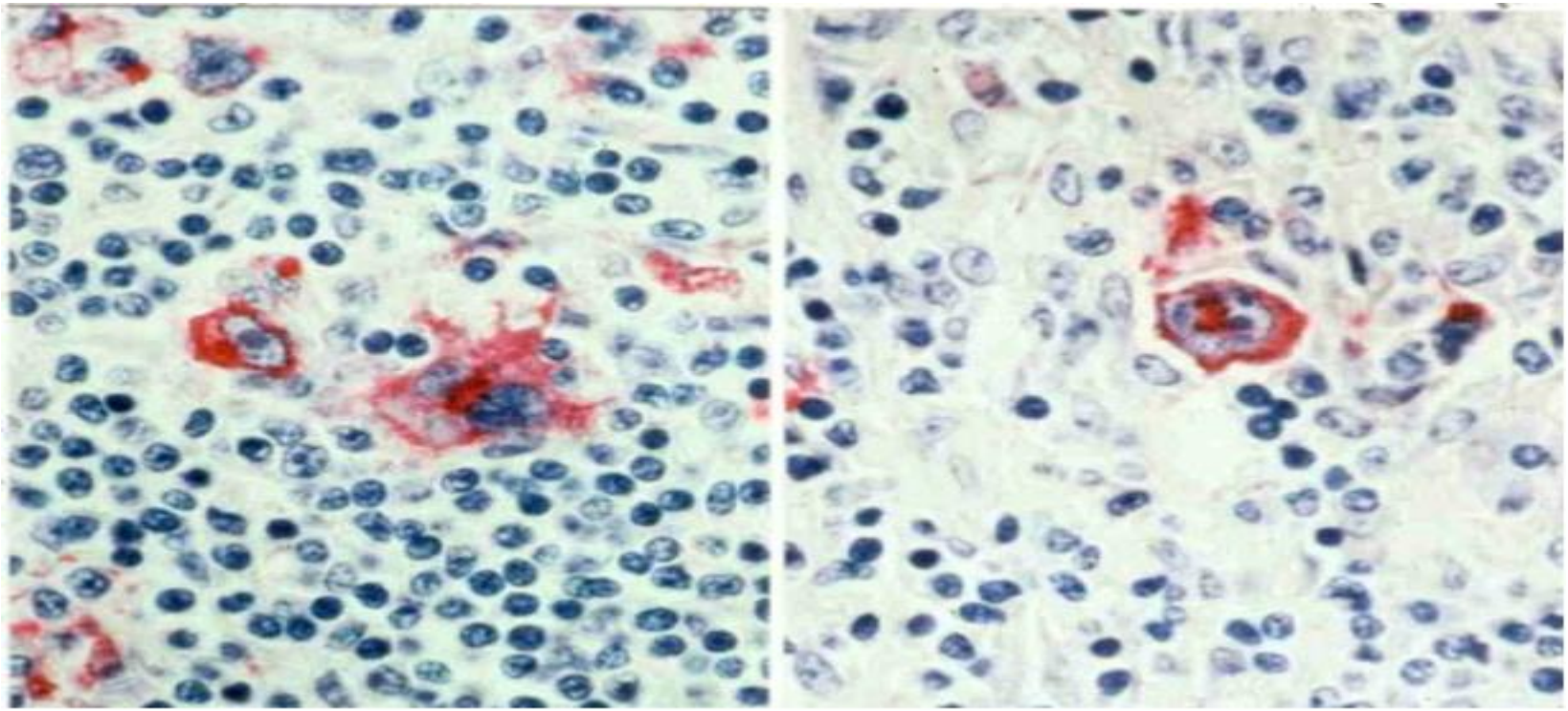
HD18 for PET-2 negative patients
Overall survival



Borchmann et al, Lancet 2017

Immunohistology of cHL

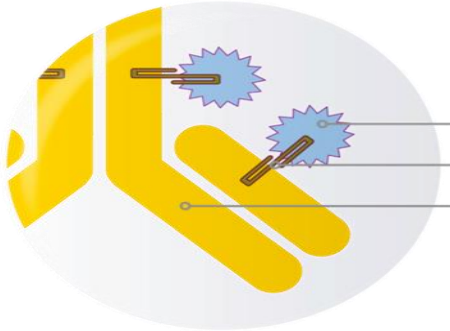
CD30 staining



Courtesy of H. Stein

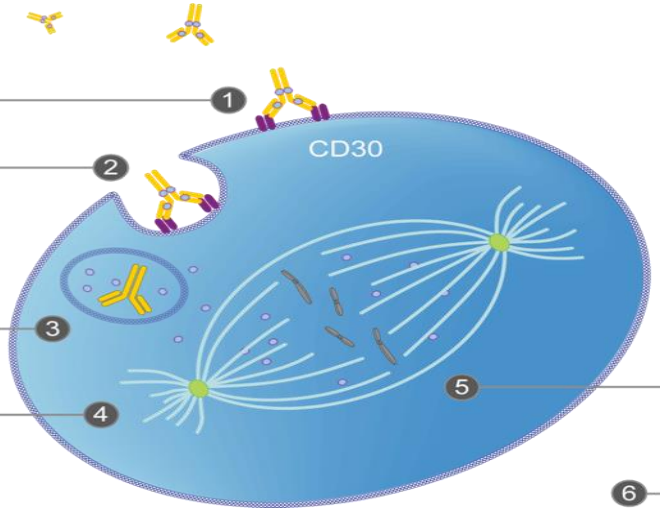
Brentuximab Vedotin (SGN-35)

Mechanism of action



Brentuximab vedotin (SGN-35) ADC

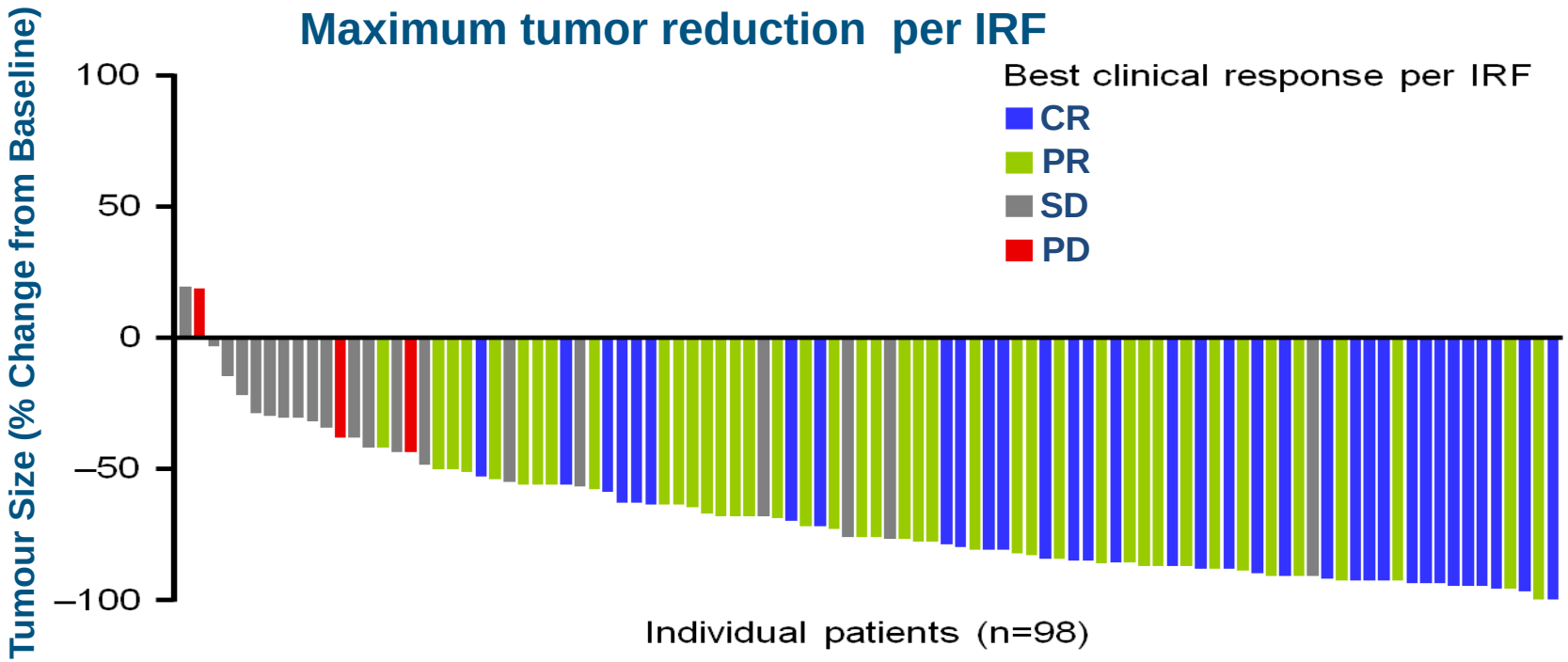
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



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

Other grade 3/4 events in ≥5% of patients:

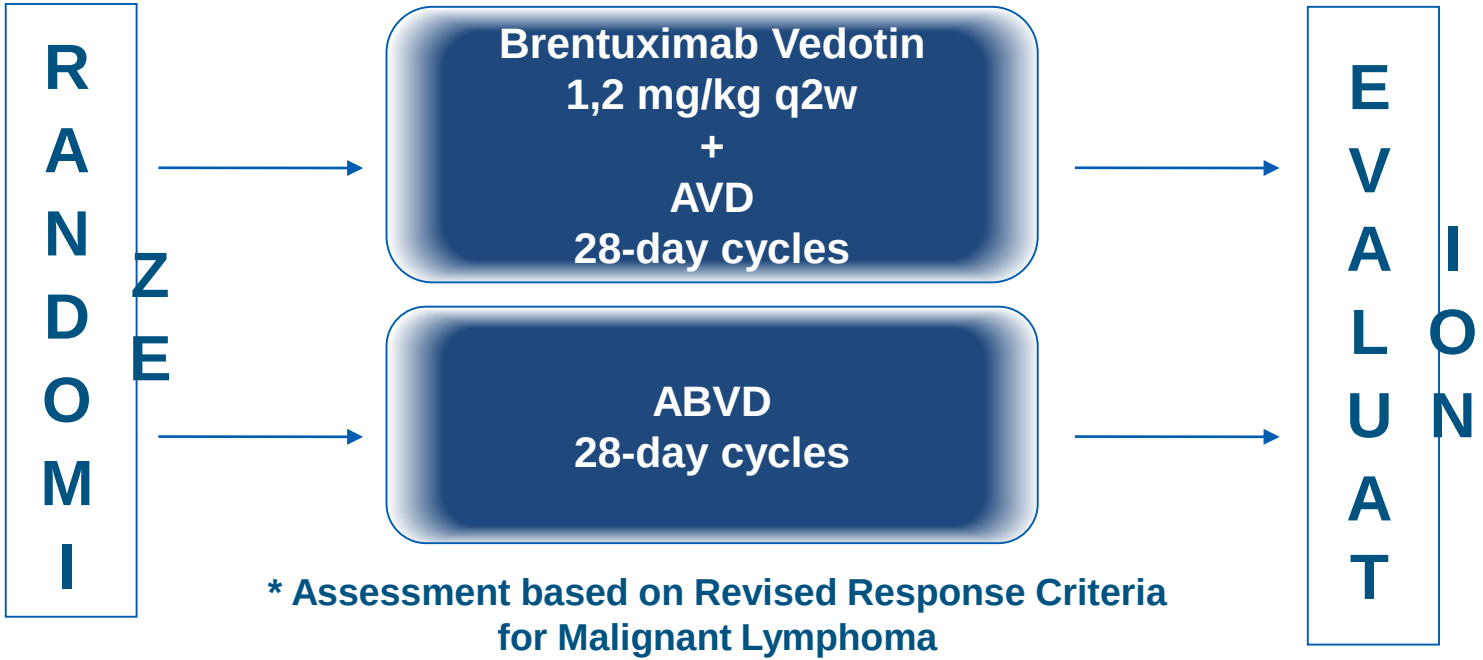
- Thrombocytopenia: 8%
- Anaemia: 6%

BV – Brentuximab Vedotin; AEs – adverse events; pts – patients

Adapted from Chen R et al; Blood, Nov 2012;120: 3689 (ASH abstract)

ECHELON-1: Phase III Trial

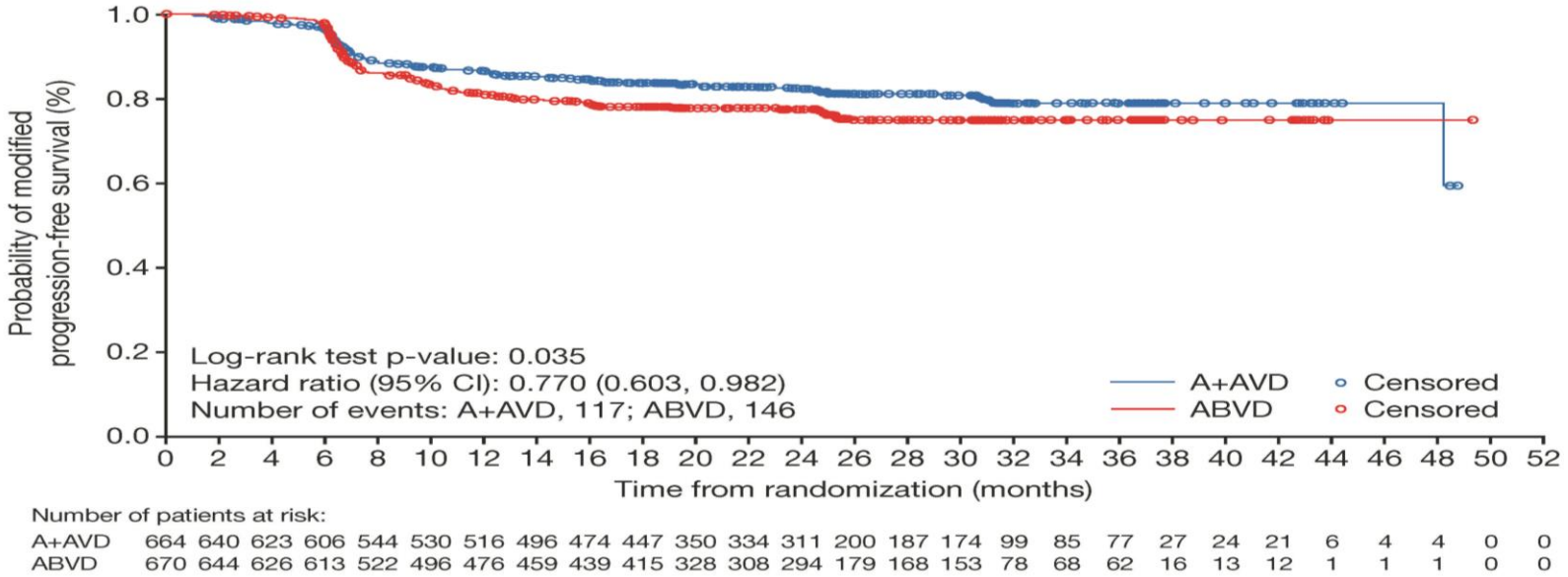
BV + AVD vs. ABVD in frontline advanced cHL



Younes et al, ASCO 2013; Chicago, US (Abstract #TPS8612)

ECHELON-1: Phase III Trial

BV + AVD vs. ABVD in frontline advanced cHL



ASH 2017, Connors et al. A6

ECHELON-1: Phase III Trial

Letters and comments

- mPFS added more pts to ABVD; 5 had Deauville-3[1]
- Discontinuation due to tox, lack of CR, new treatment without progression may obscure PFS[1,3]
- Revised calculation: 84% for A-AVD vs 82% for ABVD (ns)[1]
- Non-PET guided treatment outdated[1]
- Cost for A+AVD is $850.000 vs 18.000 for ABVD[2]
- Further therapy potentially subject to investigator bias[3]
- Not adequate for praxis changing[4]

Hilal[1], Greer[2], Crump[3], LaCasce et al[4], NEM 2018

HD21: GHSG Perspective

BV in advanced stage HL

2 x BEACOPP esc

2 x BrECADD

Centrally reviewed PET

4x BEACOPP esc

4x BrECADD

End of therapy and residual nodes > 2.5 cm:

PET positive: Rx

PET negative: Follow up

HL, Hodgkin Lymphoma; GHSG, German Hodgkin Study Group; BV, brentuximab vedotin; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; PET, positron emission tomography; RX, radiotherapy

Advanced and relapsed Hodgkin lymphoma

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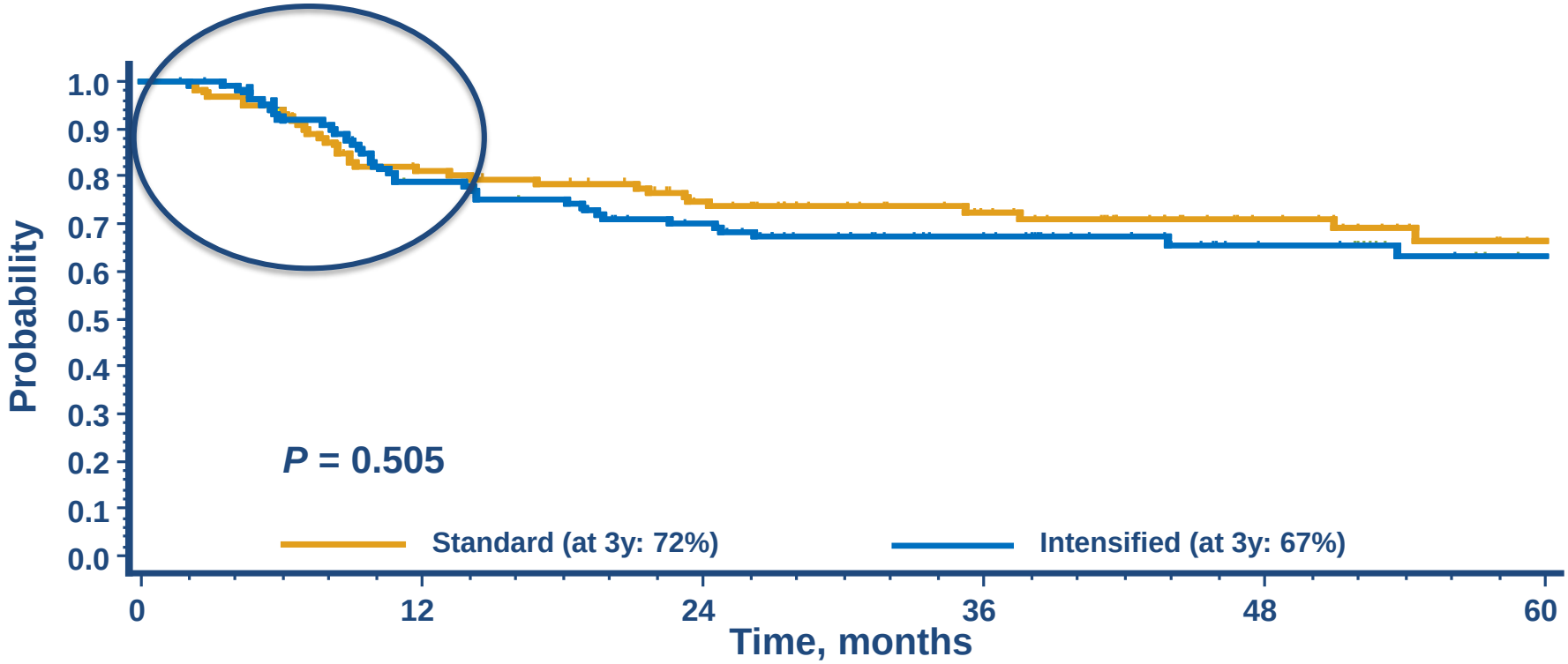
- Summary

HDR2 Study for Relapsed HL

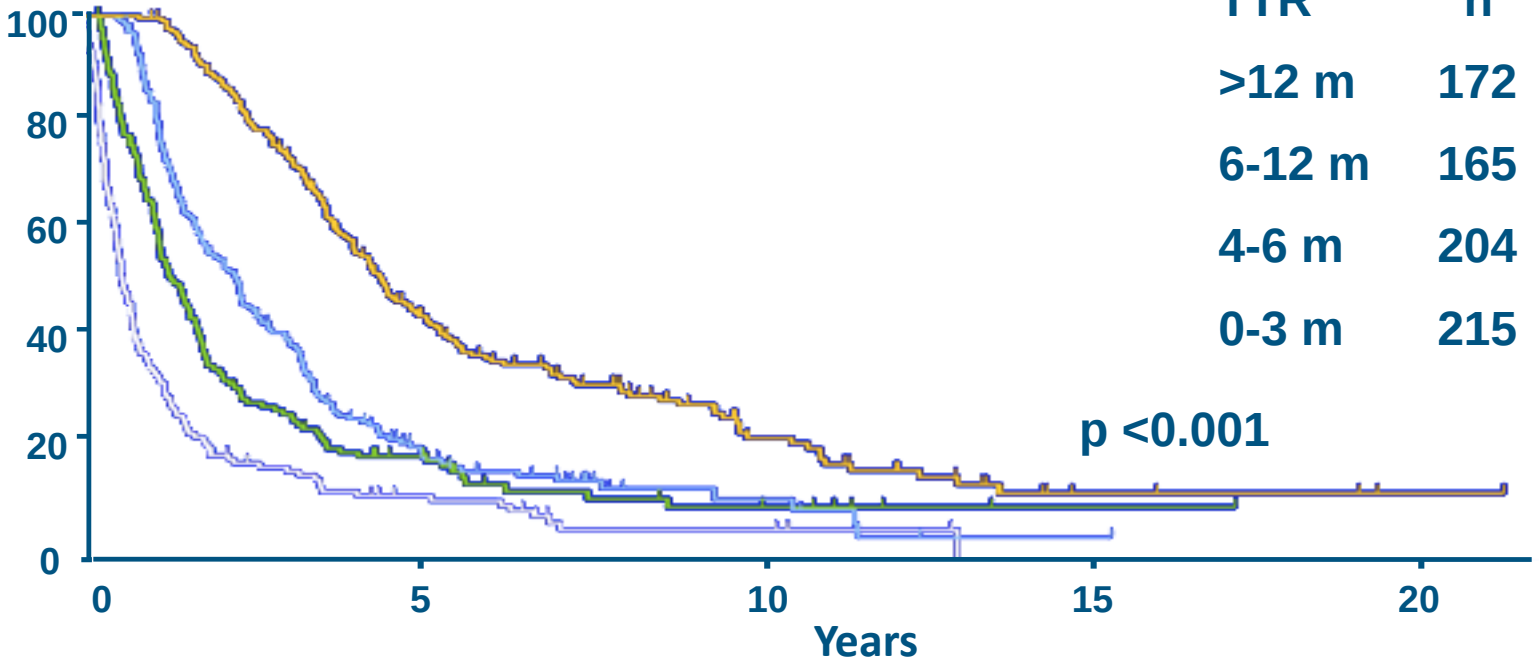
PFS by Treatment Arm (Final Analysis)



Josting A et al, JCO 2010;28(34):5074-5080

Relapse After Auto-TX

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



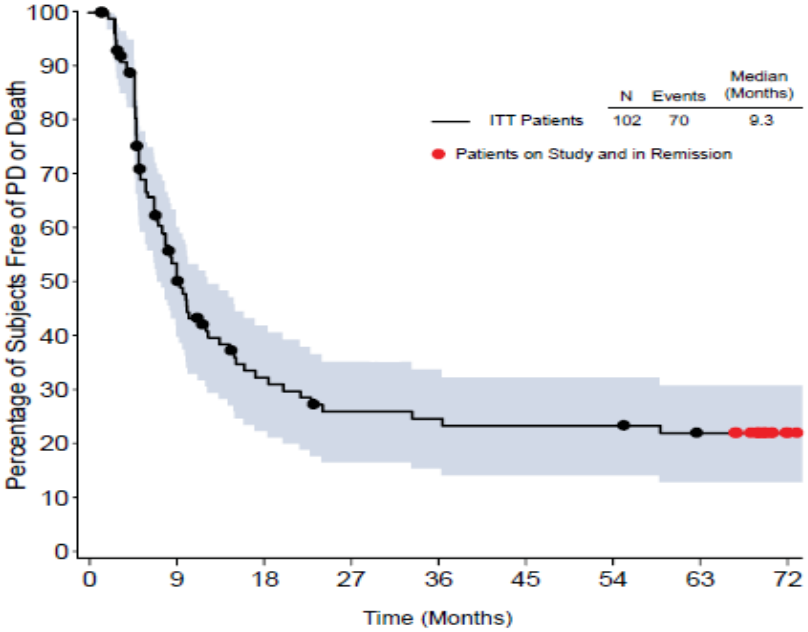
TTR	n	OS (y)
>12 m	172	4.6
6-12 m	165	2.4
4-6 m	204	1.5
0-3 m	215	0.7

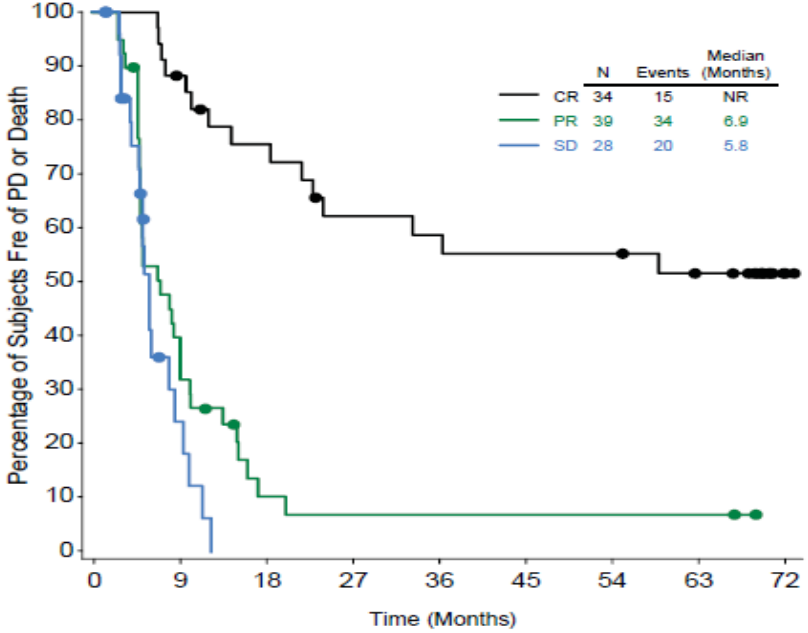
auto-TX, autologous stem cell transplant; OS, overall survival; TTR, time to relapse

Arai et al, Leuk & Lymphoma 2013:54:2531-33

Phase II Pivotal Study of BV

Progression-Free Survival



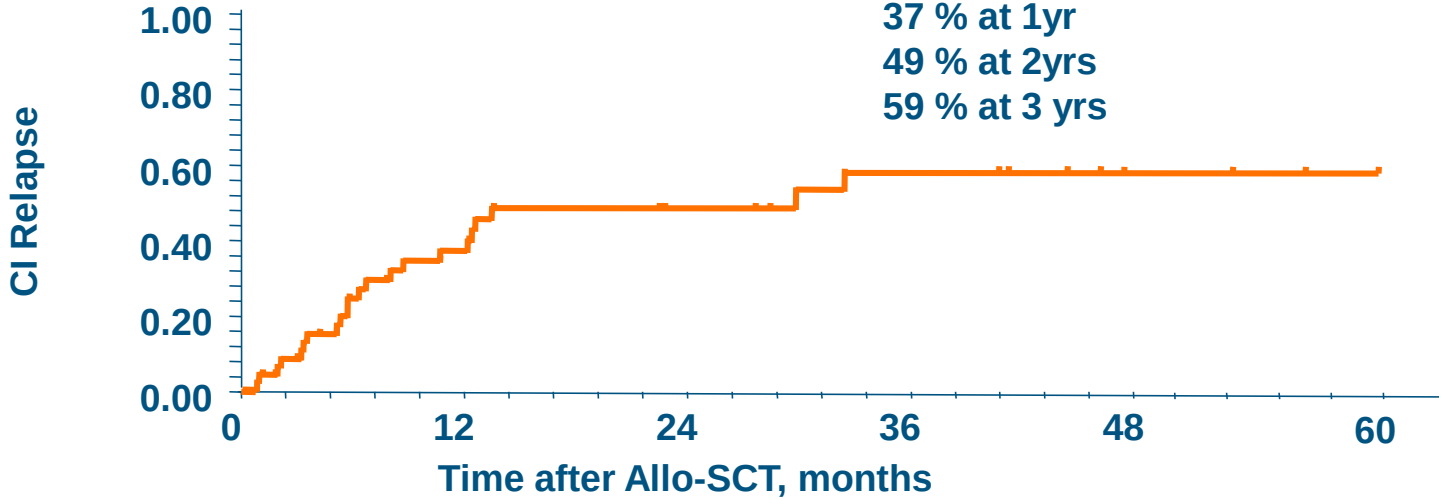


Chen, et al ASH 2015

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)

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

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

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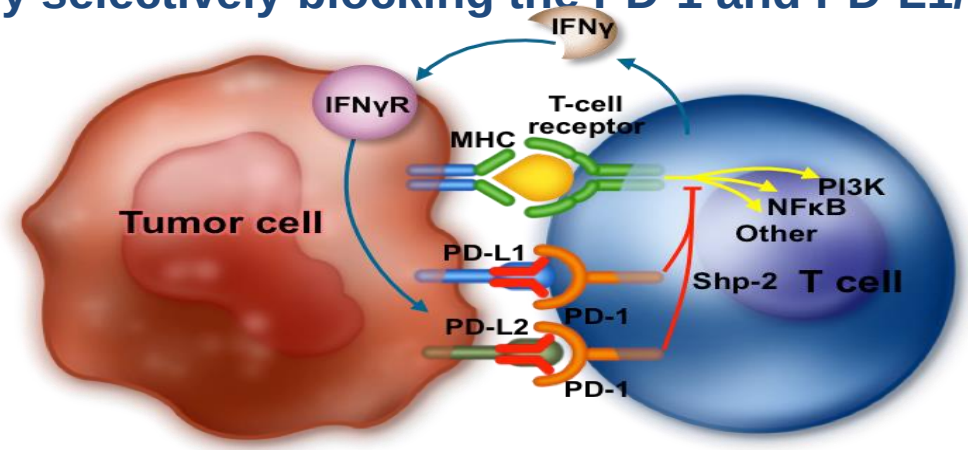
PD-1 Blockade

- 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.

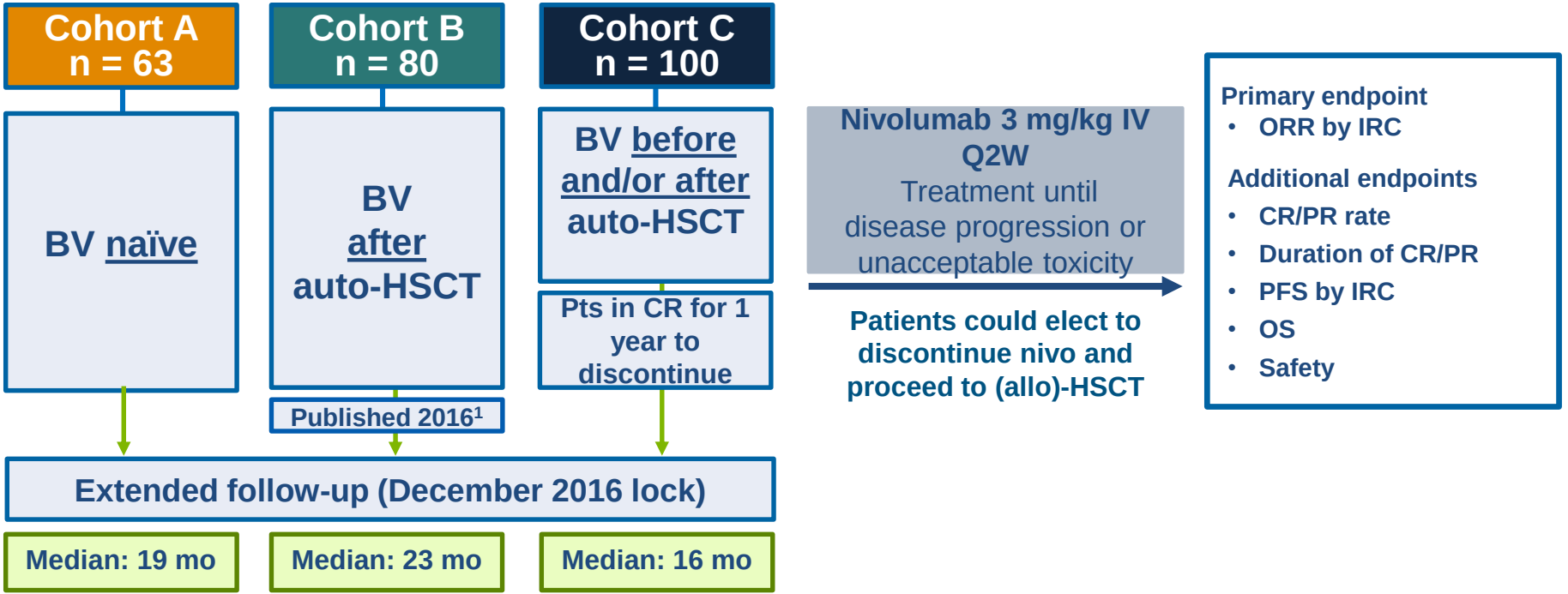


- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors

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

Phase 2 CheckMate 205

Study Design

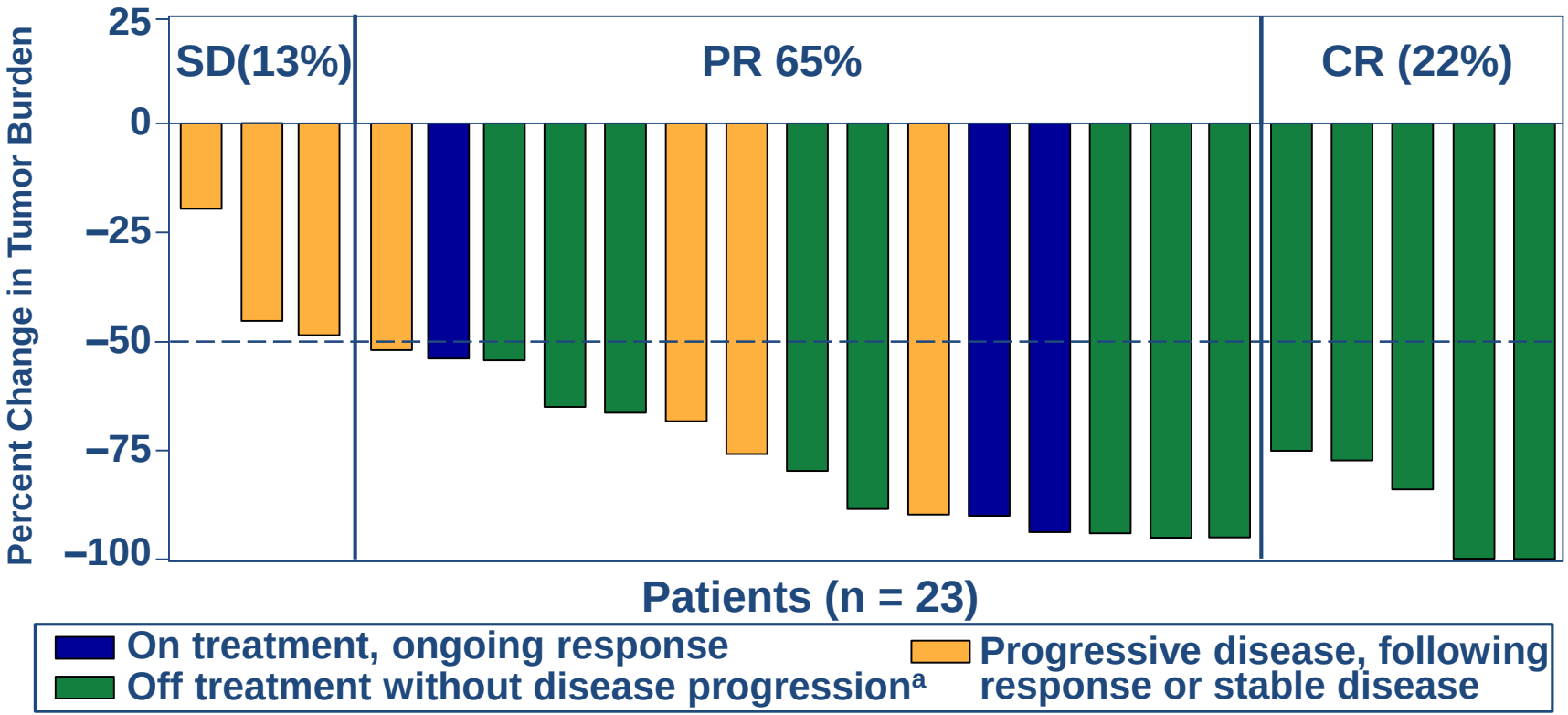


Relapsed/refractory cHL after auto-HSCT Nivolumab monotherapy

[1]Younes A et al, Lancet Oncol 2016

Nivolumab in r&r HL

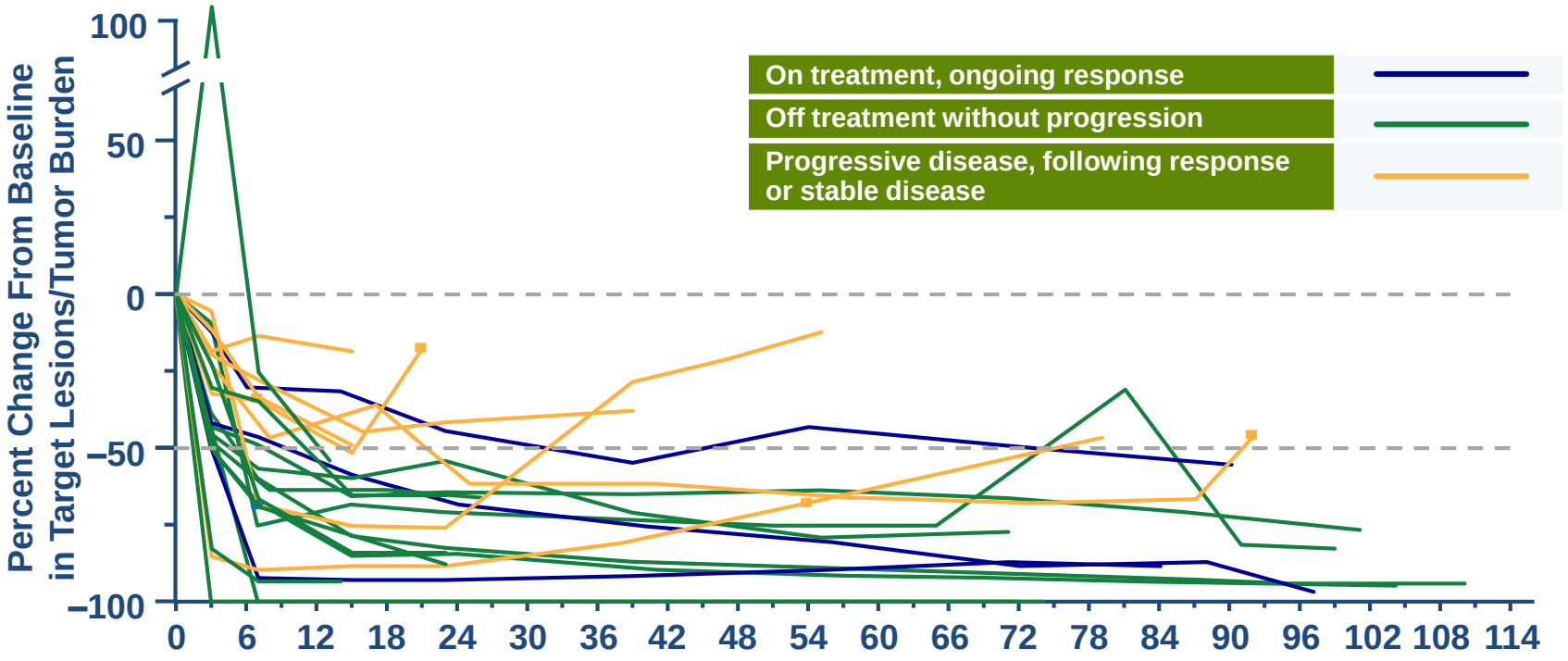
Best response



Ansell et al; ASH 2015

Nivolumab in r&r HL

Durability of response

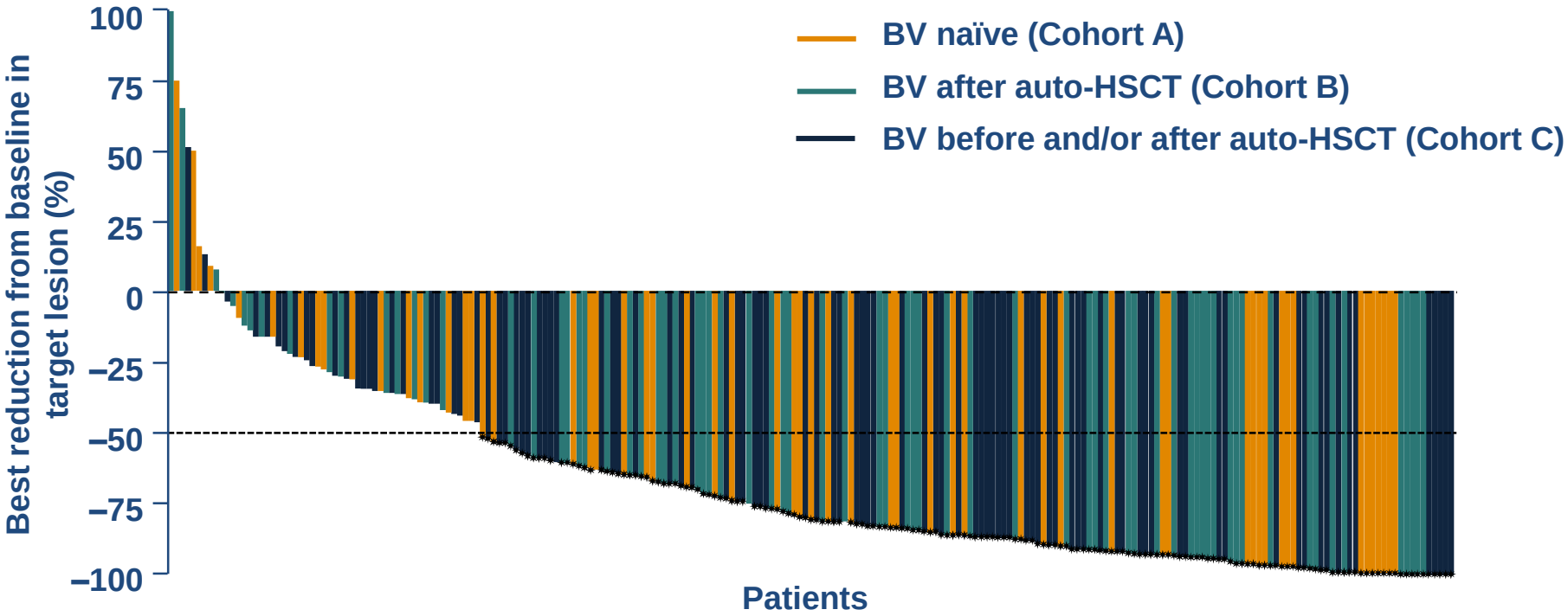


- First occurrence of new lesion

Ansell et al; ASH 2015

Phase 2 CheckMate 205

Change in Target Lesion per IRC



Asterisks (*) denote responders

Engert et al, EHA 2017

Phase 2 CheckMate 205

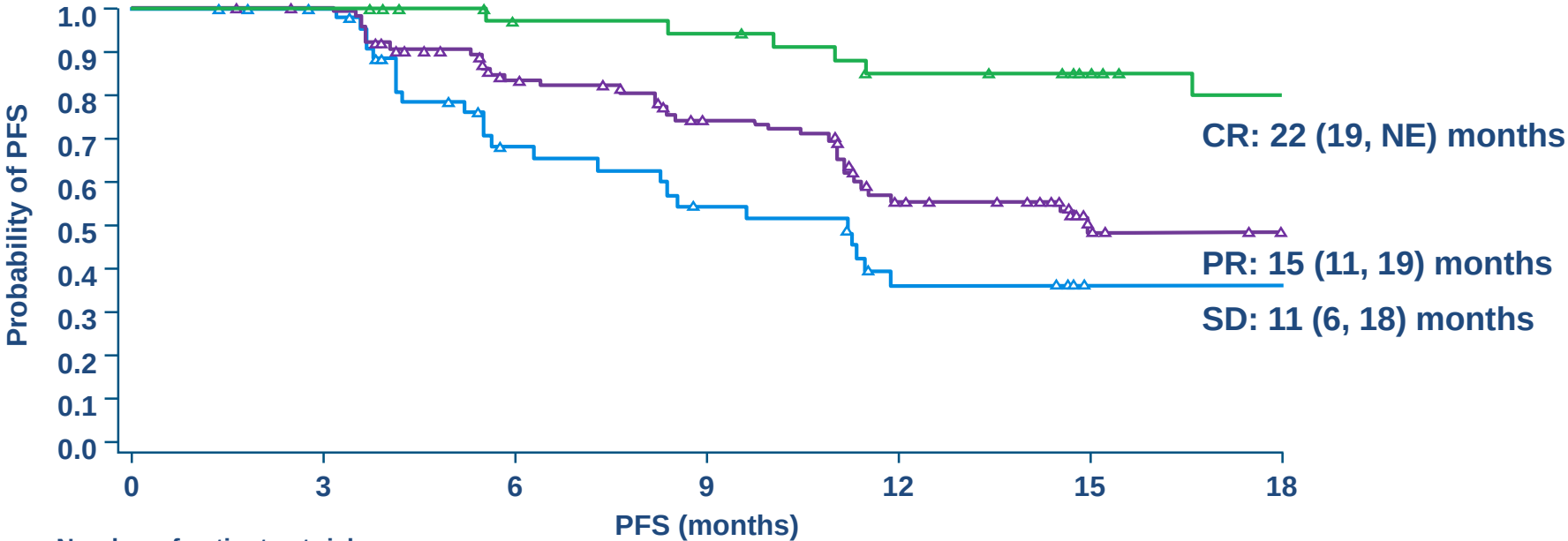
Safety Outcomes after Extended Follow-up

Patients with drug-related AEs (≥10%), serious AEs (≥1%), or AEs leading to discontinuation (≥1%)	Overall population n = 243	
Drug-related AEs, %	**Any grade**	**Grade 3–4**
Fatigue	23	1
Diarrhea	15	1
Infusion-related reaction	14	<1
Rash	12	1
Drug-related serious AEs, %		
Infusion-related reaction	2	<1
Pneumonitis	1	0
Drug-related AEs leading to discontinuation, %		
Pneumonitis	2	0
Autoimmune hepatitis	1	1

Engert et al, EHA 2017

Phase 2 CheckMate 205

PFS by Best Overall Response



Number of patients at risk

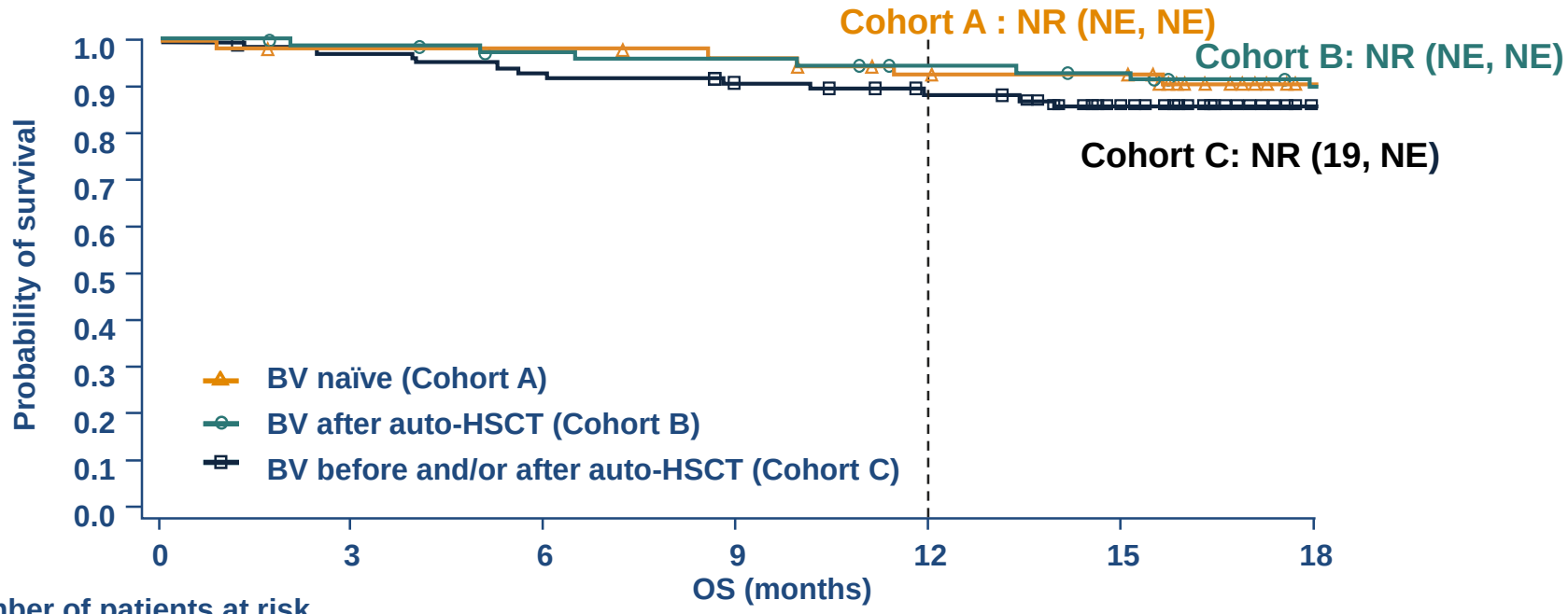
CR	40	40	33	32	27	20	16
PR	128	126	89	71	46	25	21
SD	47	44	25	19	11	8	8

Median (95% CI) PFS for overall patients (N = 243) was 15 (11, 19) months

Engert et al, EHA 2017

Phase 2 CheckMate 205

Overall Survival

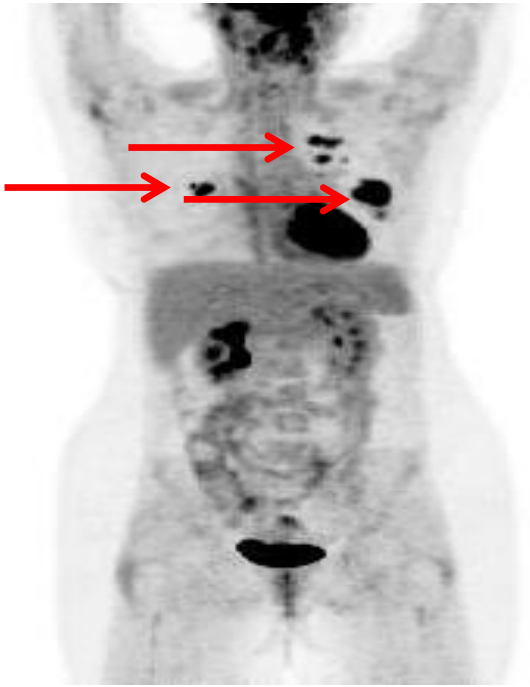


Number of patients at risk							
Cohort A	63	61	61	59	55	54	36
Cohort B	80	78	75	74	71	68	63
Cohort C	100	97	93	90	83	65	17

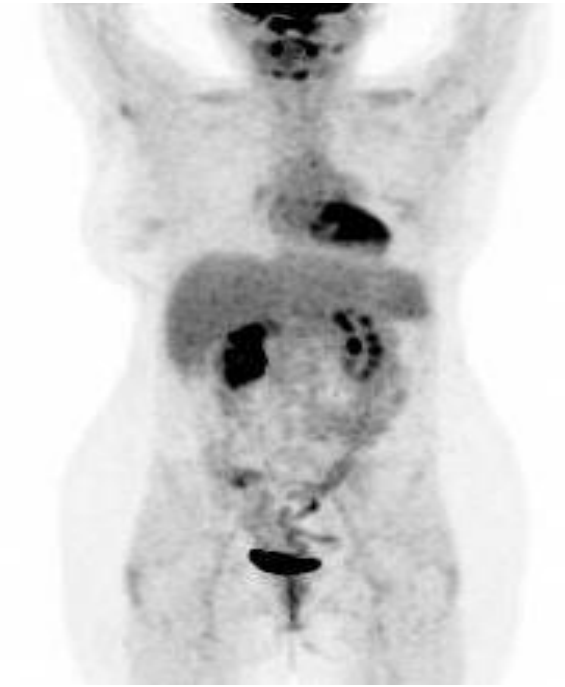
Engert et al, EHA 2017

Patient M.M.; 39 years

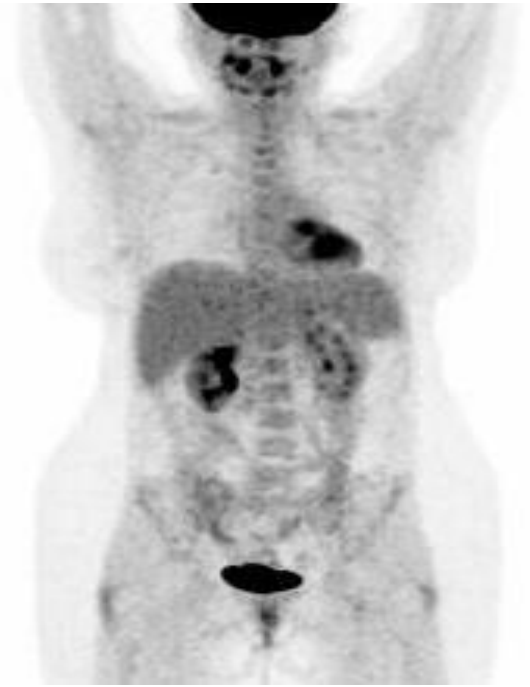
Diagnosed 2011 (5 prior therapies)



October 2014



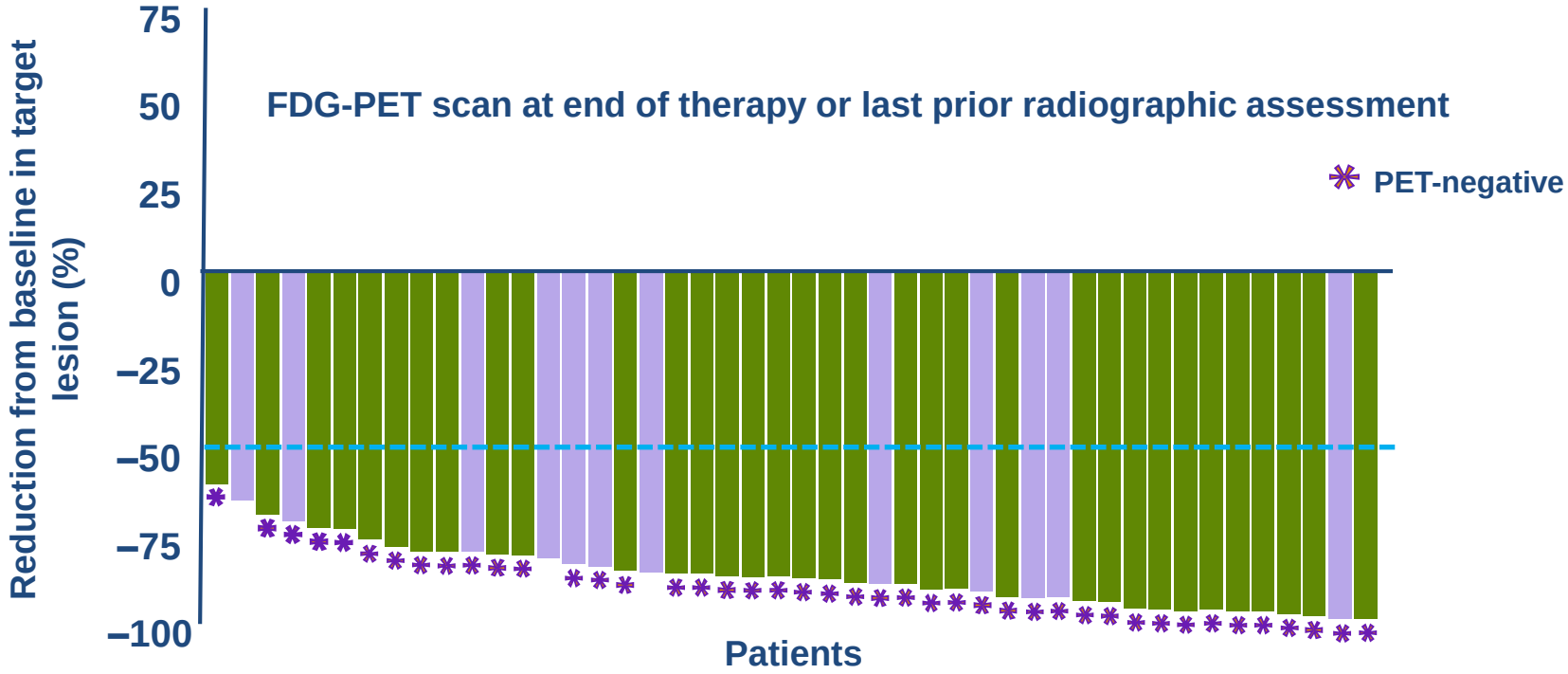
February 2015



May 2015

Nivo-AVD in advanced-stage cHL

End of Combotherapy

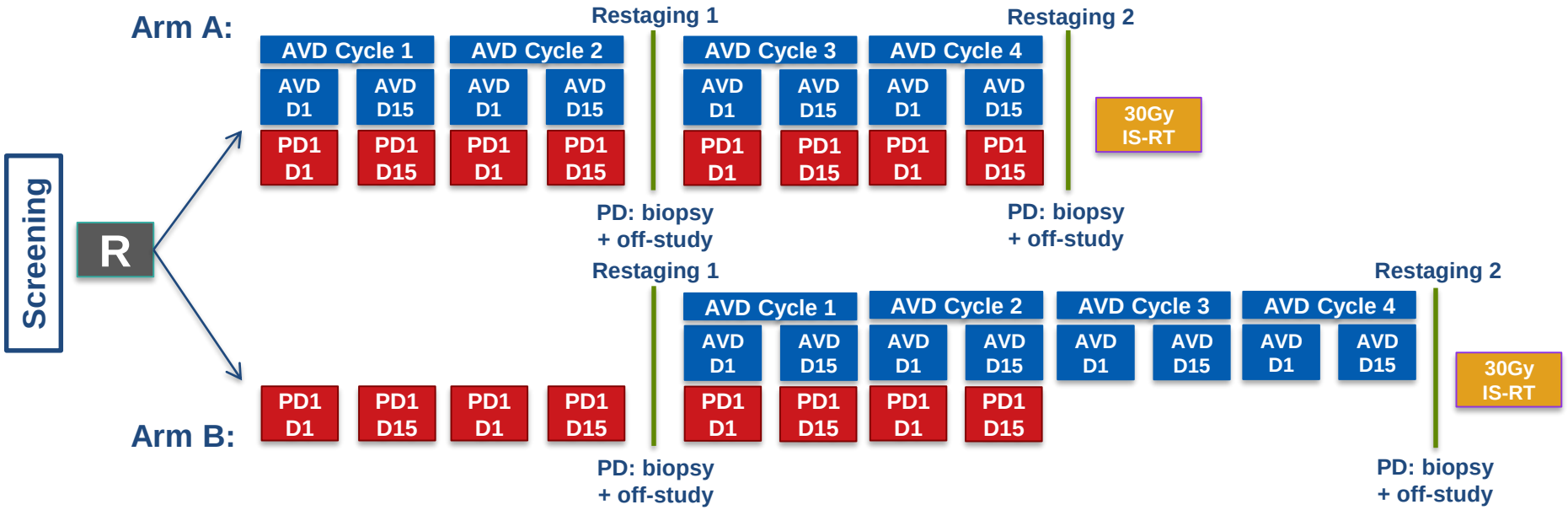


46/51 patients had available response data. Response assessed by IWG 2007 criteria

Ramchandren et al, ASH 2017

HD20 Pilot

Randomized trial in early unfavorable HL



AVD: Adriamycin, Vinblastin, Dacarbazine; PD1: anti-PD1-antibody

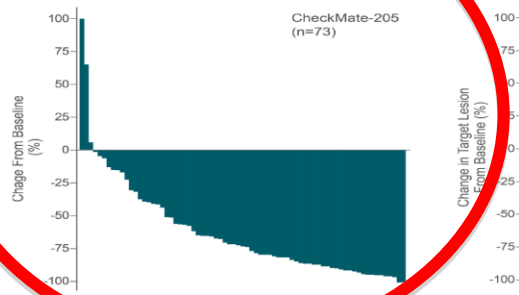
Immunomodifiers in Lymphoma
Selection

Antibody	Target	Company
Nivolumab	PD1	BMS
Pembrolizumab	PD1	MSD
REGN2810	PD1	Regeneron
Durvalumab	PD-L1	Celgene, AstraZeneca
Avelumab	PD-L1	Pfizer
Ipilimumab	CTLA-4	BMS

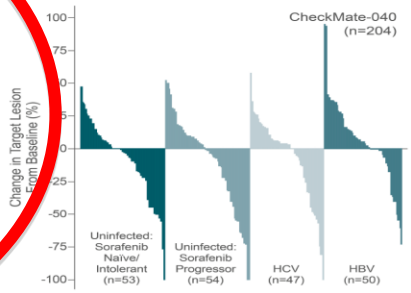
PD1 Inhibition in clinical trials

High efficacy particularely in Hodgkin Lymphoma

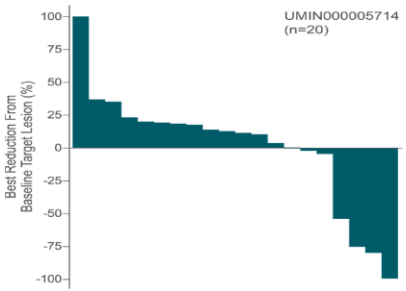
Hodgkin Lymphoma[1]



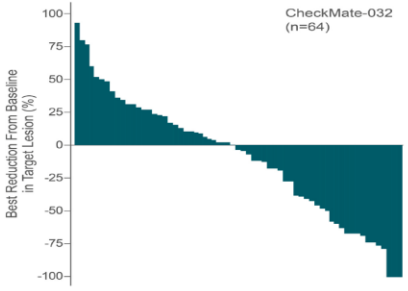
Hepatocellular Carcinoma[2]



Ovarian Cancer[3]

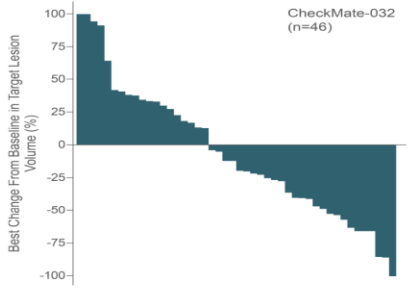


Urothelial Cancer[4]



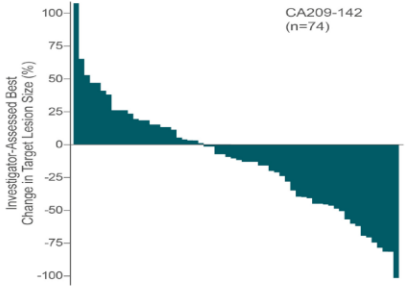
Small Cell Lung Cancer[5]

(Nivolumab 1 mg/kg BW + Ipilimumab 3 mg/kg BW)

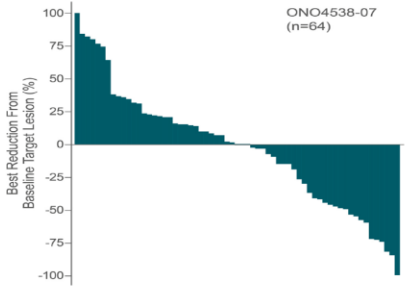


Colorectal Cancer – MSI-H[6]

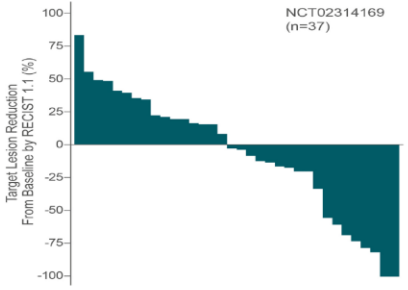
(Nivolumab 3 mg/kg BW)



Esophageal Cancer[7]



Anal Cancer[8]



1. Younes ASCO 2016, A7535. 2. Sangro ASCO 2016, A4078. 3. Hamanishi JCO 2015. 4.Sharma ASCO 2016, A4501. 5.Antonia ASCO 2016, A100. 6.Overman ASCO-GI 2017. 7. Ura et al. Poster presentation at ESMO 2015, A2301. 8. Van Morris ASCO 2016 A503

Advanced and relapsed Hodgkin lymphoma

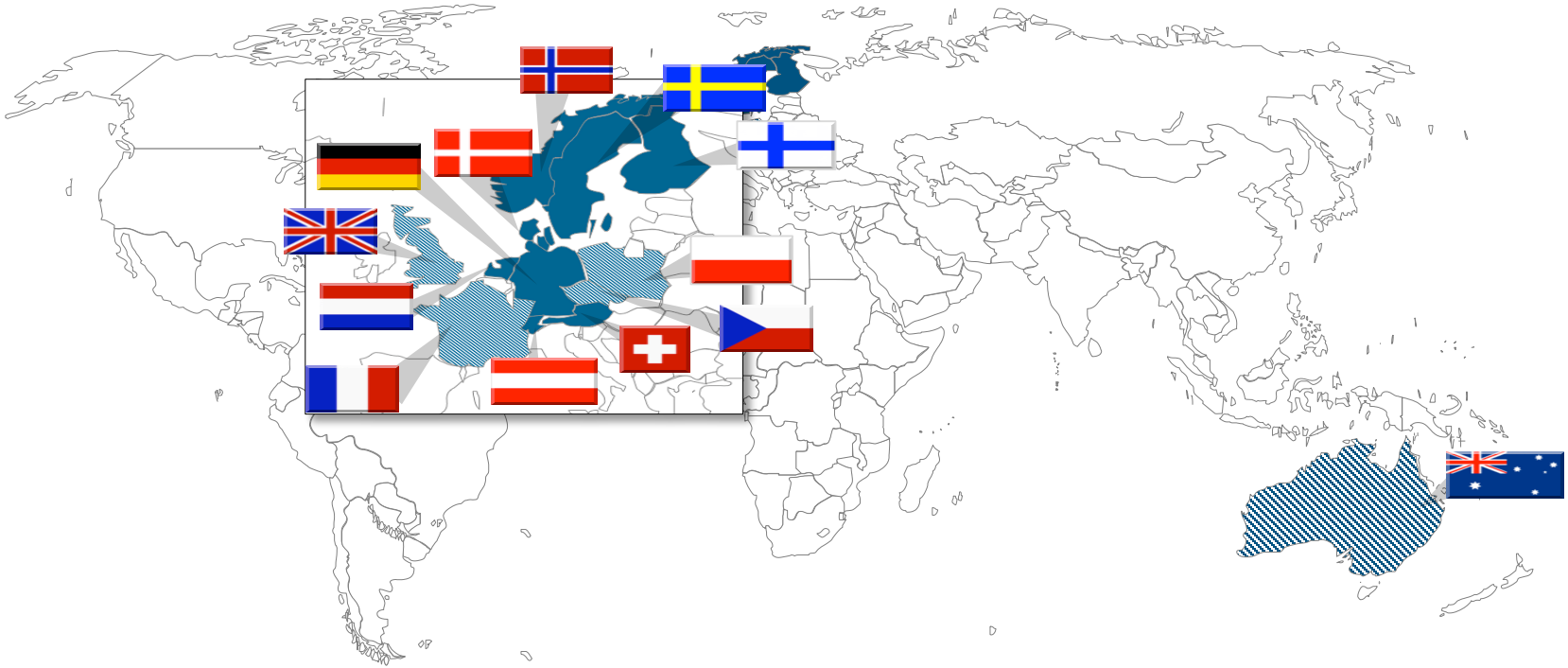
- Introduction
- Advanced stage Hodgkin lymphoma
- relapsed & refractory Hodgkin lymphoma
- Immunotherapy
- Summary

Advanced and relapsed Hodgkin Lymphoma 2018

- HL highly curable; long-term toxicity
- Early stages: 2-4xABVD+RT; „2+2“+RT PET driven
- Advanced stages: B.esc vs ABVD (15-20% better PFS and 10-15% OS vs more hematotox and infertility)
- Only 4xB.esc needed in PET- pts (3y FFTF 94.8%; OS 98.7%)
- ECHELON-1: BV-AVD vs ABVD; mPFS@2yrs 4.9%
- PD1 inhibition such as Nivo-AVD being evaluated in 1st line
- Future trials including anti-PD1 Moabs will increasingly replace chemo- and radiotherapy in HL

GHSG

Countries participating in current trials



Teilnahme an Studien der GHSG

Teilnahme, nicht aktuell/geplant

German Hodgkin Study Group
Coordination Center and Boards

Chairman:
A. Engert

Co-Chairman:
P. Borchmann

Honorary Chairman:
V. Diehl

Pathology:
M.L. Hansmann, P. Möller

Radiotherapy:
S. Marnitz-Schulze, H. Eich

Nuclear Medicine:
M. Dietlein, C. Kobe

Laboratory:
S. Borchmann

Physicians:
K. Behringer, B. Böll, P. Bröckelmann, C. Bürkle, D. Eichenauer, S. Kreissl, S. Sasse, B. v. Tresckow

Trial Coordination Center:

Head:
M. Fuchs

Trial physicians:
S. Gillesen

Data Management:
D. Armbrust, B. Koch, H. Ossadnik, B. van den Hoonaard

Project /Quality Management:
S. Kebekus, E. Louven, N. Poundeu-Tchouatieu, D. Redweik, D. Siury

Database / IT:
D. Böhmer, T. Schober, P. Zerhusen

Statistics:
H. Görgen, H. Müller, A. Plütschow

Assistant / Secretary:
K. Rust, M. Schumacher, K. Tittmann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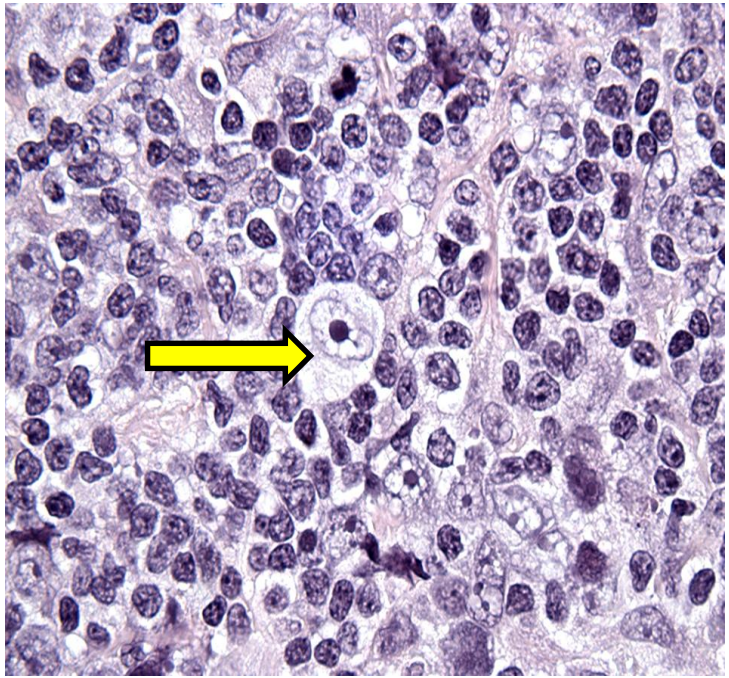
PD-1 Blockade in HL

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 genetically 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

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Role of radiation therapy in relapsed/refractory Hodgkin Lymphomas

George Mikhaeel

Professor of Radiation Oncology, Kings College London

Consultant Clinical Oncologist, Guy's & St Thomas' NHS Trust

London, UK

ILROG

INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Guy's Cancer

Size of the problem

- Primary refractory : ~10% of de novo cHL
- Relapse:
  - Limited stage: 5 – 15%
  - Advanced stage: 20 – 40%
- Salvage HD-CT + AutoSCT: 50% success

Rationale for RT for R/R cHL

- HL is one of the most radiosensitive human malignancies

- Local control after RT is high
- Large proportion of relapses (and by definition refractory disease) is in previous sites

- Most studies of combined treatment in lymphoma shows benefit for addition of RT (PFS - ?OS)
- Benefit / late effects balance is different in ref/rel situations

Complexity of Salvage Treatment: Factors to consider

- Clinical scenario:
  - Disease status & salvage Response: Primary refractory, relapse, salvage refractory
  - Site and extent of disease: Localised disease, predominant site, initial v new site
  - Salvage options: AutoSCT, BV, anti-PD1, new drugs
  - Previous treatment & RT
- Patient: age, sex, performance status, comorbidities, wishes

Role of RT in R/R cHL

When we may use RT:

1. Add to the salvage treatment if *not used* before

2. Use to help chemo if *suboptimal* response or *consolidate* its effect

3. Use if *NO* chemo/high dose options

Patient groups

- Primary refractory:
  - Failure to achieve remission with primary Rx
    - Clear Response but incomplete
    - No response / progression
  - *(Very early failure after Rx)*
- Relapse:
  - Recurrence of disease after a period of remission
- Salvage-refractory:
  - Failure to achieve remission with salvage Rx
    - Clear Response but incomplete
    - No response / progression
  - Salvage:
    - For relapsed disease
    - For primary refractory → Never entered remission

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Critical Review

The Role of Radiation Therapy in Patients With Relapsed or Refractory Hodgkin Lymphoma: Guidelines From the International Lymphoma Radiation Oncology Group

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Andrea K. Ng, MD, MPH,§ David C. Hodgson, MD, MPH, FRCPC,‖
Andrew Wirth, MD,¶ Sarah A. Milgrom, MD,#
N. George Mikhaeel, MD,** Hans Theodor Eich, MD, PhD,††
Tim Illidge, MD, PhD,‡‡ Umberto Ricardi, MD,§§ Karin Dieckmann, MD,‖‖
Craig H. Moskowitz, MD,¶¶ Ranjana Advani, MD,##
Peter M. Mauch, MD,§,‡‡‡ Lena Specht, MD, PhD,***
and Richard T. Hoppe, MD†††

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0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2018.01.011

Table 3 Treatment summaries

	Treatment summary
Refractory HL: salvage RT if CR after salvage chemotherapy (Deauville score of 1-3)	
Timing	Immediately prior to SCT
	4-12 wk following ASCT, pending hematologic recovery and resolution of acute side effects
Dose	CR (anatomic and DS 1-2) after salvage chemotherapy: 30 Gy
	CMR but residual disease >2.5 cm: can escalate dose to 36 Gy if safe
	If site has a Deauville score of 3 or is in a critical location: can escalate dose to 36 Gy if safe
	If previously irradiated, typical dose constraints should be considered, that is, bilateral lungs' V20 to <30% and V5 to <55%, mean lung dose to <13.5 Gy, and cumulative mean heart dose to <20 Gy; if a meaningful dose (≥18 Gy) cannot be administered that meets these dose constraints, then RT should be avoided
	If disseminated nodal disease treated with extended-field RT: 30-36 Gy to involved sites if toxicity profile is acceptable
Volume	All initial sites of disease are irradiated if safely able to be encompassed
	If toxicity concerns exist, then only refractory sites are irradiated unless the remaining but responsive initial disease sites are close to the refractory site or sites and their inclusion does not exacerbate toxicity
	Can consider RT to extranodal sites if RT exposure is considered safe
Refractory HL: salvage RT if PR after salvage chemotherapy (Deauville score of 4)	
Timing	For patients with metabolic or anatomic PR, RT before SCT to achieve minimal residual disease
Dose	Irradiate CR adjacent sites to 30-36 Gy and boost PR sites to 36-40 Gy
	For treatment before SCT, accelerated ISRT (18-20 Gy over period of 5 d with twice/day fractionation) followed by TLI (15-18 Gy over period of 5 d with twice/day fractionation) has proven efficacy; alternatively, once-daily fractions of 1.5-1.8 Gy can be used
Volume	Similar to patients who have CR to salvage chemotherapy
	PR site alone can be treated or also including adjacent CR sites using differential dosing (simultaneous integrated boost and so on) if the toxicity profile is acceptable
	ISRT to post-chemotherapy salvage residual sites immediately followed by TLI prior to SCT is of proven effectiveness for some patients who have disseminated nodal disease
Refractory HL: salvage RT for persistent refractory (or progressive) HL (Deauville score of 5)	
Dose	For patients with persistent refractory (or progressive) HL, alternative salvage chemotherapy and biologics including brentuximab vedotin and anti-PD1 checkpoint inhibitors may be administered
	RT is inadvisable for patients with disseminated refractory sites, because of the toxicity profile, unless extended-field pre-SCT RT is determined to be the most likely approach to engender a CMR; otherwise, RT is similar to the aforementioned CR and PR scenarios except in the following situations: 1. Considerations for pre-SCT RT are even more powerful 2. The RT dose can be escalated to 40-45 Gy to areas of refractory disease 3. An integrated (simultaneous)–boost approach is more likely to be considered in which the sites of responding disease receive a lower dose than the sites of refractory disease
Relapsed HL: salvage RT if initial stage IA-IIA HL treated without RT	
Timing	Similar to the refractory setting in which the arguments for pre-SCT vs post-SCT RT apply; patients treated with conventional chemotherapy followed by ISRT (and no SCT) should receive RT 2-4 wk after chemotherapy
Dose	CR to salvage chemotherapy: 30-36 Gy
	PR to salvage chemotherapy: 36-40 Gy
	An integrated (simultaneous) boost can be considered in which all initial sites are irradiated to 30 Gy and the resistant sites are irradiated to 36-40 Gy
Volume	Includes all sites of initial disease if considered tolerable and patient has undergone relapse within 6-12 mo using ISRT principles
	Also includes all sites of initial disease if the relapse is delayed and RT toxicities are acceptable
	Alternatively, if a delayed relapse occurs, just the relapsed sites can be irradiated if the risks of a more comprehensive volume are considered to have an adverse toxicity profile
RT only	Should only be considered in patients who are not candidates for combined-modality therapy
	Doses ranging from 30-40 Gy for patients in whom chemotherapy was minimal (eg, 3-4 cycles of ABVD); the relapse was delayed; and the disease volume was localized (eg, ≤3 contiguous sites), nonbulky, nodal, and without B symptoms
	The minimal treatment volume is ISRT, but extended fields such as the mantle, the spleen and/or para-aortics with or without the pelvis, or combinations may be considered since RT is being used as the primary and sole treatment modality

(*continued on next page*)

Table 3 (*continued*)

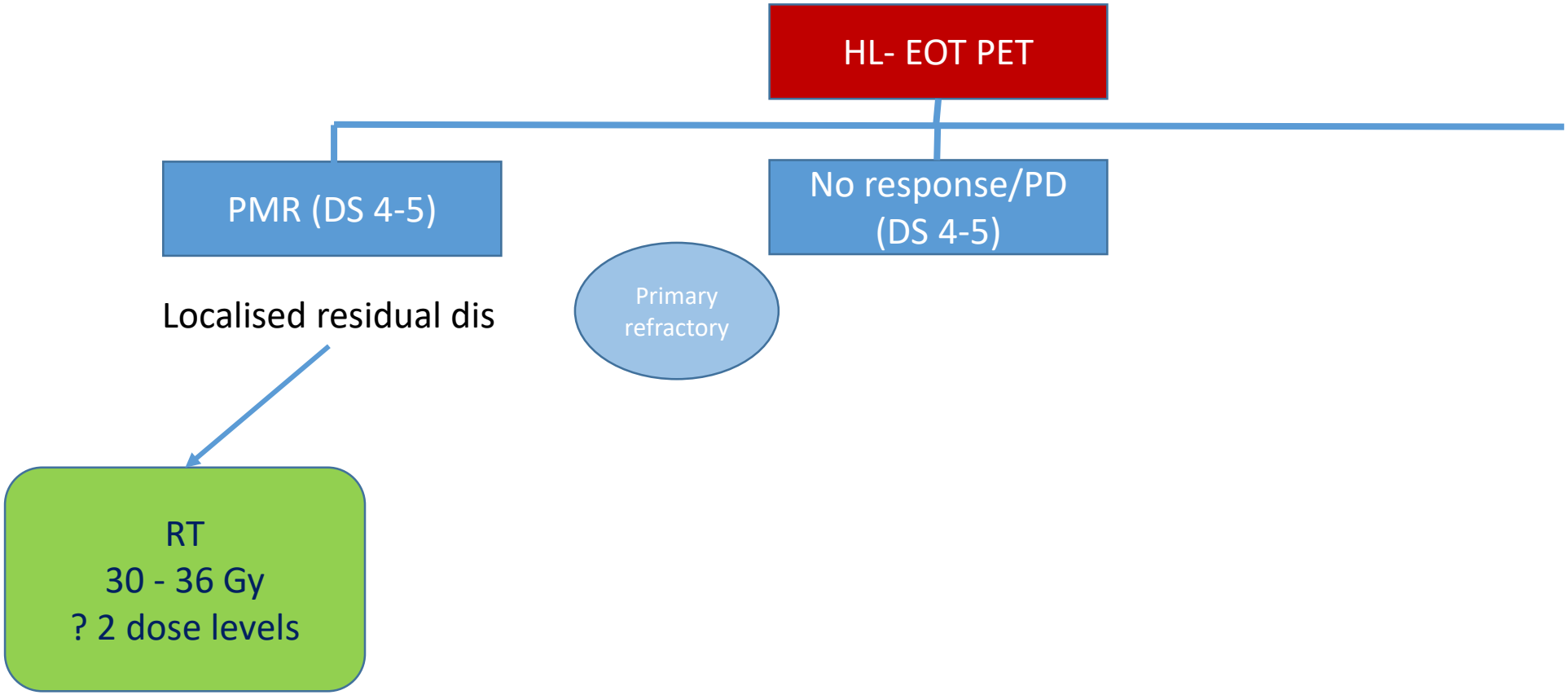
	Treatment summary
Relapsed HL: all other situations	
Timing	If administered after SCT, then RT is initiated when acute SCT morbidities and hematologic parameters have recovered, usually within 4-12 wk
	For patients who remain PET avid despite salvage chemotherapy and biologics but who are still planning to undergo SCT, pre-SCT RT is considered (either ISRT or rarely ISRT plus TLI)
Dose	CR to salvage chemotherapy: 30-36 Gy
	PR to salvage chemotherapy: 36-40 Gy
	Treat adjacent but responsive disease sites to 30 Gy and boost partially responding sites to 36-40 Gy
	For patients who have previously been irradiated, the dose constraints to the critical tissues (ie, lungs, heart, and kidneys) must be acceptable
Volume	Sites of relapsed disease and inclusion of contiguous previously involved sites particularly if the relapse is rapid (<6-12 mo)
RT only	For patients who have relapse with local and limited volume and are not candidates for systemic therapy, RT alone (36-40 Gy) is considered; the radiation doses can be limited to 30 Gy if there are concerns about toxicity
Transplant ineligible or relapse after SCT	
CR to salvage therapy	All initial sites of disease can be targeted if the toxicity profile is acceptable Otherwise, just sites of relapsed HL are irradiated, particularly if the relapse is delayed
	Treat ISRT volumes to doses of 30-36 Gy that might include integrated or sequential boosts (eg, lower doses to adjacent but nonrelapsed sites and higher doses to relapsed or bulky sites)
PR to salvage therapy	Greater attempt to treat all initially involved sites but increased dose to partially responding sites; peak doses might rarely exceed 40 Gy if relapsed bulky disease only partially responds to salvage therapy
No salvage therapy	RT volume and dose are tailored to the particular patient's tolerance with the goal of treating at-risk sites to progressively higher RT doses depending on the distribution of disease sites, normal tissue toxicity constraints based on previous exposures, and goals of therapy (ie, curative or palliative)
Refractory or relapsed nLPHL	
Timing	For patients with limited-stage relapse, particularly at delayed intervals, and then limited systemic therapy, salvage chemotherapy combined with adjuvant RT, RT alone, and observation are all considerations
Dose	30-40 Gy depending on previous chemotherapy and RT exposures, as well as normal tissue constraints
Volume	Biopsy-proven relapsed HL or all initial sites of disease depending on toxicity profile and influenced by the rapidity of the relapse
TBI	
Indication	Rarely appropriate; exceptions can include patients only partially responsive to all systemic salvage approaches and with extranodal or bone marrow disease
Dose	RT to sites of refractory or relapsed disease (fractionated doses of 18-24 Gy and rarely even higher) immediately prior to TBI (usually 12 Gy in 1.5-Gy fractions) can be considered
Volume	Whole body; patients must be counseled on treatment-associated risks
Palliative RT: when patients have relapsed HL and without systemic options	
Timing	When symptomatic or if patients will receive additional systemic therapies but need extra recovery time from previous treatment
Volume	Symptomatic sites or those that threaten to compromise organ function
Dose	Variable total doses and fractionation schedules are acceptable depending on goals and concerns about normal tissue toxicities

Abbreviations: ASCT = autologous stem cell transplantation; CMR = complete metabolic response; CR = complete response; HL = Hodgkin lymphoma; nLPHL = nodular lymphocyte predominant Hodgkin lymphoma; PET = positron emission tomography; PR = partial response; RT = radiation therapy; SCT = stem cell transplantation; TBI = total body irradiation.

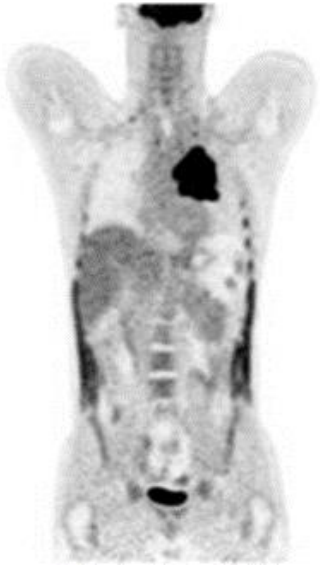
Refractory HL

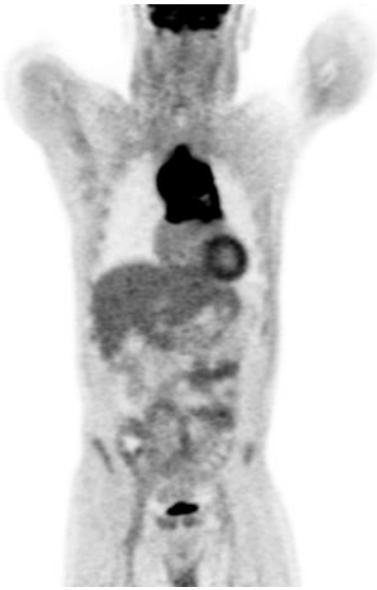
Salvage RT in setting of primary refractory HL if CR occurs after salvage chemotherapy (Deauville score of 1-3)

In patients whose disease is refractory to primary chemotherapy but who are complete responders to salvage chemotherapy, available evidence supports proceeding with ASCT (Fig. 3). In this situation, RT is an appropriate adjuvant for patients with a limited number of refractory disease sites (where all of the relapsed disease sites can be irradiated) or with a site adjacent to a critical structure (Table 2) where a local relapse could have devastating consequences. Bulky disease at relapse may also be an indication for RT (44) and can be targeted even when all sites of relapse cannot be safely irradiated. RT would not be recommended for most patients whose disease is refractory in multiple nonbulky or extranodal (extensive bony, hepatic, or pulmonary) disease sites

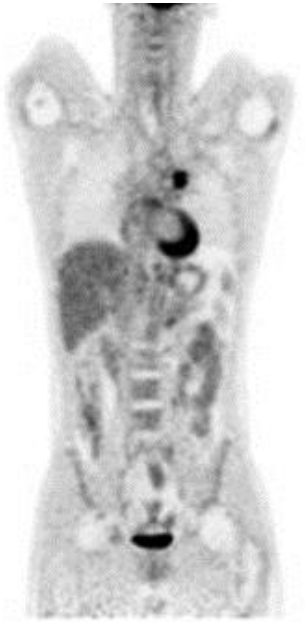

HL- EOT PET
PMR (DS 4-5)
No response/PD
(DS 4-5)
Primary
refractory
Localised residual dis
RT
30 - 36 Gy
? 2 dose levels

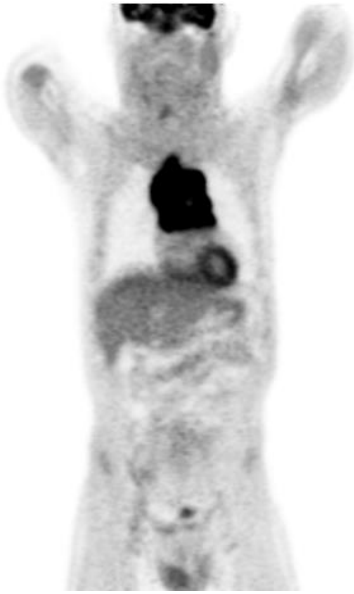
Baseline





Post chemo





DS 5
Partial Metabolic Response

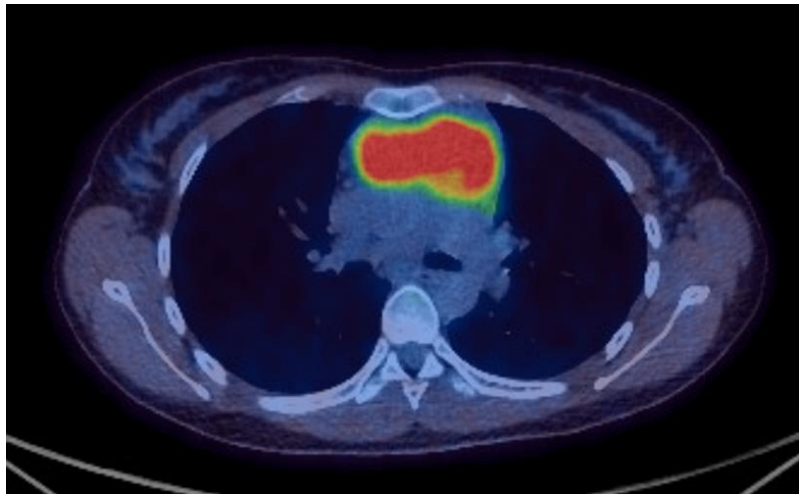
Patient 1

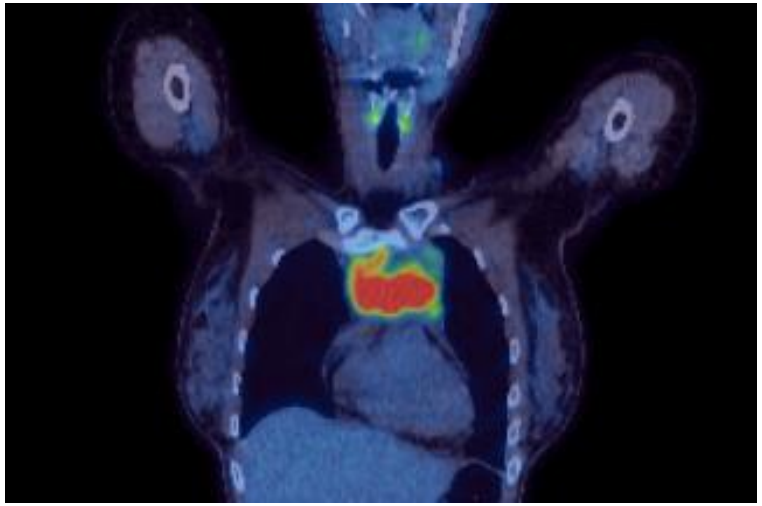
Patient 2

DS 5
No Metabolic Response

PMR after chemo – residual mass + a focus of residual activity

Pre





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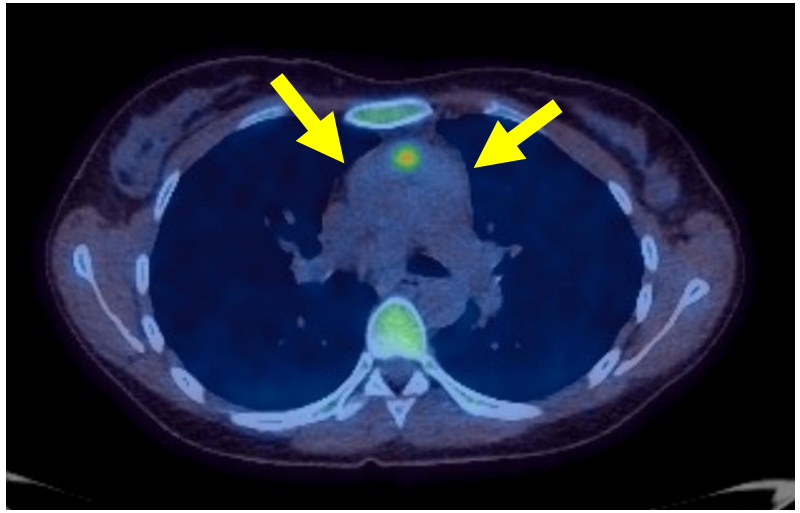
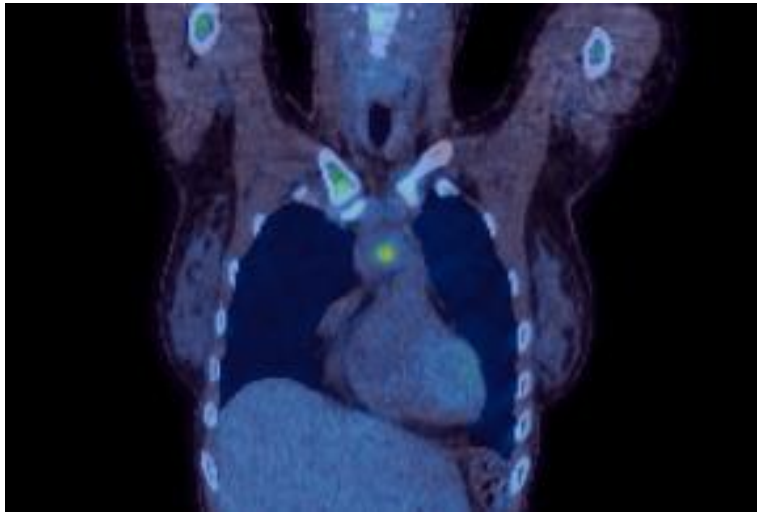
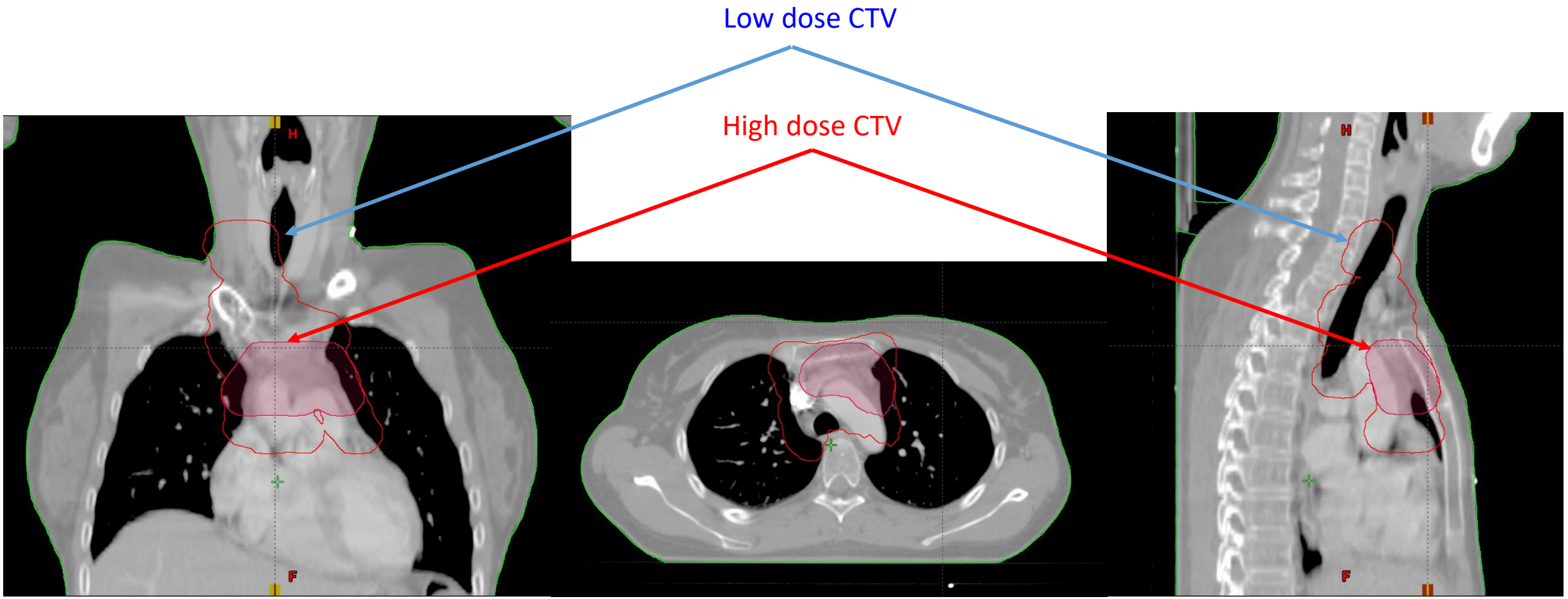


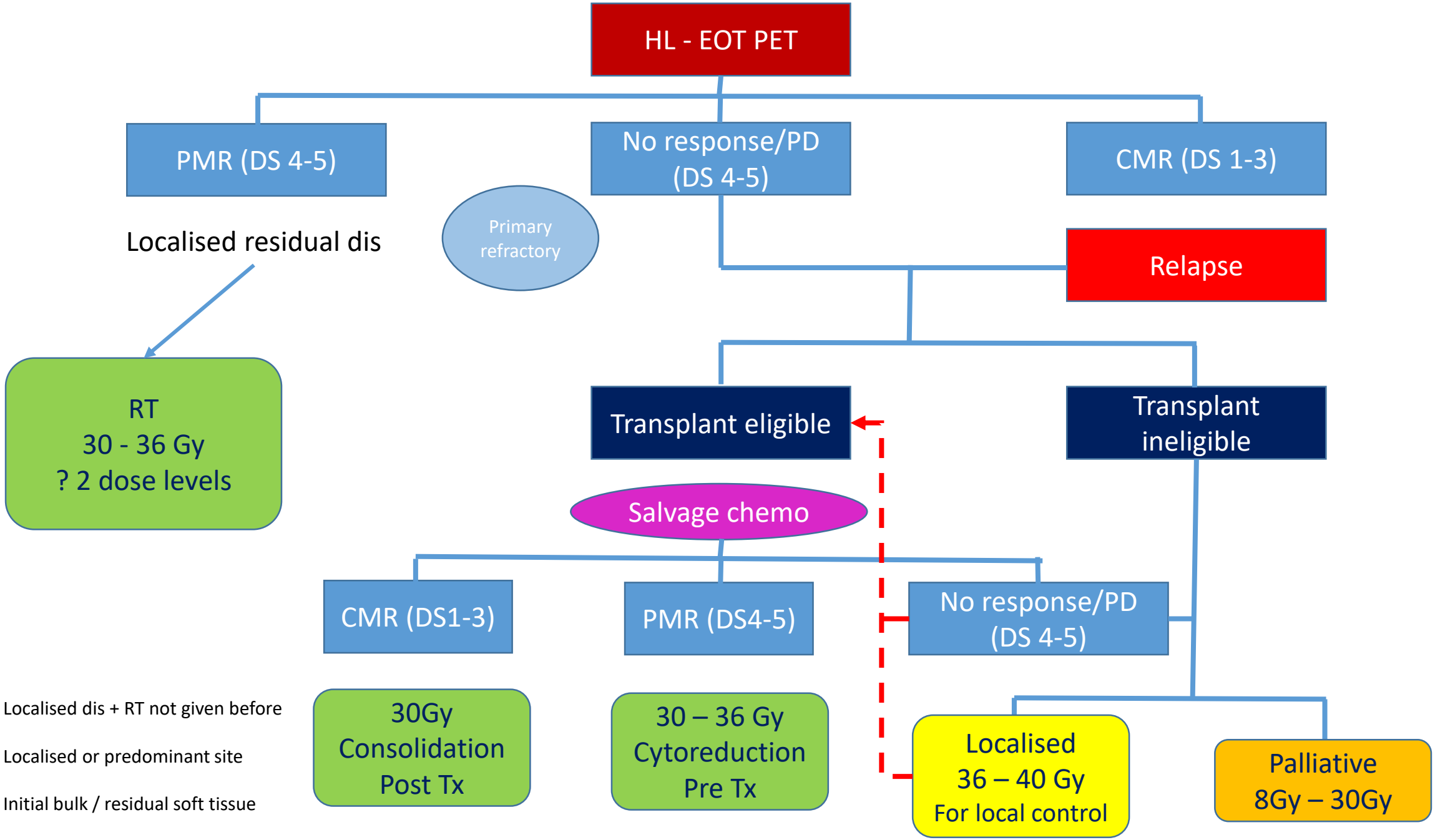


PMR after chemo – 2 dose levels:

Low dose CTV = Original disease extent

High dose CTV = Whole residual mass is included (Not PET+ focus)





- Localised dis + RT not given before
- Localised or predominant site
- Initial bulk / residual soft tissue

Indications for RT in salvage

1. Limited disease - RT not given before: *give RT regardless of Salvage response*
2. Advanced disease:
   - CMR to salvage: RT if
     - bulk
     - local control is important: Risk of Sp C Comp, SVCO, airway obst or hydronephrosis
   - Partial or Poor Response to salvage
3. Relapse after Transplant or Transplant ineligible
4. Palliation

RT alone or CMT alone salvage

- RT alone: Limited disease +
  - limited chemo + PET-ve and no RT + early relapse in original sites (RAPID study approach)
  - Relapse post transplant (RT not given before)
  - Unfit for further chemo

- CMT alone (no transplant): Limited disease +
  - Late relapse (e.g. 5ys) + CMR to salvage chemo

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
- Timing of harvest

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

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

Disease control

Pneumonitis

Volumes & Doses

- Volumes:
  - limited stage disease (initially + relapse): cover all sites of disease
  - Advanced stage disease initially + limited relapse: sites of relapse only
  - Advanced stage disease initially + on relapse: bulk or residual or slow response

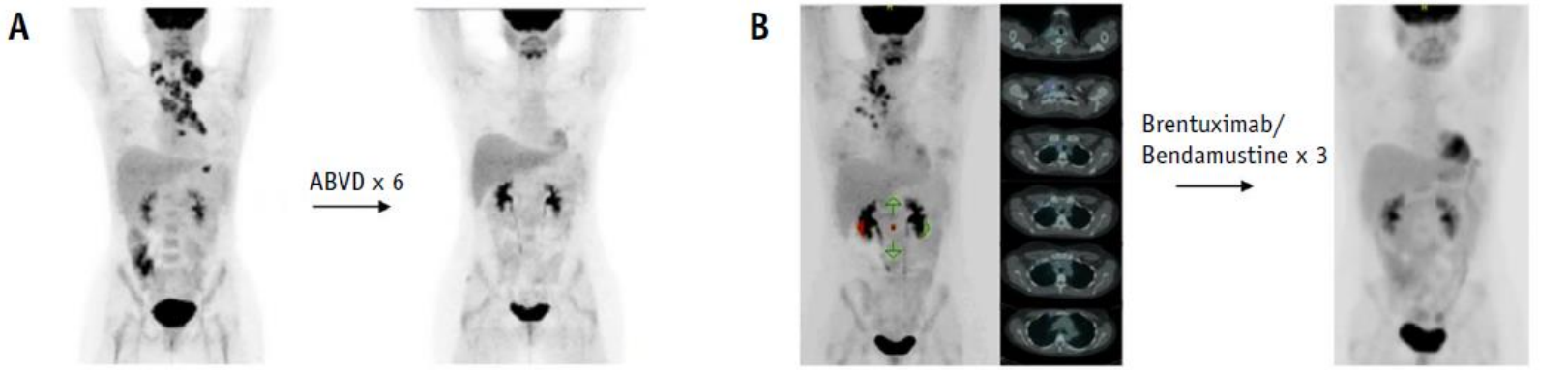
- Doses:
  - Good response to salvage: 30 – 36 Gy
  - Suboptimal response: 36 – 40 Gy (??44Gy for very refractory dis)
  - Use 2 dose levels (integrated boost)

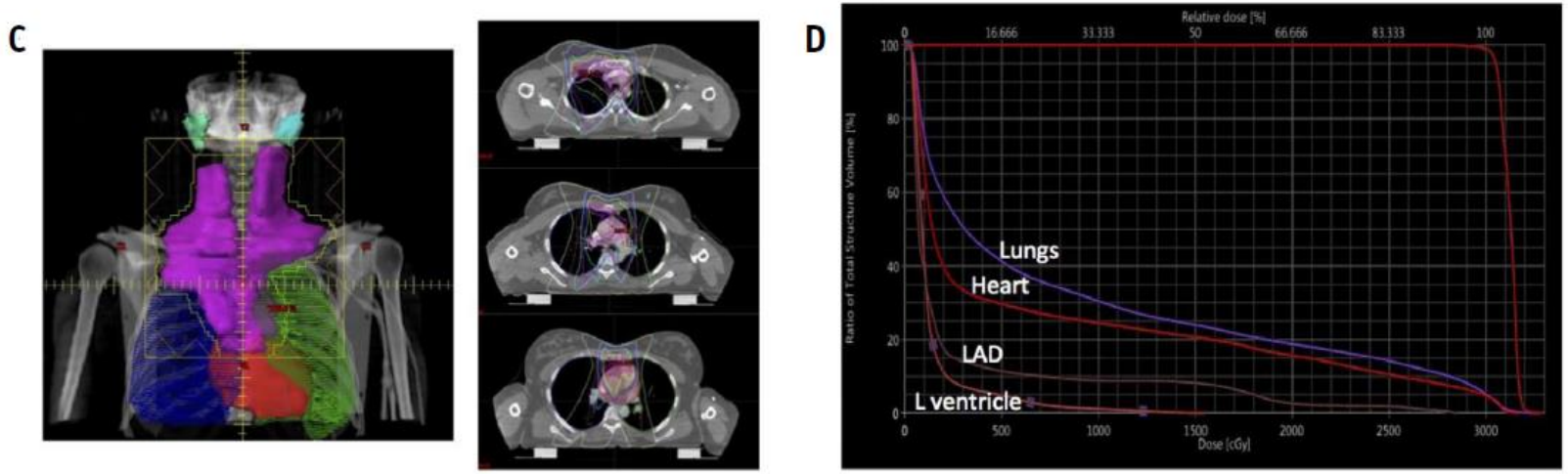
Dose Constraints

Organ	Constraint	Primary Rx	Salvage responsive	Salvage refractory
Lung	Dmean	10-12Gy	13.5	13.5
	V20	25%	30%	35%
	V5	45%	55%	60%
Heart	Dmean	5-10Gy	15Gy	20Gy

Limited disease (initially + relapse) – CMR to salvage

30 Gy IMRT



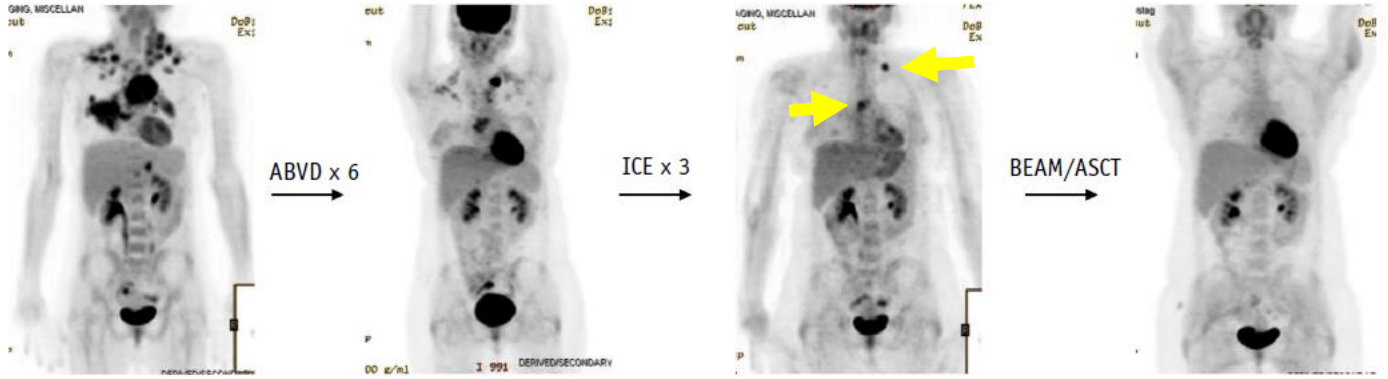


	Lungs	Heart	Left Ventricle
Mean dose	8.5 Gy	6.8 Gy	1.3 Gy
V20	18.7%	15.6%	
V15	23.9%	20.5%	
V5	41.3%	29.6%	

Advanced stage disease – Primary refractory - PMR to salvage

30.6 Gy and 37.4Gy IMRT

A



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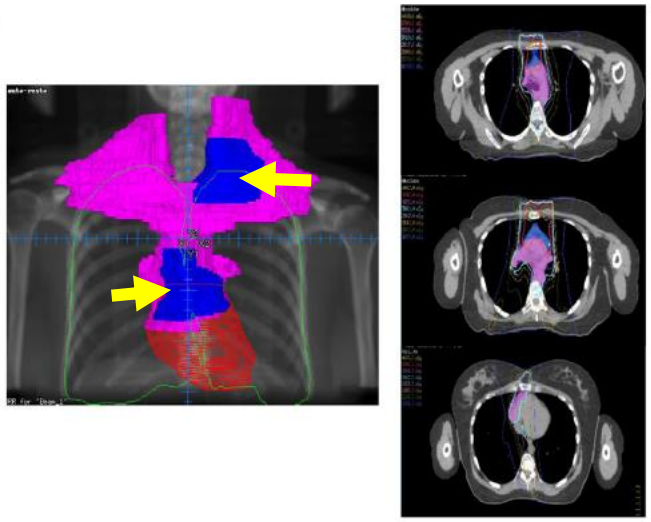

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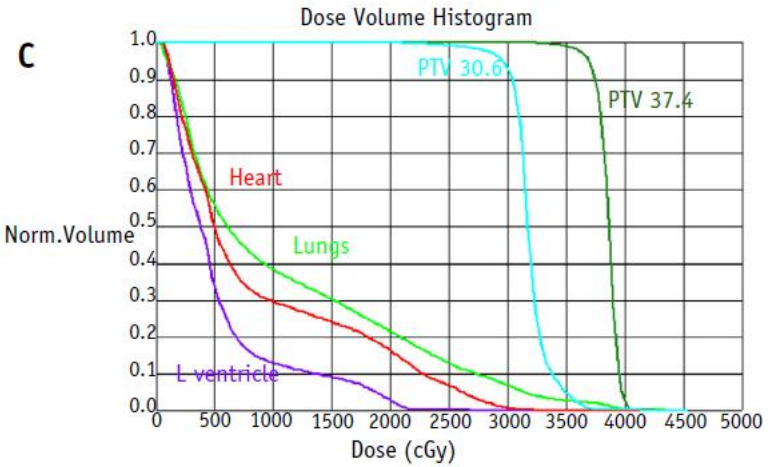
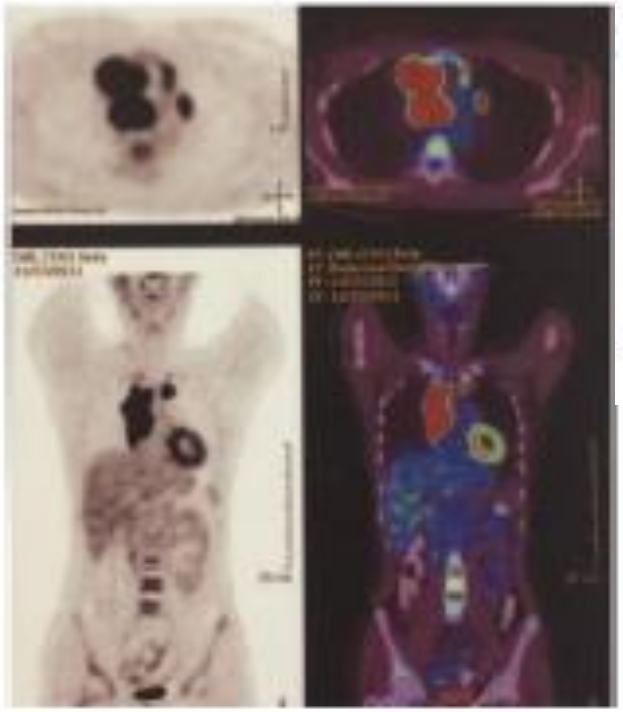
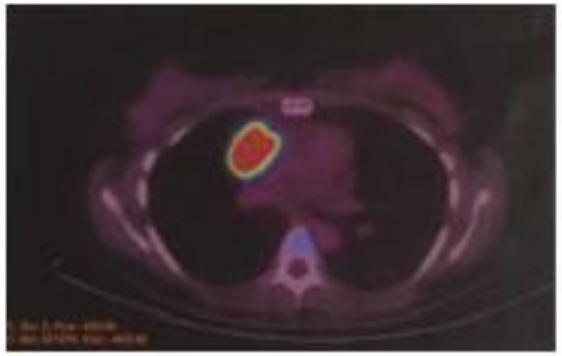


	Lungs	Heart	Left Ventricle
Mean dose	10.8 Gy	8.7 Gy	5.0 Gy
V20	22%	16%	
V15	30%	25%	
V5	55%	50%	

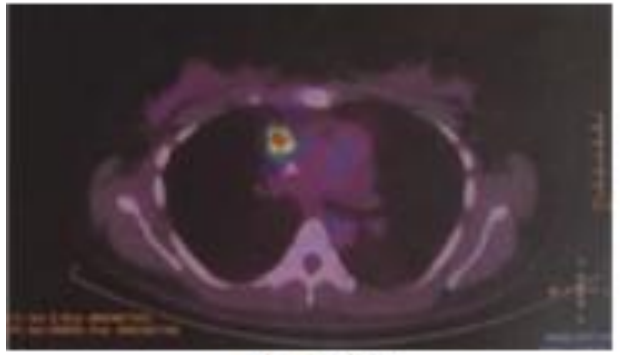
Limited disease – Refractory to salvage

30 Gy / 40 Gy IMRT

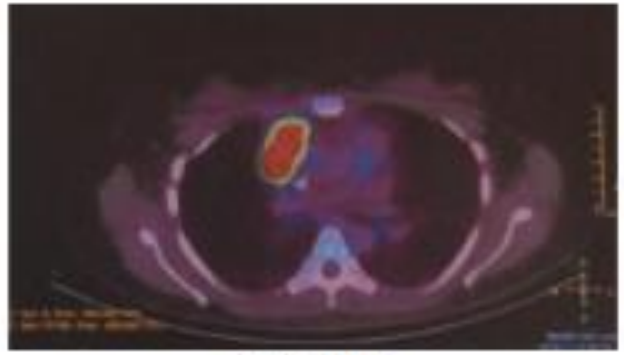




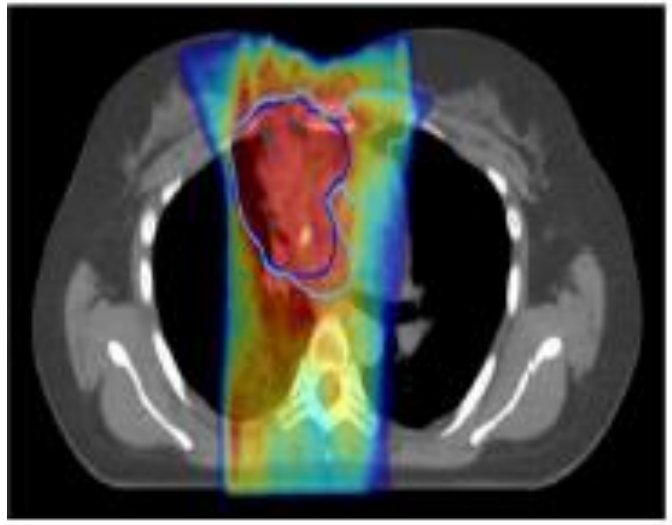
At relapse



After 2 IGEV



After 4 IGEV



Questions, controversies and variation in practice

- Peri-transplant RT:
  - Timing of peri-transplant RT
  - Excellent PMR (minimum DS 4): timing of RT: pre vs post Tx
  - Starting post-Tx RT early enough
- RT volume
- Dose of RT:
  - How much higher it should be for refractory disease?
- Salvage-refractory:
  - If response to RT: does AutoSCT work?
- Radiation Oncology:
  - Variation in RO input in transplant/salvage MDM
  - Variation in RO attitude to role of RT in salvage

Thank you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Radiation therapy for cHL: volumes, doses and techniques

Umberto Ricardi

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UNIVERSITY OF TURIN

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RT in classical Hodgkin Lymphoma

- 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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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 (VOLUMES)
  - Lowest target dose necessary for the highest chance of local lymphoma control (DOSES)
  - Lowest possible risk of significant long-term side effects (TECHNIQUES)

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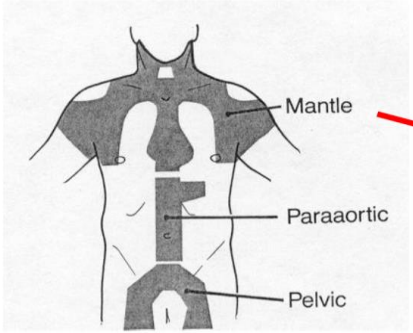
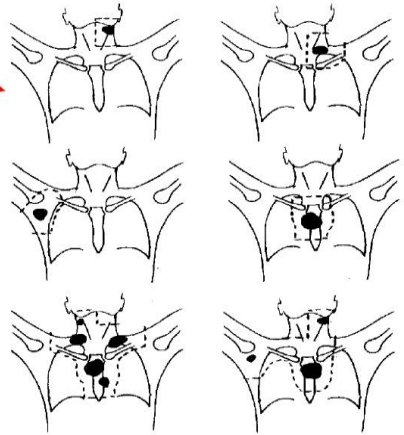
UNIVERSITY OF TURIN

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

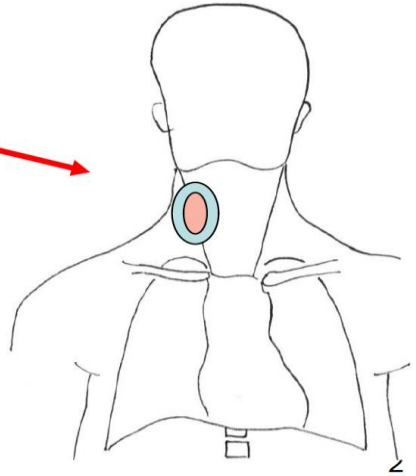
EFRT

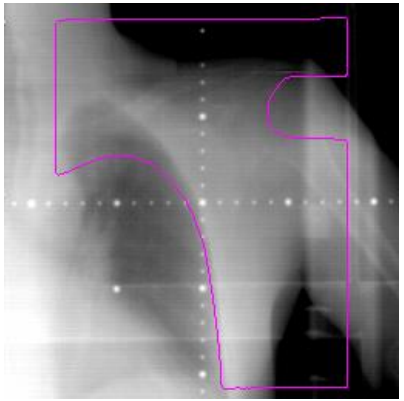


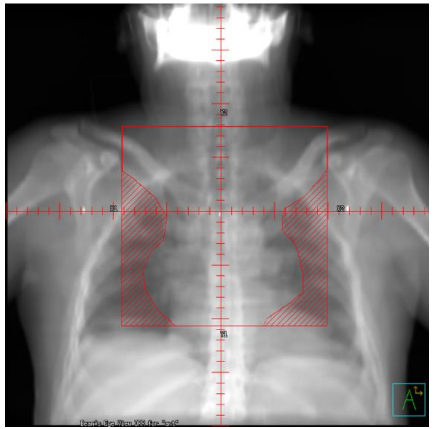
IFRT



INRT







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

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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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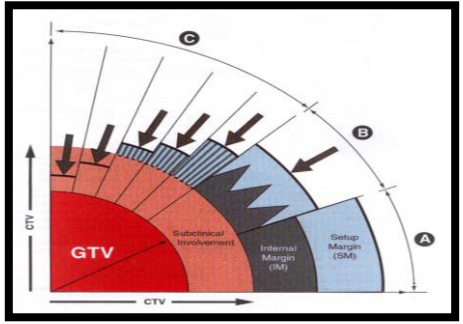
Treatment Volume Principles



- 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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Modern RT for lymphoma

- 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

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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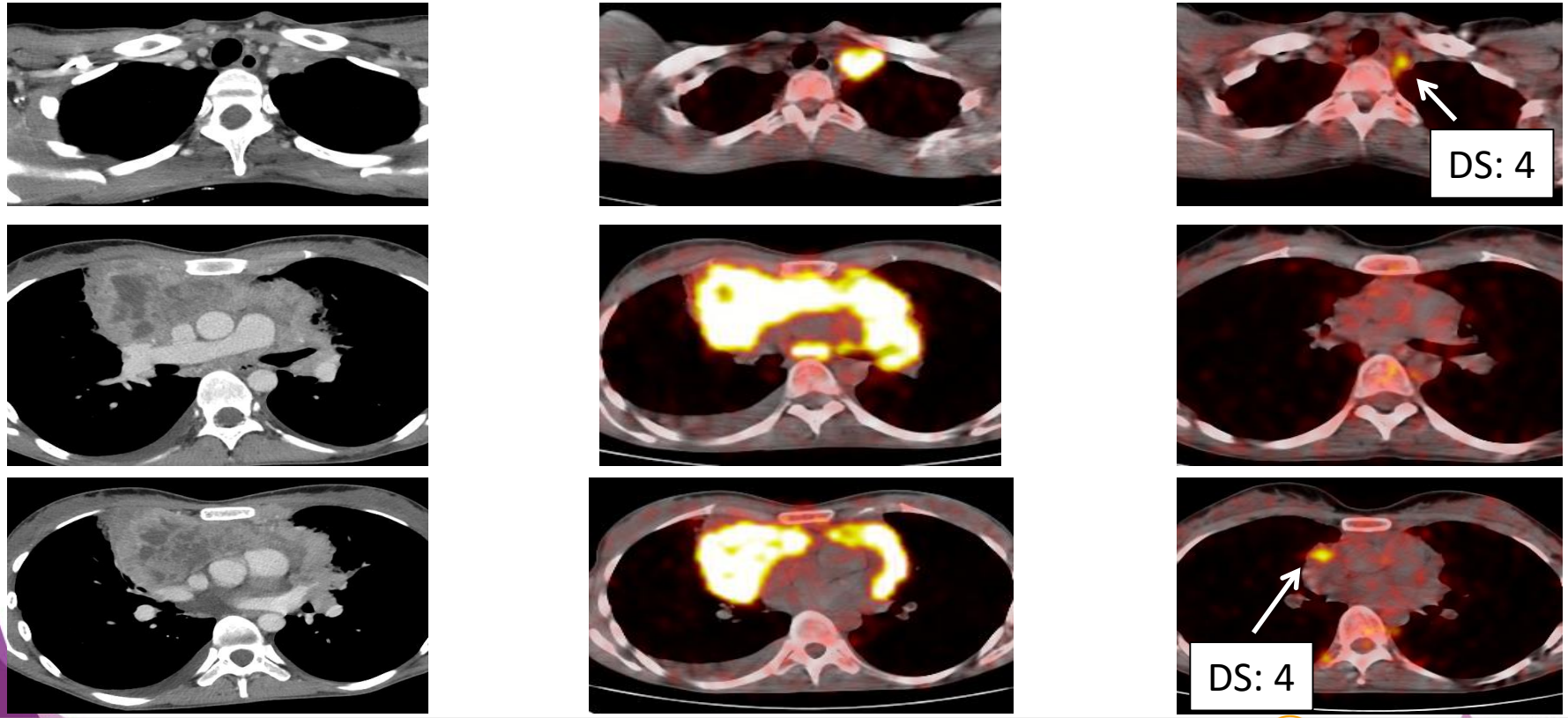
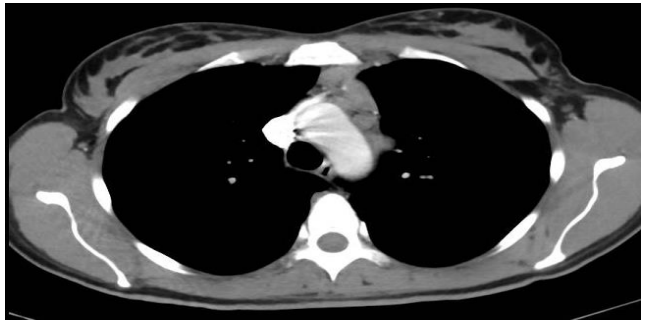
CT scan
(diagnosis)

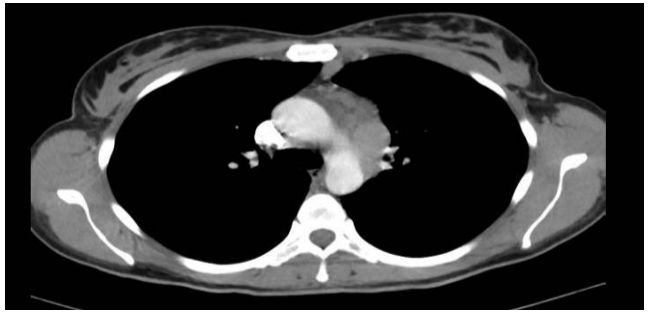
PET/CT scan
(diagnosis)

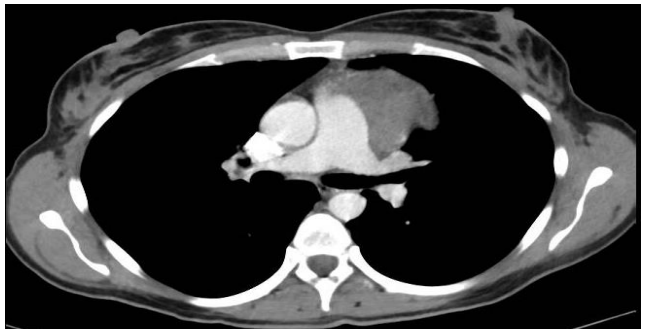
PET/CT scan
(end of chemo)



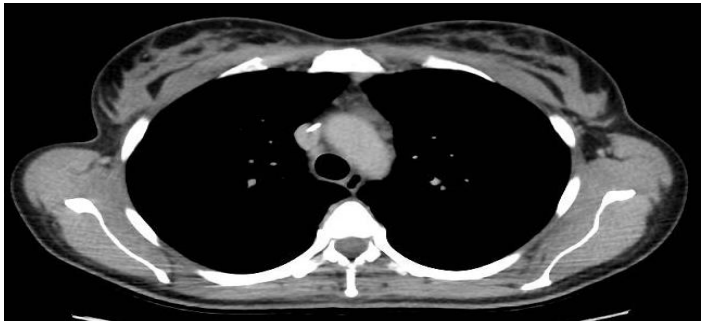
Baseline

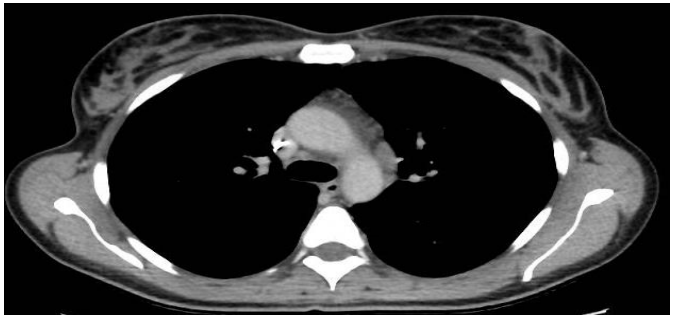


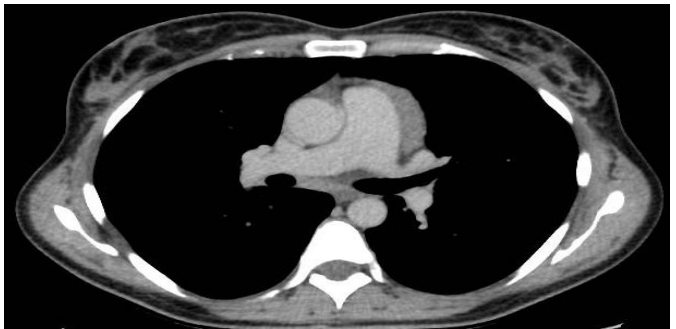




After 3 ABVD

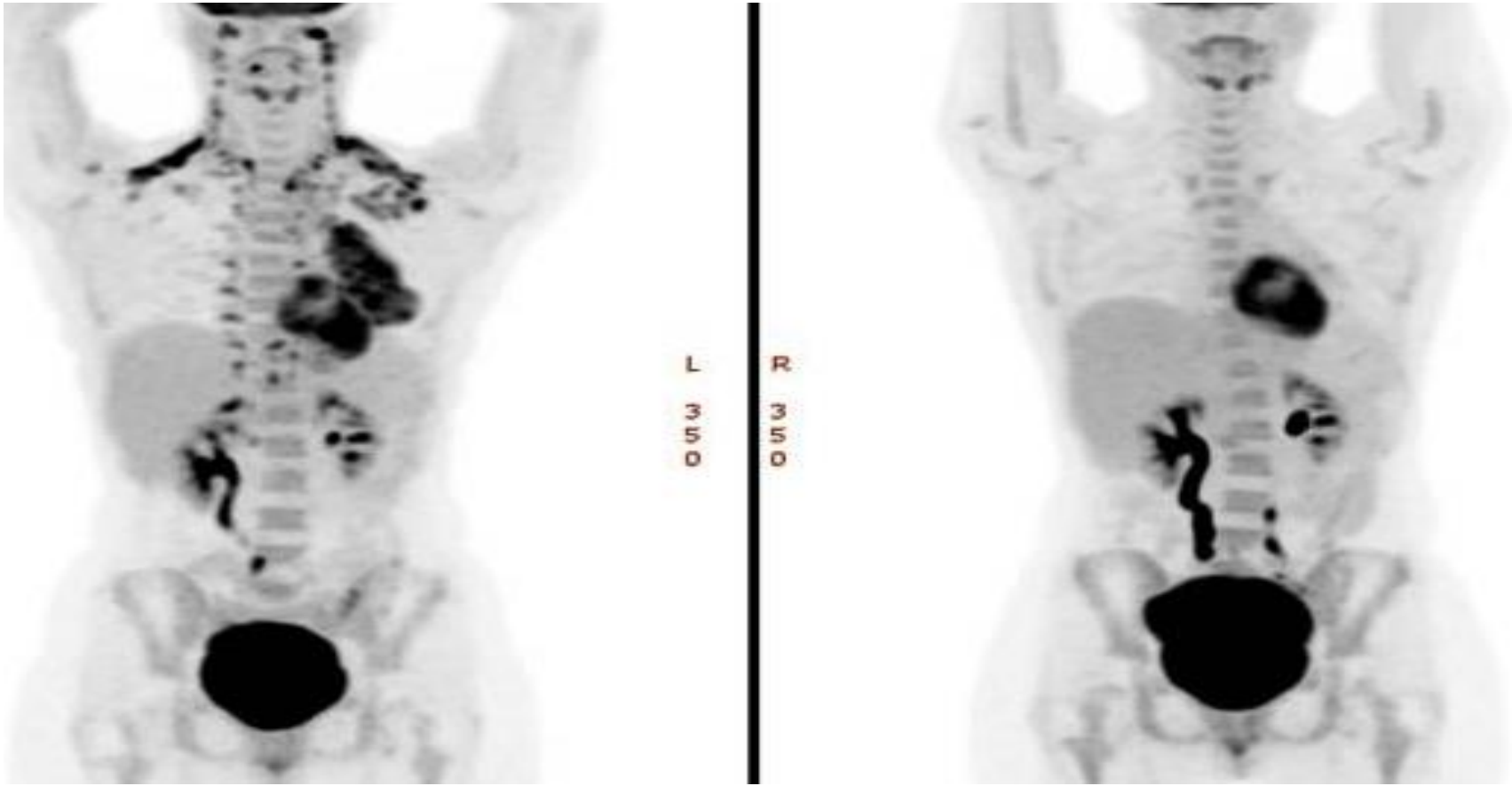






Baseline

After ABVD



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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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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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

- Depending on image-guidance in treatment delivery

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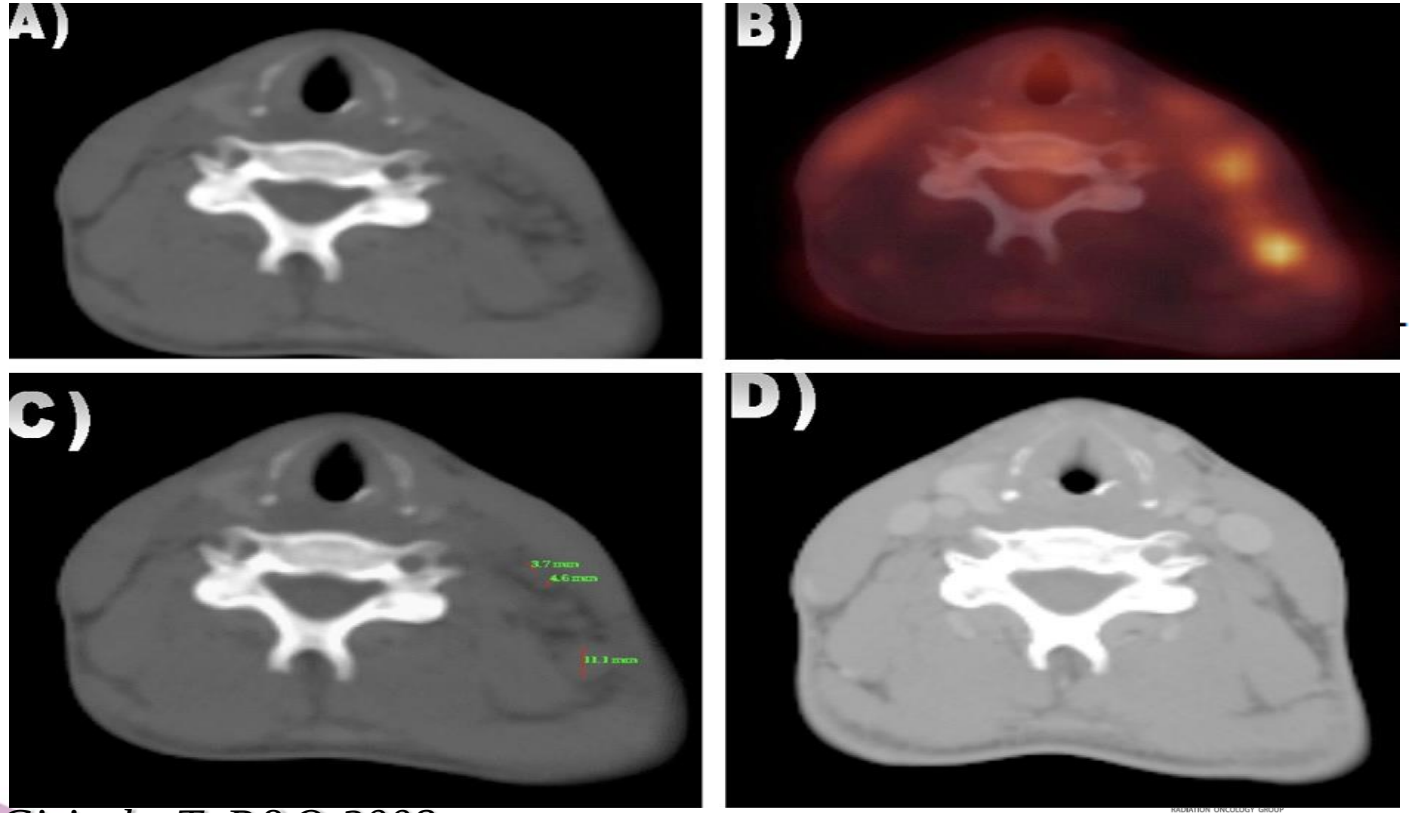
EORTC Lymphoma Group pioneered conformal RT for HL:

Involved node radiotherapy (INRT)



Girinsky T, R&O 2008

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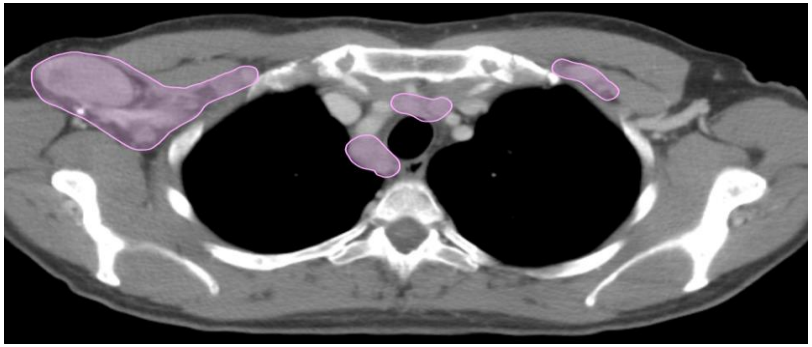
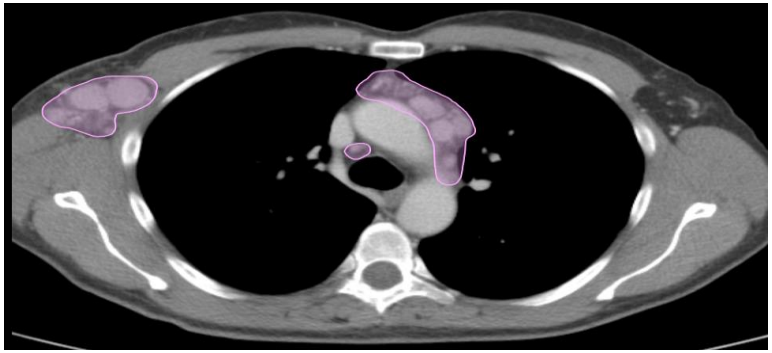
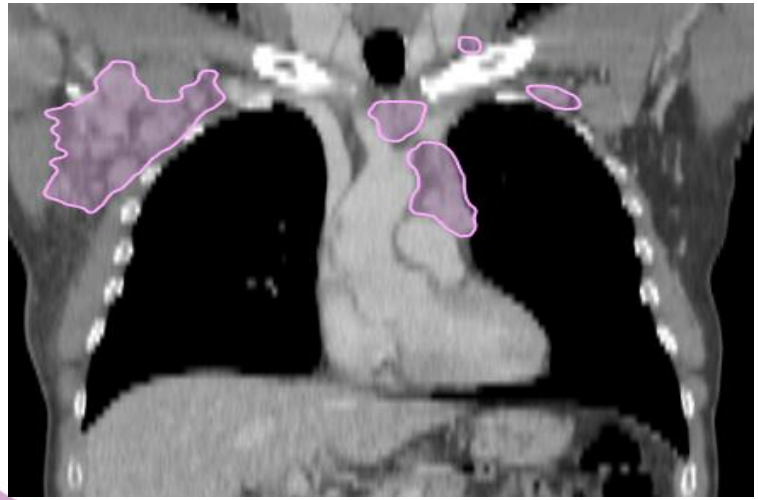
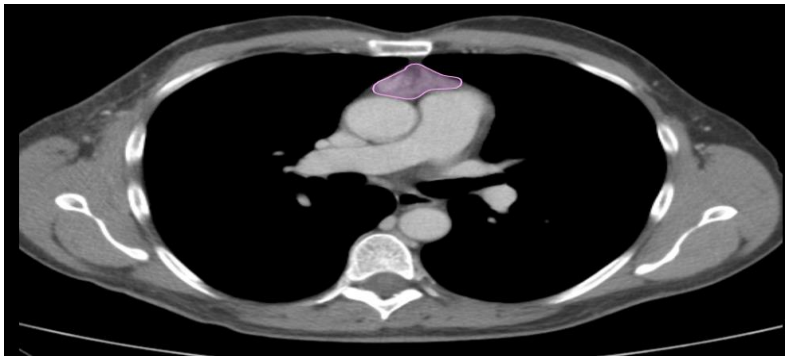
GTV on pre-chemotherapy CT









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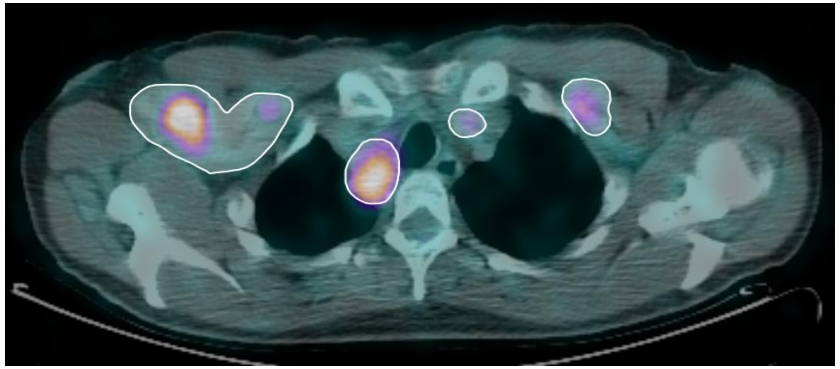
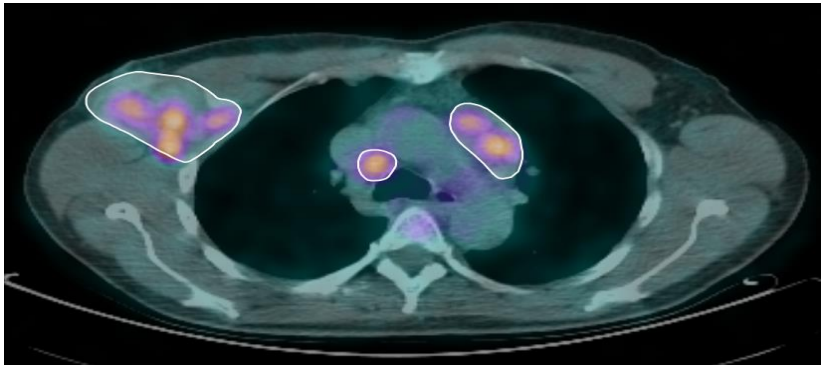
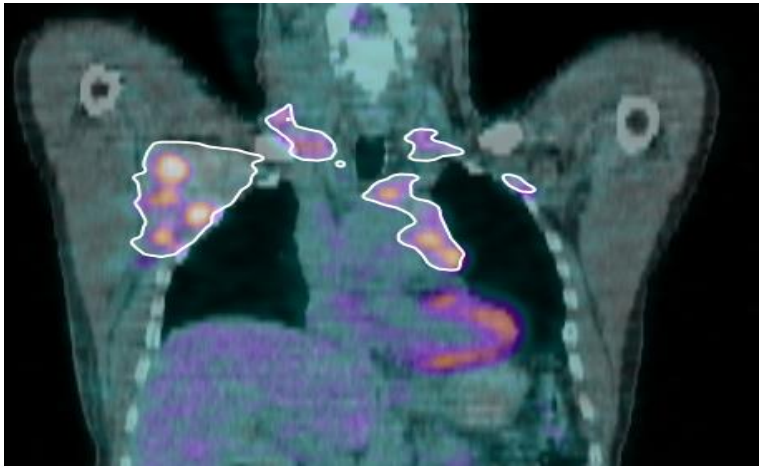
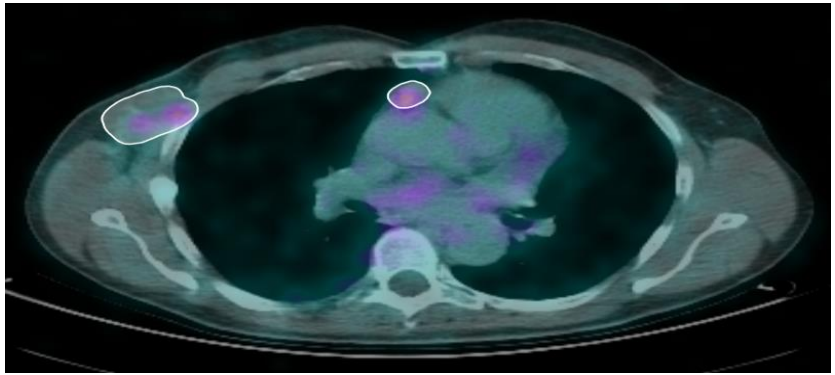
GTV on pre-chemotherapy PET









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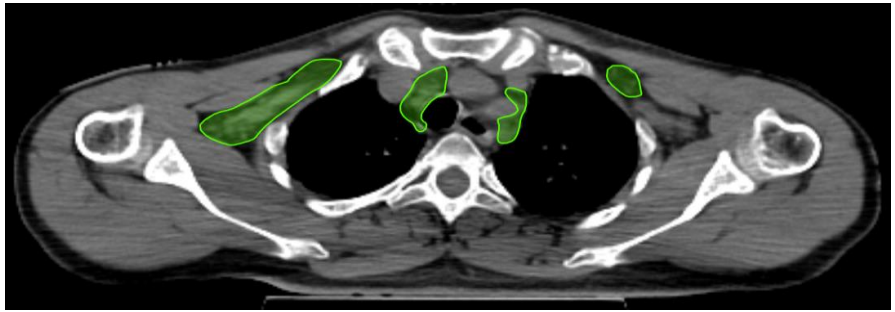
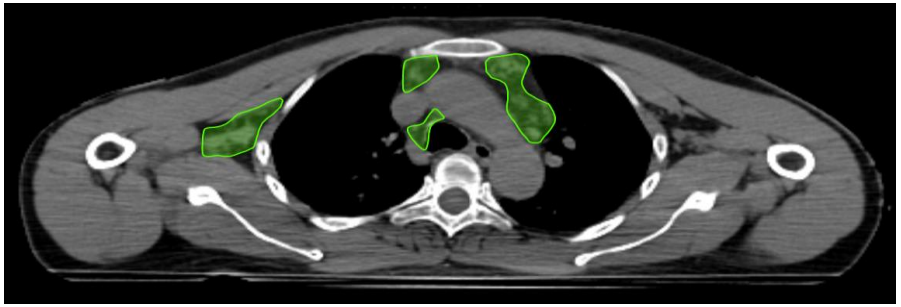
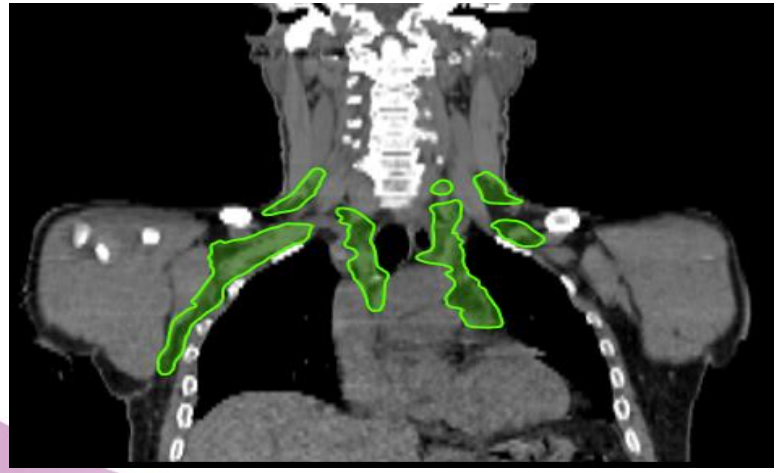
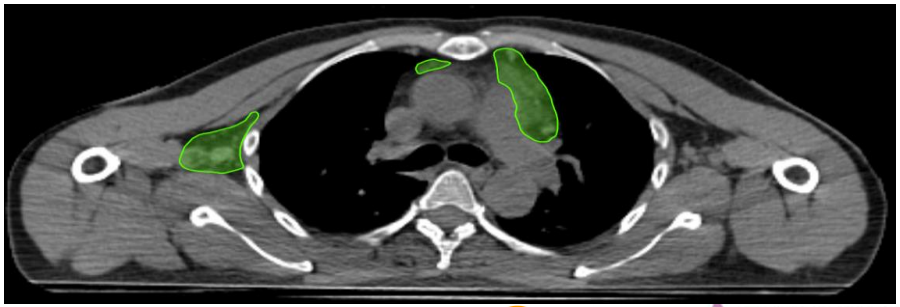
GTV_{CT} and GTV_{PET} import on planning CT→ CTV definition by modifying GTVs according to response and normal tissues displacement → **INRT**









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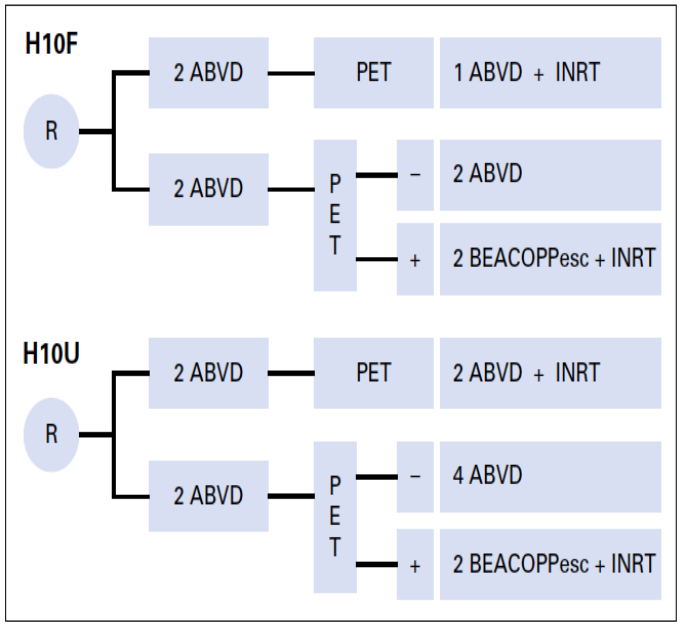
Early Positron Emission Tomography Response–Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial

Marc P.E. André, Théodore Girinsky, Massimo Federico, Oumédaly Reman, Catherine Fortpied, Manuel Gotti, Olivier Casasnovas, Pauline Brice, Richard van der Maazen, Alessandro Re, Véronique Edeline, Christophe Fermé, Gustaaf van Imhoff, Francesco Merli, Réda Bouabdallah, Catherine Sebban, Lena Specht, Aspasia Stamatoullas, Richard Delarue, Valeria Fiaccadori, Monica Bellei, Tiana Raveloarivahy, Annibale Versari, Martin Hutchings, Michel Meignan, and John Raemaekers

VOLUME 35 · NUMBER 16 · JUNE 1, 2017

JOURNAL OF CLINICAL ONCOLOGY



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 J., JCO 2014

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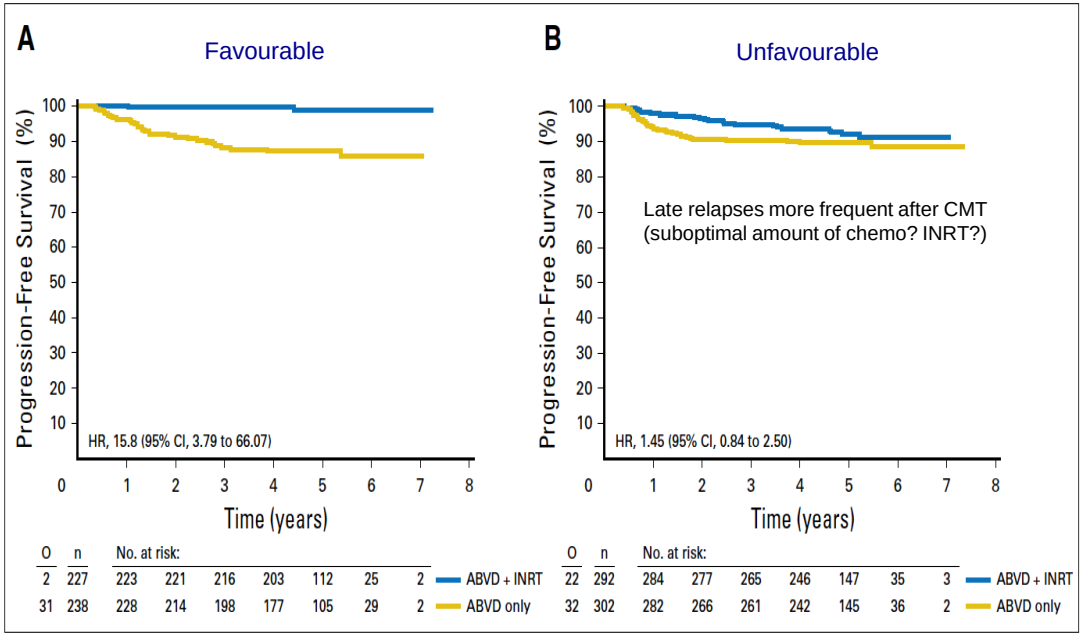
e-PET negative patients
Non inferiority of ABVD only could not be demonstrated;
risk of relapse is increased when INRT is omitted

465 F pts:
30/238 developed relapse after chemo only vs **2/227 after CMT**

595 U pts:
30/302 relapsed after chemo only vs **16/292 after CMT**



◇ 5-year PFS rates in the F group were 99.0% versus 87.1% (HR, 15.8; 95% CI, 3.8 to 66.1) in favor of ABVD + INRT

◇ U group: 92.1% versus 89.6% (HR, 1.45; 95% CI, 0.8 to 2.5) in favor of ABVD + INRT

Involved Site Radiotherapy (ISRT)

- 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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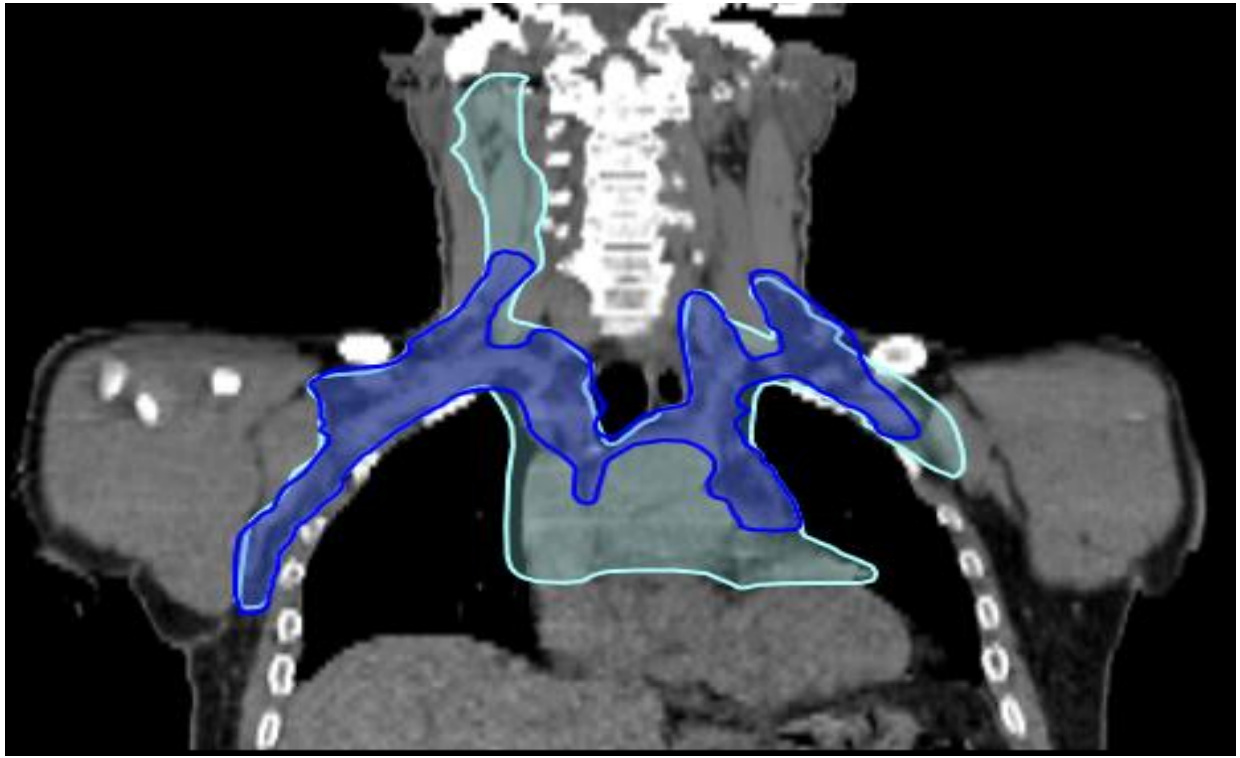
ISRT vs IFRT



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

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Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma

Jessica L. Conway, MD,*,† Joseph M. Connors, MD,*
Scott Tyldesley, MD,*,† Kerry J. Savage, MD,*
Belinda A. Campbell, MD,‡ Yvonne Y. Zheng, MEng, MSc,§
Jeremy Hamm, MSc,§ and Tom Pickles, MD*,†

- *British of Columbia Cancer Agency*
- *Period of analysis: 1961-2009 (>5 years of follow up)*
- *Median RT dose: 35 Gy*
- *Median follow up: 18 years*

- ***SFRT = IFRT; ISRT; INRT***

Table 2 SBC characteristics

Characteristic	MRT (n = 231)	SFRT (n = 185)	CO (n = 318)
Number of SBC	40 (17.3%)	5 (2.7%)	9 (2.8%)
Median age at SBC diagnosis, y (range)	46 (30-79)	46 (44-55)	53 (42-56)
Median time to SBC from HL diagnosis, y (range)	22 (12-37)	9 (7-35)	21 (6-33)

Abbreviations: CO = chemotherapy only; HL = Hodgkin lymphoma; MRT = mantle field radiation; SBC = secondary breast cancer; SFRT = small field radiation.

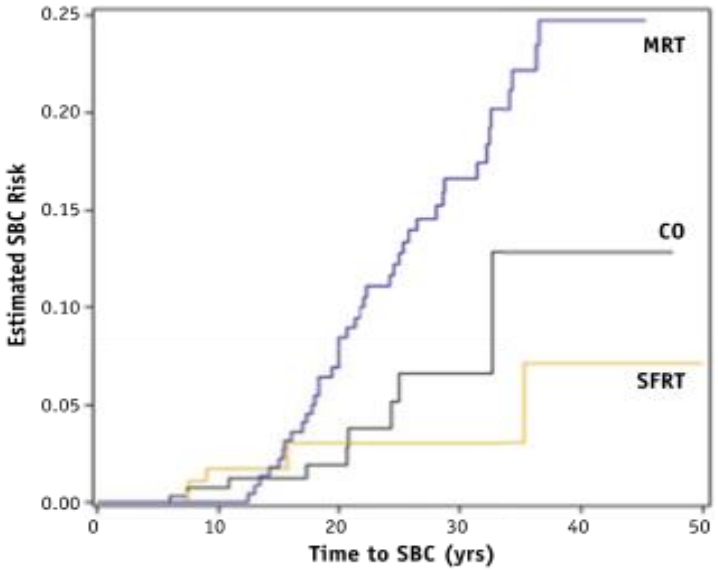

Fig. 2. Cumulative incidence: death and loss to follow-up as competing risks. *Abbreviations:* CO = chemotherapy only; MRT = mantle field radiation; SBC = secondary breast cancer; SFRT = small field radiation.

Conway JL et al. IJROBP 2017

Optimal radiation doses

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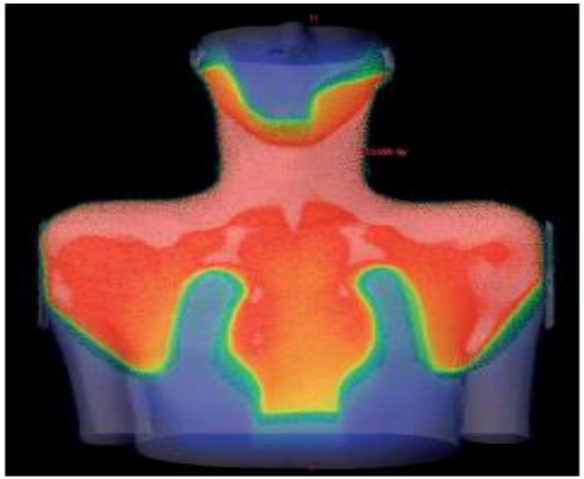
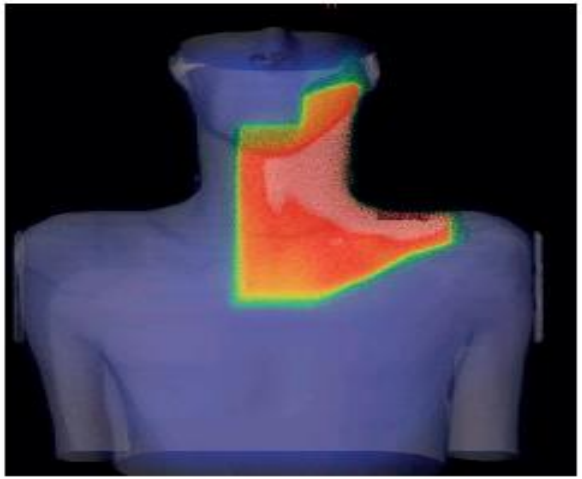
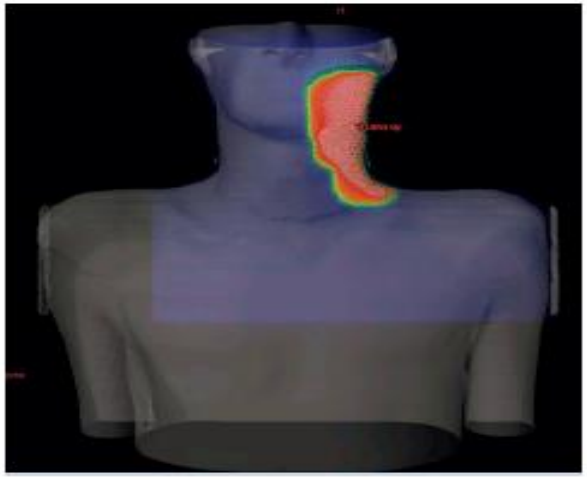
Mantle field, Involved field, Involved Node



40 Gy



36 Gy



20-30 Gy

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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

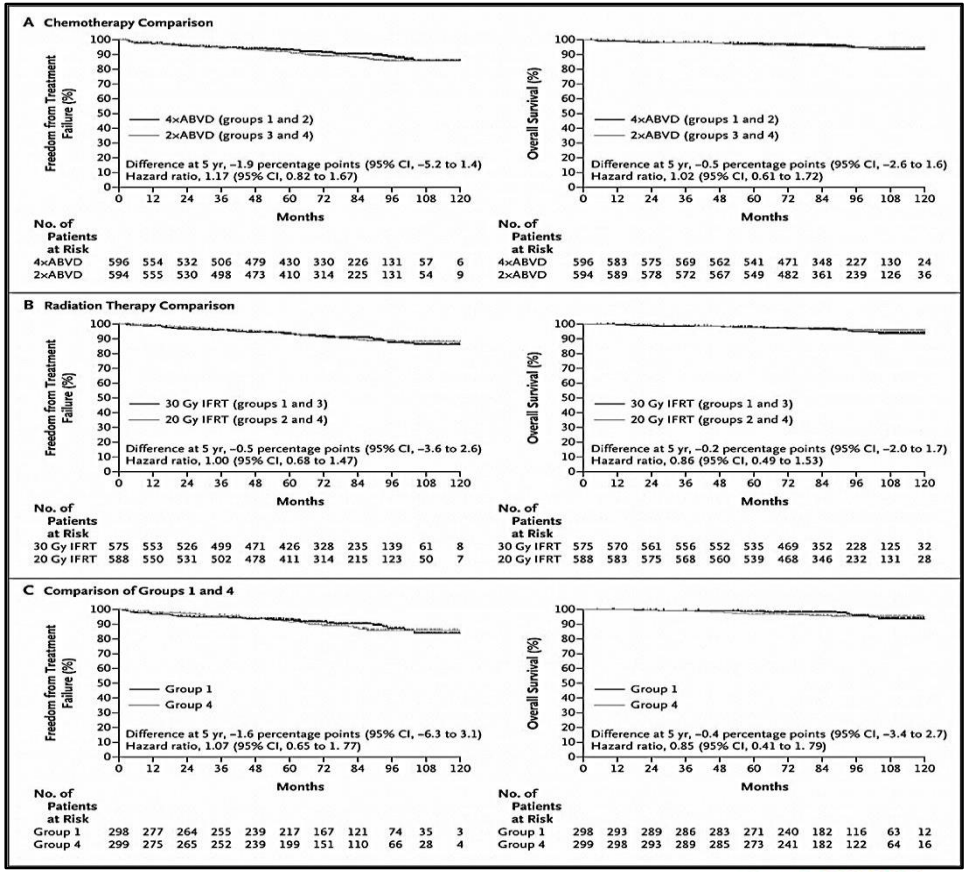
ABVD

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

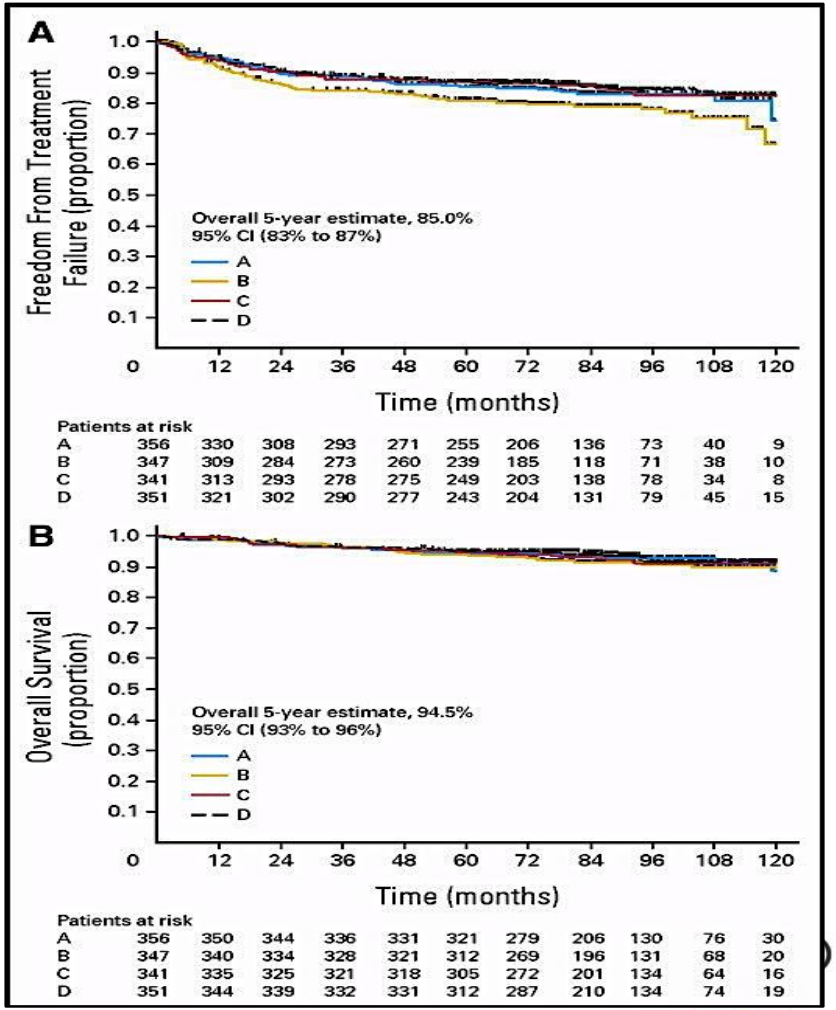
4 ABVD 4 BEACOPP

Involved field RT

20 Gy 30 Gy

ABVD x 4 + 20 Gy inferior on FFTF

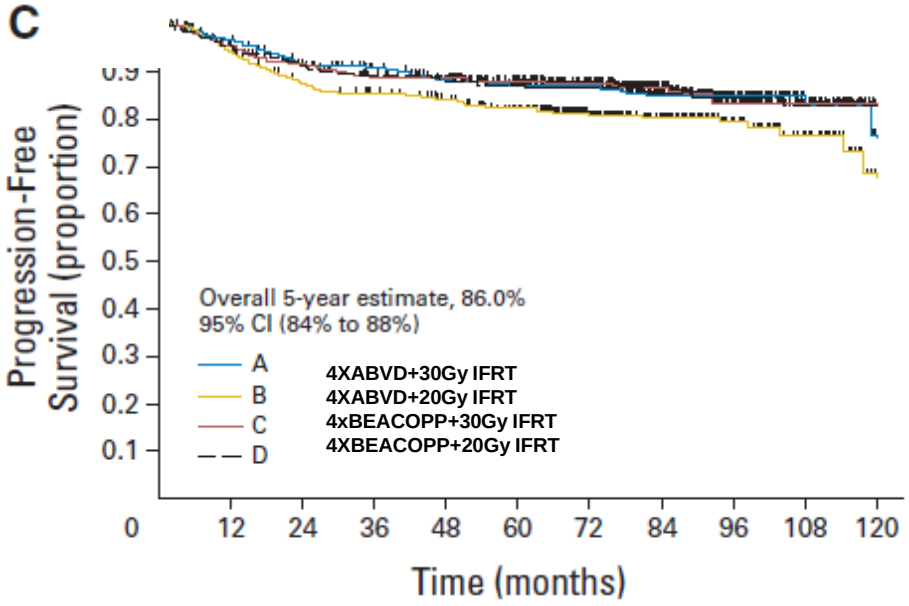
Eich H T et al. J Clin Oncol 2010;28:4199-4206



Memorial Sloan Kettering Cancer Center

Background

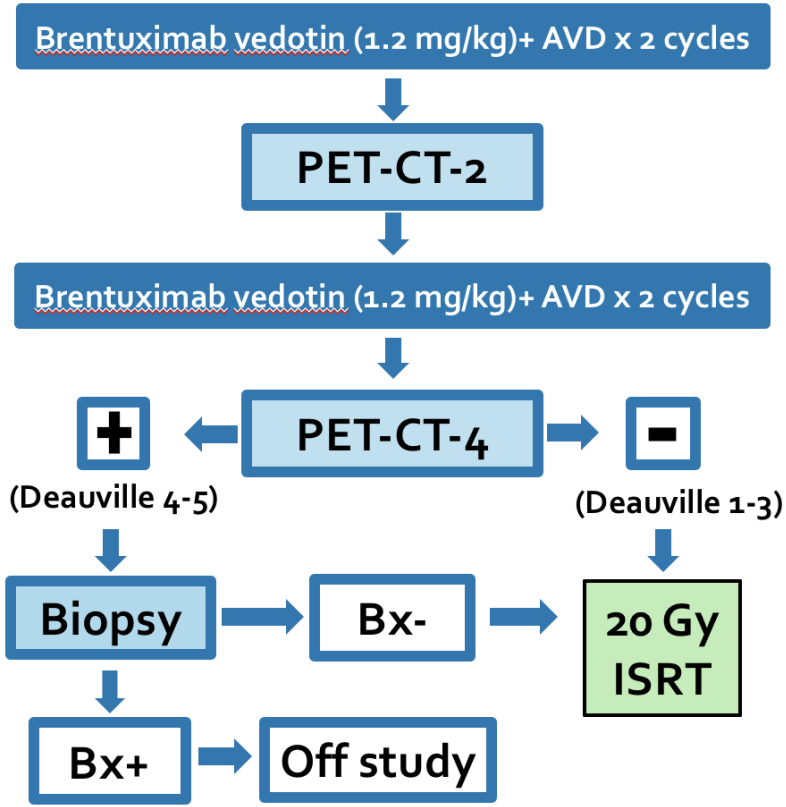
- In HD11, 30Gy was superior to 20Gy after 4 cycles of ABVD
- In HD11, there was no difference between 30Gy and 20Gy after 4 cycles of BEACOPP
- Hypothesis: The addition of brentuximab vedotin will allow for reduction in ISRT dose to minimize late effects of treatment



Eich et al, JCO 2010;28: 4199-4206.

Cohort 2 Study Design, N=29

COHORT 2



Eligibility:

- Histologically confirmed cHL
- Stage I or II
- At least 1 unfavorable risk feature:
  - **Bulky mediastinal mass (>7cm in MTD or MCD)**
  - ESR ≥ 50mm/h, or ESR ≥ 30mm/h in patient with B-symptoms
  - Extranodal involvement
  - 3 or more lymph node sites (per GHSG definition)
  - Infradiaphragmatic disease

MSKCC Disease Bulk Definition:
Kumar et al, Haematologica, 2016

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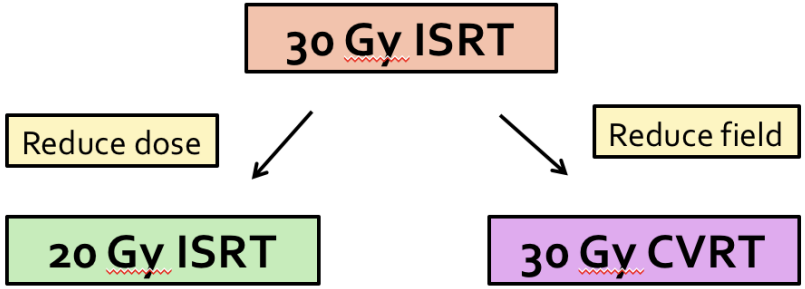
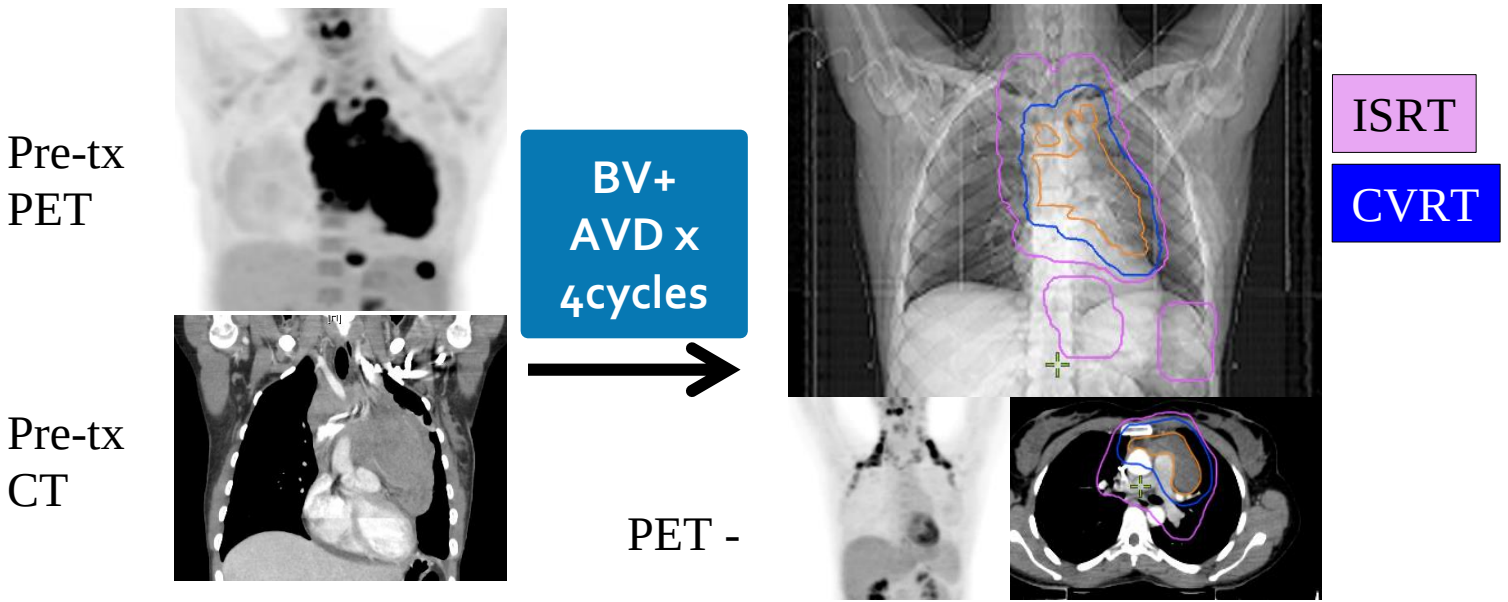
Rationale for 30Gy CVRT

- Change one variable at a time (dose vs. field) to isolate effect
- Did not have efficacy data available from cohort 2 prior to enrollment of cohort 3



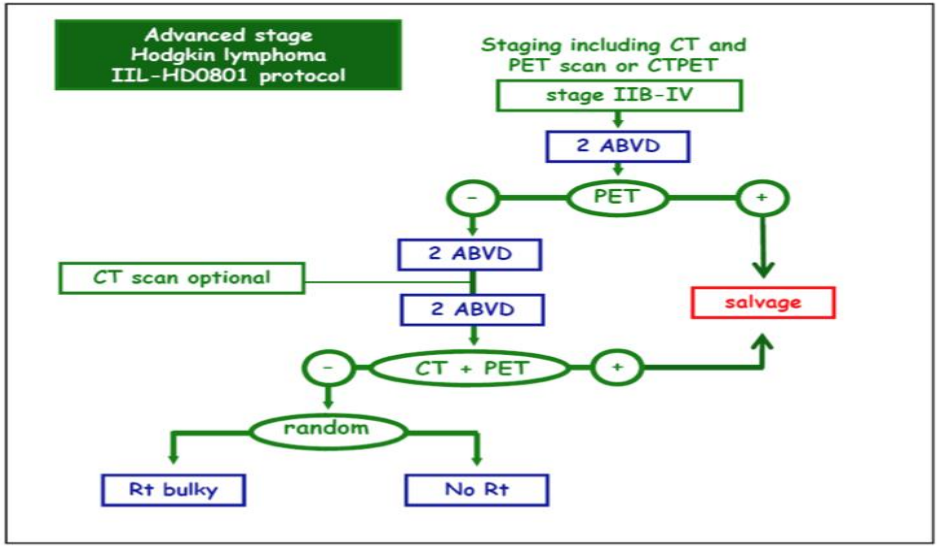
Future Directions

- COHORT 3: BV+AVD x 4 cycles of 30Gy CVRT (enrolled 25 of 29)
  - CVRT: Treat only post-chemotherapy, PET-negative residual CT abnormalities **≥ 1.5cm** in any dimension

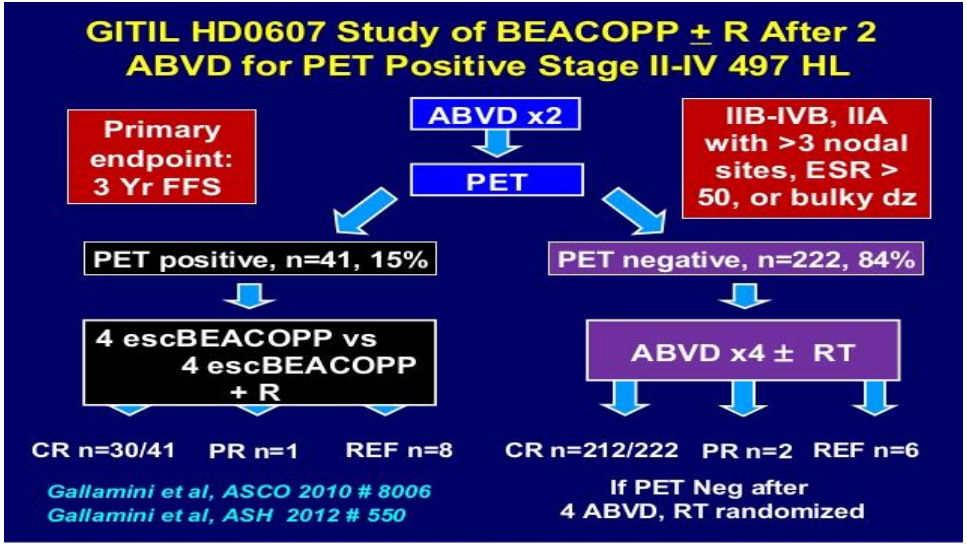


ROLE OF CONSOLIDATIVE RT TO BULKY LESIONS IN THE "^{18}FDG-PET AGE"

FIL HD 0801



GITIL HD 0607



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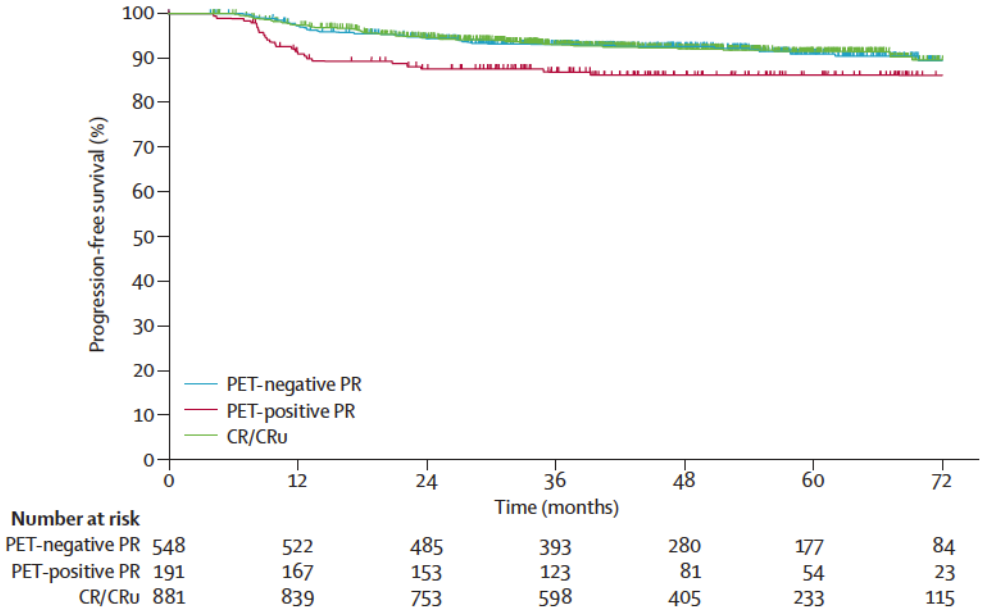
Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial

Engert et al. JCO 2017

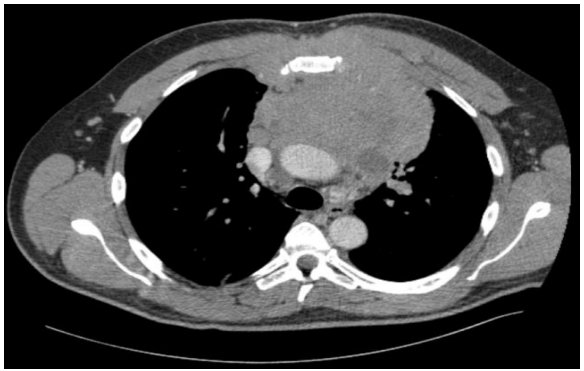


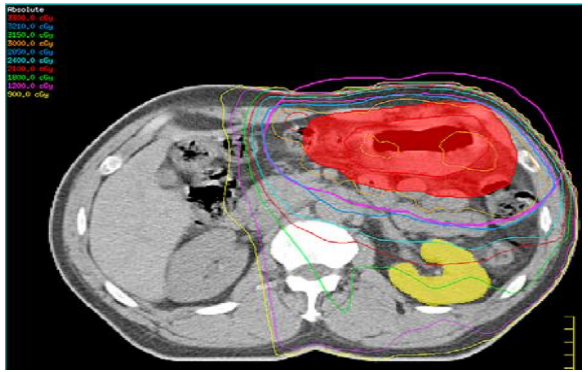
Additional RT (30 Gy) given only to patients with PET+ residual disease > 2.5 cm

Advanced conformal RT in lymphoma

The question is whether modern highly conformal RT will lead to a further reduction in late toxicity

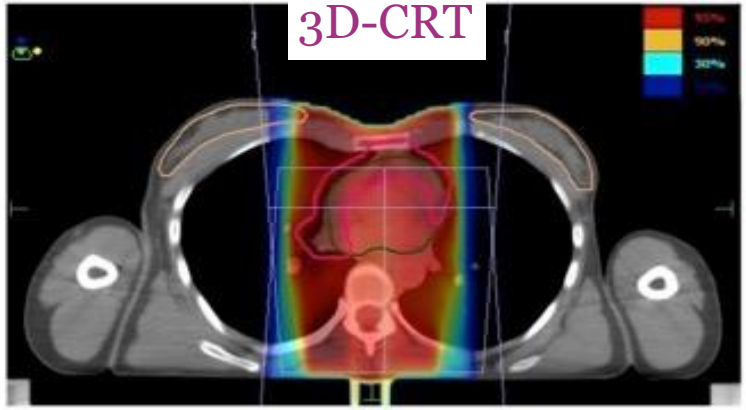
This is especially relevant for patients receiving irradiation with target volumes in close proximity to critical organs at risk (heart, lung, liver, kidney)

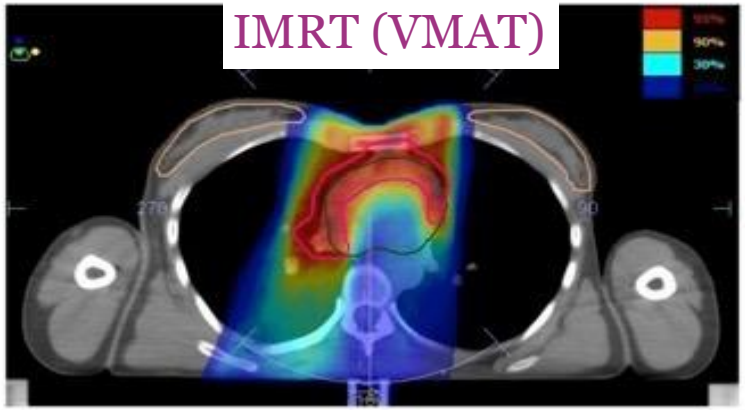




IMRT

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





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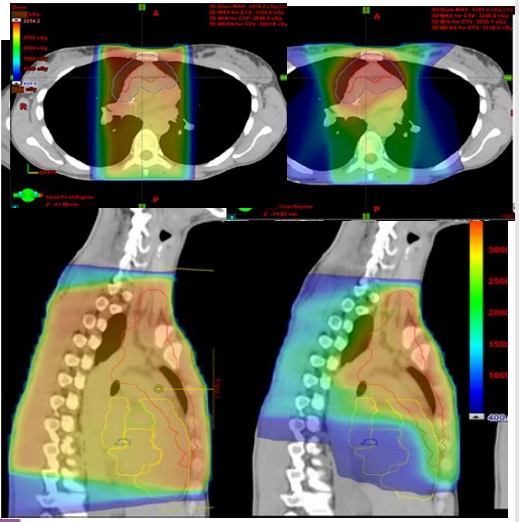
IMRT vs 3D-CRT in lymphoma

- Dosimetry: better PTV coverage (conformity index) and/or significantly better sparing effect for different OAR
    - both for the traditional IFRT and for the more recent concept of limited volumes RT (INRT, ISRT)

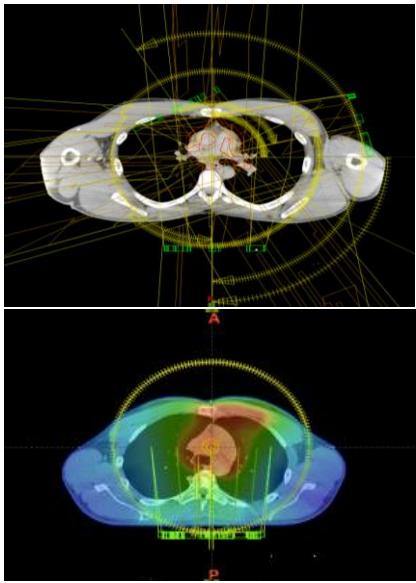
Effective Dose Reduction to Cardiac Structures Using Protons Compared With 3DCRT and IMRT in Mediastinal Hodgkin Lymphoma

B. Hoppe, IJROBP 2012



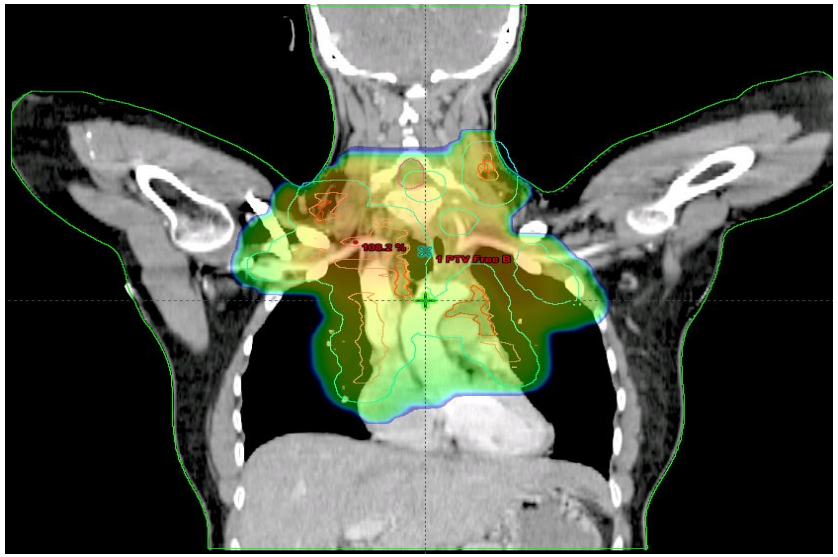
3D-CRT IMRT

Cardiac subunit	3DCRT	IMRT
Heart	21 Gy (15–25)	12 Gy (10–19)
Left ventricle	13 Gy (8–21)	5 Gy (4–15)
Right ventricle	17 Gy (15–24)	11 Gy (8–18)
Left atrium	28 Gy (22–30)	15 Gy (11–21)
Right atrium	24 Gy (18–31)	17 Gy (11–25)
Mitral valve	28 Gy (20–30)	9 Gy (5–17)
Tricuspid valve	19 Gy (7–31)	13 Gy (6–26)
Aortic valve	30 Gy (26–31)	18 Gy (10–26)
Pulmonic valve	31 Gy (26–32)	28 Gy (19–31)
Left anterior descending artery	18 Gy (8–25)	10 Gy (4–21)
Left circumflex artery	30 Gy (21–31)	16 Gy (9–20)
Right circumflex artery	29 Gy (21–31)	22 Gy (11–30)
Pulmonary artery	31 Gy (28–32)	29 Gy (24–31)
Superior vena cava	31 Gy (31–32)	31 Gy (29–32)
Ascending aorta	31 Gy (27–32)	29 Gy (21–30)
Clinical target volume	107% (104–111)	105% (102–110)
Planned target volume	106% (103–110)	104% (102–108)

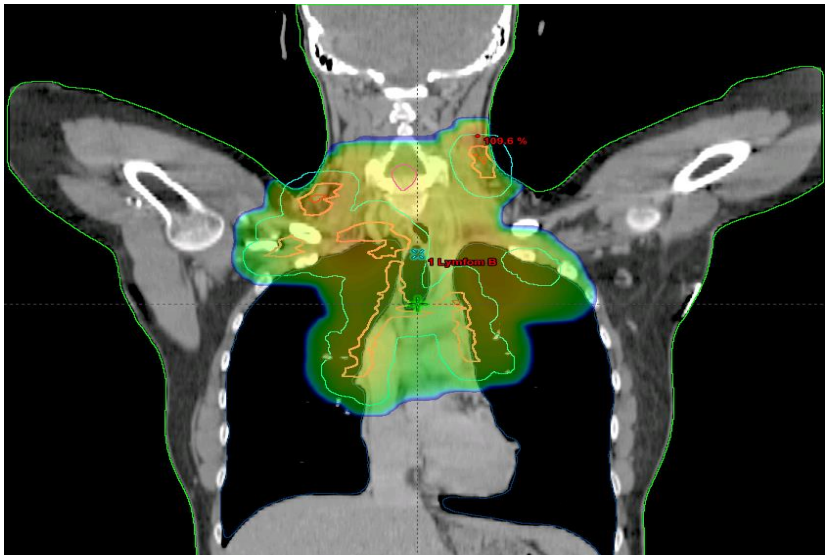


Breath hold decreases the exposure of healthy tissues

- **Free breathing**



- **Deep inspiration breath-hold**



Notice lung volume and heart position

Courtesy Dr. M. Aznar

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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 (QUANTEC)

- Fear of late effects secondary to low-dose exposure of larger volumes of healthy tissues

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Specific dose constraints in lymphoma RT

- 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

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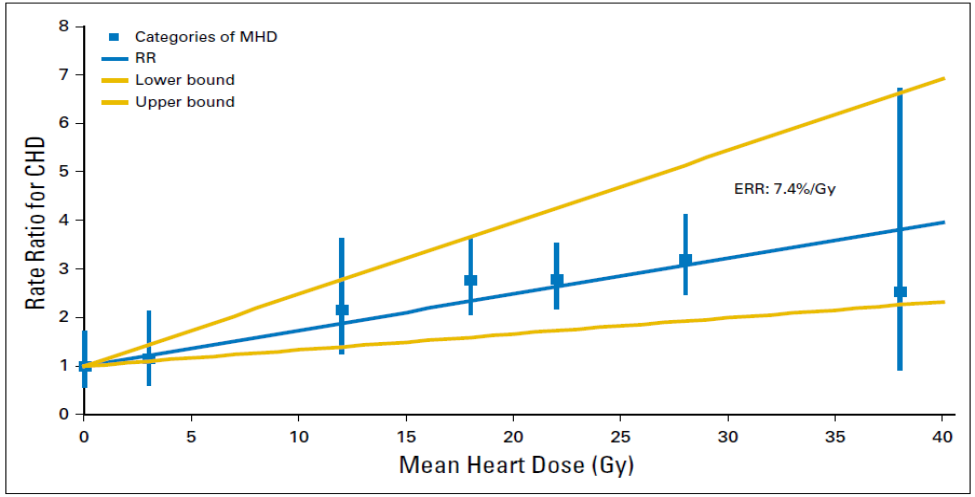
UNIVERSITY OF TURIN

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

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

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



J Clin Oncol 2016

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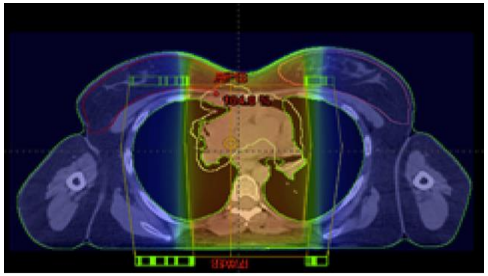
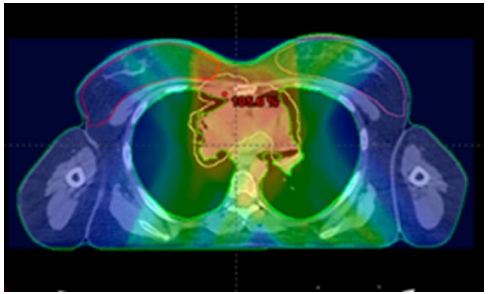
Second Cancers: IMRT vs. 3D-CRT

- Larger volumes of normal tissues exposed to low radiation doses (IMRT)





Secondary cancer risk models for RT optimization in HL

Results change when using different radiobiological models (linear, non-linear models)

IMRT may be optimized taking into account secondary cancers risk

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]

Radiation Oncology 2012, 7:186

Optimizing IMRT
with "intelligent" beam orientation

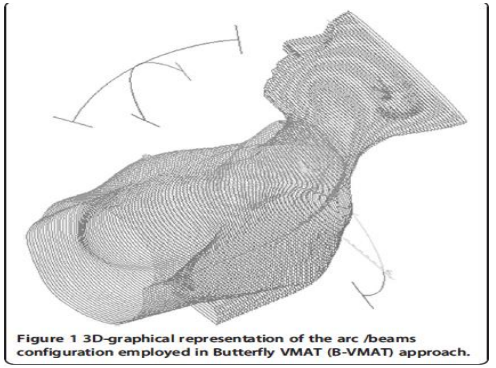


Figure 1 3D-graphical representation of the arc /beams configuration employed in Butterfly VMAT (B-VMAT) approach.

Conclusions:

- Optimized multiarc VMAT able to achieve the most balanced compromise between higher conformation around the target and smaller volumes of OAR exposed to lower doses

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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

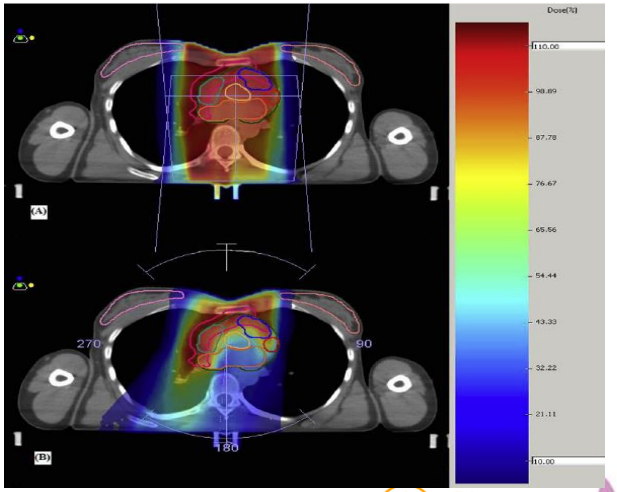
Andrea Riccardo Filippi, MD,* Riccardo Ragona, MSc,* Cristina Piva, MD,* Davide Scafa, MD,* Christian Fiandra, MSc,* Marco Fusella, MSc,† Francesca Romana Giglioli, MSc,† Frank Lohr, MD,‡ and Umberto Ricardi, MD*

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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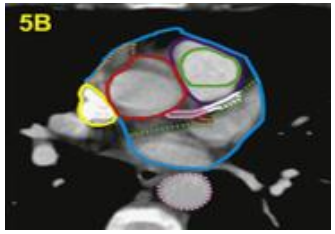
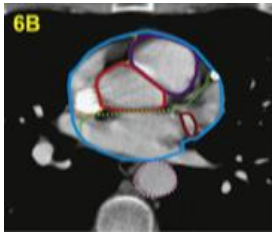
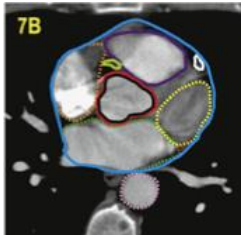
Optimized VMAT: cardiovascular disease







Cardiac subunits: heart atlas (Feng, 2011)

Absolute Excess Risk (AER)

	Mean AER and SD		
	3D-CRT	VMAT	*p* value
Cardiac diseases	0.74 ± 1.50	0.37 ± 0.45	0.038
Aortic valve	2.15 ± 2.27	0.26 ± 0.63	<0.0001
Pulmonic valve	3.13 ± 3.24	1.36 ± 1.88	<0.0001
Mitral valve	0.29 ± 1.10	0.003 ± 0.007	0.12
Tricuspid valve	0.73 ± 2.11	0.07 ± 0.36	0.045
All valves	1.57+/- 2.55	0.42+/- 1.14	<0.0001

Filippi et al, IJROBP 2015

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Optimized VMAT: second cancers

	Mean OED and SD		
	3D-CRT	VMAT	*p* value
Lung			
All	2.16 ± 0.84	2.28 ± 0.73	0.025
No Neck	1.59 ± 0.73	1.91 ± 0.62	0.001
Unilateral Neck	2.31 ± 0.85	2.46 ± 0.81	0.03
Bilateral Neck	2.33 ± 0.76	2.22 ± 0.57	0.23
Breast			
All	0.22 ± 0.15	0.22 ± 0.16	0.72
No Neck	0.17 ± 0.13	0.20 ± 0.13	0.34
Unilateral Neck	0.26 ± 0.18	0.25 ± 0.19	0.88
Bilateral Neck	0.20 ± 0.12	0.16 ± 0.09	0.02
Thyroid			
All	3.29 ± 1.77	3.34 ± 1.75	0.35
No Neck	0.30 ± 0.16	0.41 ± 0.36	0.29
Unilateral Neck	3.65 ± 0.83	3.73 ± 0.81	0.48
Bilateral Neck	4.83 ± 0.62	4.83 ± 0.68	0.94

Filippi et al, IJROBP 2015

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Optimisation: cardiac constraints

- Mean heart dose is the most used parameter (D_{mean} < 5 Gy; 5-15 Gy: acceptable; > 15 Gy: omitting RT or plan modification), with whole heart evaluated as a single structure
- Other dosimetric parameters (V_5, V_{10}, V_{30}) are highly correlated with mean dose
- Very few data on toxicity according to specific contraints to different cardiac sub-units
- Different cardiac structures definition

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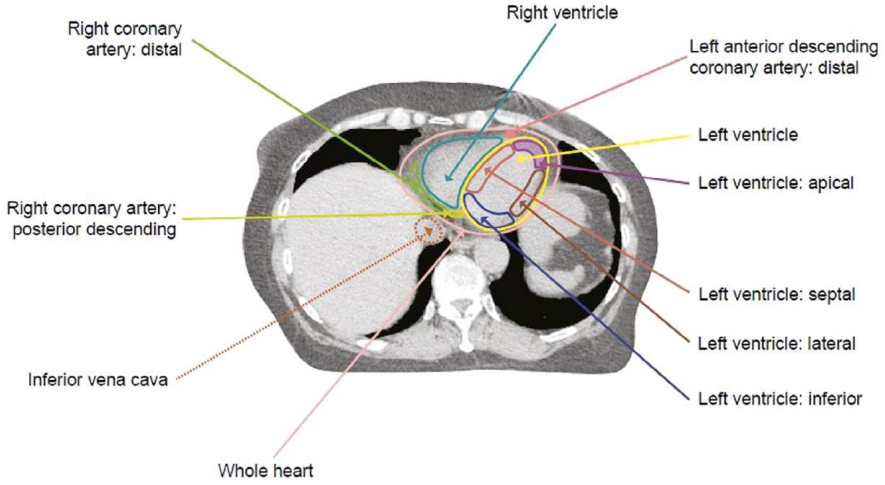
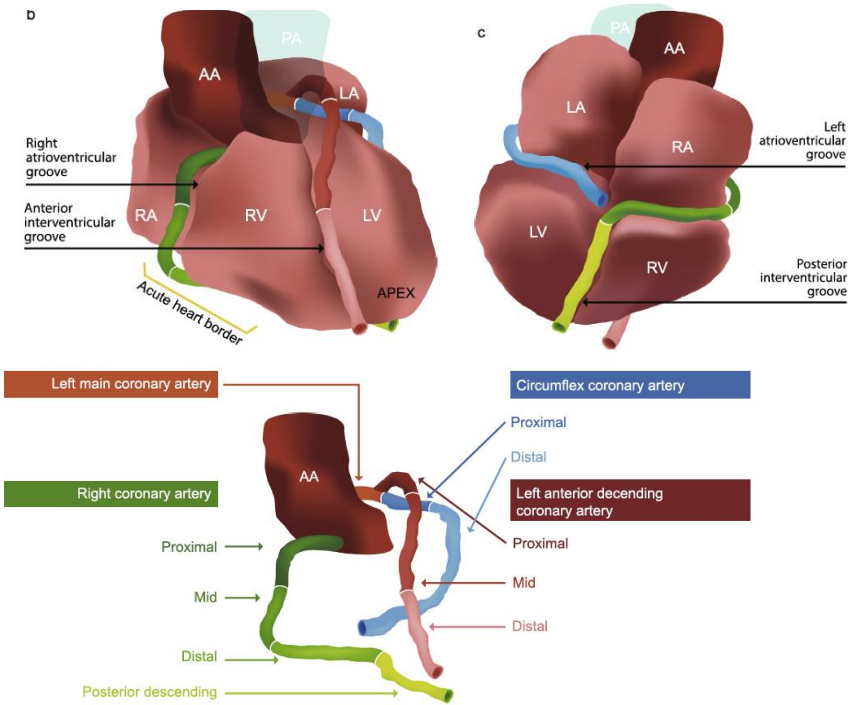
A cardiac contouring atlas for radiotherapy

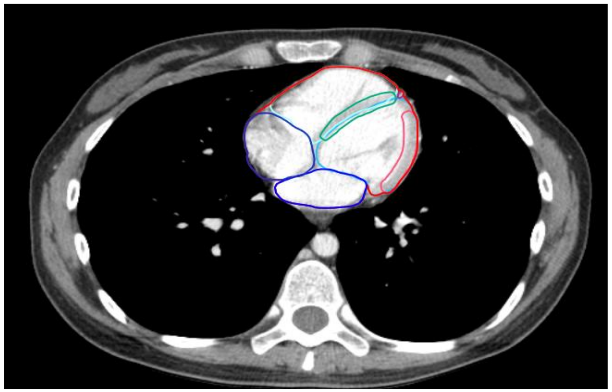
Frances Duane[a,b,*], Marianne C. Aznar[a], Freddie Bartlett[c], David J. Cutter[a], Sarah C. Darby[a], Reshma Jagsi[d], Ebbe L. Lorenzen[e], Orla McArdle[f], Paul McGale[a], Saul Myerson[g], Kazem Rahimi[h], Sindu Vivekanandan[i], Samantha Warren[j], Carolyn W. Taylor[a]

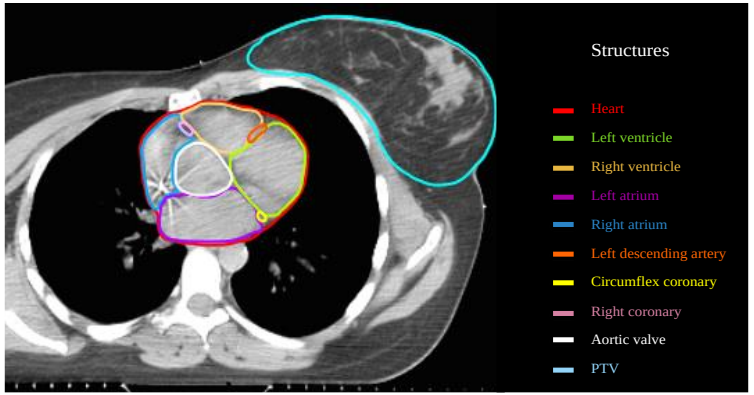
Radiotherapy and Oncology 122 (2017) 416–422

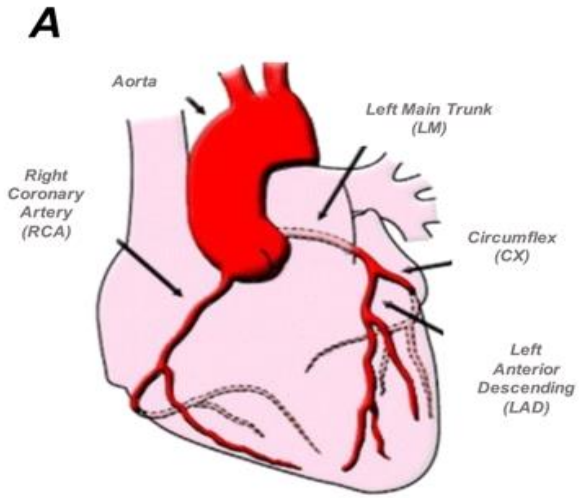


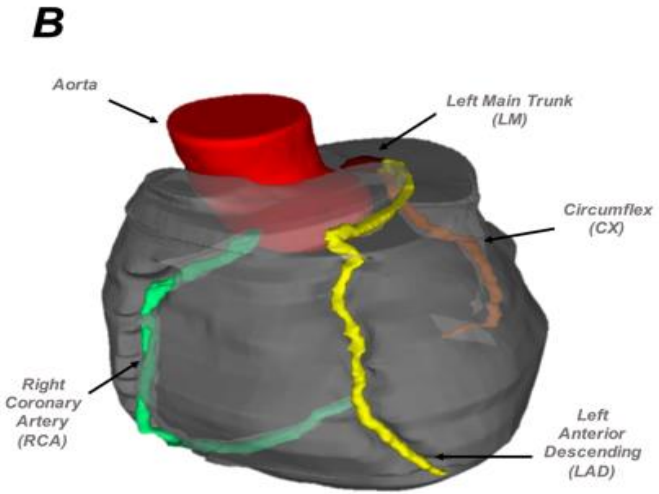


DETAILED CONTOURING OF CARDIAC SUB-STRUCTURES









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Choosing wisely…

- Even low doses to normal tissues, previously considered safe, may result in significant risks of morbidity in long-term survivors
- Doses to all normal structures should be kept as low as possible (some structures are more critical than others)
- No two lymphomas are the same with regard to localization and extent of disease (individual patient/target geometry)
- The decision should be made at the individual patient level (degree of modulation; individual treatment goals and toxicity considerations)

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Between the 'Lines

Journal of the National Comprehensive Cancer Network

Are Advanced Radiation Therapy Technologies Required for Treating Patients With Hodgkin Lymphoma?

Richard T. Hoppe, MD

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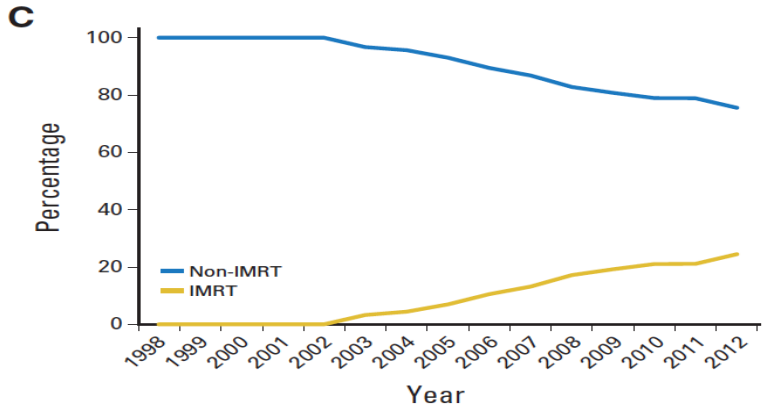
Big Data: National Cancer Database

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

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

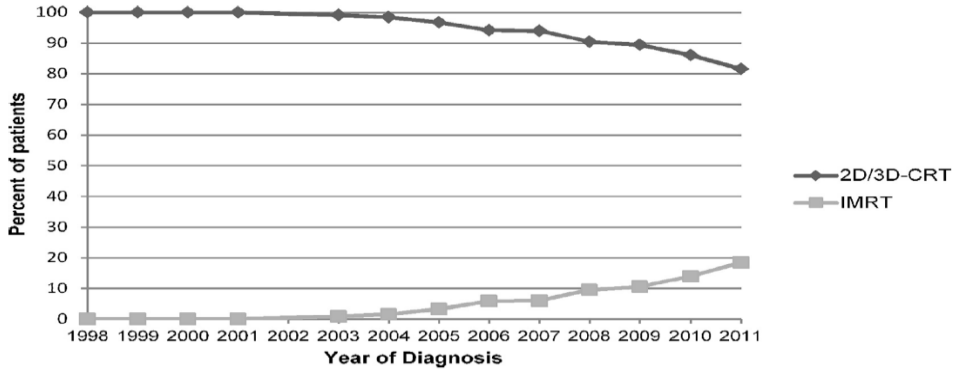


VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

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

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



Radiotherapy and Oncology 118 (2016) 52–59

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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

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

- Smaller treatment volumes, lower radiation dose and advanced conformal radiotherapy can certainly allow a safer radiation delivery, when needed

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CANCER RESEARCH UK | MANCHESTER CENTRE

MANCHESTER 1824 The University of Manchester

The Christie NHS NHS Foundation Trust

Indolent lymphomas : Treatment approaches to primary and relapsed / refractory disease

Tim Illidge
BSc PhD FRCR FRCP FRCPath
Head of Division of Cancer Sciences
University of Manchester

LRG International Lymphoma Radiation Oncology Group

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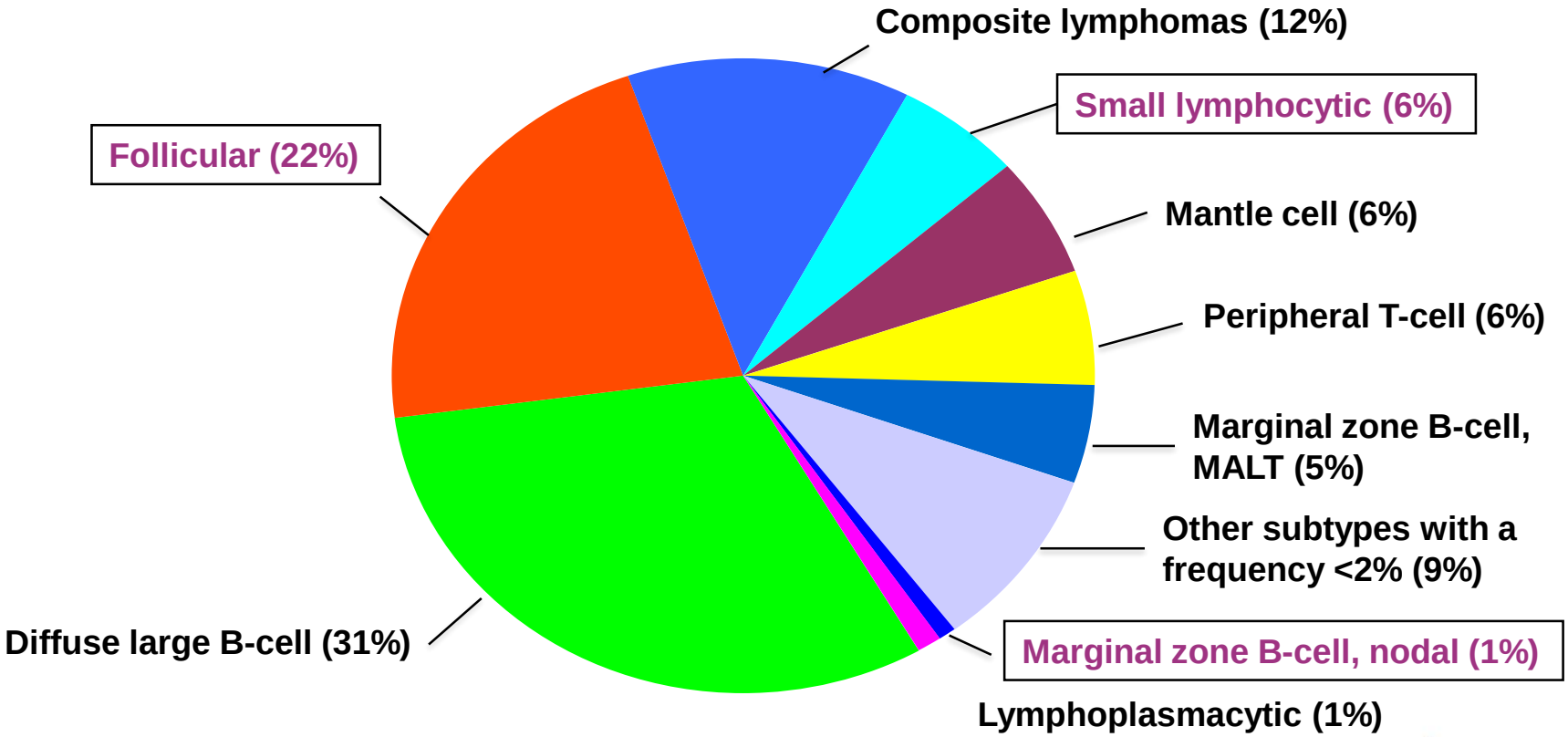
Frequency of NHL Subtypes in Adults



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

Follicular Lymphoma (FL) is the Second Most Common Type of NHL, Accounting for 22% of NHL

Median survival

~ 14 years

33% of FL cases turn into more aggressive diffuse large B-cell lymphoma (DLBCL)

- **Median** age at diagnosis is 62 year
- **Much more common in Caucasians** than in Blacks or Asians – rare in some parts of the world eg Far East and parts of Africa

1. Datamonitor 2012 epidemiology data

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Outline of talk

- Early stage – Is Radiotherapy still standard ?
- Advanced stage
  - Low volume asymptomatic – Is watch and wait still standard ?
  - High volume or symptomatic : standards of care in Immuno-chemotherapy ?
- Relapsed / refractory disease – How do we predict patients who may require different treatment approaches ?
- Radioimmunotherapy – Is there still an opportunity ?
- Targeted Therapies – Is there life with and after PI3K inhibitors ?

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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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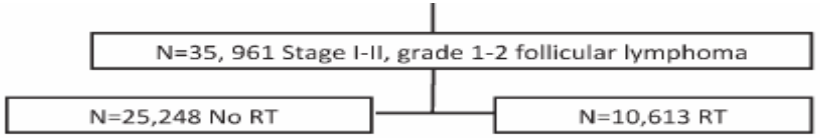
Radiotherapy in Early stage Low Grade lymphomas

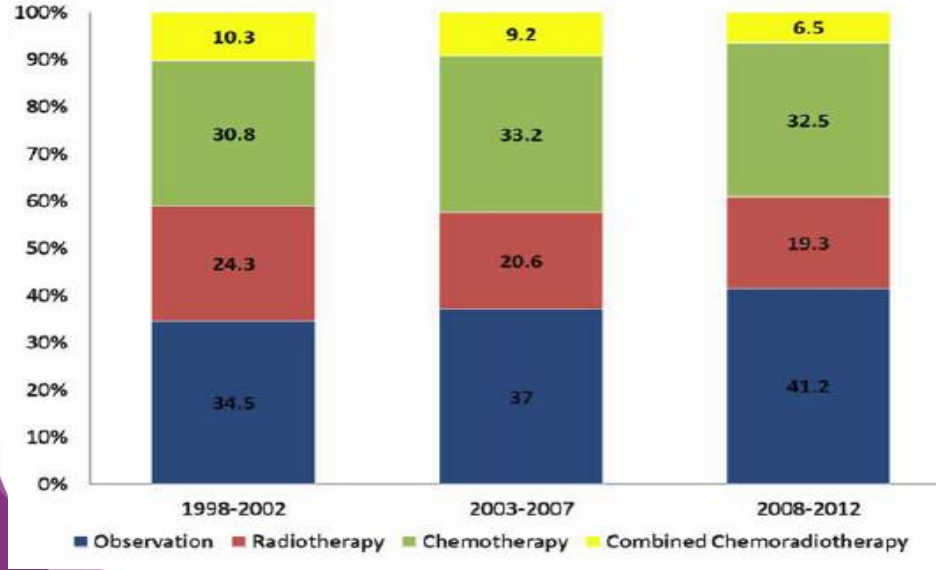
- Radical treatment
  - stage I and contiguous II

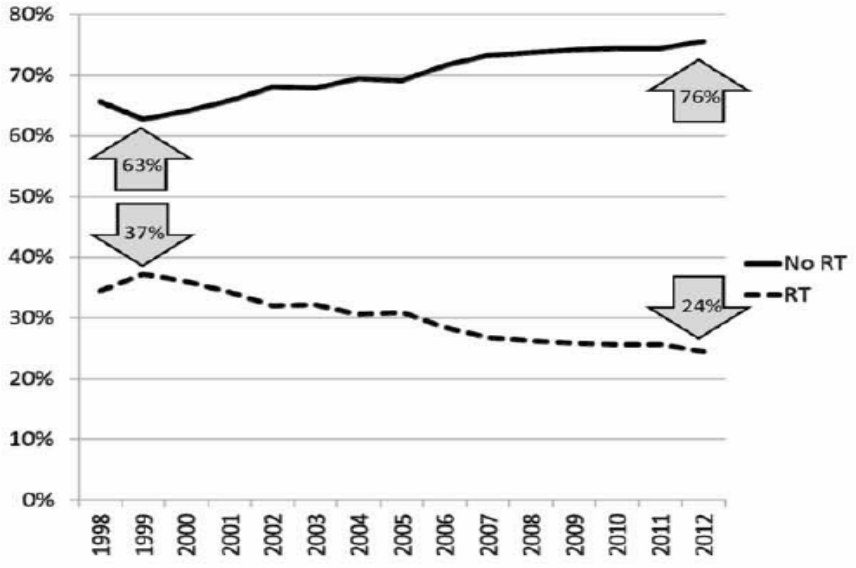
What Is the Optimal Management of Early-Stage Low-Grade Follicular Lymphoma in the Modern Era?

John A. Vargo, MD[1]; Beant S. Gill, MD[1]; Goundappa K. Balasubramani, PhD[2]; and Sushil Beriwal, MD[1]

Cancer 2015;121:3325-34.







Improved Survival in Patients With Early Stage Low-Grade Follicular Lymphoma Treated With Radiation

Cancer 2010;116:3843–51.

A Surveillance, Epidemiology, and End Results Database Analysis

Thomas J. Pugh, MD; Ari Ballonoff, MD; Francis Newman, MS; and Rachel Rabinovitch, MD

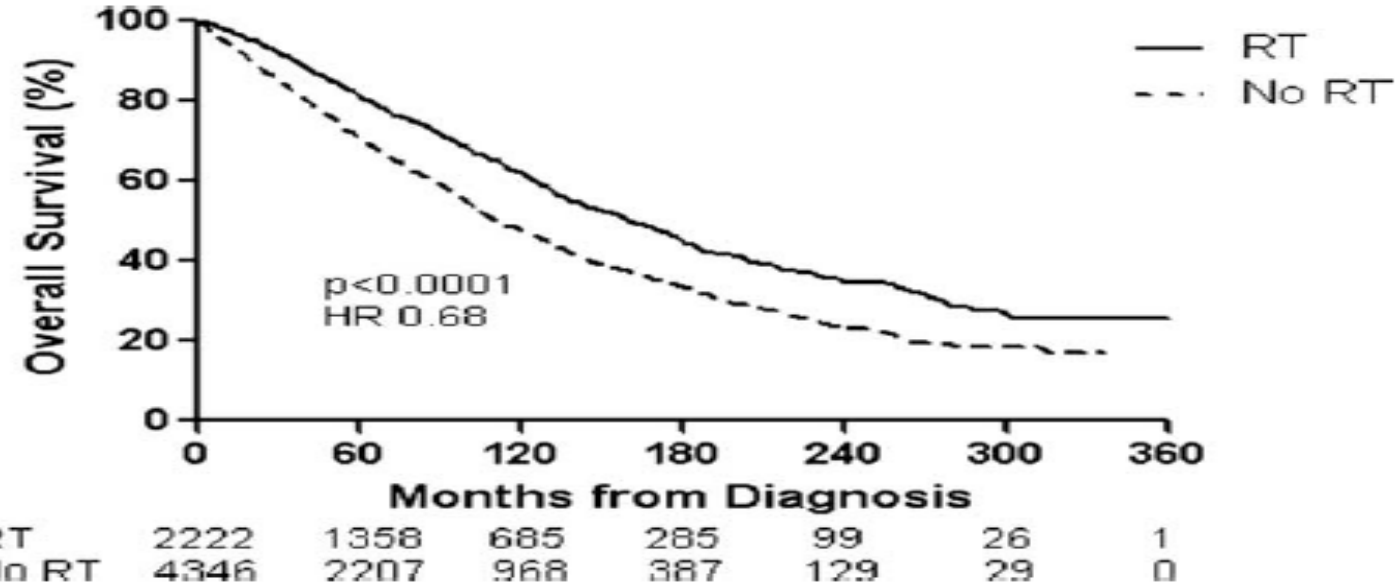


Figure 2. Overall survival in patients with low-grade, stage I-II follicular lymphoma treated with or without upfront external beam radiation therapy (RT) is shown. HR indicates hazard ratio.

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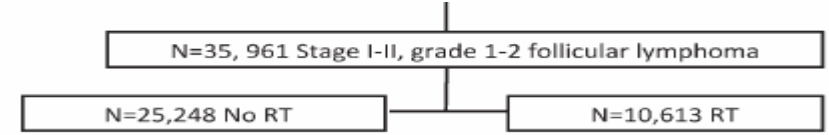
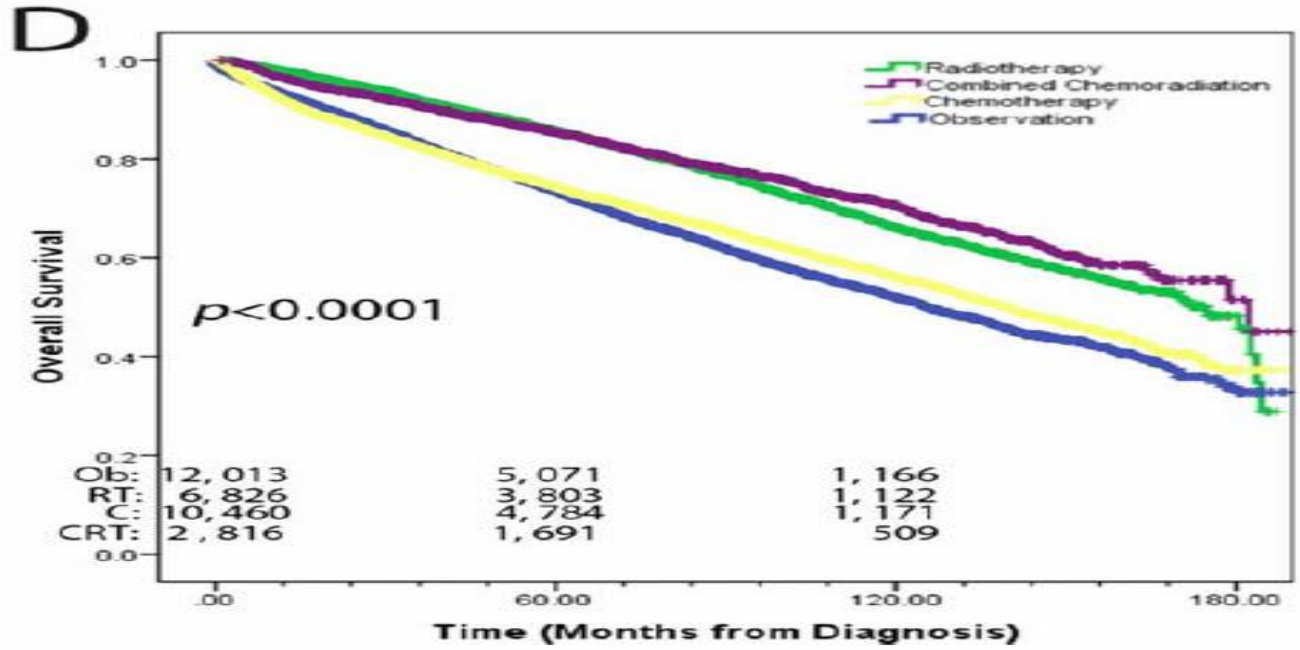
What Is the Optimal Management of Early-Stage Low-Grade Follicular Lymphoma in the Modern Era?

Cancer 2015;121:3325-34.

John A. Vargo, MD[1]; Beant S. Gill, MD[1]; Goundappa K. Balasubramani, PhD[2]; and Sushil Beriwal, MD[1]





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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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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.

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.

- 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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Is there a role for adjuvant chemotherapy with ISRT in localised FL ?

Series of randomized trials, small and -ve

BNLI study chlorambucil – ve but persistent improvement

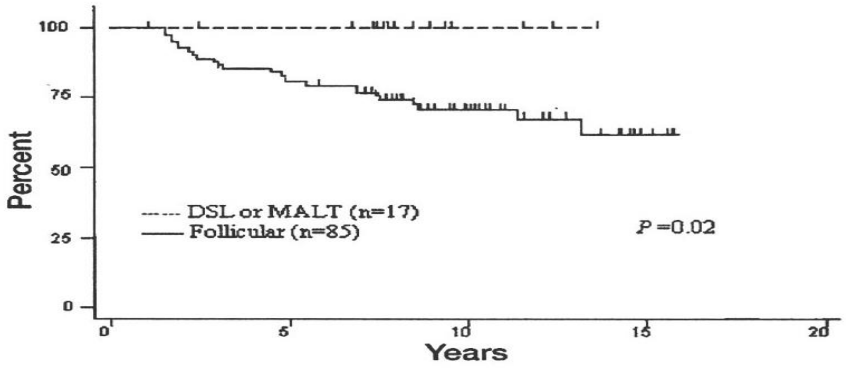
MDACC phase II Seymour JCO 2003

- Better than historical controls
- Better in high risk groups

Prospective Australian trial: IFRT +/- RCVP

Macmanus, Seymour : presented at Lugano 2017

	10y FFTF
All	72%
Stage II	70%
Bulk ≥ 5cm	65%
Age > 60	64%

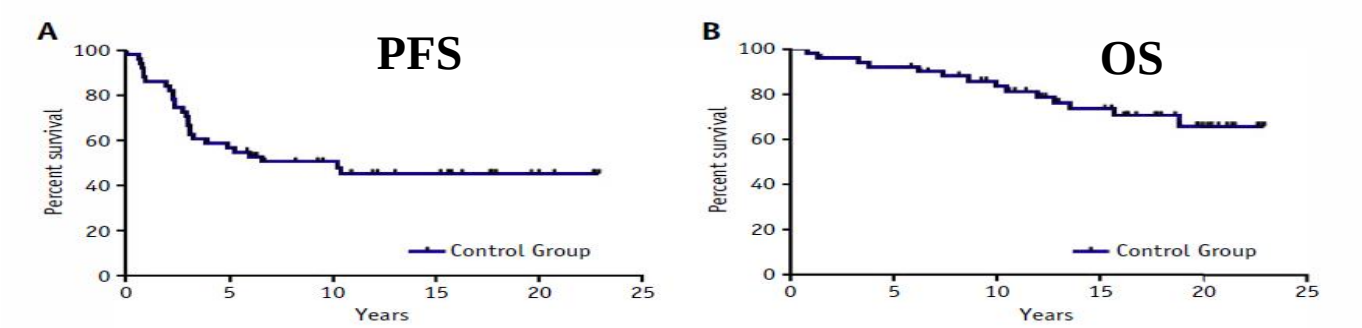


Addition of Rituximab to Involved-Field Radiation Therapy Prolongs Progression-free Survival in Stage I-II Follicular Lymphoma: Results of a Multicenter Study

Marco Ruella, MD,*,† Andrea Riccardo Filippi, MD,§ et al

Int J Radiation Oncol Biol Phys, Vol. 94, No. 4, pp. 783–791, 2016

n=51



n=43

Median f/u 16.7yrs

Median f/u 8.6yrs

36-40Gy: R weekly x4

Advanced stage disease : Goals of therapy versus toxicity / tolerability in Follicular Lymphoma

- Advanced 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, tumor burden, patient preferences.

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Follicular Lymphoma International Prognostic Index (FLIPI and F2) –

important to record but not yet influencing management

No Nodal regions > 4

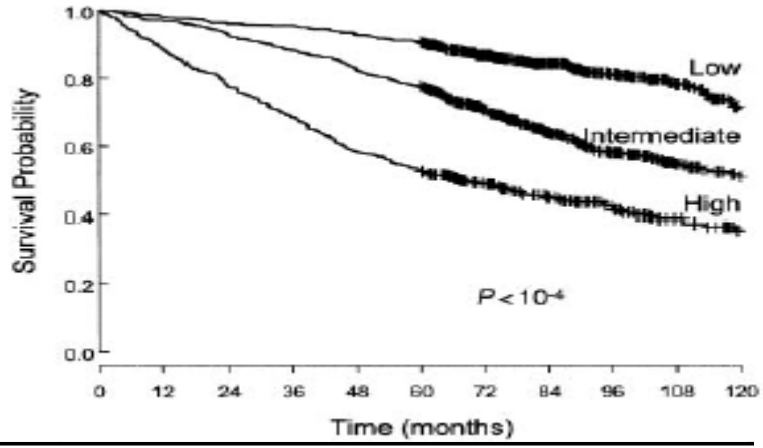
L Elevated LDH

A Age > 60

S Stage III/IV

H Haemoglobulin < 12 g/dl

F2 **Serum B2 microglobulin**



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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Established definitions of when treatment required – is this still the right approach ?

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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Rituximab has changed the landscape in Follicular Lymphoma

- Watch and wait versus rituximab – is watch and wait still the correct approach ?
- Rituximab – chemotherapy – what is the optimal immunochemotherapy ?
- Rituximab maintenance – is 2 years standard of care and should this be with subcutaneous Rituximab ?
- Rituximab biosimilars – is this cost effective approach inevitable ?

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Is Watch and wait the correct approach in the modern era ?

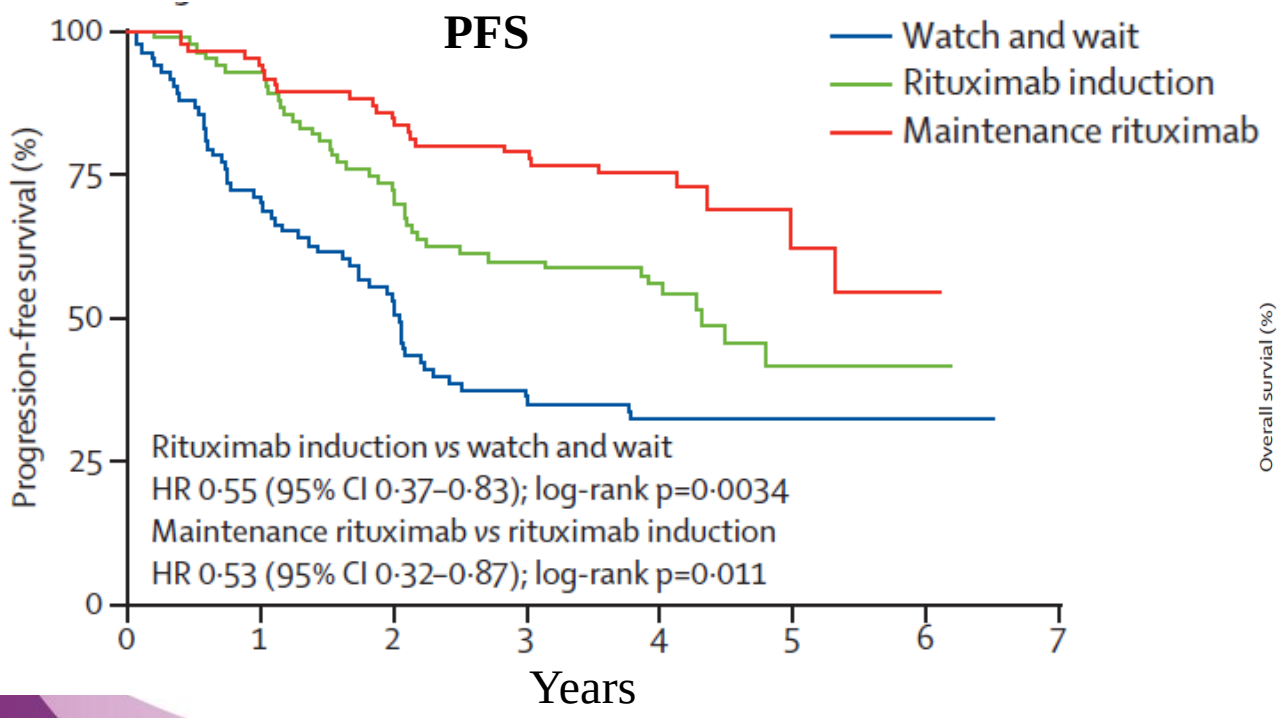
- Advanced stage
  - The natural history of follicular lymphoma, many patients over the age of 70 never require treatment.
  - Does Rituximab immunotherapy make a difference?

Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial

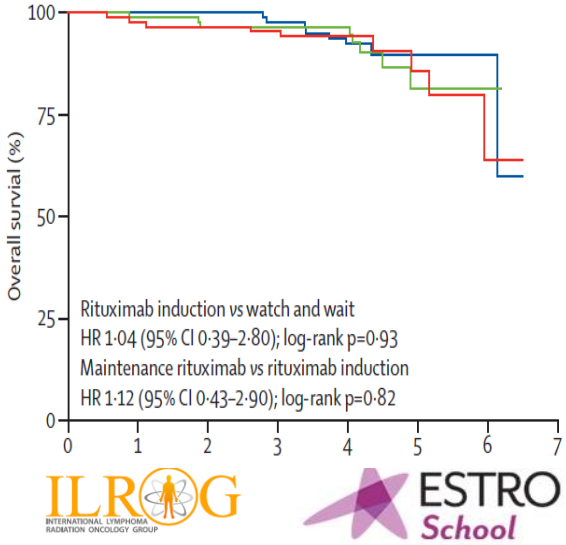
Lancet Oncol 2014; 15: 424–35

Kirit M Ardeshna, Wendi Qian, Paul Smith, Nivette Braganca, Lisa Lowry, Pip Patrick, June Warden, Lindsey Stevens, Christopher F E Pocock, Fiona Miall, David Cunningham, John Davies, Andrew Jack, Richard Stephens, Jan Walewski, Burhan Ferhanoglu, Ken Bradstock, David C Linch

PFS



Overall survival



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QUALITY OF LIFE VALUES FOR ECONOMIC ASSESSMENT

Health state	Utility score	Source
Asymptomatic follicular lymphoma	0.8800	Unpublished data from Wild *et al*. 2005 for "disease free" patients from ScHARR
Symptomatic follicular lymphoma	0.8050	Unpublished data from Wild *et al*. 2005 for "progression free" patients from ScHARR
Progressive disease	0.7363	Unpublished data from Wild *et al*. 2005 for "disease progression" from ScHARR

Initial treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Rituximab induction	£38,355		11.31		
Rituximab induction + maintenance	£47,969	£9,614	11.45	0.14	£69,406
Watchful waiting	£48,147	£9,793	10.98	Dominated	Dominated

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Non-Hodgkin's lymphoma: diagnosis and management

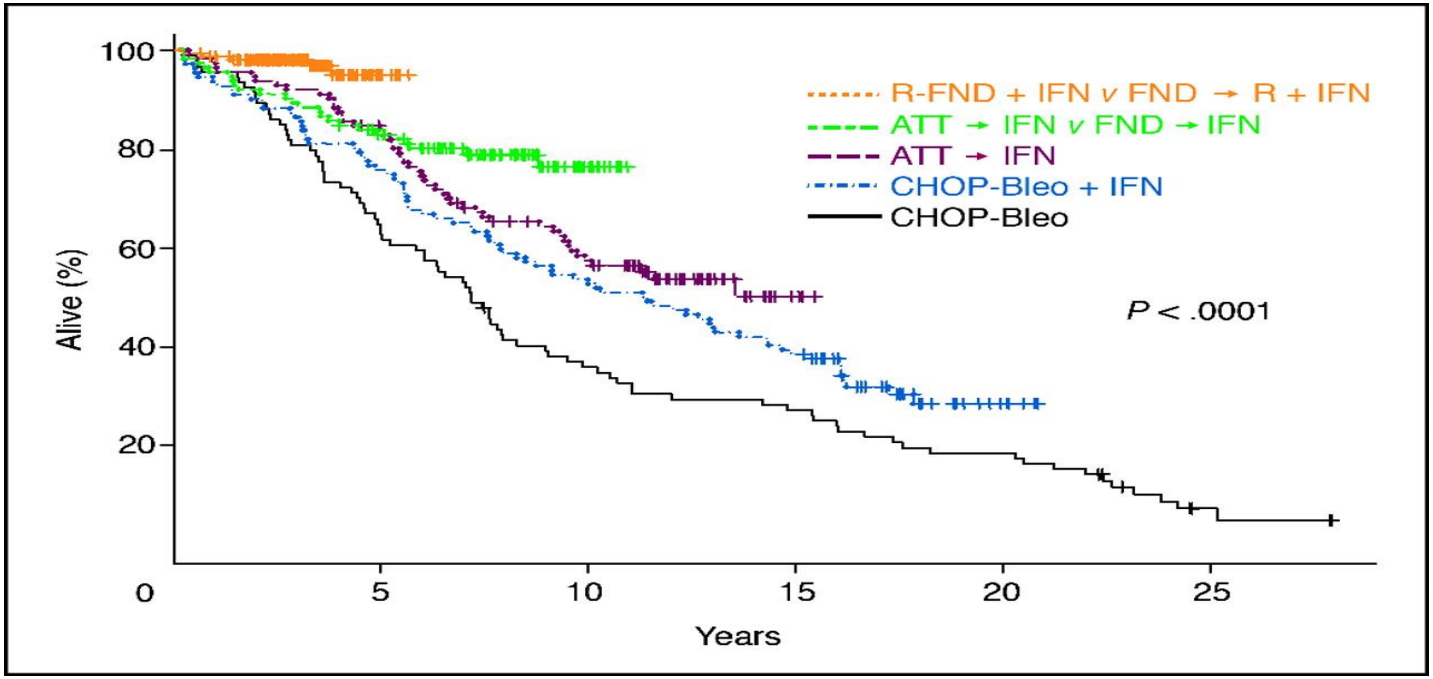
NICE guideline: methods, evidence and recommendations

Recommendations	Offer local radiotherapy as first-line treatment to people with localised stage IIA follicular lymphoma.
	Offer FDG-PET-CT imaging to confirm staging for people diagnosed with: • stage I or localised stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field
Recommendation	Offer rituximab induction therapy[a] to people with advanced-stage (stages III and IV) follicular lymphoma who are asymptomatic.

Rituximab-Chemotherapy in Untreated Advanced Follicular NHL

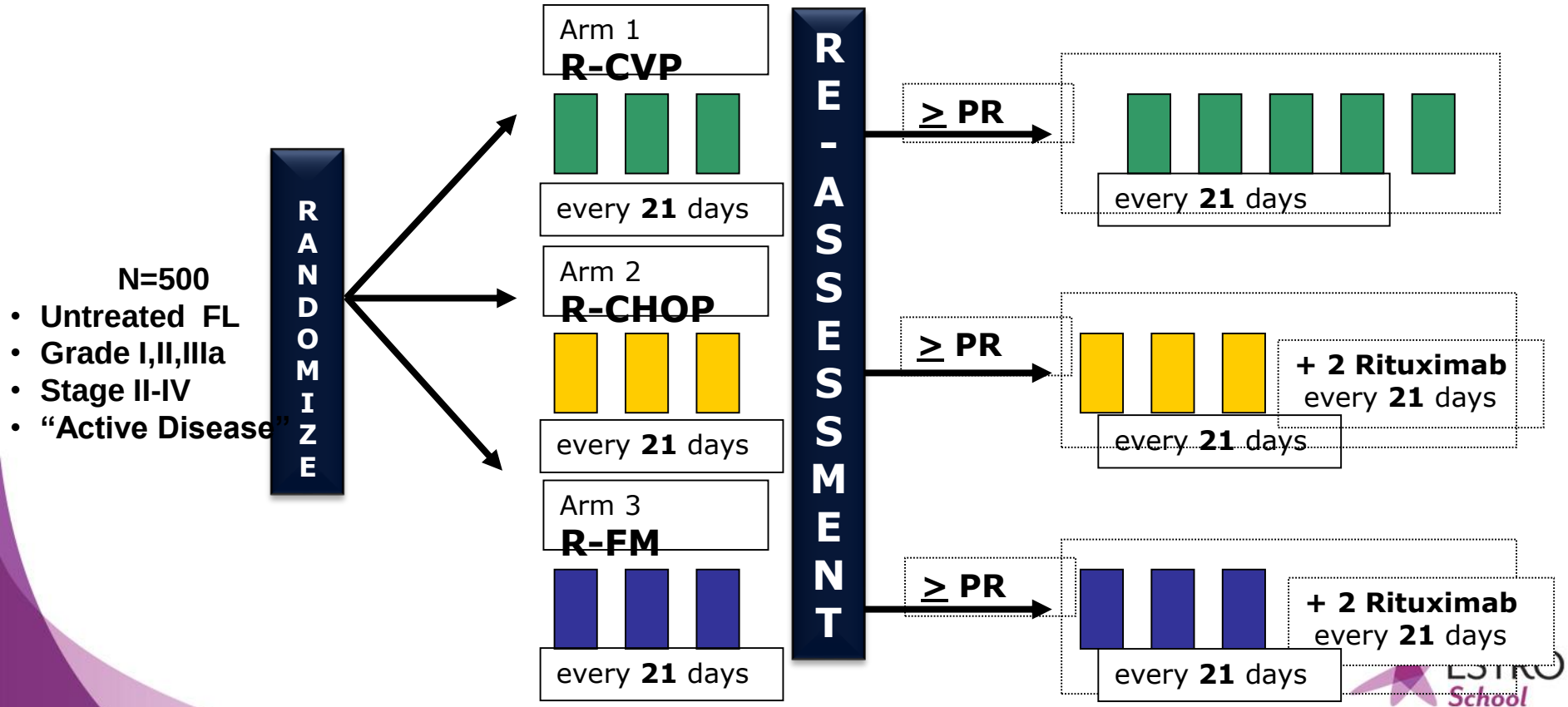
Study	Treatment, n	Median FU, months	ORR %	CR, %	Median TTP/ TTF/ EFS, mo	OS, %
Marcus et al. 2008	CVP, 159	53	57	10	15	77
	R-CVP, 162		81	41	34	83
					P<.0001	*P*=.0290
Hiddemann et al. 2005	CHOP-IFN, 205	18	90	17	29	90
	R-CHOP-IFN, 223		96	20	NR	95
					P<.001	*P*=.016
Herold et al. 2007	MCP-IFN, 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

Overall Survival Following Frontline Study Entry

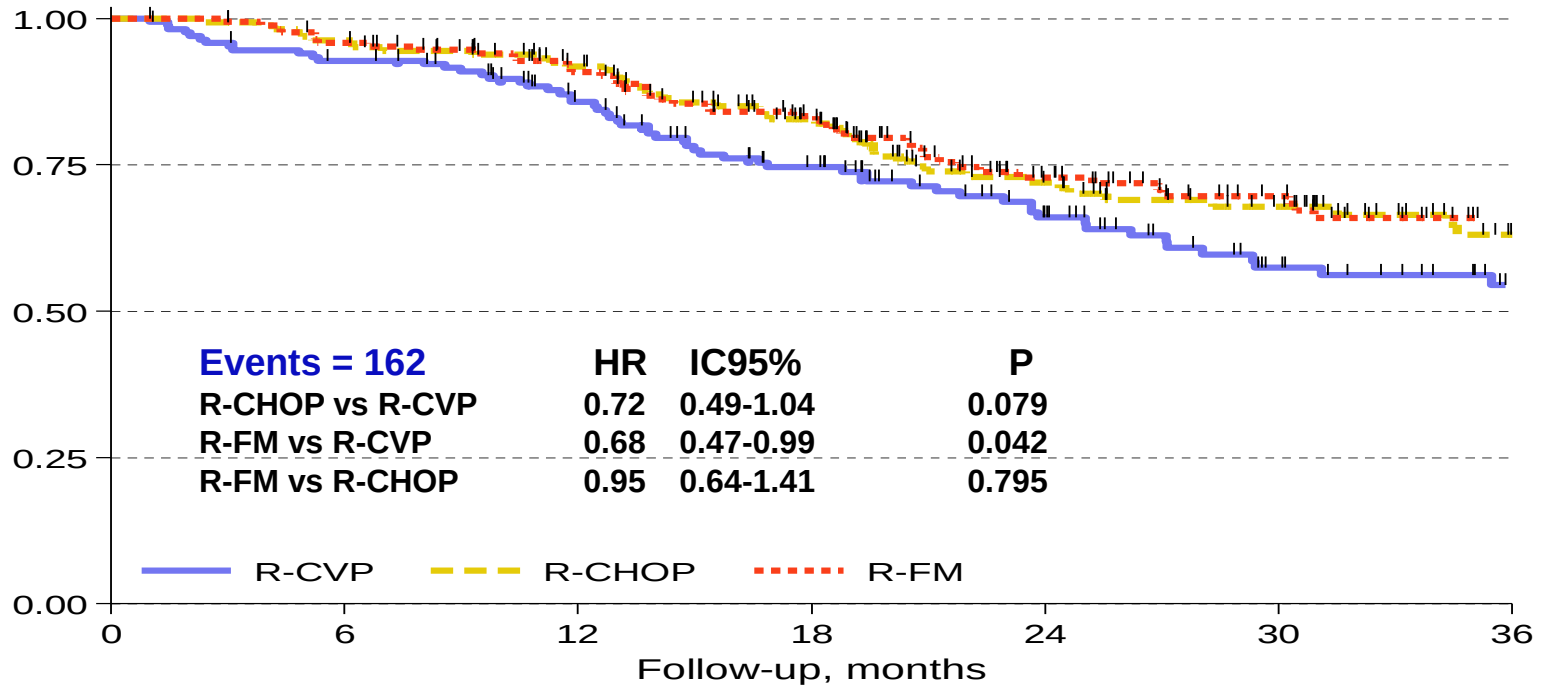


Liu Q, Mclaughlin P et al. JCO 2006;24:1582-1589

FOLL-05 Study Federico, M et al. JCO 2013.

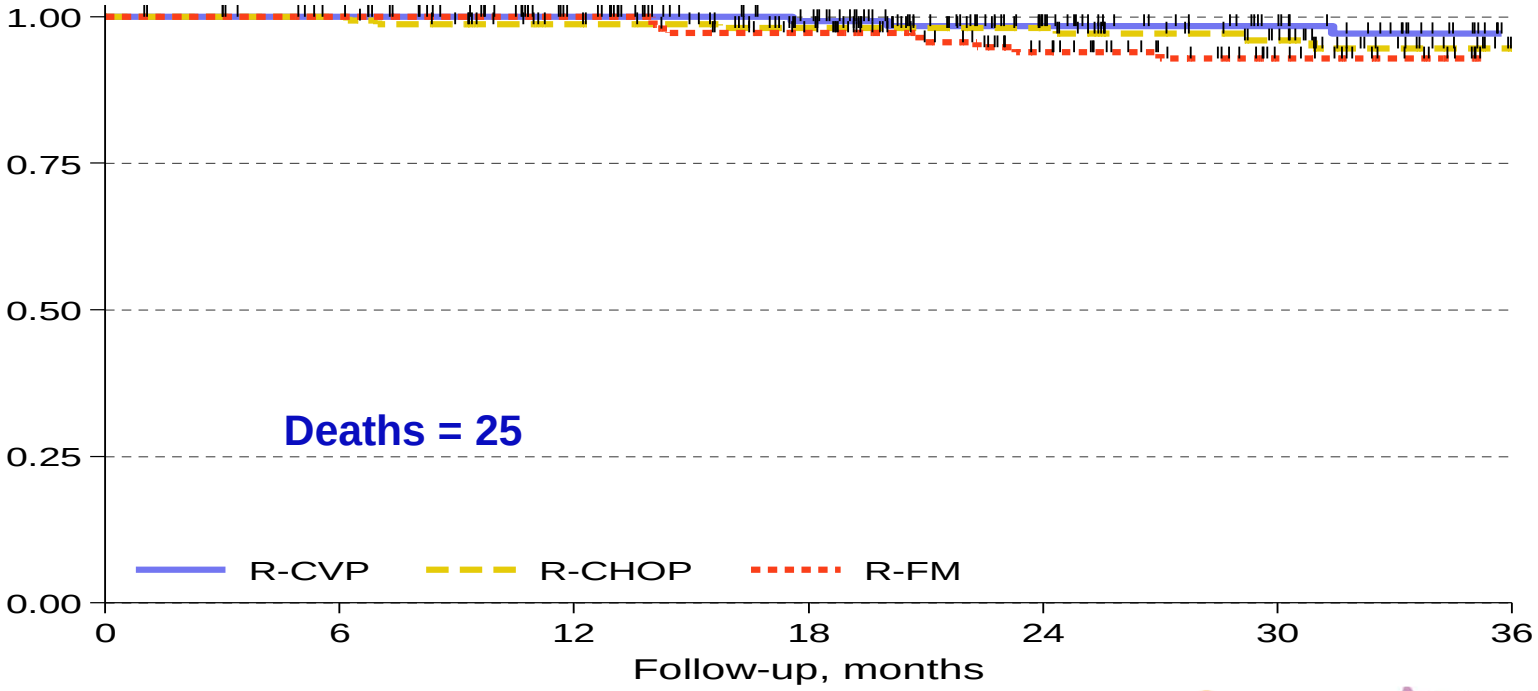


FOLL-05 PFS by arm (N=504)

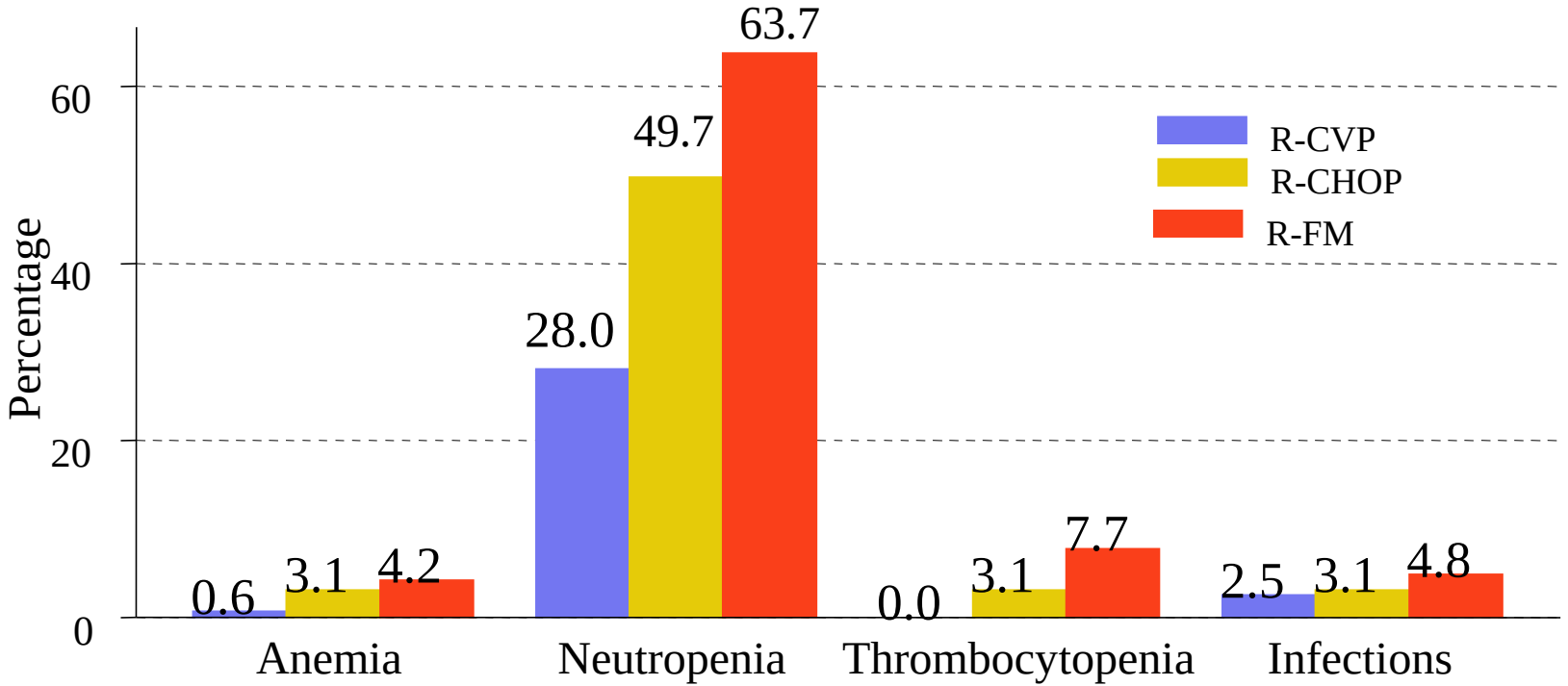


Federico, M et al. JCO 2013.

FOLL-05 Overall Survival Federico, M et al. JCO 2013.



Acute and late Toxicities



Overall, 23 second malignancies were registered during follow-up: four in R-CVP, five in R-CHOP, and 14 in R-FM

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BR vs. R-CHOP The StiL Study

Eligible patients:

- CD20+ FL, Waldenstrom's macroglobulinemia (WM), marginal-zone lymphoma (MZL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL); elderly
- No previous treatment
- Stage III or IV

RANDOMIZE

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/m² Days 1-5
Rituximab 375 mg/m² Day 1

- **Primary objective**
  - **To prove the noninferiority of BR vs. R-CHOP defined as a decrease of <10% in PFS after 3 years**
- **Secondary objectives**
  - **Response rates, time to next treatment, event-free survival, OS**
  - **Acute and late toxicities, infectious complications**
  - **Stem cell mobilization capacity in younger patients**

Rummel M et al. Lancet, 381.1203 - 1210.

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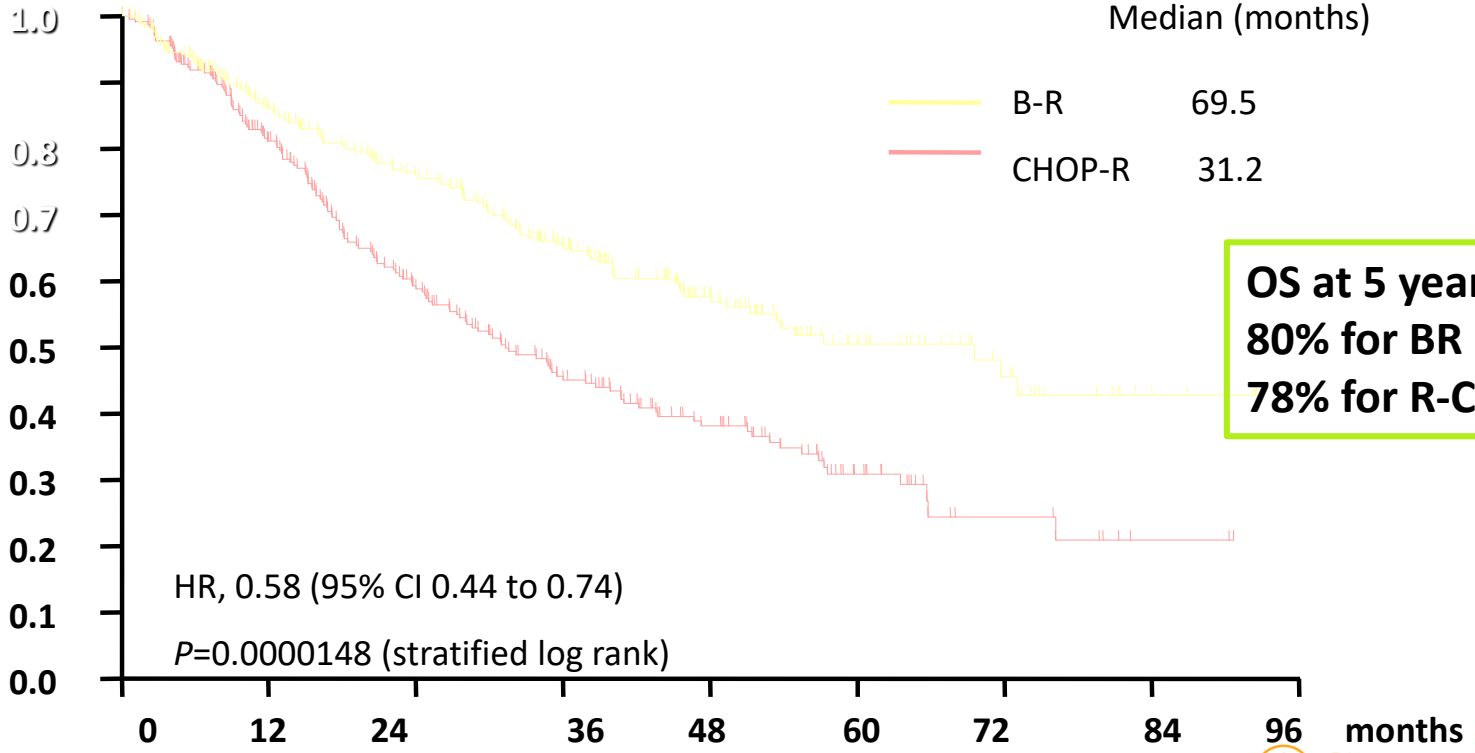
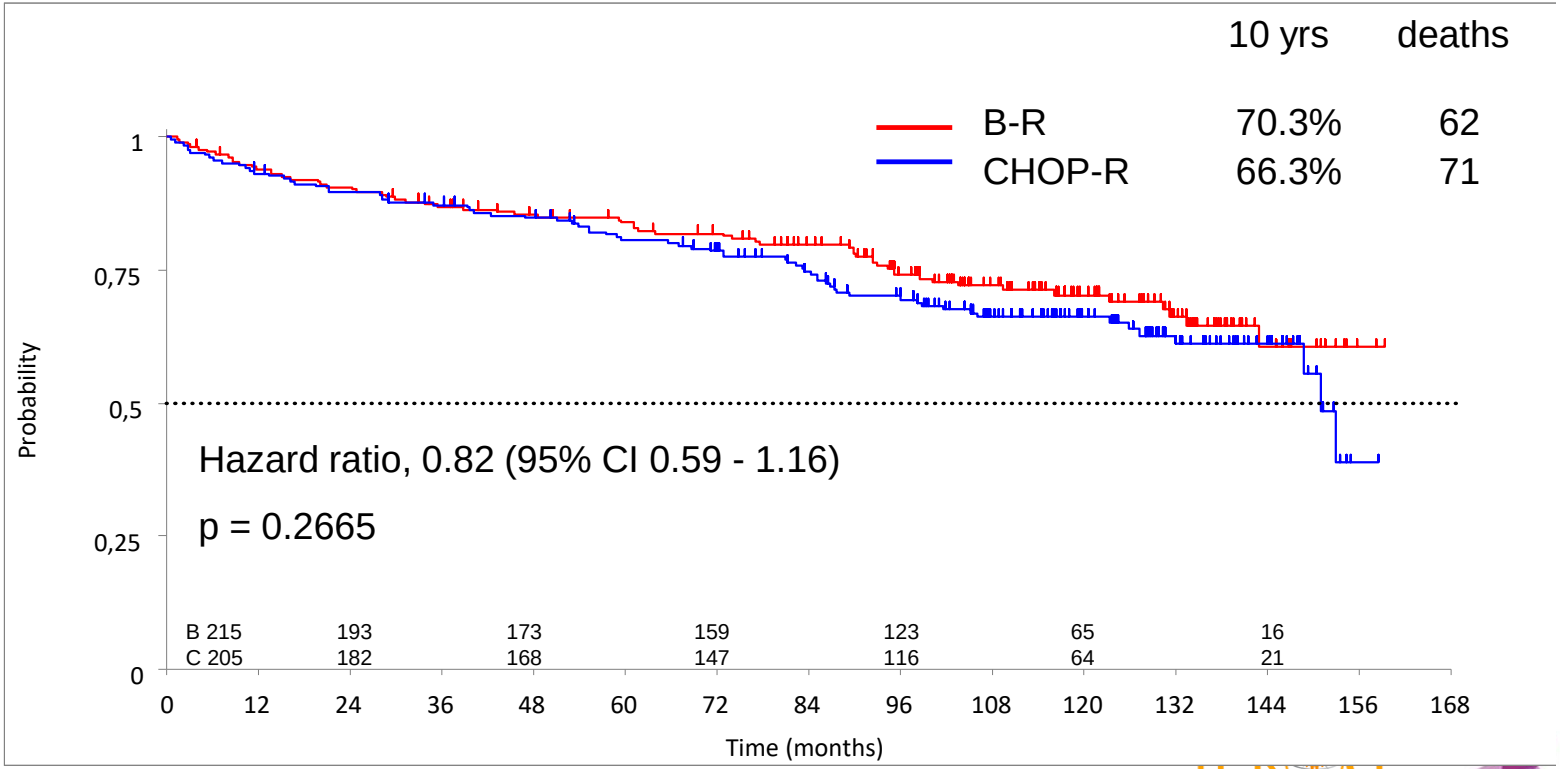
BR vs. R-CHOP
PFS 45 Months of Follow-Up



OS at 5 years was 80% for BR and 78% for R-CHOP

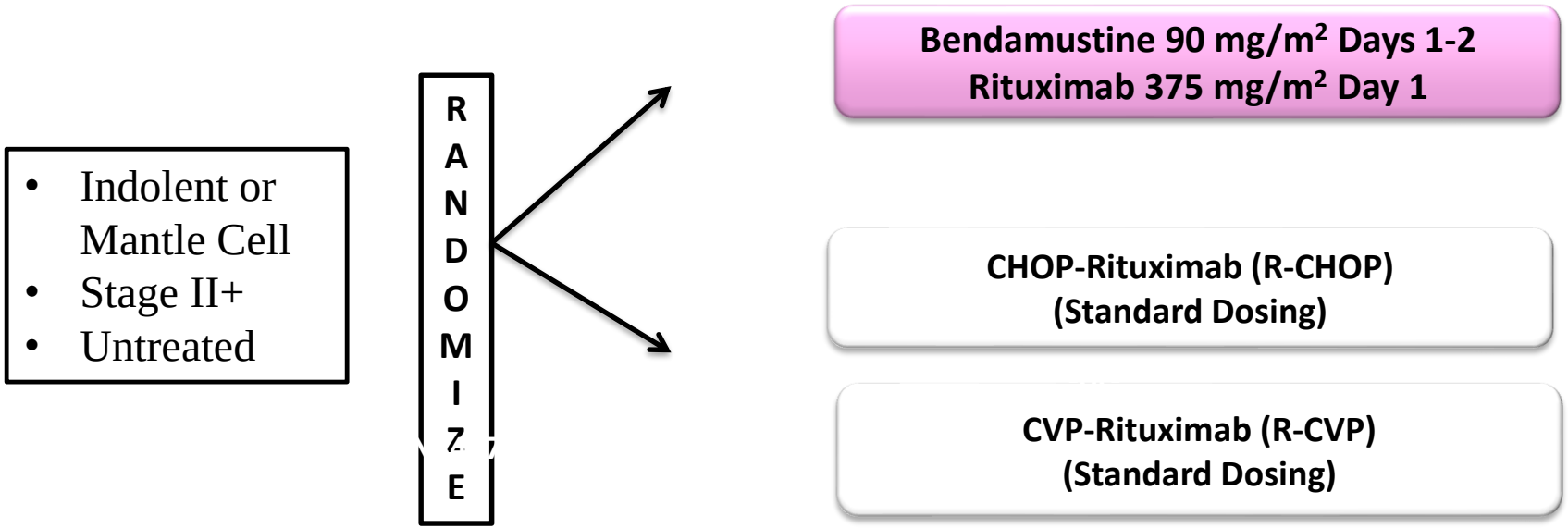
Rummel M et al. Lancet, 381.1203 - 1210.

Long-term follow up: Overall survival



Rummel M, et al ASCO 2017

Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study.



- Primary Objective: Determine if BR is non-inferior (CR rate) to standard tx (R-CHOP or R-CVP)

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Flinn, I. et al Blood. 2014 May 8;123(19):2944-52.

Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study.

Efficacy

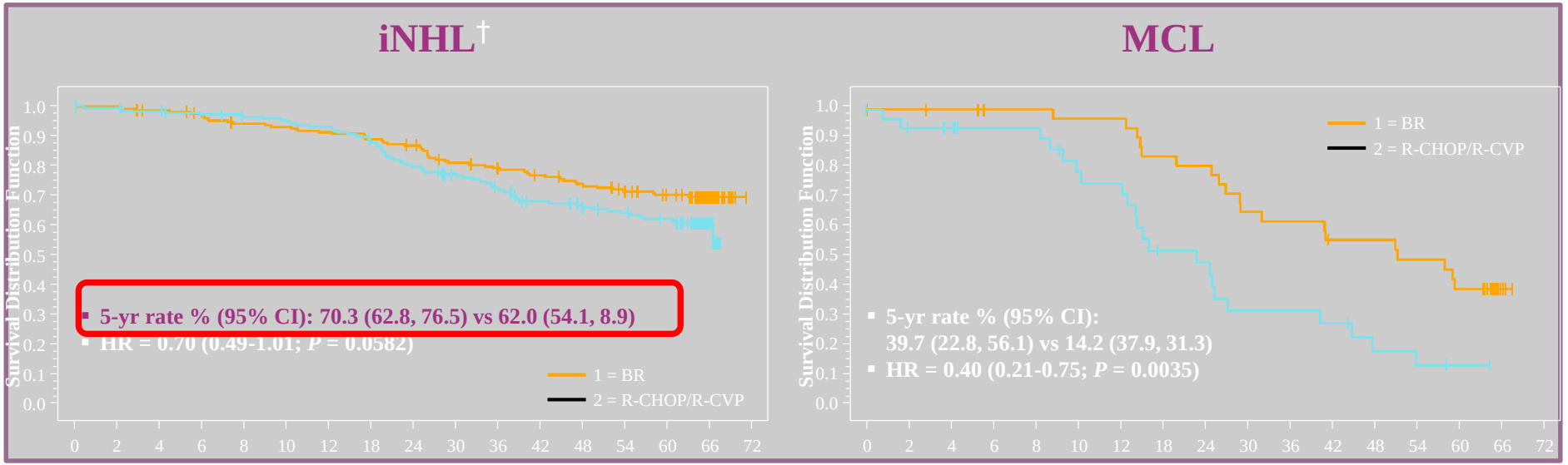
Overall Response	BR	R-CHOP/R-CVP
Overall Response Rate	97%	91%
Complete Response	31%	25%
Partial Response	65%	66%

Toxicity

Toxicity	BR	R-CHOP	R-CVP
Vomiting	25-29%	13%	13%%
Infections (Gr3+)	7-12%	5%	7%
Rash	12-18%	7%	9%
Neuropathy	4%	20%	26%
Alopecia	4%	51%	21%
Neutropenia (Gr3+)	39-49%	86%	56%
Lymphopenia (Gr3+)	61-63%	33%	28%
Platelets (Gr3+)	5-10%	12%	2%

Flinn, I. et al Blood. 2014 May 8;123(19):2944-52.

Progression-Free Survival by Lymphoma Type



At Risk

1.	187	182	176	170	165	163	160	156	151	139	134	129	122	116	110	34	0
2.	186	175	172	168	165	162	159	149	135	126	118	107	101	97	92	11	0

At Risk

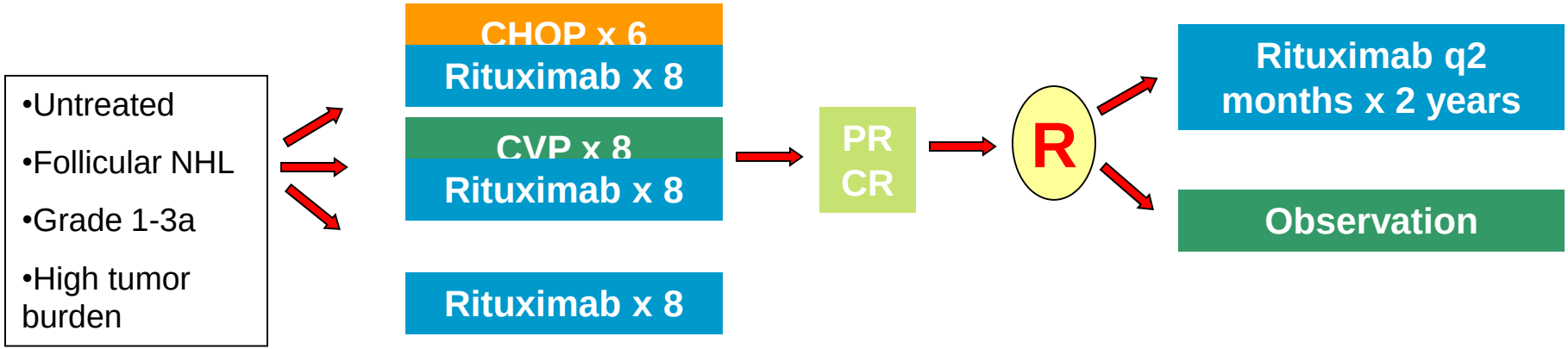
1.	37	36	34	32	32	31	31	27	26	21	20	17	17	15	12	3	0
2.	37	30	29	26	26	21	20	13	12	8	8	7	4	3	2	0	0

Progression-Free Survival (months)

*BR vs R-CHOP/R-CVP.
†Not including MCL.

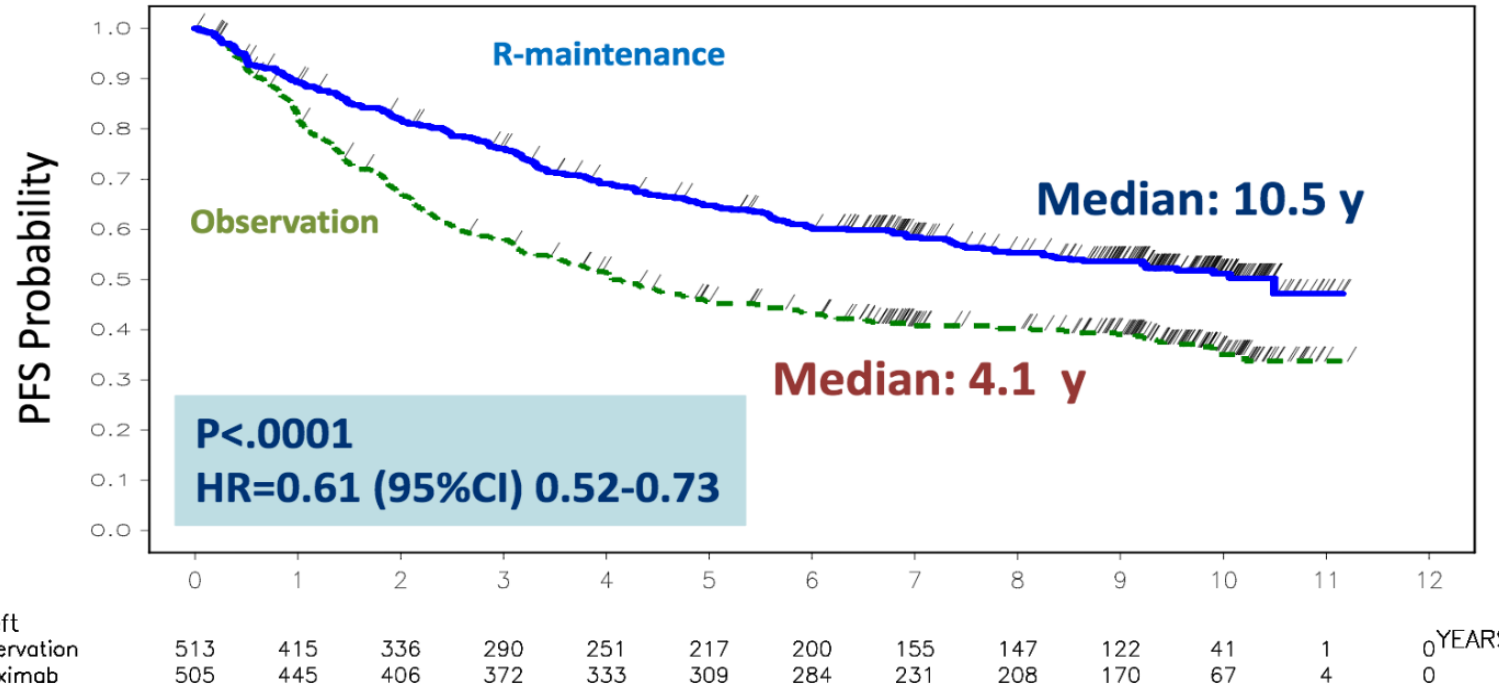
Flinn I, et al, ASCO 2017

PRIMA Study – Rituximab maintenance

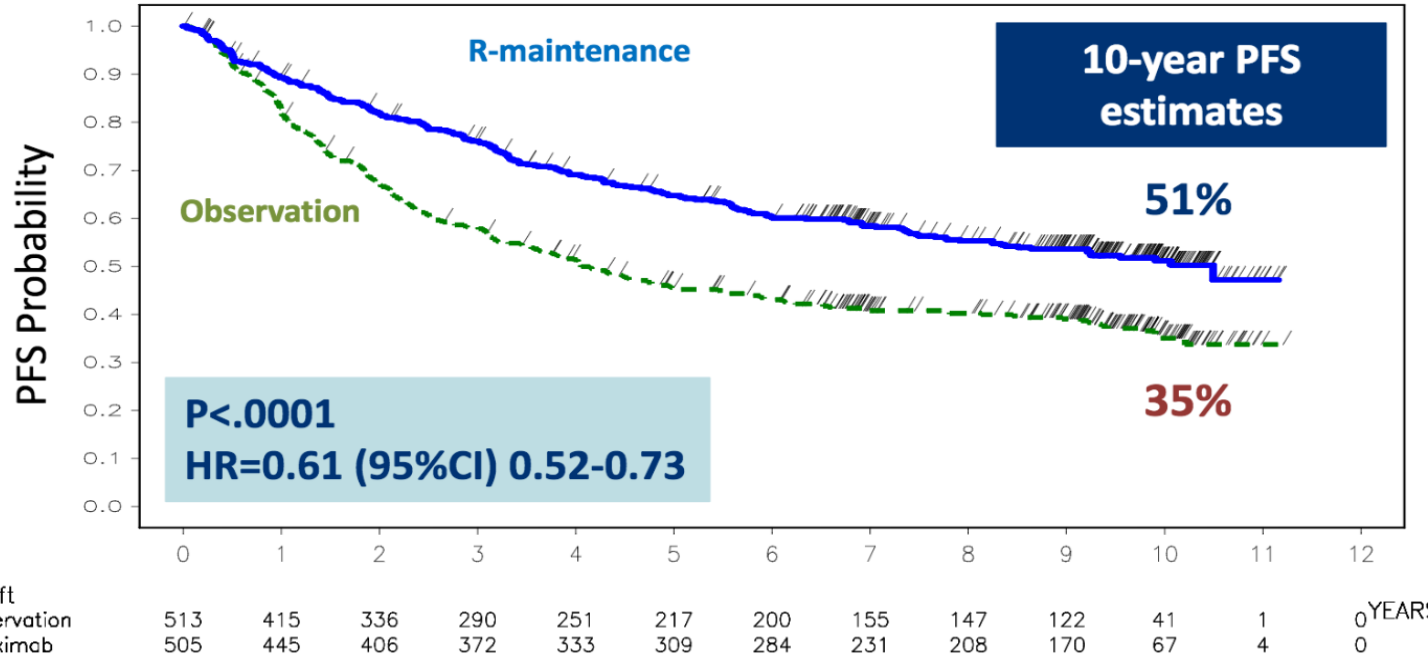


Salles, G. et al. J Clin Oncol 28:15s, 2010

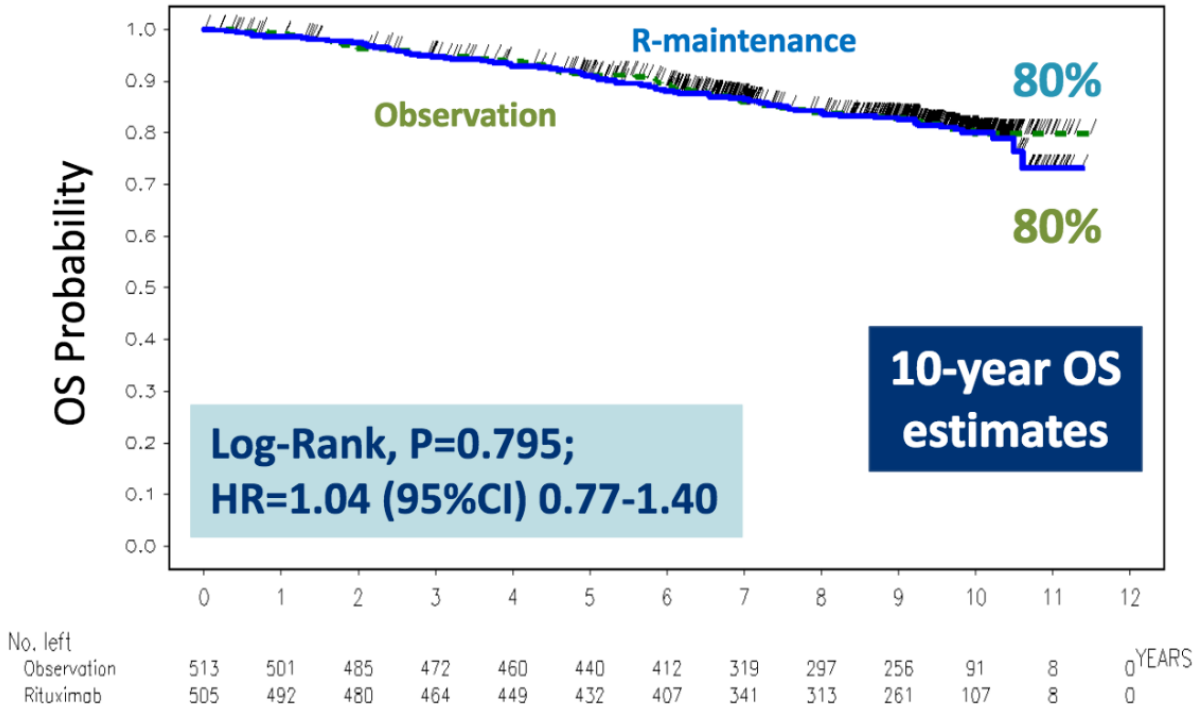
PRIMA : Progression Free Survival at 10 years (from randomization)



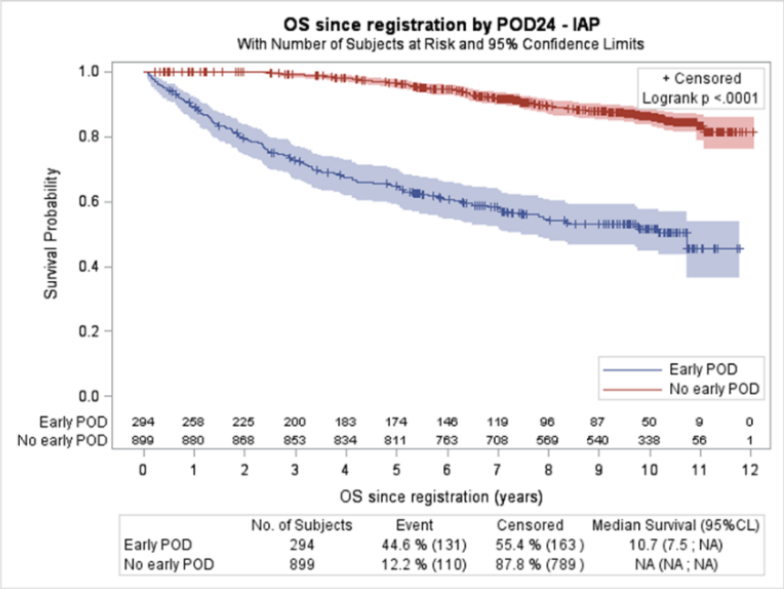
PRIMA : Progression Free Survival at 10 years (from randomization)



PRIMA : Overall Survival at 10 years (from randomization)



PRIMA : EFS 24 (EFS18 after randomization)



Failed by month 18 after randomization (EFS 24)	
Observation	**R-maintenance**
144 (28%)	**83 (16%)**

Long term OS of pts in the observation and maintenance groups are identical

→ The **smaller** group of pts who progress during R- maintenance represents pts **more difficult to salvage**

Conclusions

- With 10 years of follow-up,
  - the benefit of R-maintenance in term of PFS persist
  - this benefit exists independently of initial pts characteristics (age, FLIPI)

- No new safety signals have occurred

- Those pts with a high tumor burden have a 80% chance of survival at 10 years but there is no OS benefit associated with R-maintenance

- Half of the patients having received R-maintenance
  - are free of disease progression (38% risk reduction)
  - **have not received any new anti-lymphoma treatment (33% risk reduction)**

Toxicity considerations of Rituxumab after Bendamustine

- Despite the fact that Gallium was not designed to detect differences in chemotherapy platforms, the fatal AE rate in GALLIUM drew attention
  - 5% in BR(O) plus maintenance patients
  - 2% in R(O)-CHOP plus maintenance patients
- Virtually all "excess" fatal AE's occurred during maintenance or later
- Raising concern that
  - MR after BR (or MO after BO) is adding toxicity that may not justify any efficacy benefit
- Additionally, remains unproven that an efficacy benefit exists for MR

Early Relapse of Follicular Lymphoma After Rituximab Plus CHOP Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. Casulo C et al J Clin Oncol. 2015 Aug 10;33(23):2516-22

- 20% of patients with follicular lymphoma (FL) experience progression of disease (POD) within 2 years of initial chemoimmunotherapy.
- National LymphoCare Study to identify whether prognostic FL factors are associated with early POD and whether patients with early POD are at high risk for death.
- 588 patients with stage 2 to 4 FL received first-line R-CHOP.
- Two groups were defined: patients with early POD 2 years or less after diagnosis and those without POD within 2 years, the reference group.

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Early Relapse of Follicular Lymphoma After Rituximab Plus CHOP Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. Casulo C et al J Clin Oncol. 2015 Aug 10;33(23):2516-22

- 588 patients, 19% (n = 110) had early POD, 71% (n = 420) in reference group, 8% (n = 46) were lost to follow-up, and 2% (n = 12) died without POD less than 2 years after diagnosis.

- Five-year overall survival was lower in the early-POD group than in the reference group (50% v 90%). Trend maintained after adjusted for FLIPI (HR 6.44; 95% CI, 4.33 to 9.58). Results were similar for the validation set (FL IPI-adjusted hazard ratio, 19.8).

- Patients with FL who received first-line R-CHOP, POD within 2 years after diagnosis associated with poor outcomes and should be further validated as a standard end point of chemo-immunotherapy trials of untreated FL.

This high-risk FL population warrants further study in directed prospective clinical trials

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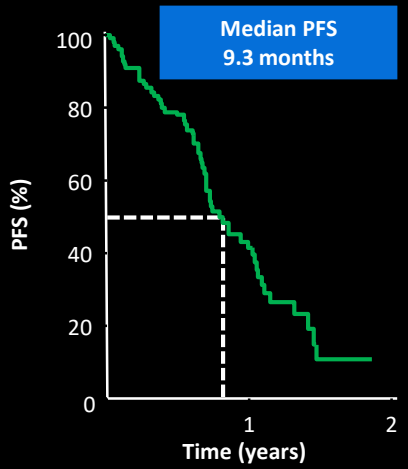
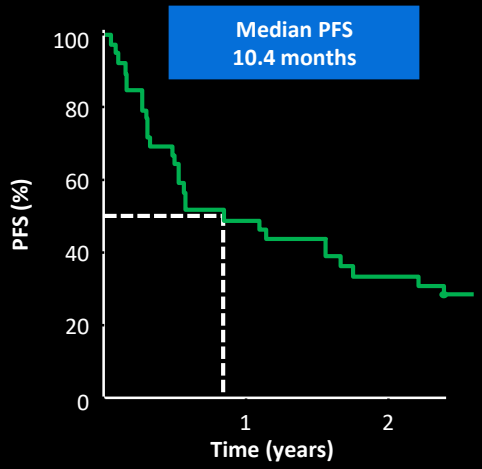
Unmet need in iNHL – relapsed and refractory disease

Effective current treatment options limited, with no standard of care currently identified

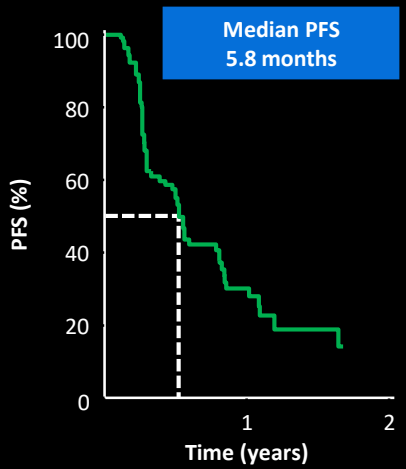
Bendamustine monotherapy[3]



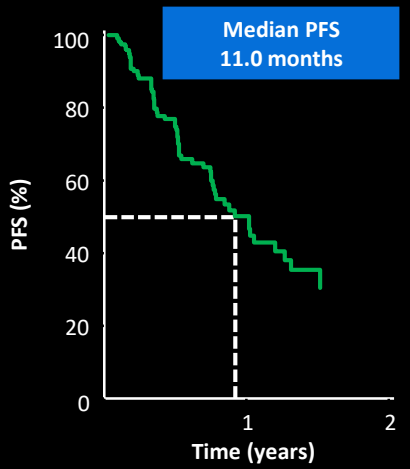
Radioimmunoconjugate (^{131}I-tositumomab)[4]



Ofatumumab monotherapy[5]

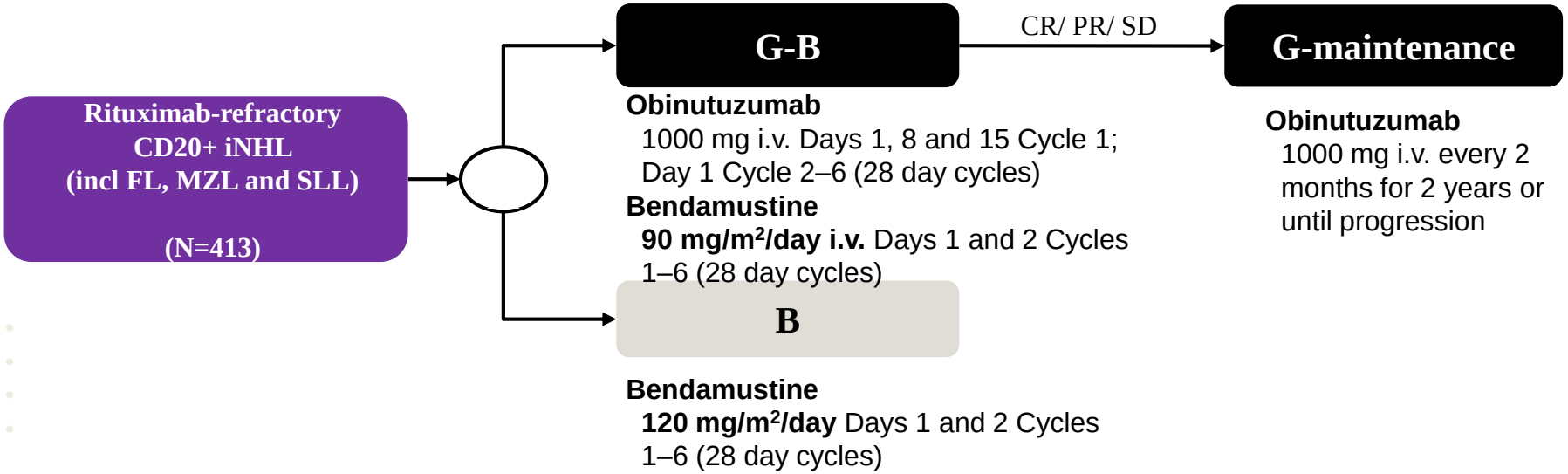


Idelalisib monotherapy[6]



1. The NHL Classification Project. *Blood* 1997; 89: 3909–3918
2. Fowler NH. *Pharmacy and Therapeutics* 2011; 36: 590–598
3. Kahl B, et al. *Cancer* 2010;116:106–114
4. Horning SJ, et al. *J Clin Oncol* 2005;23:712–719
5. Czuczman MS, et al. *Blood* 2012;119:3698–704
6. Gopal AK, et al. *N Engl J Med* 2014;370:1008–1018

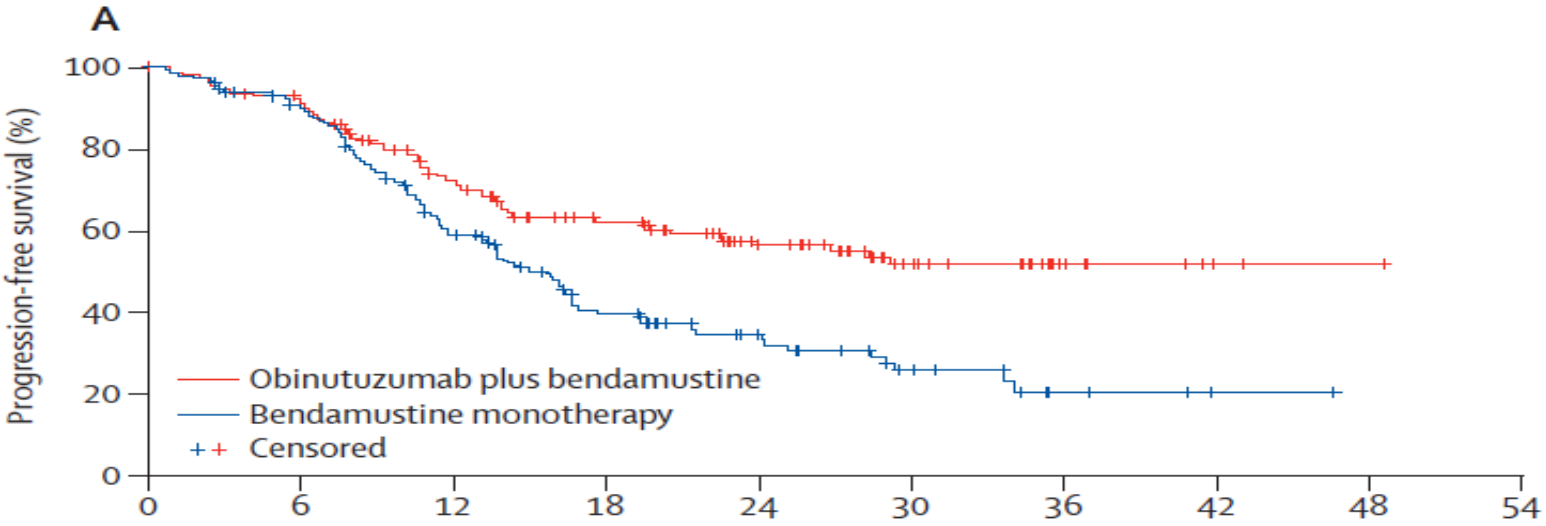
Relapsed Follicular Lymphoma
Gadolin: Bendamustine vs Bendamustine + Obinutuzumab



- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

Sehn, L. et al. Lancet

Gadolin Study (Bendamustine and Obinutuzumab) an option in relapsed disease
Progression Free Survival (IRC)

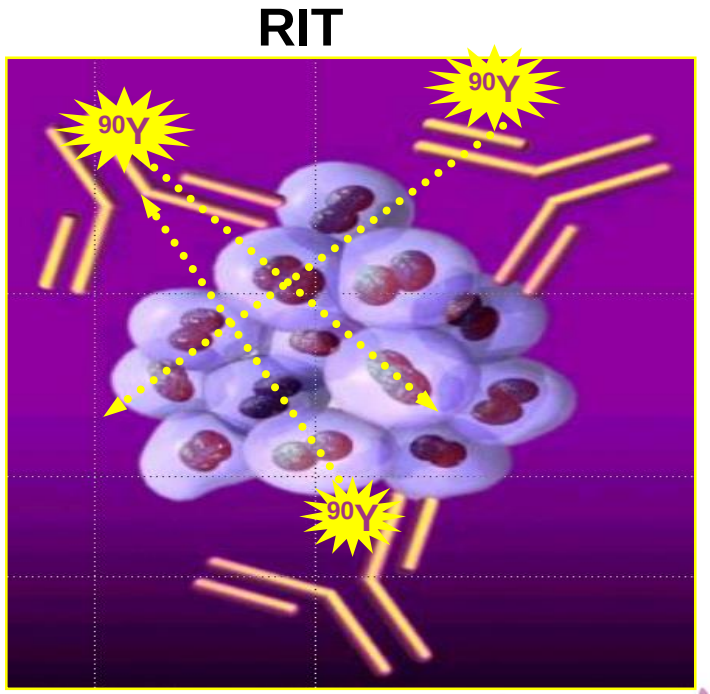


- The addition of obinutuzumab also improved PFS in patients that were refractory to both alkylators and rituximab (double refractory) (HR 0.56 (0.40–0.78))

Sehn, L. et al. Lancet Onc. 2016

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



ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

Role of RIT in Follicular lymphoma

- RIT simple and effective treatment; most active single drug apprach in NHL, unique mechanism of action
  - Effective (high response rate, durable remission) and underused single treatment in relapsed and rituximab refractory disease (131I Tositumomab, 90Y Ibritumumab tuxetan)
  - Phase II data as single agents Zevalin RIT in untreated follicular lymphoma show high response rates and durable remission
  - Patients in Phase 3 randomised ^{90}Y-ibritumomab arm had a greater than 5-year advantage in time to next treatment in FIT trial as consolidation
  - Novel Radioimmunconjugates are being developed but pathways to registration and routine clinical use are challenging.

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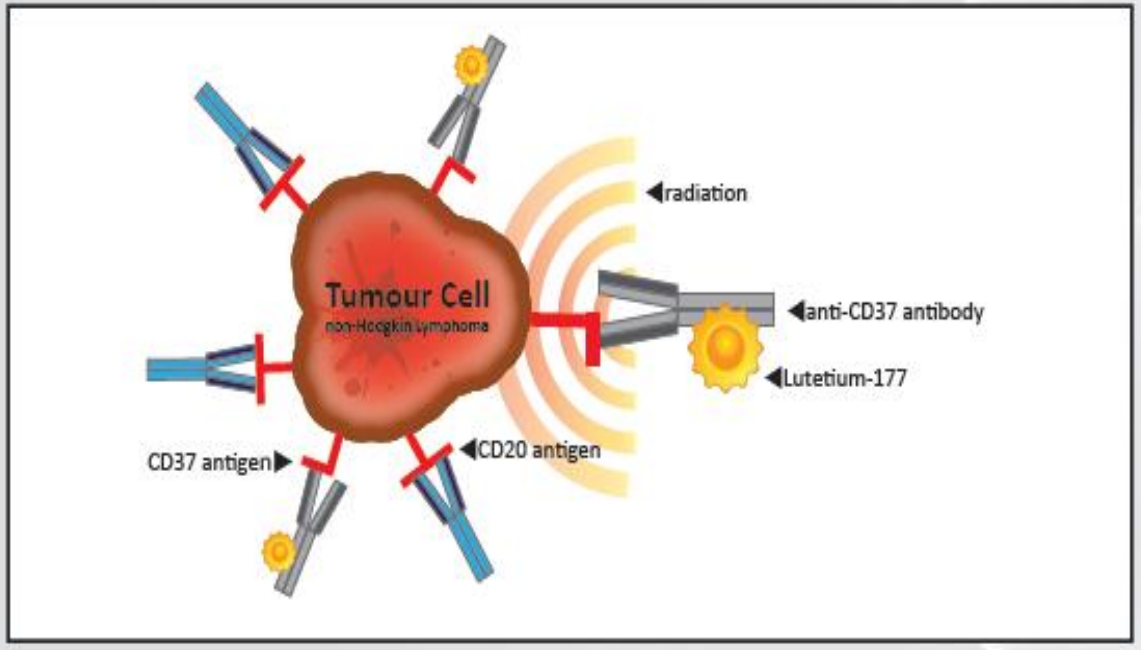
Results of a phase 1 study of ^{177}Lu-DOTA-HH1 anti body radionuclide (Betalutin) conjugate for patients with relapsed CD37$_+$ non-Hodgkin lymphomas – Lugano 2015



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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LYMRIT 37-01: Updated results of a phase I/II study of ^{177}Lu-lilotomab satetraxetan, a novel CD37-targeted antibody-radionuclide-conjugate in relapsed NHL patients

A Kolstad, MD, PhD[1], U Madsbu, MD[2], M Beasley, MD[3], M Bayne, MD[4], T Illidge, MD[5], N O'Rourke, MD[6], I Lagerlöf MD[7], R Hájek MD[8], W Jurczak MD[9], E Willenbacher MD[10], J Blakkisrud, PhD[11], A Muftuler Løndalen, MD[2], L Rojkjaer, MD[12], L Baylor Curtis MSc[12], M Bloma MSc[12], S Turner PhD[12], N Bolstad, MD[13], S Spetalen, MD[14], M Erlanson, MD, PhD[15], S Nygaard Rudå[1] and H Holte Jr. MD, PhD[1]

[1]Department of Oncology, Oslo University Hospital, Radiumhospitalet, Oslo, Norway; [2]Dept of Radiology and Nuclear Medicine, Oslo University Hospital, Radiumhospitalet, Oslo, Norway; [3]Bristol Cancer Centre, Bristol, United Kingdom; [4]Dorset Cancer Centre, Poole, United Kingdom; [5]University of Manchester, Manchester, United Kingdom; [6]Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; [7]University Hospital Linköping, Sweden; [8]University Hospital Ostrava, Czech Republic; [9]Malopolska Medical Center, Krakow, Poland; [10]University Clinic Innsbruck, Austria; [11]The Intervention Centre, Oslo University Hospital, Oslo, Norway; [12]Nordic Nanovector ASA, Oslo, Norway; [13]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway; [14]Department of Pathology, Oslo University Hospital, Radiumhospitalet, Oslo, Norway; [15]Dept of Oncology, Norrland University Hospital, Umeå, Sweden.

Figure 5. Best percent change in tumour size from baseline (n=46)

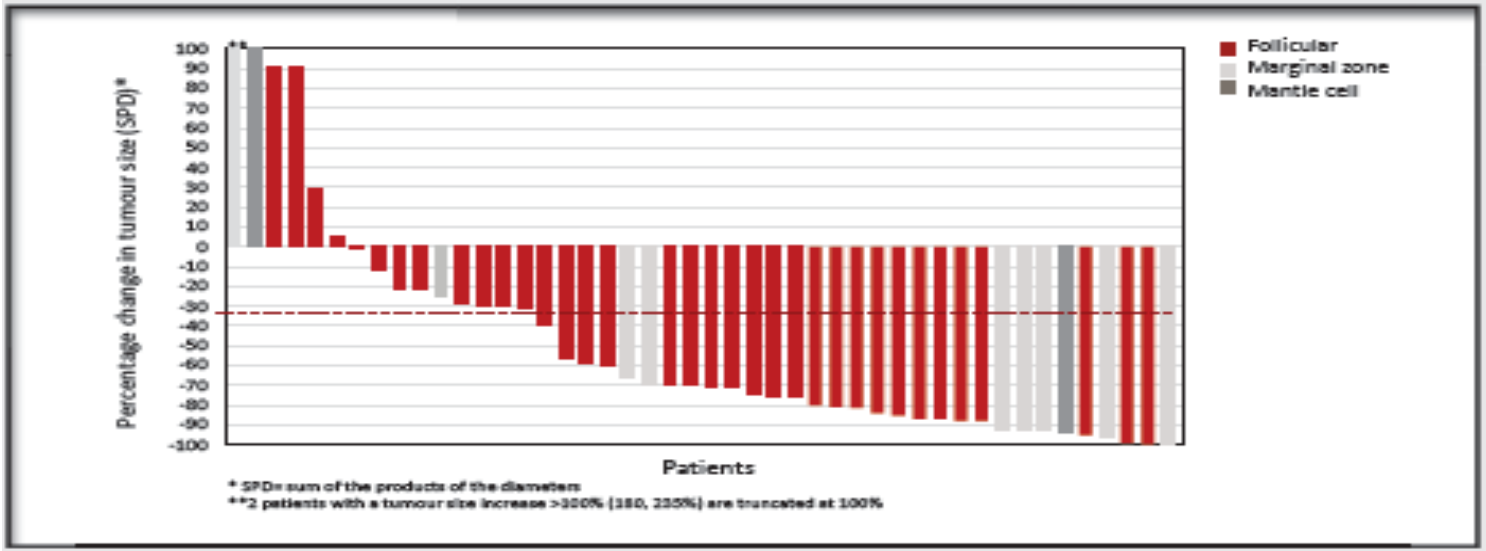

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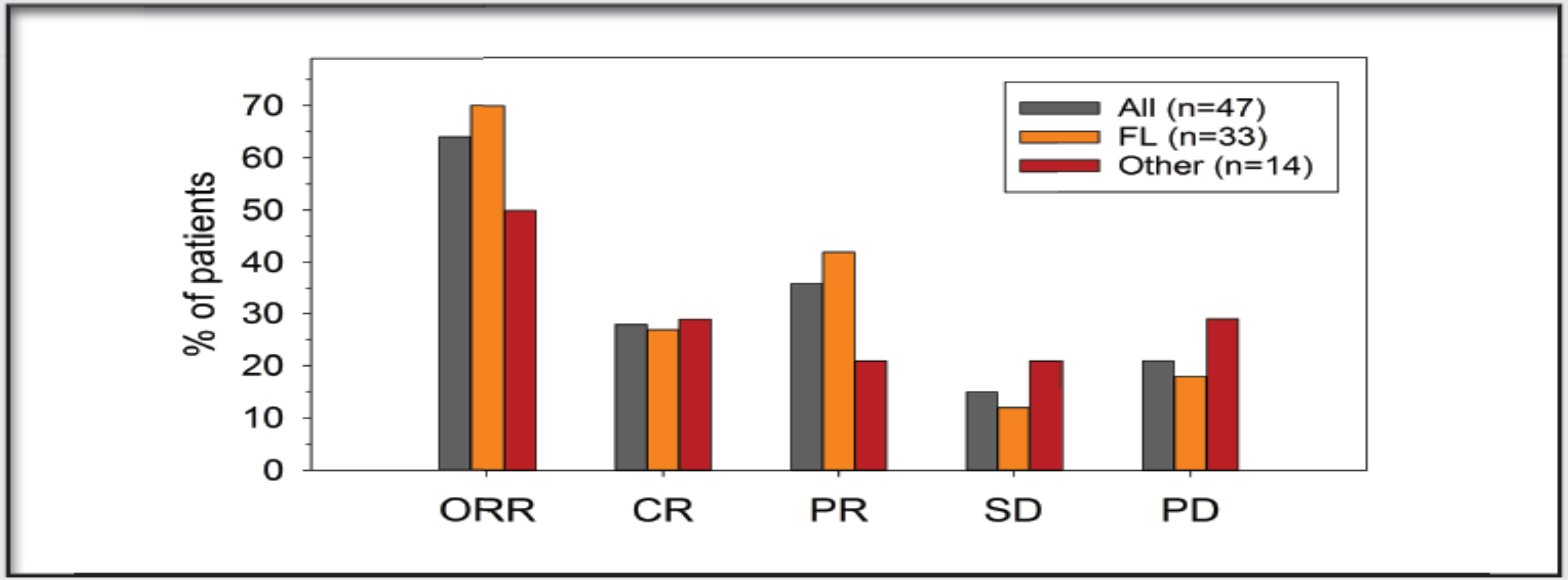
Figure 4. Overall response rate



Idelalisib: Selective PI3K Inhibitor Phase II in Refractory iNHL

Ritux + Alkylator Refractory Indolent NHL

Idelalisib 150 mg BID continuously

Long Term follow-up

- Tumor assessments:
  - Weeks 0, 8, 16, 24, 36, 48
  - Every 12 weeks thereafter
  - Evaluated by Independent Review Committee
    - 2 radiologists with adjudication if needed
    - clinical review

- Primary endpoint:
  - Overall Response Rate (ORR)
- Secondary endpoints:
  - Duration of Response (DOR)
  - Progression Free Survival (PFS)
  - Safety
  - Quality of life

Gopal A, et al. NEJM 2014

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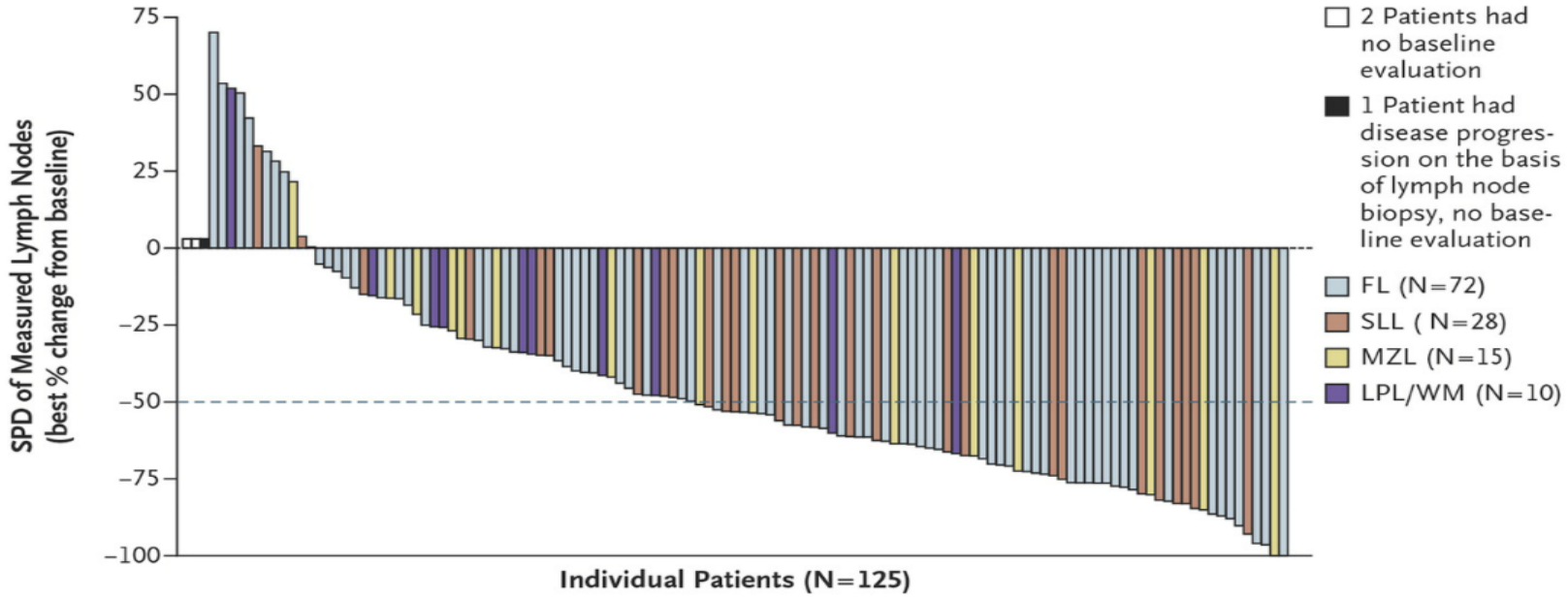
Idelalisib: Selective PI3K Inhibitor :Tumour Response



Gopal A, et al. NEJM 2014

Progression Free Survival

Historical Control:
Bendamustine: DOR 10mo

Gopal A, et al. NEJM 2014

Adverse Events

Event or Abnormality	Grade	
	Any	≥3
	no. (%)	
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

Gopal A, et al. NEJM 2014

Pi3Ki: Duvelisib

- Inhibitor of PI3K- delta and gamma isoforms.
- Phase II study: Dynamo
  - Rituximab refractory
  - Refractory to alkylator or radioimmunotherapy
  - Primary endpoint: ORR

- Safety:
  - Neutropenia: 28%
  - Diarrhea: 15%
  - Grade 3 infection: 20%
  - CMV: 2.3%

	FL N=83	SLL N=28	MZL N=18	Overall N=129
ORR, %	41	68	33	46
DoR (months), median	9.2	9.9	NE	9.9
PFS (months), median	8.3	11.3	NE	8.4
TTR (months), median	1.9	1.9	3.6	1.9
OS (months), median	18.4	NE	NE	18.4

ABBREVIATIONS: DoR = duration of response; FL = follicular lymphoma; MZL = marginal zone lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SLL = small lymphocytic lymphoma; TTR = time to response; NE = not estimable

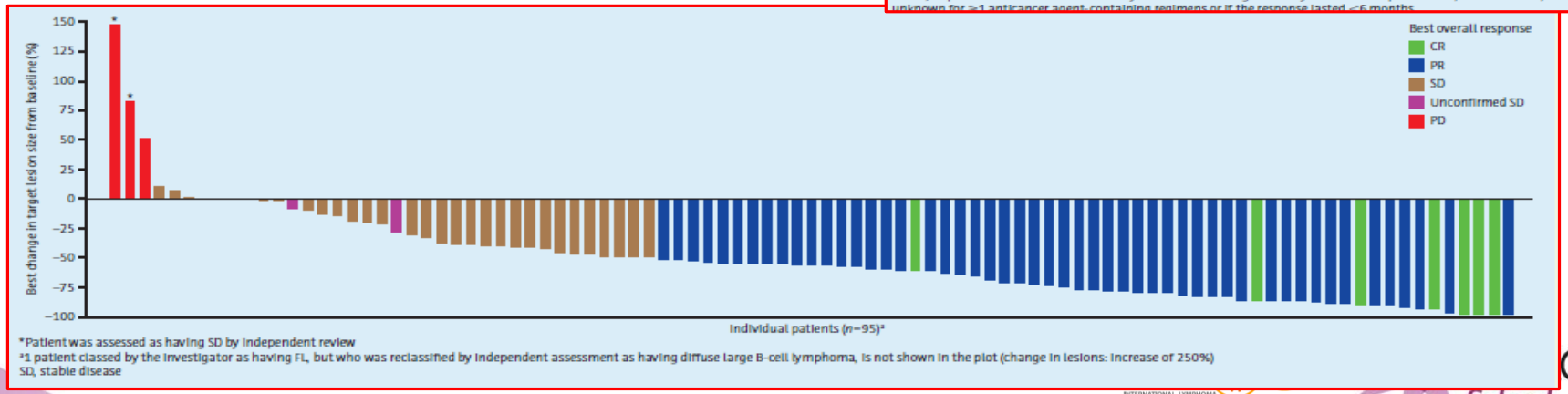
Flinn, I et al. ASH 2016

PI3Ki: Copanalisib (BAY 80-6946)

- Inhibitor of PI3K- alpha and beta isoforms.
- Phase II study:
  - 142 pts, relapsed or refractory to ≥ 2 lines of therapy.
  - IV on days 1,8, and 15.
  - Primary endpoint: ORR
  - Results:
    - ORR 61%, CR 15% (n=104 fl pts)
    - Median PFS: 11.2 months

	Total (*N*=104)
Median (range) prior anticancer therapy lines	3 (2-8)
Median (range) time since last systemic therapy until PD[a], months	8.54 (0-108)
>6 months, *n* (%)	47 (45.2)
Prior rituximab, *n* (%)	104 (100)
Refractory against last regimen, *n* (%)	65 (62.5)
Refractory against last regimen with[b], *n* (%)	
rituximab	59 (56.7)
alkylating agent	39 (37.5)
both rituximab and alkylating agent	43 (41.3)

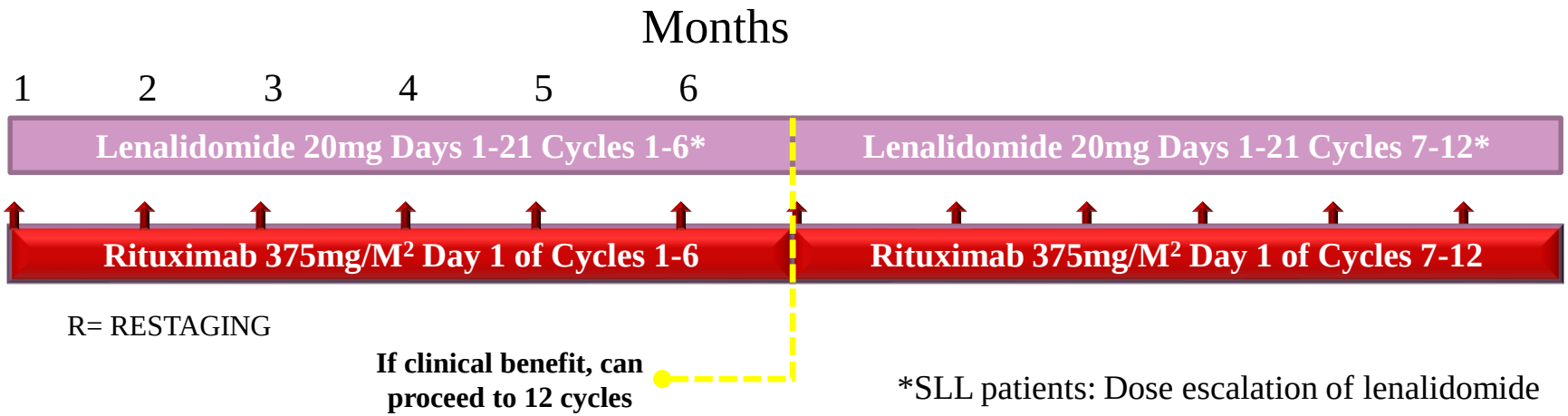
[a]*n*=93; [b]A patient was considered refractory to an anticancer agent if they had a best response of PD, stable disease, or unknown for ≥1 anticancer agent-containing regimens or if the response lasted <6 months



*Patient was assessed as having SD by independent review
[a]1 patient classed by the investigator as having FL, but who was reclassified by independent assessment as having diffuse large B-cell lymphoma, is not shown in the plot (change in lesions: increase of 250%)
SD, stable disease

Dryling, M. et al ASH 2016

Phase II Study of R2 in Follicular Lymphoma: Study Design



*SLL patients: Dose escalation of lenalidomide starting with cycle 1: (10mg, 15mg, 20mg)

- Planned Enrollment
  - N= 50 Follicular lymphoma (grade I/II)
  - N=30 Small lymphocytic lymphoma
  - N=30 Marginal zone lymphoma
- Groups analyzed independently for response and toxicity

Fowler N, et al ASH 2012.

Response Rates

	SLL (N=30)	Marginal (N=27)*	Follicular (N=46)*	All Patients Eval (N=103)	All Patients 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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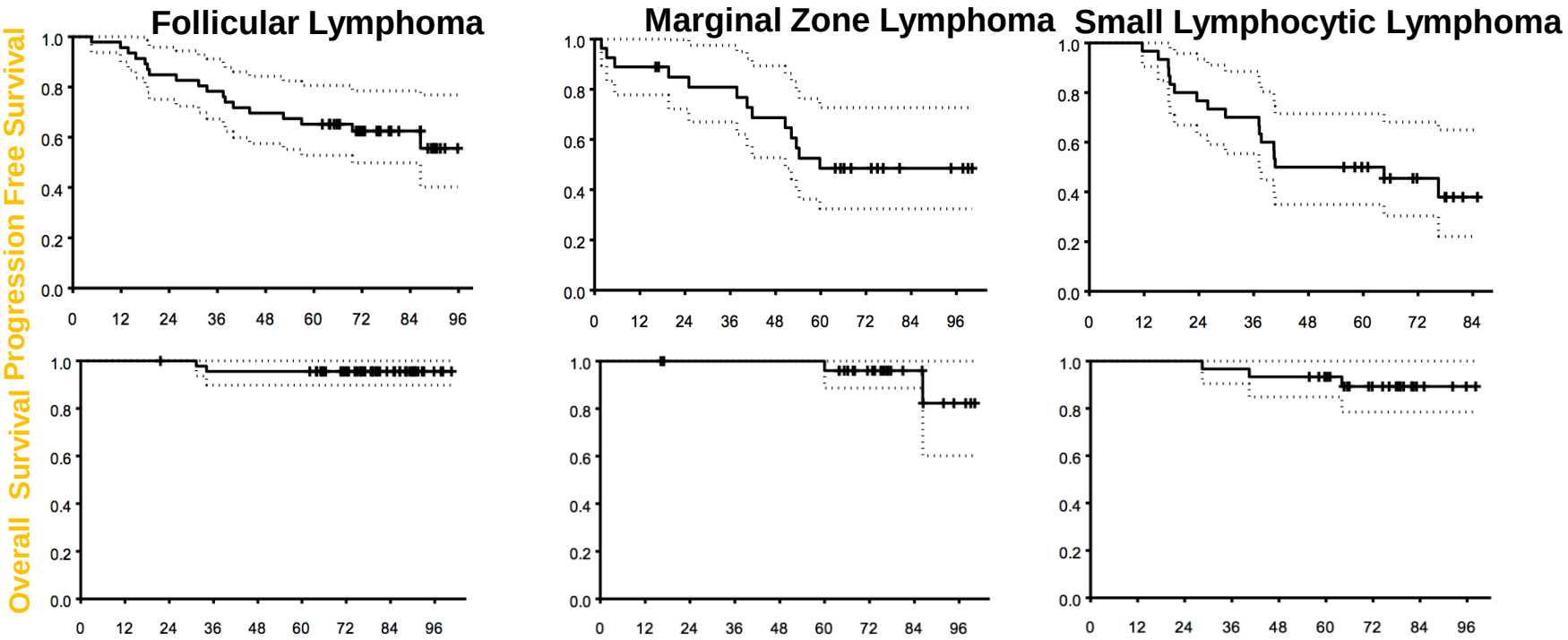
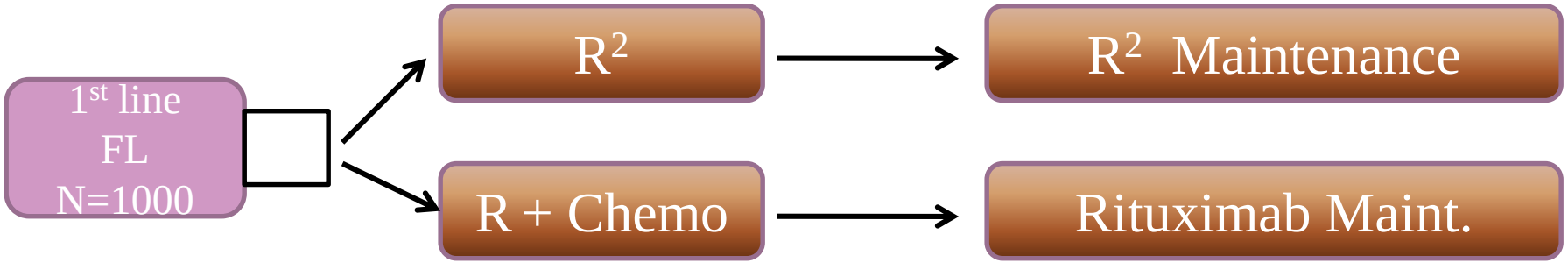
R2 in Indolent NHL : Long Term FU



Fowler N, et al. ASCO 2017

RELEVANCE Study Design

(Rituximab and LEnalidomide versus Any ChEmotherapy)



- R+Chemo:
  - Investigator's choice of R-CHOP, R-CVP, BR
- Lenalidomide 20mg for 6 cycles, then 10mg if CR

RELEVANCE Study Design

(Rituximab and LEnalidomide versus Any ChEmotherapy

- 1,030 patients were enrolled, with 513 in the R^2 arm and 517 in the R-chemo arm (the control group).

- Baseline characteristics were similar between the two groups: median age was 59, with 49% men in both groups; approximately 85% of patients had grade 1 or 2 disease, and the remainder had grade 3A disease.

- The co-primary endpoint—complete remission/complete remission unconfirmed (CR/Cru)/partial response—was 84% with R^2 versus 89% with R-chemo; SPD reduction greater than or equal to 50% was reported in 81% of patients in the R^2 group versus 90% in the R-chemo group.

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RELEVANCE Study Design

(Rituximab and LEnalidomide versus Any ChEmotherapy

- Median follow-up of 37.9 months, the interim progression-free survival (PFS) by an independent review committee was 77% in the R^2 arm versus 78% in the R-chemo arm (HR 1.10, 95% CI [0.85, 1.43]; p = 0.48).

- Discontinuations due to treatment were also similar between the two groups, with 157 in the R^2 group versus 146 in the R-chemo group, with the most frequent reasons due to progression and toxicity.

Conclusions

- Outcomes are improving in patients with indolent NHL.
- Immunochemotherapy combinations have been extremely effective, but likely have reached a “plateau” and for majority of patients have life expectancy similar to aged matched control.
- Different approaches are required for POD-24 – early consideration of transplantation approaches and novel agents
- Novel non-cytotoxic drugs as single agents are active in iNHL.
- Next generation regimens combine biological and targeted agents.
- Mechanistic and biomarker studies are still lacking in the majority of studies, but are <u>essential</u> to optimize therapy.

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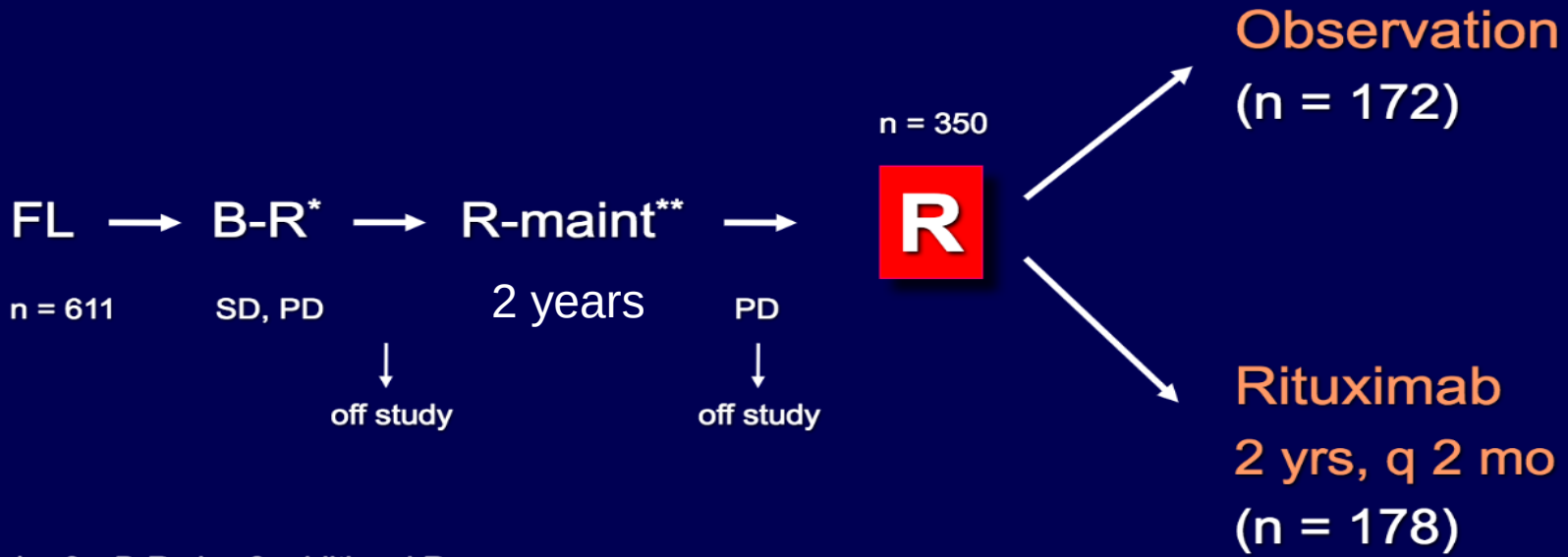
B-R + 2 years versus B-R + 4 years Rituximab

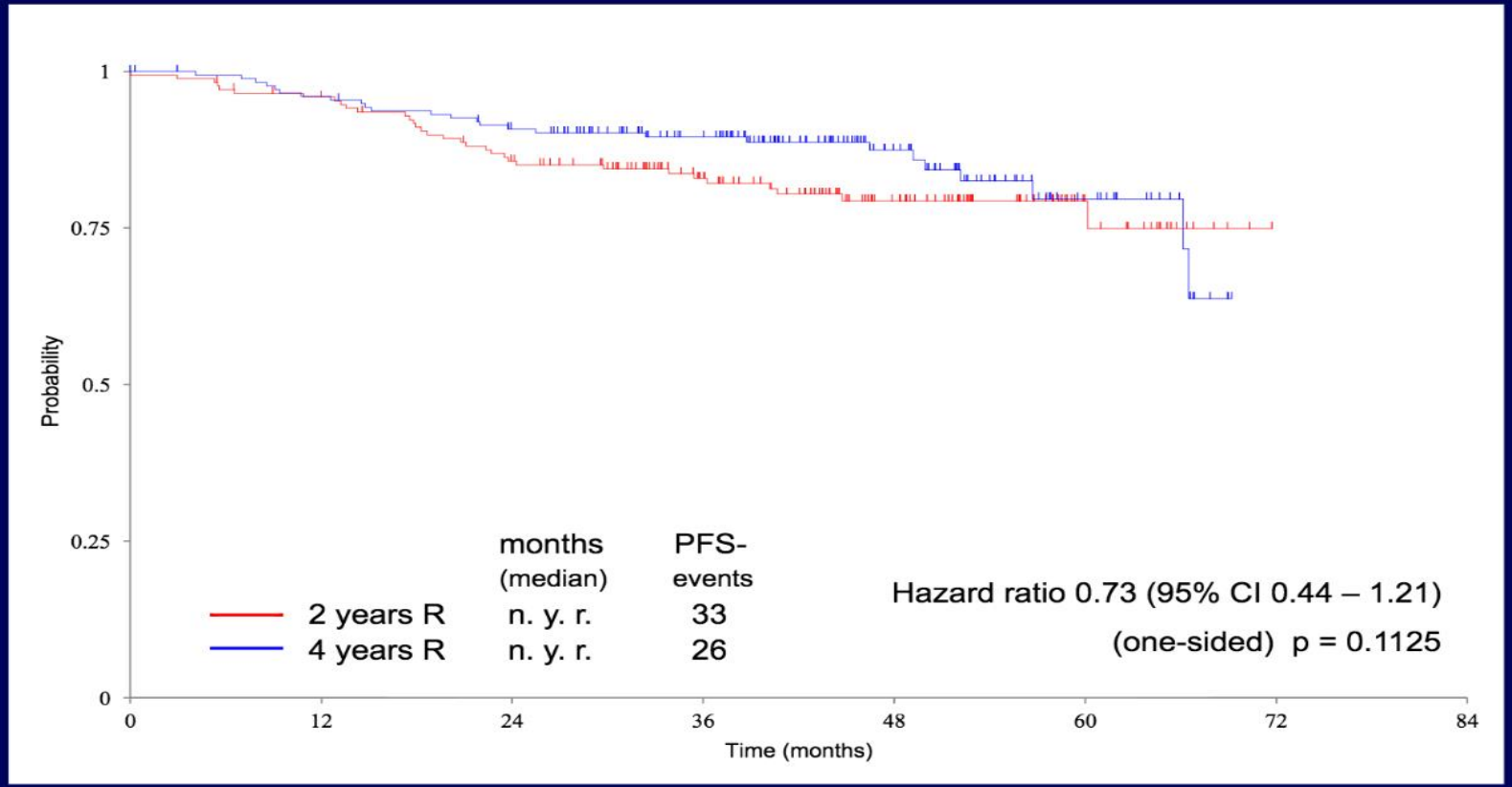
StiL NHL 7-2008 - MAINTAIN



* 6 x B-R plus 2 additional R

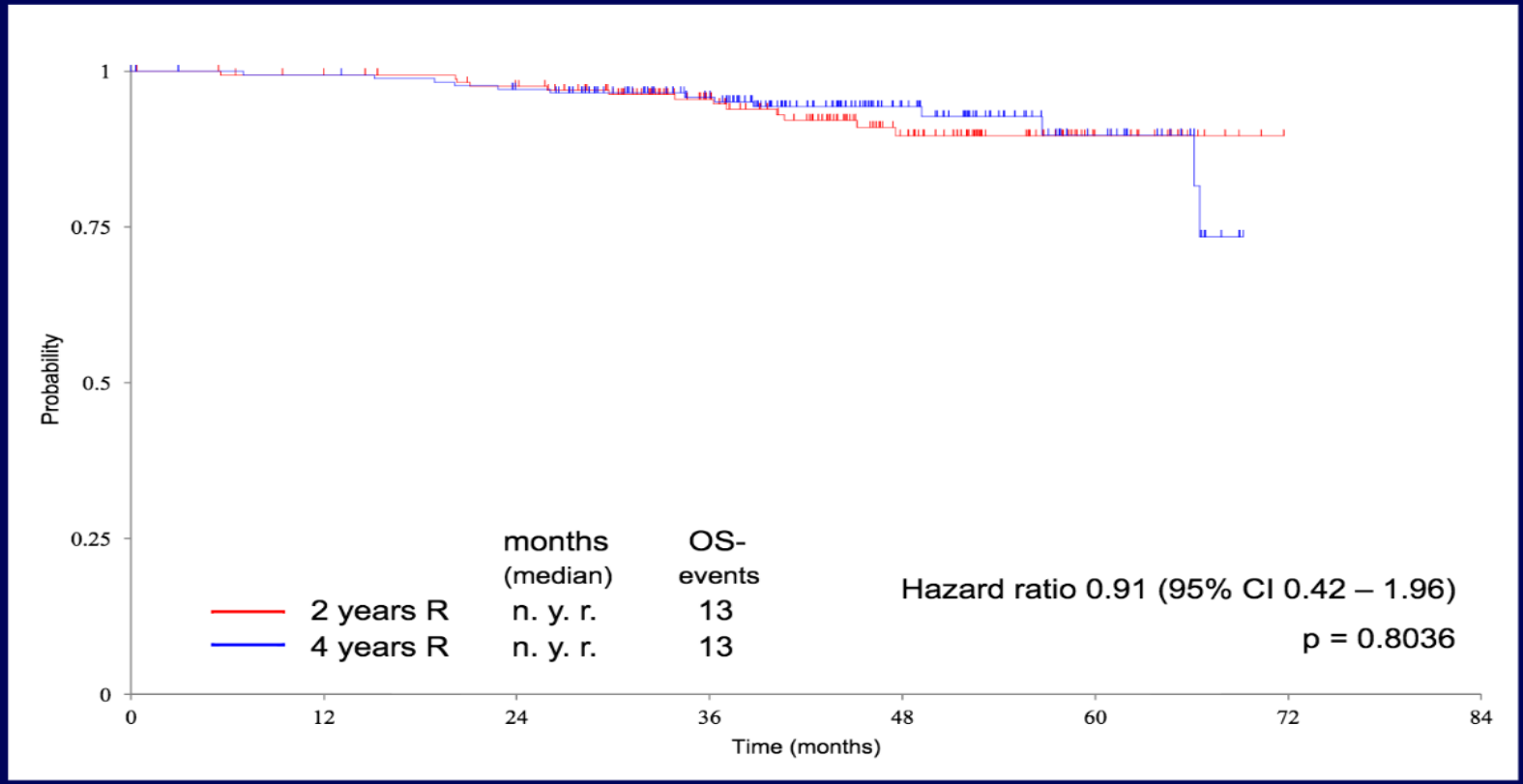
** R-maintenance q 2 months for 2 years

Progression-free survival from randomization (n = 350)



Pts at risk						
Observation	172	161	141	106	62	18
R-maintenance	178	168	155	123	61	22

Overall survival from randomization



Pts at risk						
Observation	172	166	159	120	67	18
R-maintenance	178	174	167	135	65	24

Fatal infections (75 months follow-up)

- Total of 17 pts (2.8%) died from infection (13 not rand., 1 in 2 yrs, 3 in 4 yrs)
- Median age at registration: 71 years
- 9 died after a relapse and a 2nd-line treatment
- 7 were primary refractory and died early due to an infection
- 10 died in ongoing remission
- Infections:
  - 8 Pneumonia
  - 6 Sepsis
  - 1 Fungal infection
  - 1 PcP (72 yrs, 5 cycles B-R, died at the end of induction after 5 months)
  - 1 PML (41 yrs, 19 cycles R-maint., ongoing remission, on treatment 3 ½ yrs)

Cross-study comparison: NHL7 vs NHL1

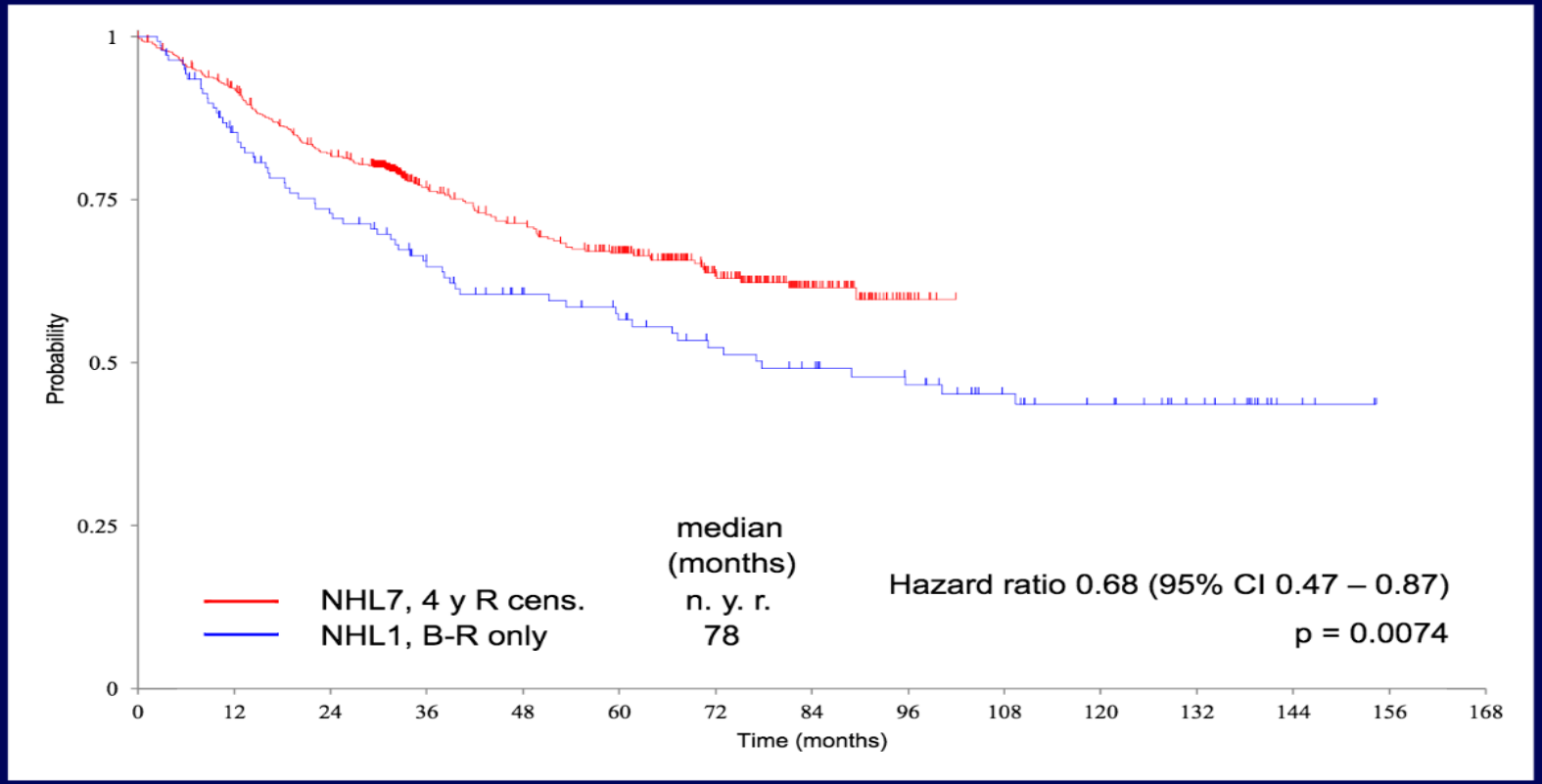
Is 2 years R-maintenance after B-R meaningful?

StiL NHL7-2008 (this study: MAINTAIN trial, B-R + 2 or 4 yrs R-maint.)
(all patients, but 4 yrs R patients censored at time of randomization)

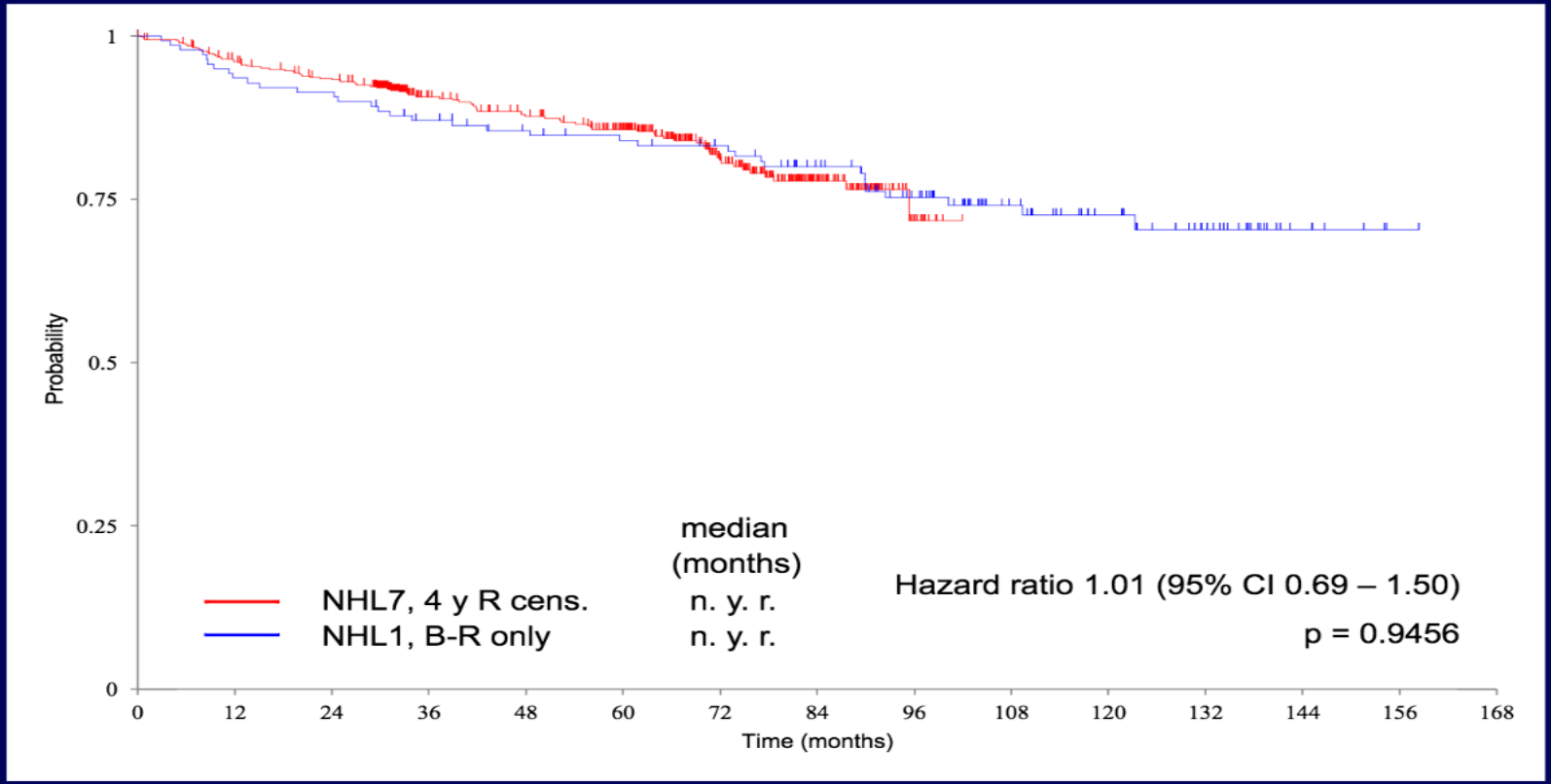
versus

StiL NHL1-2003 (previous study, B-R vs CHOP-R, no R-maintenance)
(all follicular lymphoma patients with B-R as published in Lancet 2013)

PFS comparison: NHL 1 (B-R, foll.) vs. NHL 7 (4y R cens.)



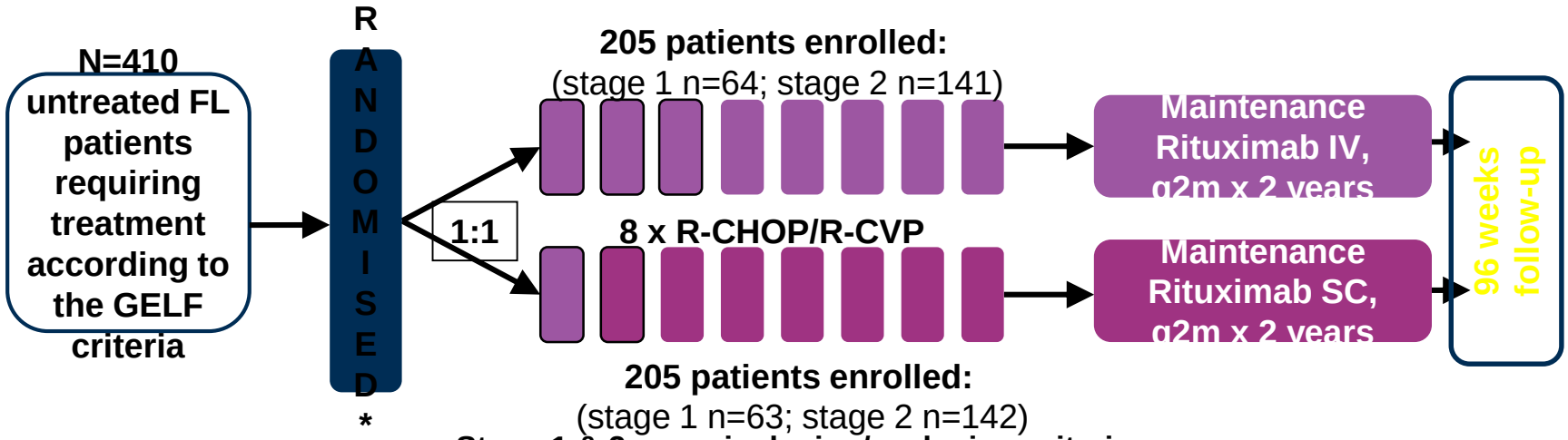
OS comparison: NHL 1 (B-R, foll.) vs. NHL 7 (4y R cens.)



Conclusions

- 4 years R-maintenance prolonged PFS after B-R compared with only 2 years (HR 0.73), however, this difference was not statistically significant
- No difference in overall survival between the two R-maintenance arms
- We selected patients who may not be suitable for R-maintenance by excluding those with toxicity or events from randomization
- After randomization less events than expected were observed
- This study confirmed the high anti-lymphoma activity of B-R
- With the limitation of a non-randomized comparison we were able to demonstrate that B-R can be further improved by R-maintenance with regard to PFS, but this did not translate into a better survival rate

SABRINA: 2-stage randomised phase III study in untreated FL



Rituximab IV (375 mg/m²)

Rituximab SC (1400 mg)

- ~~Stage 1 & 2 same inclusion/exclusion criteria~~
- Stage 1 & 2 same design, except PK (more intensive in stage 1)
- Pooled stage 1 & 2 data analysis pre-planned to allow assessing efficacy and safety in most robust patient population

Focus on pooled stage 1 & 2 data

*Patients stratified according to Follicular Lymphoma International Prognostic (FLIPI) score, chemotherapy and region;
CR = complete response; GELF = Groupe d'Etudes des Lymphomes Folliculaires; PK = pharmacokinetic; PR = partial response; CHOP = cyclophosphamide/doxorubicin/vincristine/prednisone; CVP = cyclophosphamide/vincristine/prednisone; IV = intravenous

Davies A, et al. Lancet Oncol 2014

Summary and conclusions from SABRINA

Pharmacokinetic

- Non-inferior C_{trough} with the fixed dose of rituximab SC of 1400 mg compared with rituximab IV 375 mg/m^2 given every 3 weeks

Efficacy

- ORR and CR/CRu comparable, indicating the switch to the SC route of administration did not impair rituximab's anti-lymphoma activity

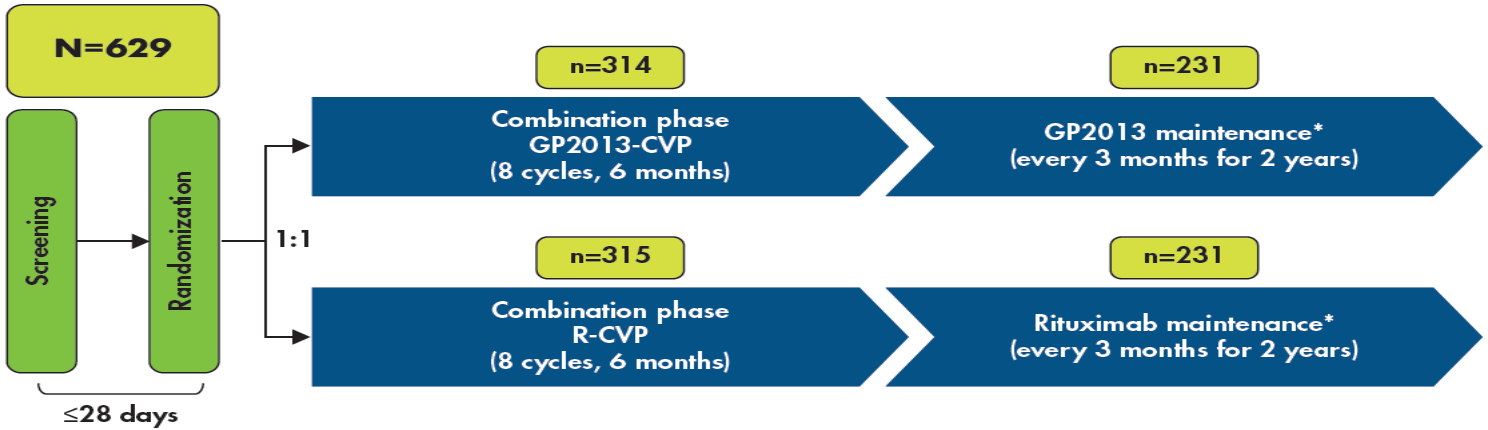
Safety

- Rituximab SC safety profile comparable to that of rituximab IV

Data from additional patients in stage 2 confirm that rituximab SC 1400 mg has a benefit/risk profile comparable to rituximab IV 375 mg/m^2

A Phase III Efficacy and Safety Study of the Proposed Rituximab Biosimilar GP2013 versus Rituximab in 629 Patients with Previously Untreated Advanced Follicular Lymphoma

Figure 3. Study design

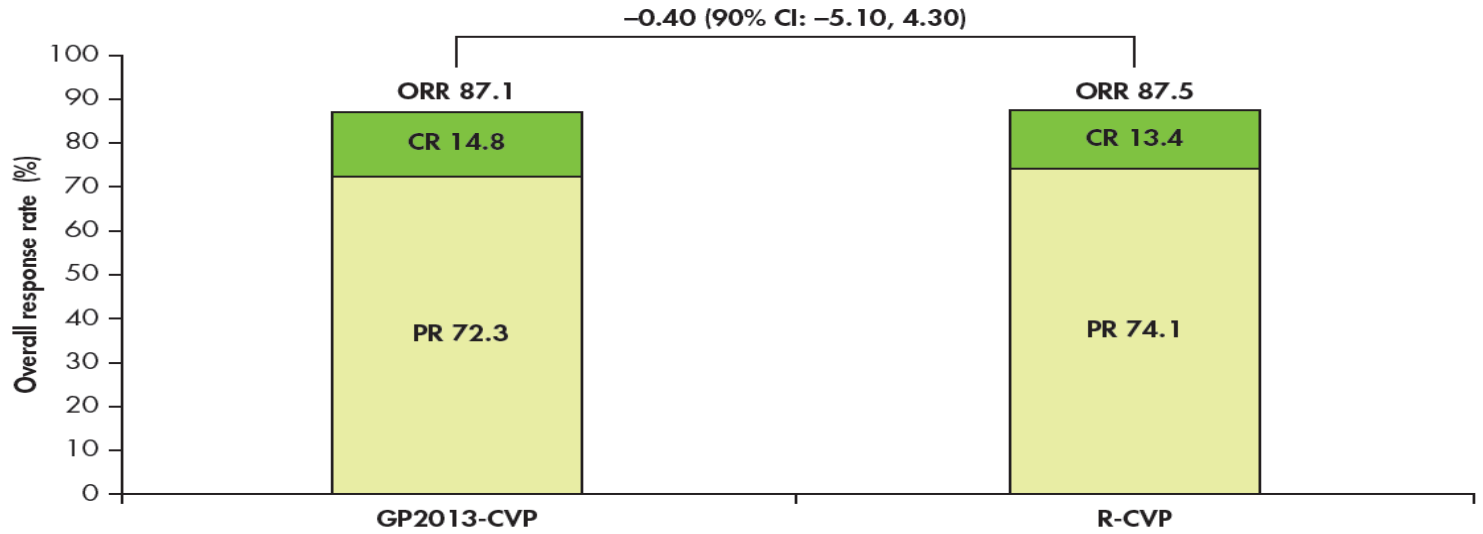


GP2013 (375 mg/m²) + cyclophosphamide (750 mg/m² i.v D1) + vincristine (1.4 mg/m² D1) + prednisone (100 mg p.o. D1–D5)
Rituximab (375 mg/m²) + cyclophosphamide (750 mg/m² i.v D1) + vincristine (1.4 mg/m² D1) + prednisone (100 mg p.o. D1–D5)
*For responders (partial or complete response) treated with GP2013-CVP or R-CVP, according to the original treatment assignment
R-CVP, Rituximab-CVP

RESULTS

A Phase III Efficacy and Safety Study of the Proposed Rituximab Biosimilar GP2013 versus Rituximab in 629 Patients with Previously Untreated Advanced Follicular Lymphoma

Figure 4. Primary efficacy analysis of overall response rate (CR or PR) based on central blinded review (PPS)



CR, complete response; GP2013-CVP, GP2013 plus cyclophosphamide, vincristine, prednisone; PPS, per protocol set; PR, partial response; R-CVP, Rituximab-CVP

POD 24

- **Abstract 0412: Validation of POD24 As a Robust Early Clinical Endpoint of Poor Survival in Follicular Lymphoma: Results from the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) Investigation Using Individual Data from 5,453 Patients on 13 Clinical Trials**

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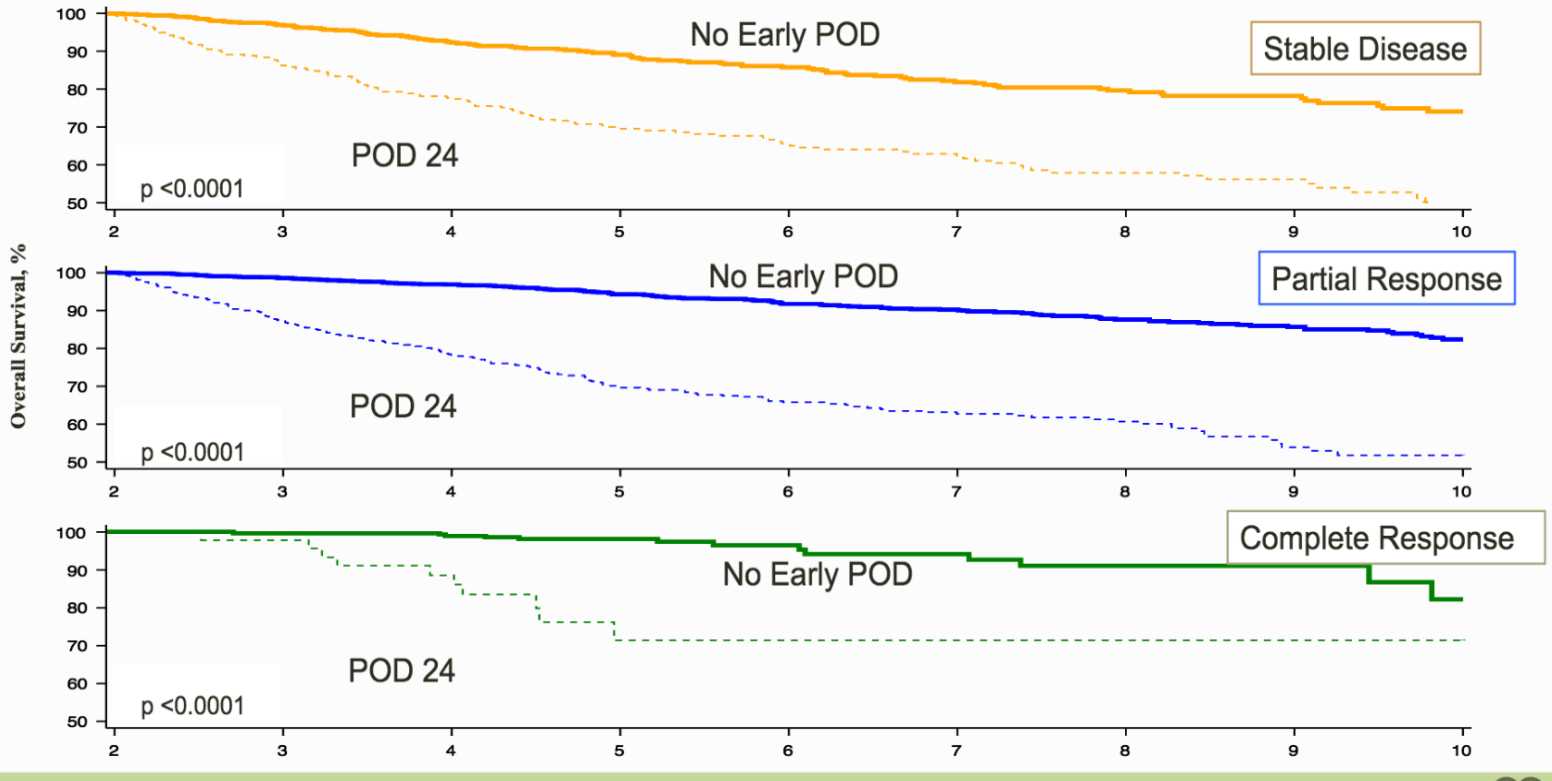
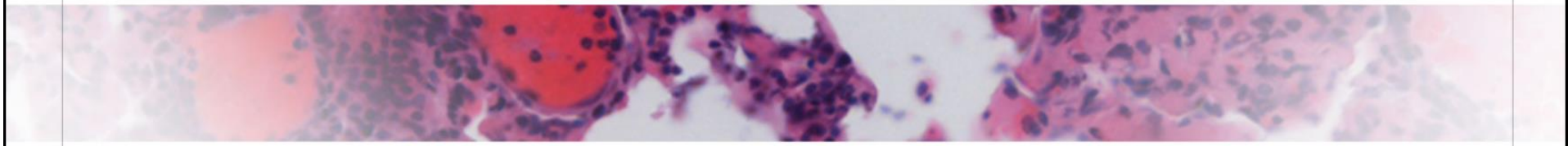
Landmark OS by First Response



American Society *of* Hematology

Helping hematologists conquer blood diseases worldwide



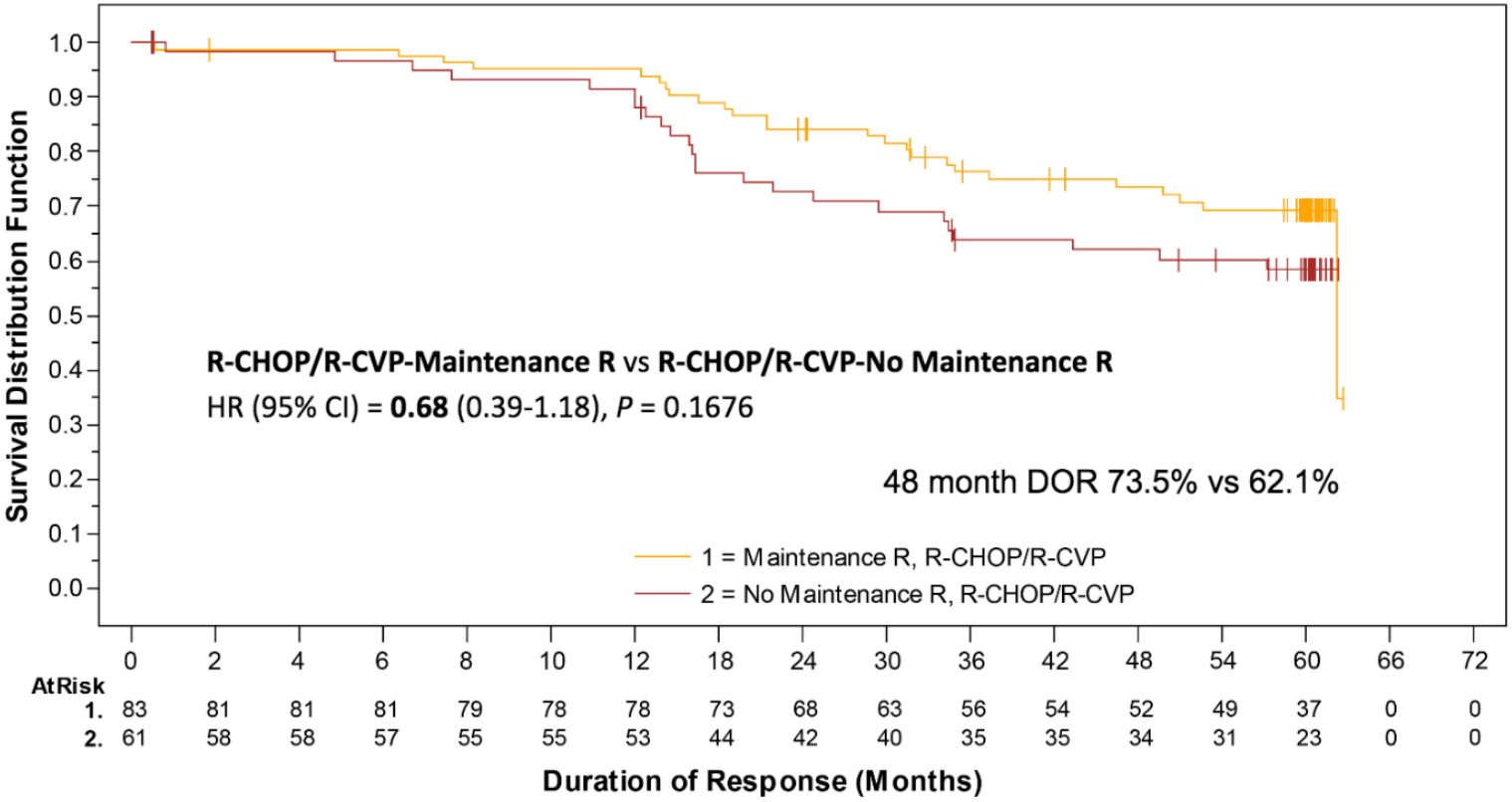
Assessment of Maintenance Rituximab After First-Line Bendamustine-Rituximab in Patients With Follicular Lymphoma: An Analysis From the BRIGHT Trial

Presented by Brad Kahl on behalf of BRIGHT Trial Contributors

Background

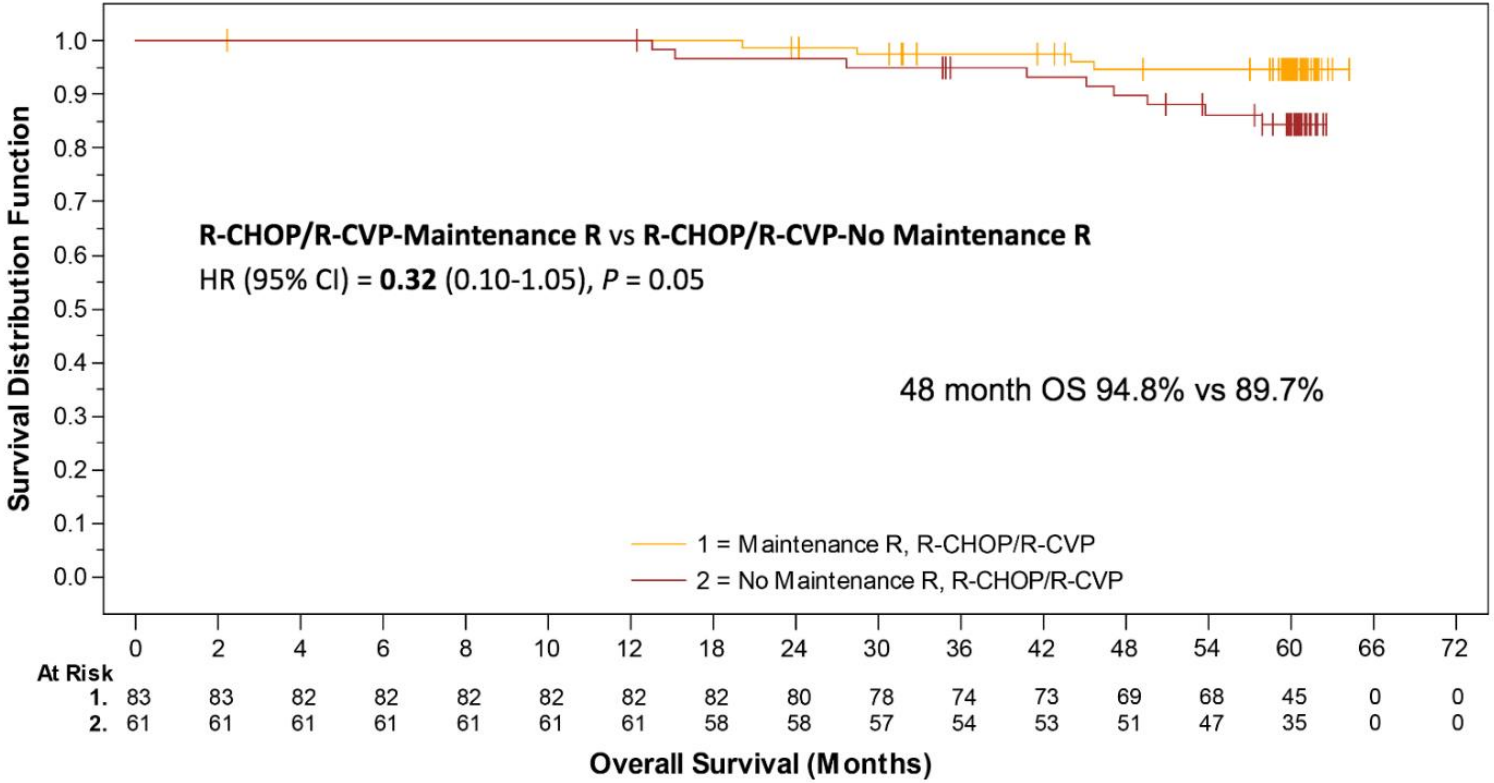
- Given widespread use of BR as initial therapy in FL and given widespread use of MR in FL
  - Important to determine the impact of MR after BR for both
    - Efficacy and toxicity
- The design of the BRIGHT trial permits an ad hoc analysis on the use of maintenance R among patients with FL in the BRIGHT study
  - Due to data collection procedures used in the BRIGHT study, this analysis is essentially limited to addressing efficacy

Duration of Response in FL*: R-CHOP/R-CVP



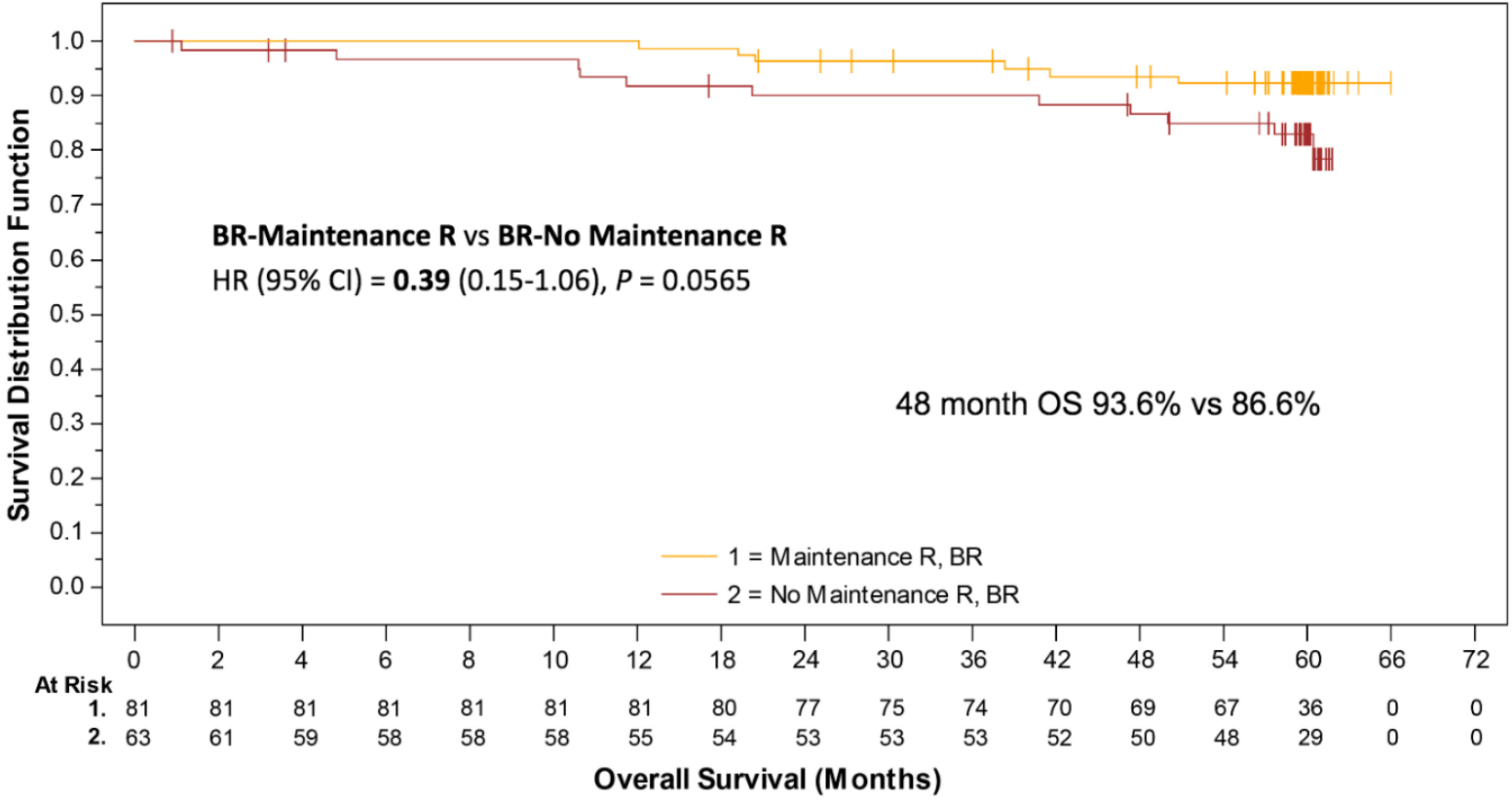
*FL patients with CR or PR. CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CI: confidence interval; CR: complete response; CVP: cyclophosphamide, vincristine, and prednisone; FL: follicular lymphoma; HR: hazard ratio; PR: partial response; R: rituximab

Overall Survival in FL*: R-CHOP/R-CVP



*FL patients with CR or PR. CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CI: confidence interval; CR: complete response; CVP: cyclophosphamide, vincristine, and prednisone; FL: follicular lymphoma; HR: hazard ratio; PR: partial response; R: rituximab

Overall Survival in FL*: BR



*FL patients with CR or PR.
B: bendamustine; CI: confidence interval; CR: complete response; FL: follicular lymphoma; HR: hazard ratio;

Summary and Conclusions

- Limitations to data
  - Since maintenance R was administered at investigator's discretion, selection bias may contribute to the observed results
  - We can not comment on toxicities that may have been influenced by the MR
    - Unable to provide a full accounting of the risk-benefit ratio

Conclusions

- No signal that OS was negatively influenced by MR in responding patients
  - If anything, data favors MR
  - Reassurance regarding fatal AE rate
- DOR was significantly longer in BR treated patients receiving maintenance R
- Consistent with previous trials, maintenance R also showed a tendency toward improved DOR after R-CHOP/R-CVP
- The overall improvement in DOR in the maintenance R patients appears to be at least as great following BR as following R-CHOP/R-CVP

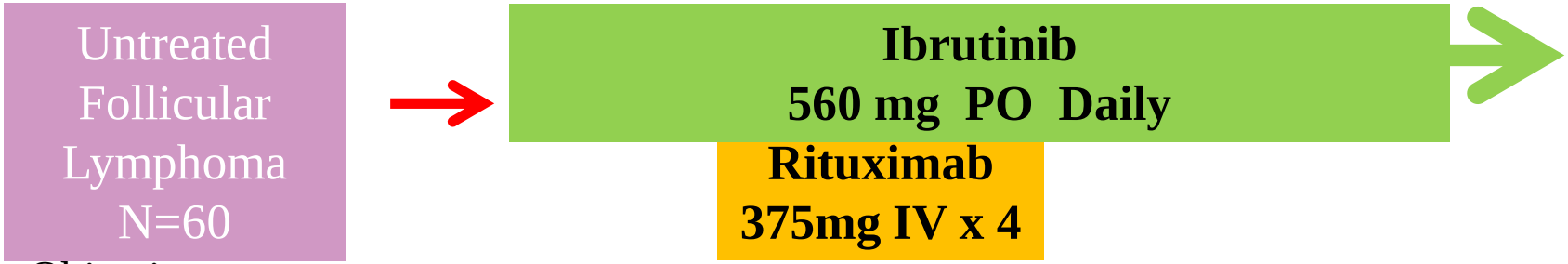
Alliance Phase II Study of Rituximab + Lenalidomide in Follicular Lymphoma: Responses

Response, n (%)	Overall (N = 57)	FLIPI 0-1 (n = 17)	FLIPI 2 (n = 36)	FLIPI 3 (n = 2)
ORR	53 (93)	16 (94)	33 (92)	2 (100)
CR	41 (72)	13 (77)	25 (70)	2 (100)
PR	12 (21)	3 (18)	8 (22)	--
SD	2 (4)	0 (0)	2 (6)	--
Unevaluable	2 (4)	1 (6)	1 (3)	--

- 4 additional patients in PET-CR but not confirmed by bone marrow biopsy
- There was no significant association between CR rate and FLIPI score, presence of bulky disease, or grade

Martin P, et al. ICML 2013. Abstract 063.

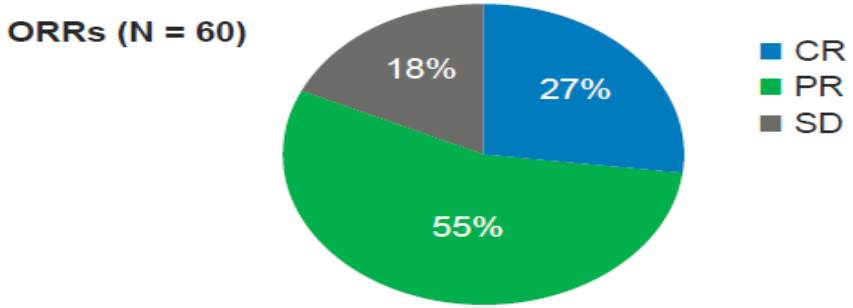
Frontline Ibrutinib + Rituximab Follicular Lymphoma



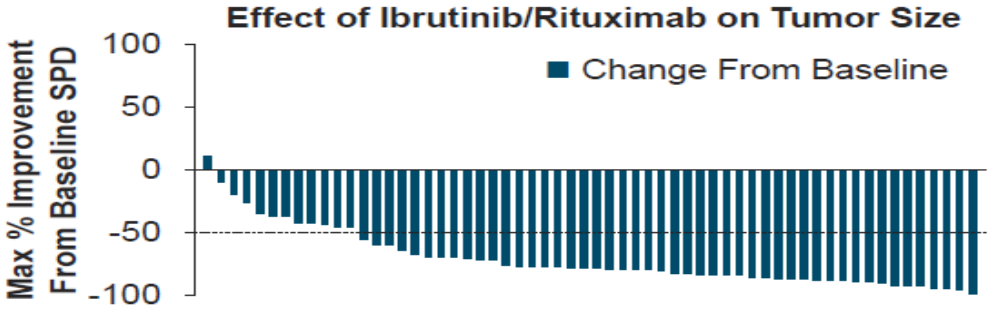
- Objectives
  - Primary
    - Evaluate the ORR (CR+PR)
  - Secondary
    - Duration of response, PFS
    - Safety

PI: N. Fowler

Frontline Ibrutinib + Rituximab Follicular Lymphoma



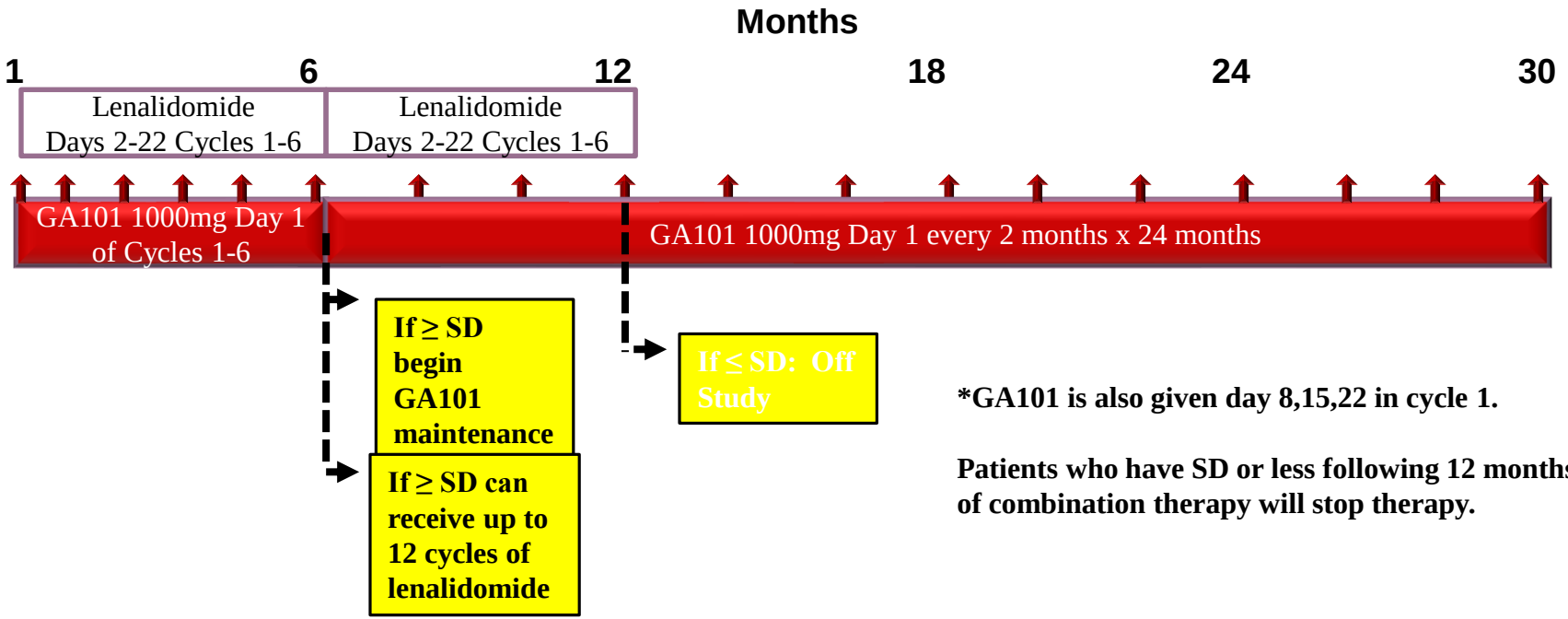
ORR: 82% (27% CR + 55% PR)



- Median target lesion SPD at baseline was 24 cm^2 (range, 2.2-135.5)

Fowler NH et al. American Society of Hematology 2015 Annual Meeting (ASH 2015). Abstract 470.

Lenalidomide + Obinutuzimab in Relapsed iNHL



***GA101 is also given day 8,15,22 in cycle 1.**

Patients who have SD or less following 12 months of combination therapy will stop therapy.

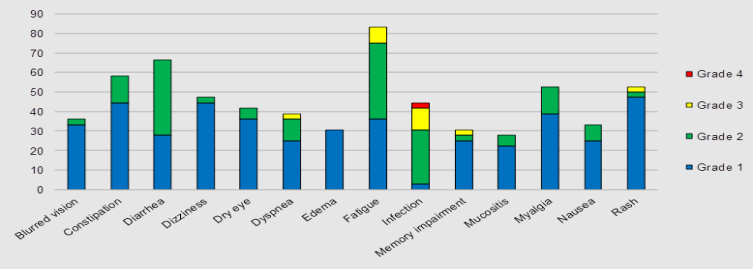
Fowler N, et al. ASCO 2017

Lenalidomide + Obinituzimab: Results

Overall Response: 100%

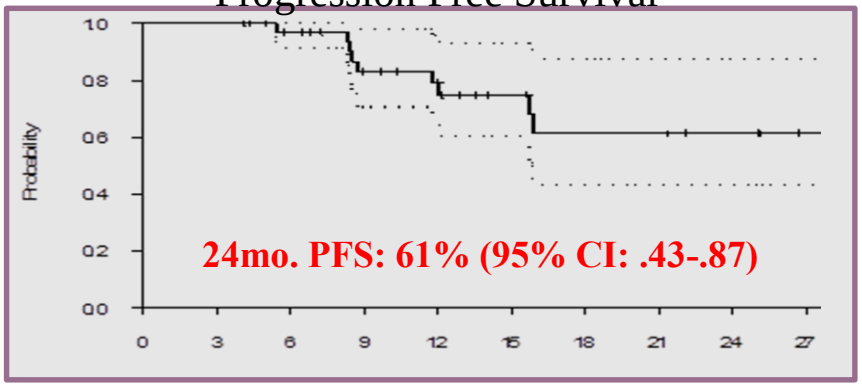
Best Response	N (%)
Complete Remission (CR / Cru)	28 (78%)
Partial Remission	8 (22%)
Stable Disease	0
Progression	0

Adverse Events



- Grade 3+ neutropenia: 27%

Progression Free Survival



- Median # of prior therapies: 2
- Lenalidomide + obinutuzumab was well tolerated with 100% ORR and no unexpected toxicity.

Also see: Morchhauser F. et al. ICML. Wed. June 14th

Fowler N, et al. ASCO 2017

Pembrolizumab + Rituximab

- Phase II, single arm study
- Subjects received rituximab (375 mg/m^2 IV) on days 1, 8, 15, and 22 of cycle 1 and pembrolizumab (200mg IV) every 3 weeks for up to 16 infusions starting on day 2 of cycle 1.

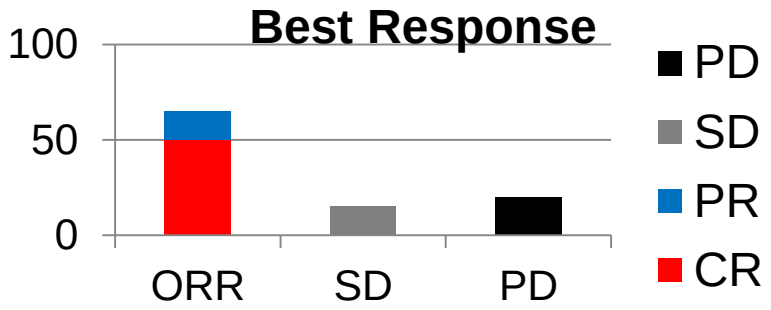
[redacted]

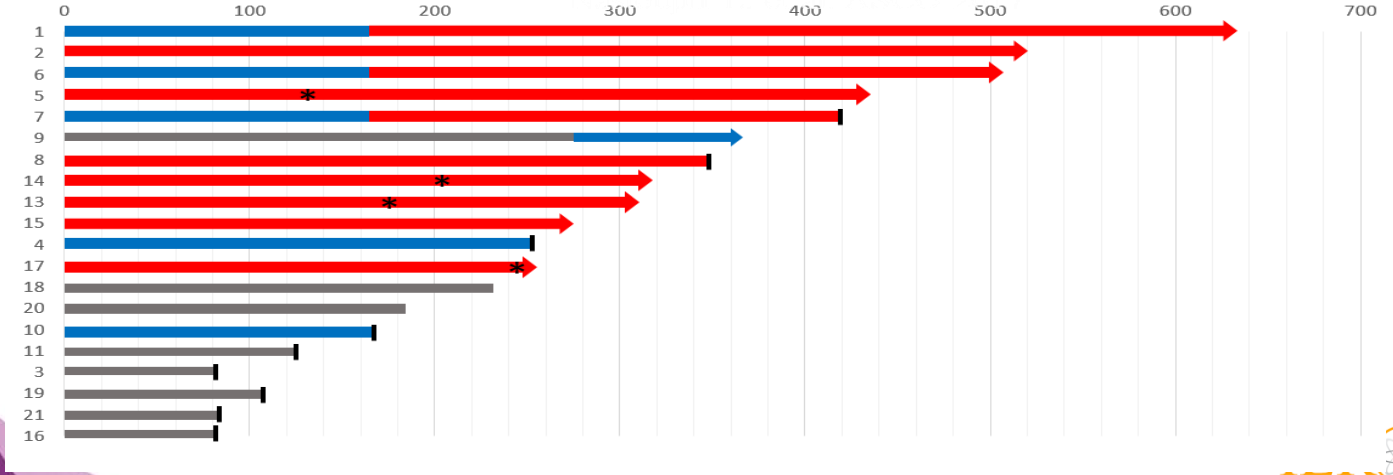
Primary Endpoint
Overall Response Rate (ORR)

Nastoupil L. et al. ASCO 2017

Efficacy

- 20 evaluable for response
- **ORR was 65%** (CR N=10/PR N=3)
- **CR rate was 50%**
- 3 patients with stable disease and 4 with progressive disease as best response





Nastoupil L. et al. ASCO 2017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Radiation Therapy for Indolent Nodal non Hodgkin Lymphoma:
Volumes, doses and techniques

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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Indolent Lymphomas
Treatment of stage I and II

- Standard: Involved Field Radiotherapy (IFRT), historically 36-40 Gy
- 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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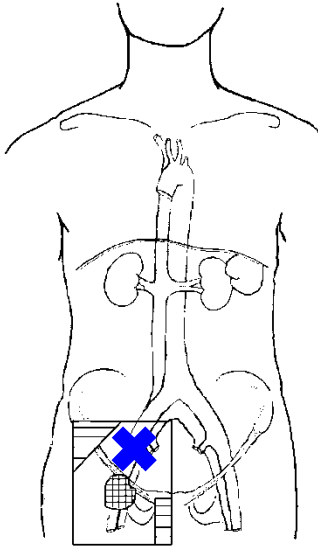
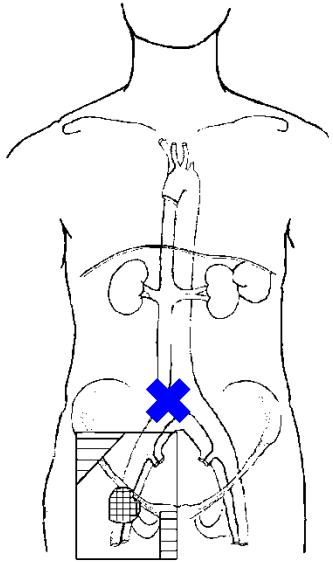
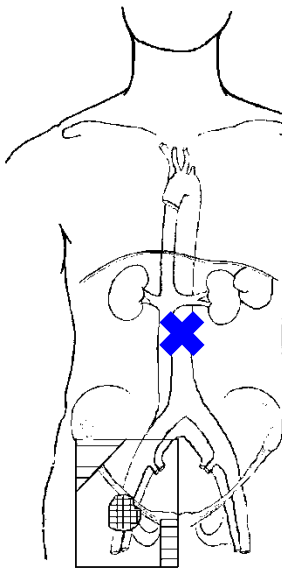
Relapse Locations in Relation to RT Fields



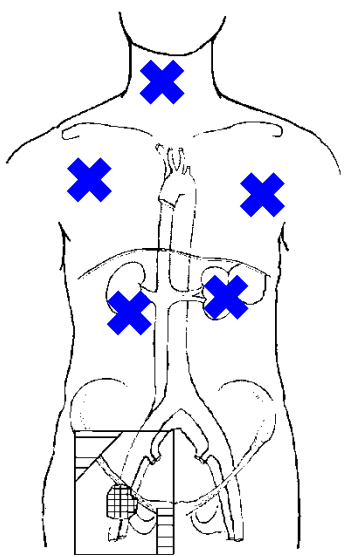
In-Field



Marginal (<5cm)



Next Echelon (contiguous)



Distant

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What Volume should be treated with radiotherapy?

Extended Field vs Involved Field vs Involved Site/Node

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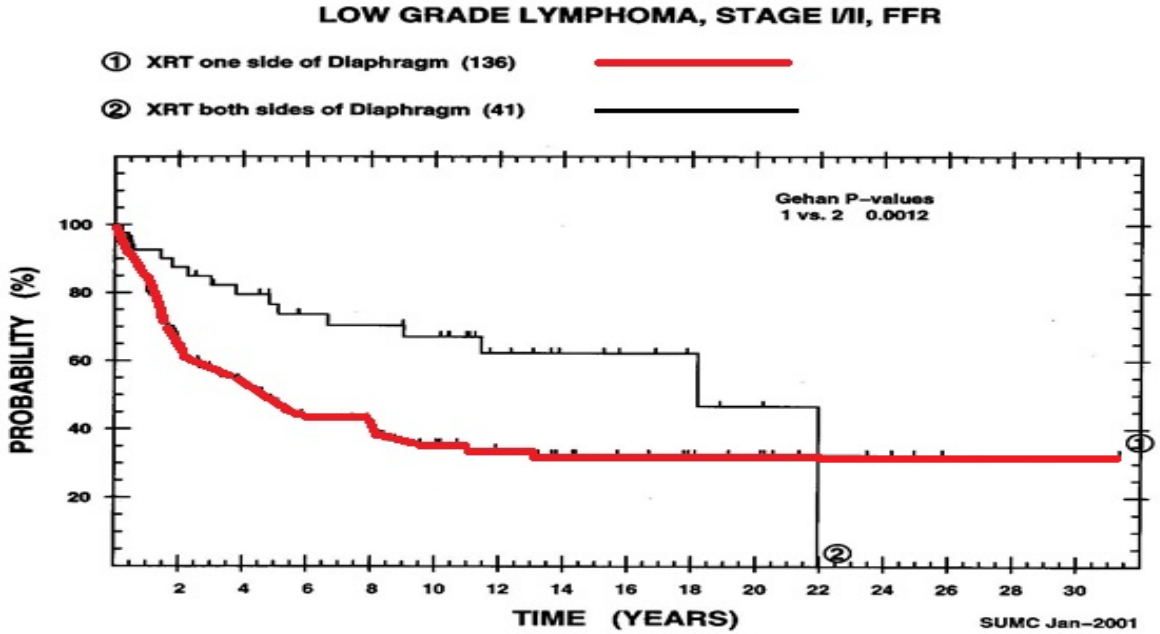
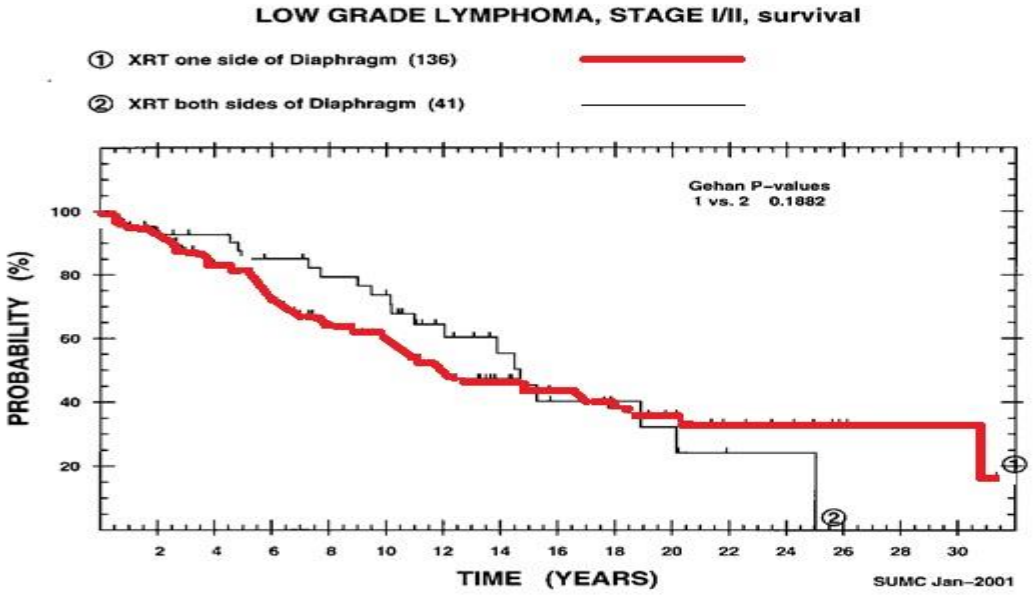
Stanford Follicular Lymphoma: Effect of Treatment Volume on Freedom from Relapse



Approx 30% difference at 10y

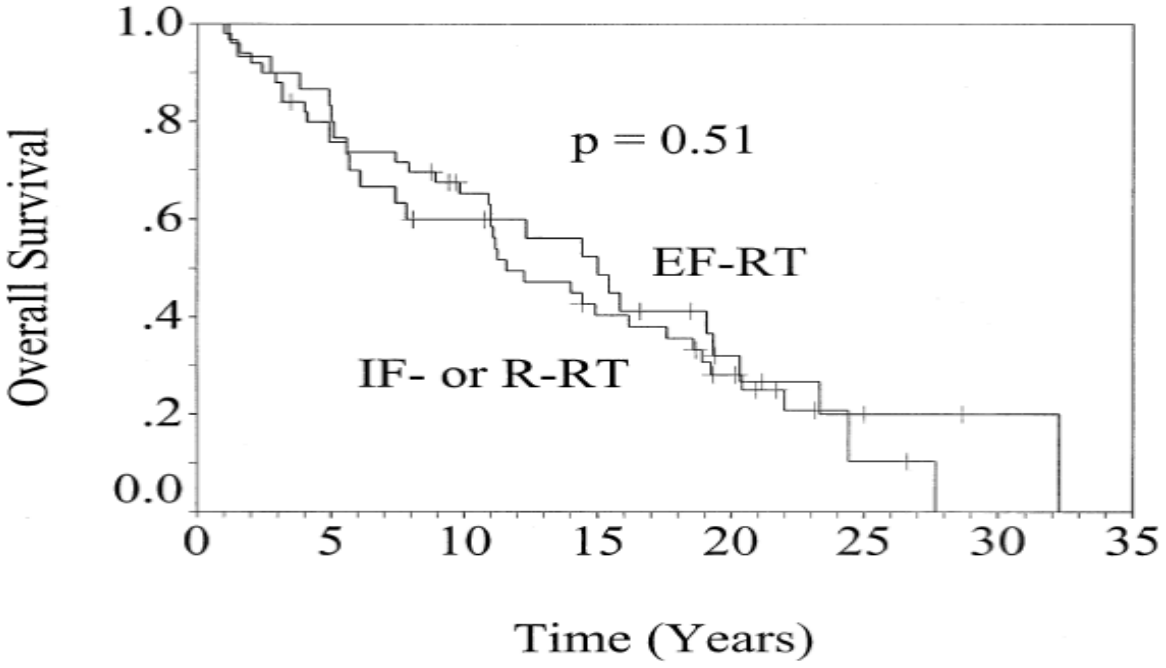
Mac Manus and Hoppe JCO 14; 1282-1290 1996

Stanford Follicular Lymphoma: Effect of Treatment Volume on Overall Survival



Mac Manus and Hoppe JCO 14; 1282-1290 1996

EFRT do not protect from relapses



Wilder et al, IJROBB, 2001

Involved Node vs Involved Region in FL

- IRRT = involved lymph node group plus ≥1 adjacent, uninvolved lymph node group(s).
- INRT=involved lymph node(s) with margins ≤5 cm.
- 237 pts: INRT 95, IRRT 142
- Median follow-up, 7.3 years

Campbell BA et al . Involved regional radiotherapy versus involved node radiotherapy
Cancer 116, 3797, 2010

- After INRT, 1% of patients had a regional-only recurrence
- No effect of field size on PFS or OS

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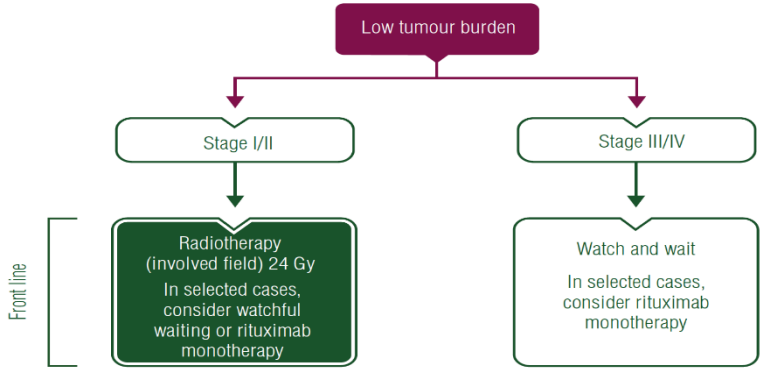
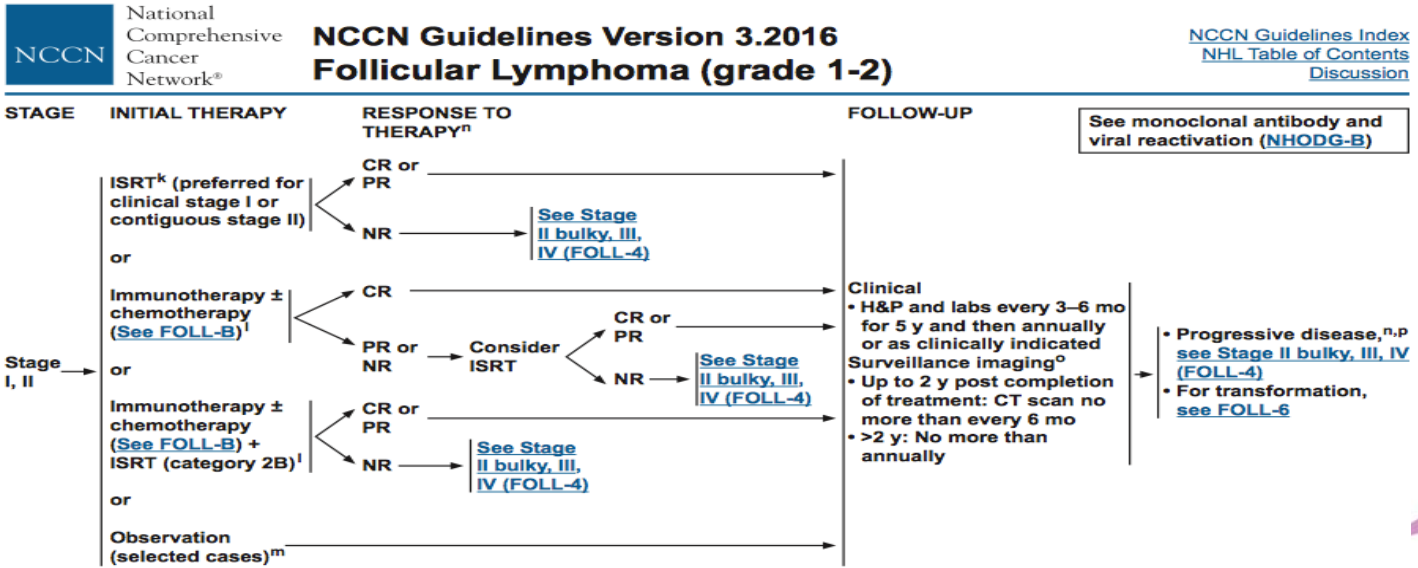
clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v83–v90, 2016
doi:10.1093/annonc/mdw400

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4], U. Vitolo[5] & M. Ladetto[6], on behalf of the ESMO Guidelines Committee*





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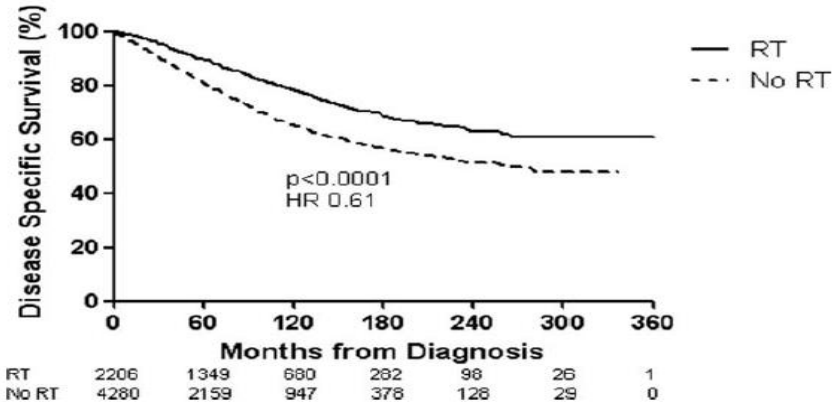
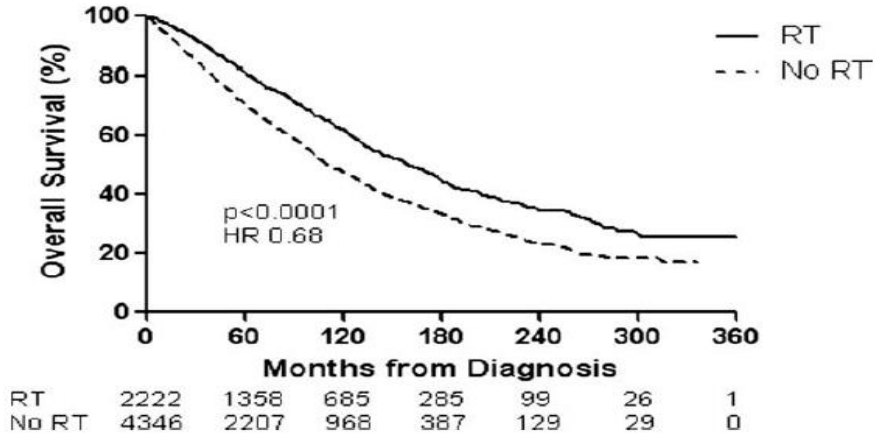
Improved Survival in Patients With Early Stage Low-Grade Follicular Lymphoma Treated With Radiation

Cancer 2010;116:3843–51

A Surveillance, Epidemiology, and End Results Database Analysis

Thomas J. Pugh, MD; Ari Ballonoff, MD; Francis Newman, MS; and Rachel Rabinovitch, MD





Radiation Therapy has low toxicity, high efficacy (but under-utilised)

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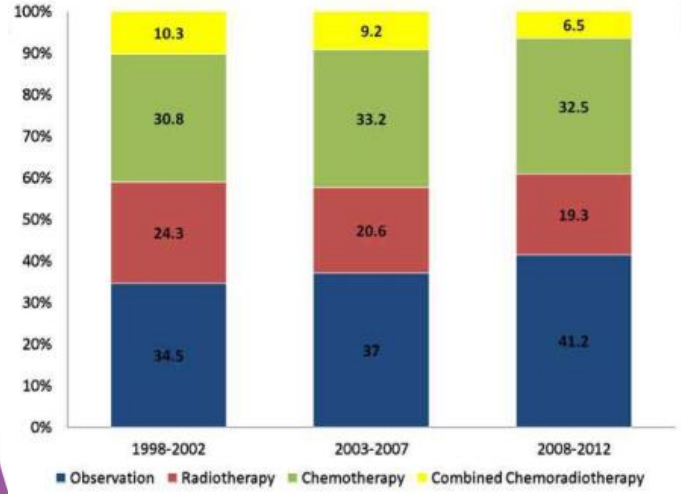
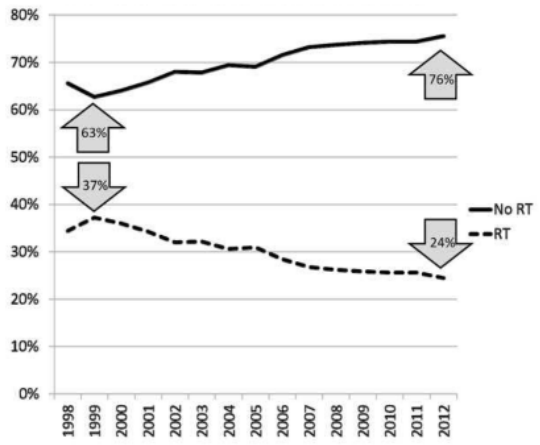
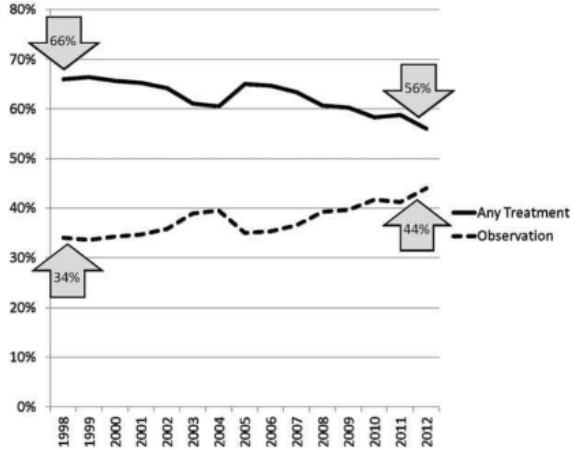
What Is the Optimal Management of Early-Stage Low-Grade Follicular Lymphoma in the Modern Era?

John A. Vargo, MD[1]; Beant S. Gill, MD[1]; Goundappa K. Balasubramani, PhD[2]; and Sushil Beriwal, MD[1]

National Cancer Data Base retrospective cohort study: 35961 pts with nodal and extranodal, AJCC stage I to II, WHO grade 1-2 follicular lymphoma who were diagnosed between 1998 and 2012.







CONCLUSIONS: RT is an increasingly underused treatment approach in the era of modern therapy for patients with early-stage follicular lymphoma.

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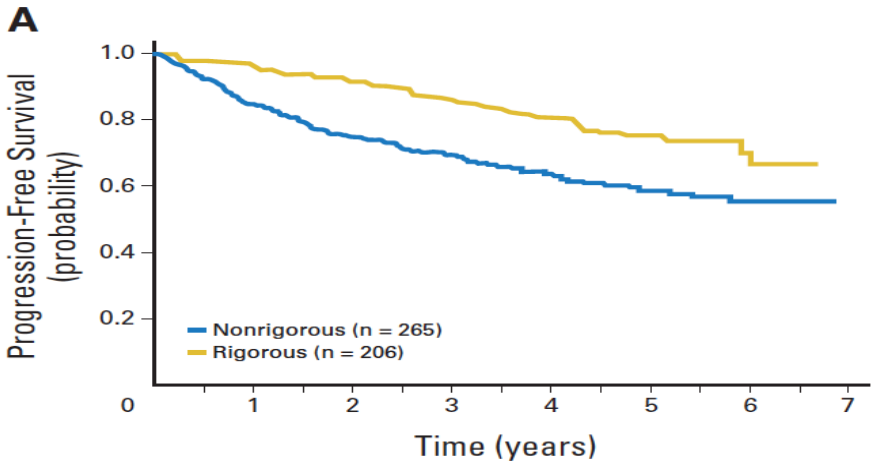
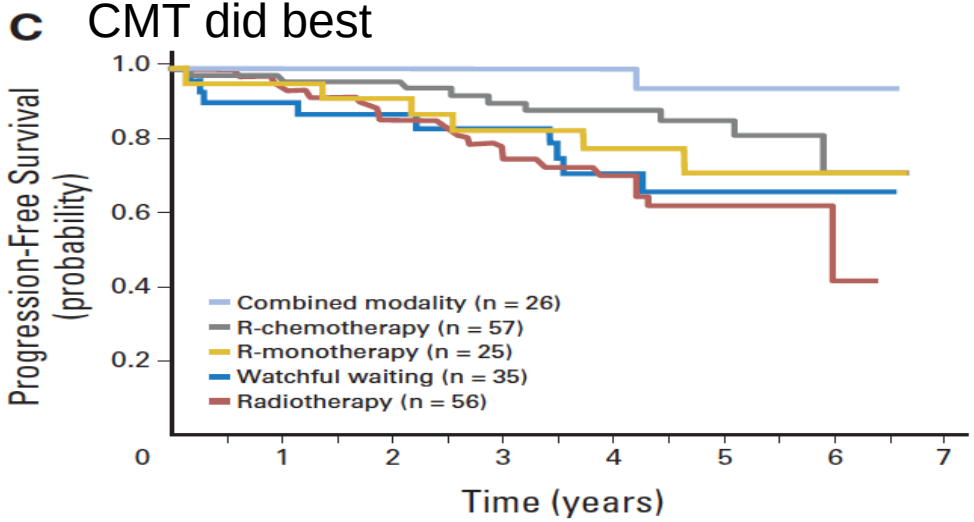
Effectiveness of First-Line Management Strategies for Stage I Follicular Lymphoma: Analysis of the National LymphoCare Study

Jonathan W. Friedberg, Michelle Byrtek, Brian K. Link, Christopher Flowers, Michael Taylor, John Hainsworth, James R. Cerhan, Andrew D. Zelenetz, Jamie Hirata, and Thomas P. Miller

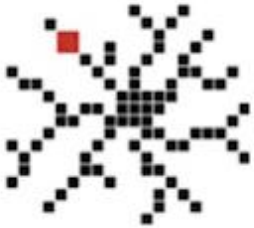
J Clin Oncol 30:3368-3375. © 2012

Chemo and R-Chemo better than RT (?)
CMT did best





Of 471 patients with stage I follicular lymphoma, 206 patients underwent rigorous staging



14th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 14-17, 2017

Outcome of curative radiotherapy for localised follicular lymphoma in the era of ^{18}F-FDG PET-CT staging: an international collaborative study on behalf of ILROG.

Jessica L. Brady MBBCh FRCR*[1], Michael S. Binkley MD MS*[2], Carla Hajj MD[3], Monica Chelius MD[3], Karen Chau BA[3], Mario Levis MD[4] , Seo Hee Choi MD[11], Chang Ok Suh MD[11], Sara Hardy MD[10], Louis S Constine MD[10], Anders Krog Vistisen MD[8], Scott Bratman MD PhD[2], Gabriele Reinartz MD[9], Hans Eich MD[9], Masahiko Oguchi MD[5], Youlia Kirova MD[6], Andrea Ng MD[7], Victoria S Warbey[1] Tarec El-Galaly MD[8], Andrea Riccardo Filippi MD[4], Umberto Ricardi MD[4], Joachim Yahalom MD[3], Richard T. Hoppe MD[2], N. George Mikhaeel MBBCh, MSc, FRCR[1]

Hypothesis: more accurate staging will lead to better patients selection for tretament with ISRT, with consequent improvement in clinical results

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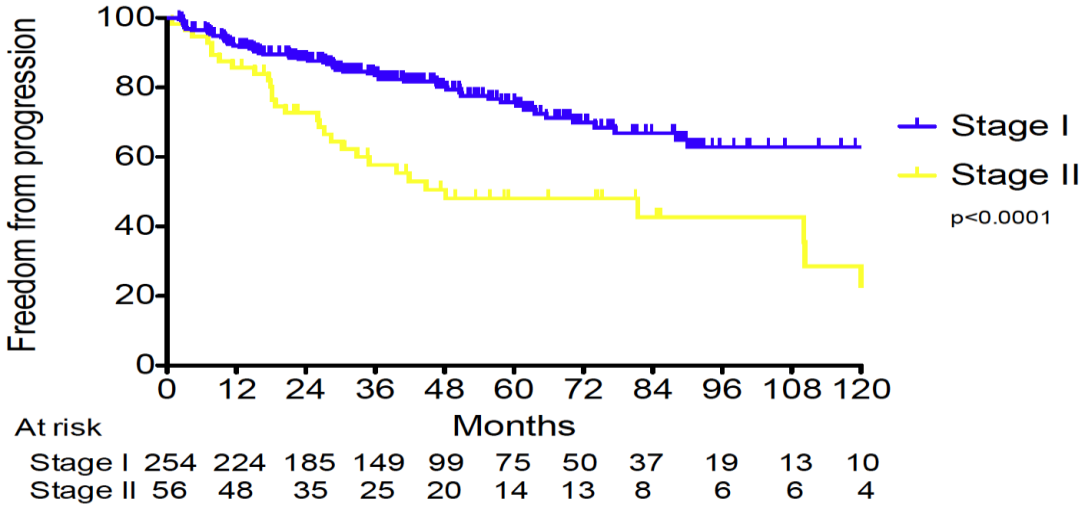
RESULTS

- **310 pts** treated from 2000-2016 at 11 centres were eligible

- Median RT dose was **30 Gy** (range 24-36)
- Median follow up was **50 months** (range 3.2-174.6)

- 222/310 (71.6%) pts remain **disease free**
- Only 1 case of grade 3 toxicity
- 6 pts relapsed in field (1.9%) and 2 had marginal recurrences (0.6%)
- 80 pts (25.8 %) relapsed at distant sites (90.9% of all relapses)



5 yrs FFP and OS were 70.2% & 95.8%

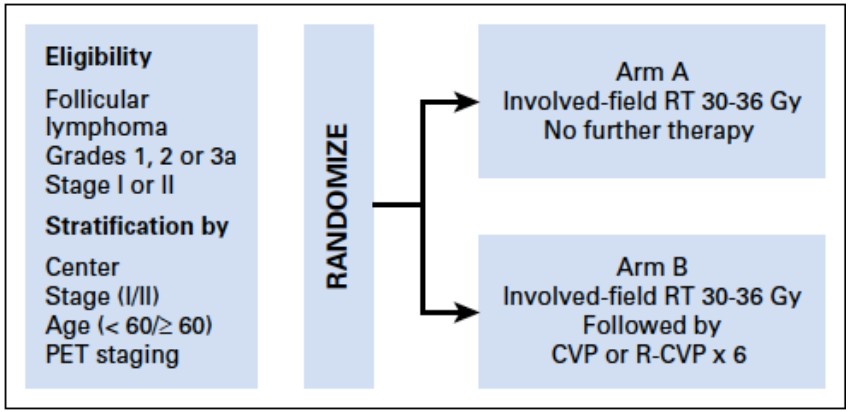
5 yrs FFP was 74.3% for stage I vs 48.1% for stage II (p<0.0001)

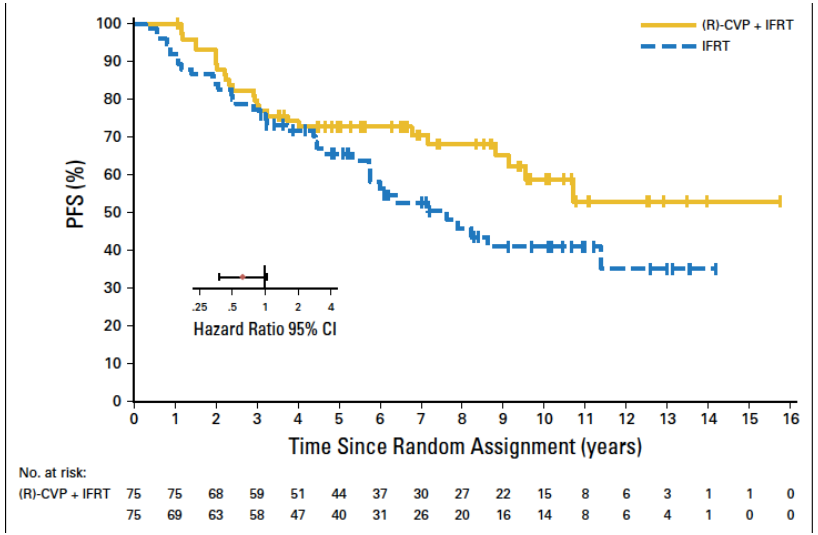
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

J Clin Oncol 36. © 2018

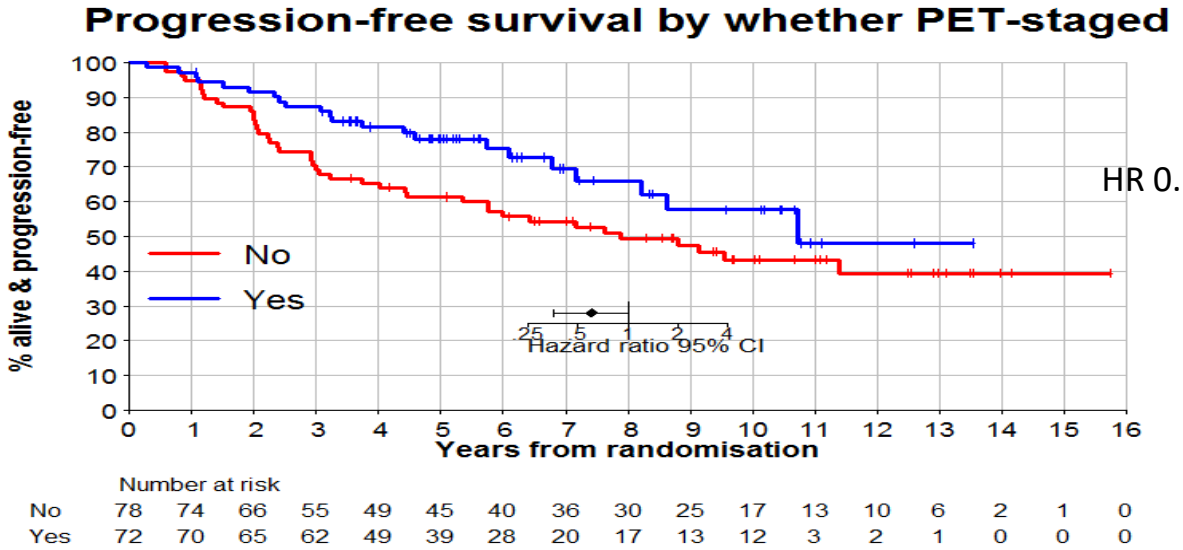
Randomized Trial of Systemic Therapy After Involved-Field Radiotherapy in Patients With Early-Stage Follicular Lymphoma: TROG 99.03

Michael MacManus, Richard Fisher, Daniel Roos, Peter O'Brien, Andrew Macann, Sidney Davis, Richard Tsang, David Christie, Bev McClure, David Joseph, Jayasingham Jayamohan, and John F. Seymour





Effect of PET



HR 0.61 P = 0.056

Modern RT in Indolent Lymphoma

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

- 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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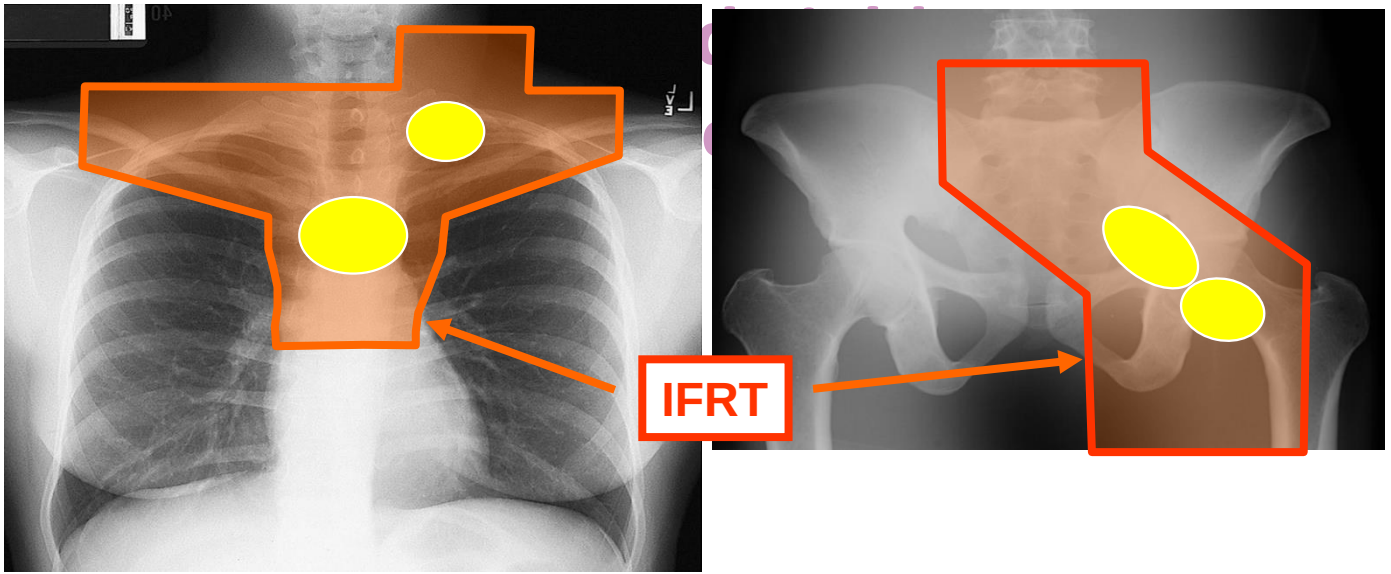
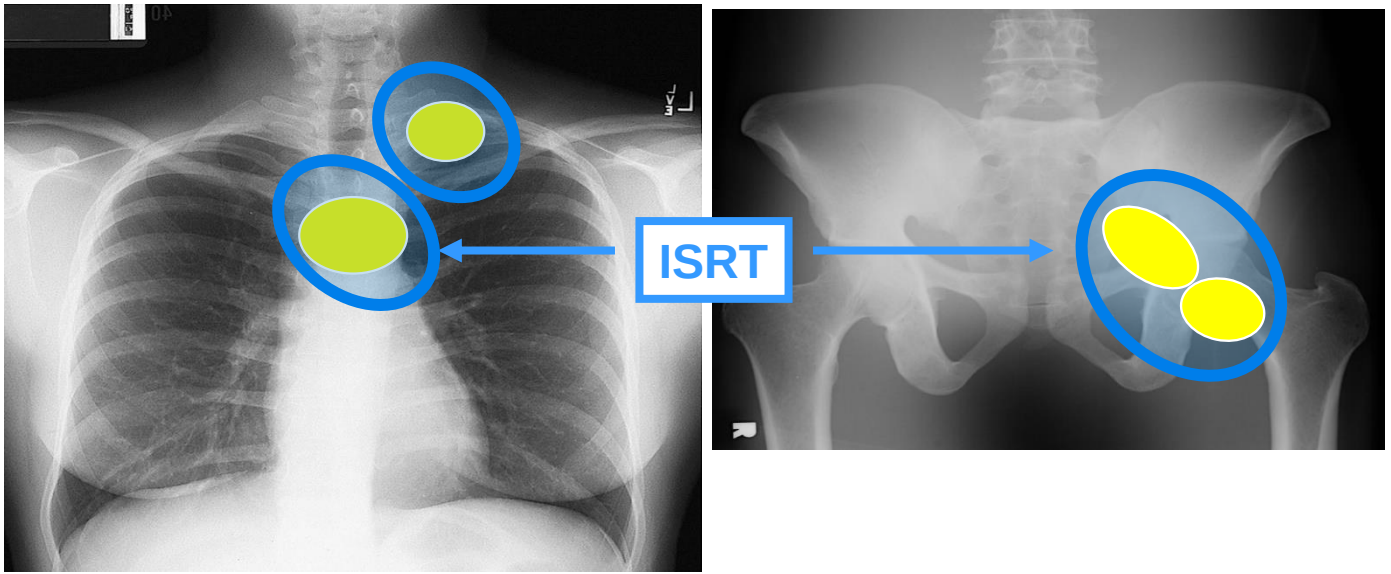
Development of Radiation Volumes



Involved Site

3D planning, based on lymphoma volume



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

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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

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

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Gross tumor volume (GTV) (ICRU 83)

- Gross demonstrable extent and location of the tumor (lymphoma)

- **Determination of Gross Tumor Volume**

Imaging abnormalities obtained before any intervention should be outlined on the simulation study and included in 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

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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

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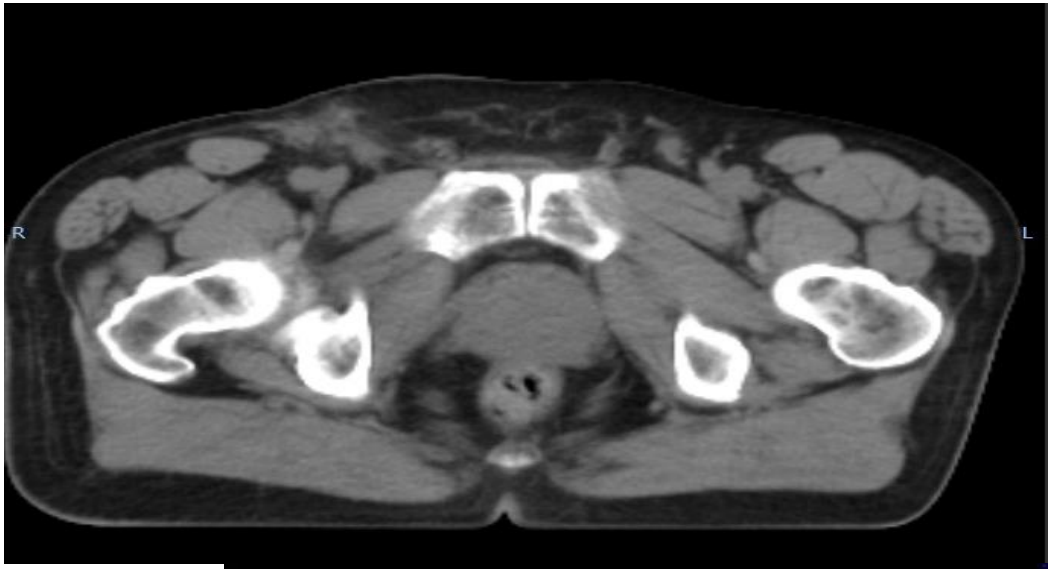

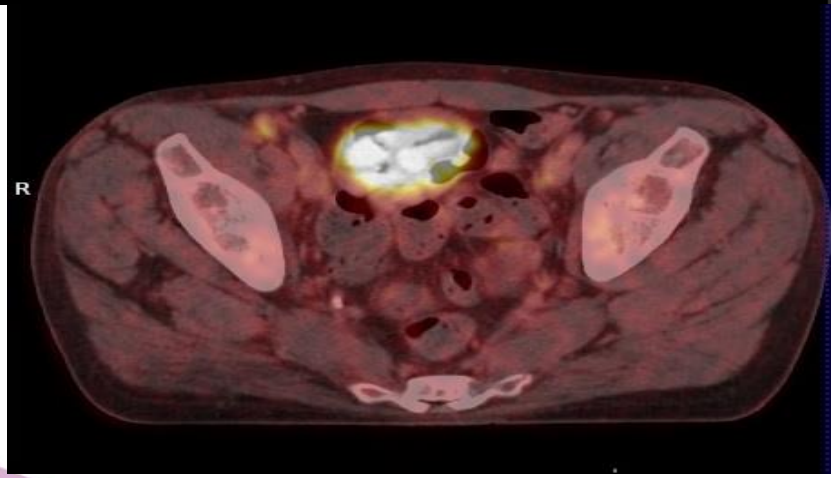

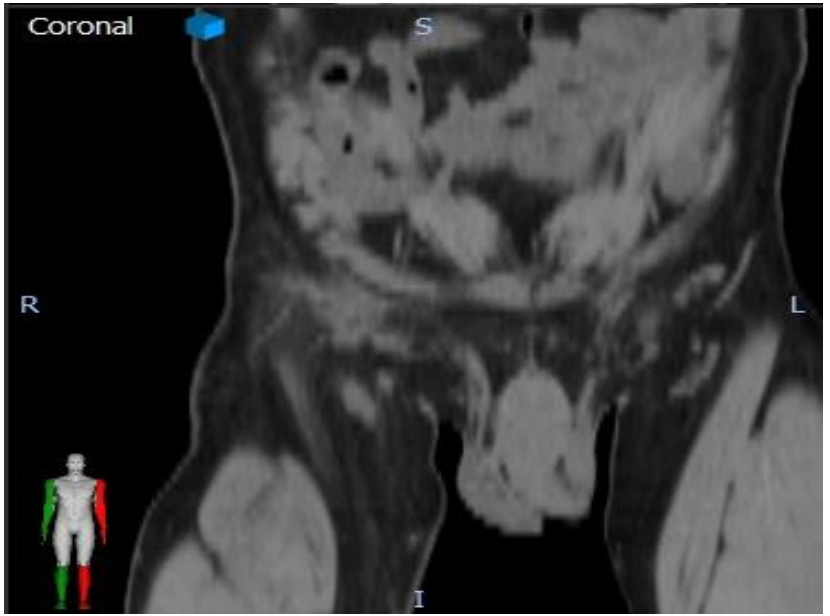

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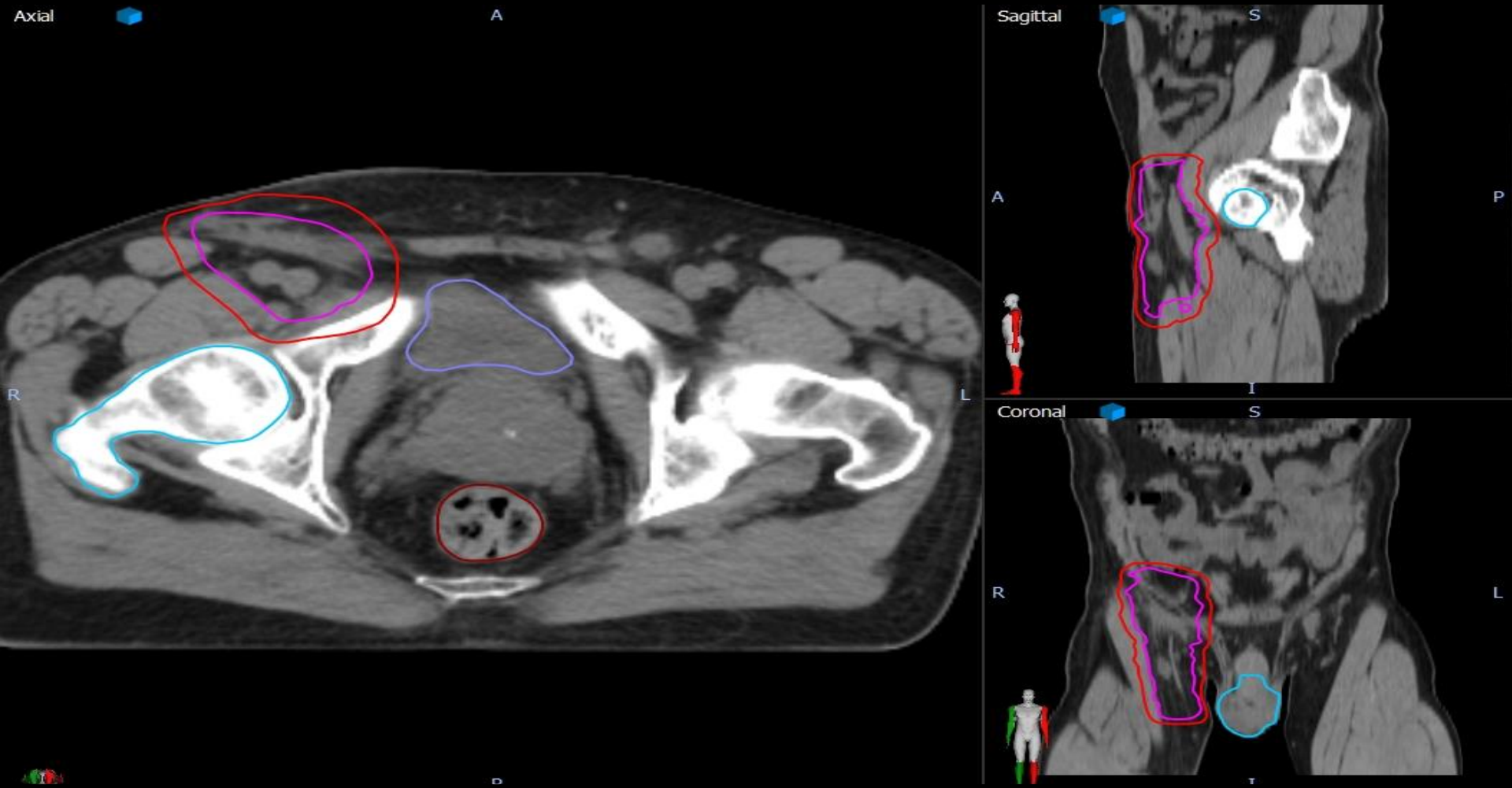
Axial
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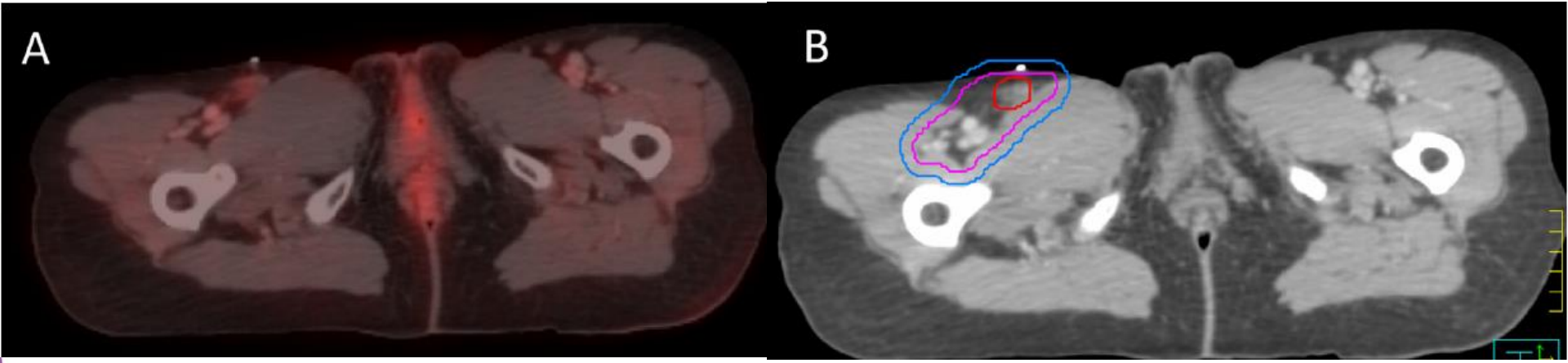
Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

ISRT: Localized indolent lymphoma



The CTV must be designed to encompass suspected subclinical disease based on the pre intervention GTV imaging

The CTV should incorporate GTV and include adjacent lymph nodes in that site and margin dictated by the clinical situation

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

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- “Rigorous staging” is required to determine appropriate patients to consider ISRT, including BM biopsy and FDG-PET scan

- ISRT remains treatment of choice for stage I/II indolent lymphomas and results in long term progression free survival and possible “cure” for patients still in remission past 10 years

Considerations on RT dose

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Reducing doses for FL

- Early series: doses often ≥40 Gy
- PMH Toronto series: no dose response above 30 Gy
- Toronto data: plateau in FL after 20 Gy
- EORTC: no improvement in control of FL >25 Gy
- Girinsky/Haas: High response rates with 2 Gy x 2

- Informative RCTs needed to answer dose question

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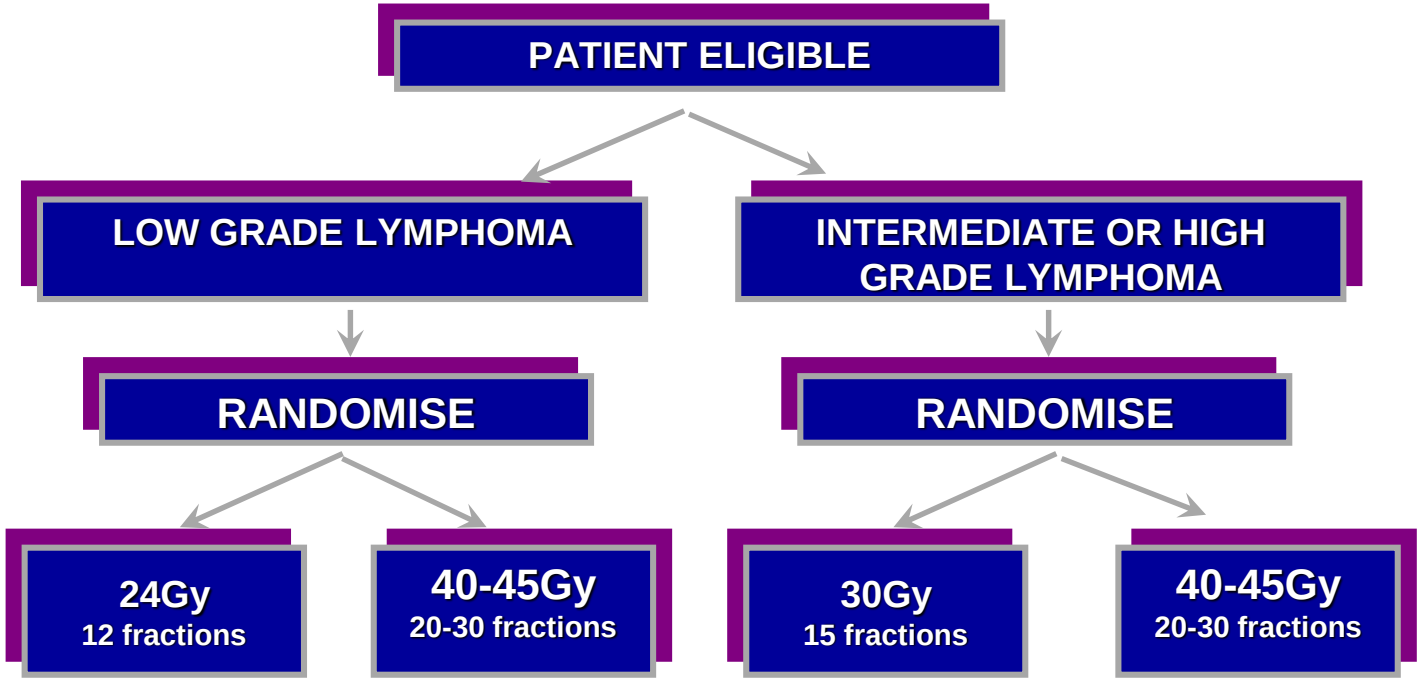
Reduced dose radiotherapy for NHL : A randomised phase III trial

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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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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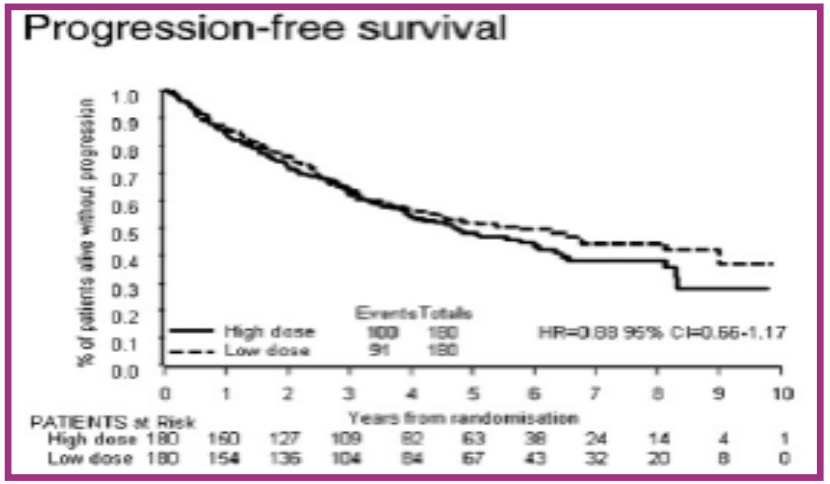
Reduced RT dose in NHL

A randomised phase III trial

Median follow-up time: 5.6 years

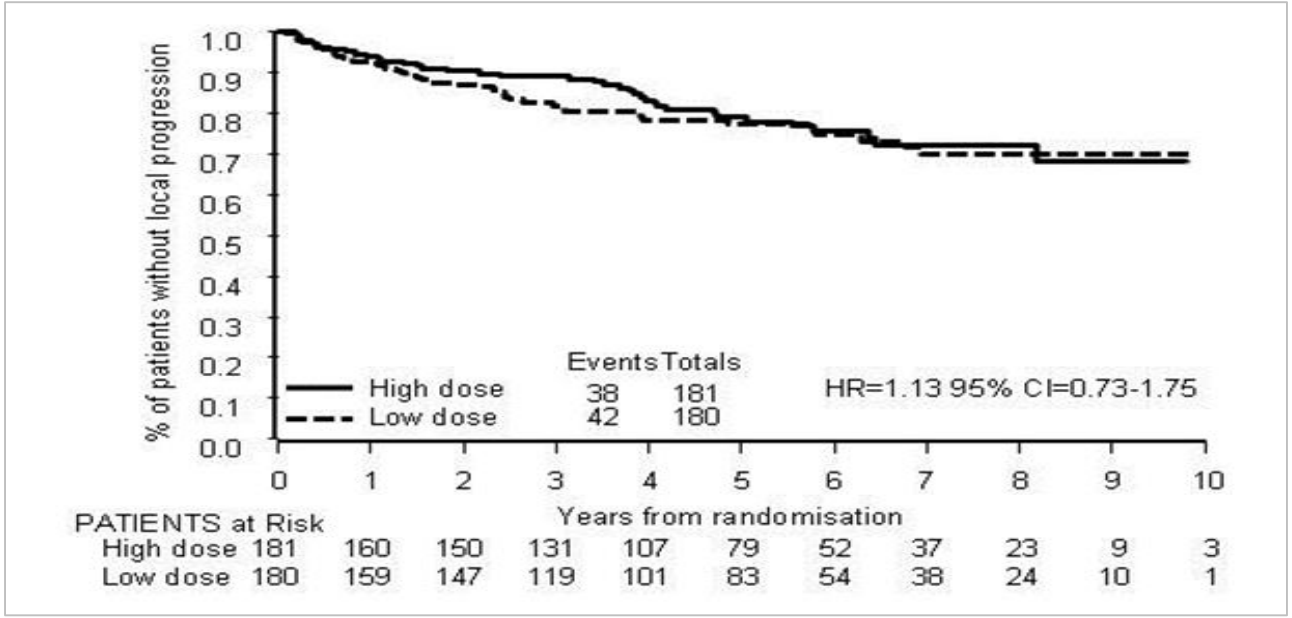
ORR: 92% in 24 Gy arm *vs* 93% in 40-45 Gy arm

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



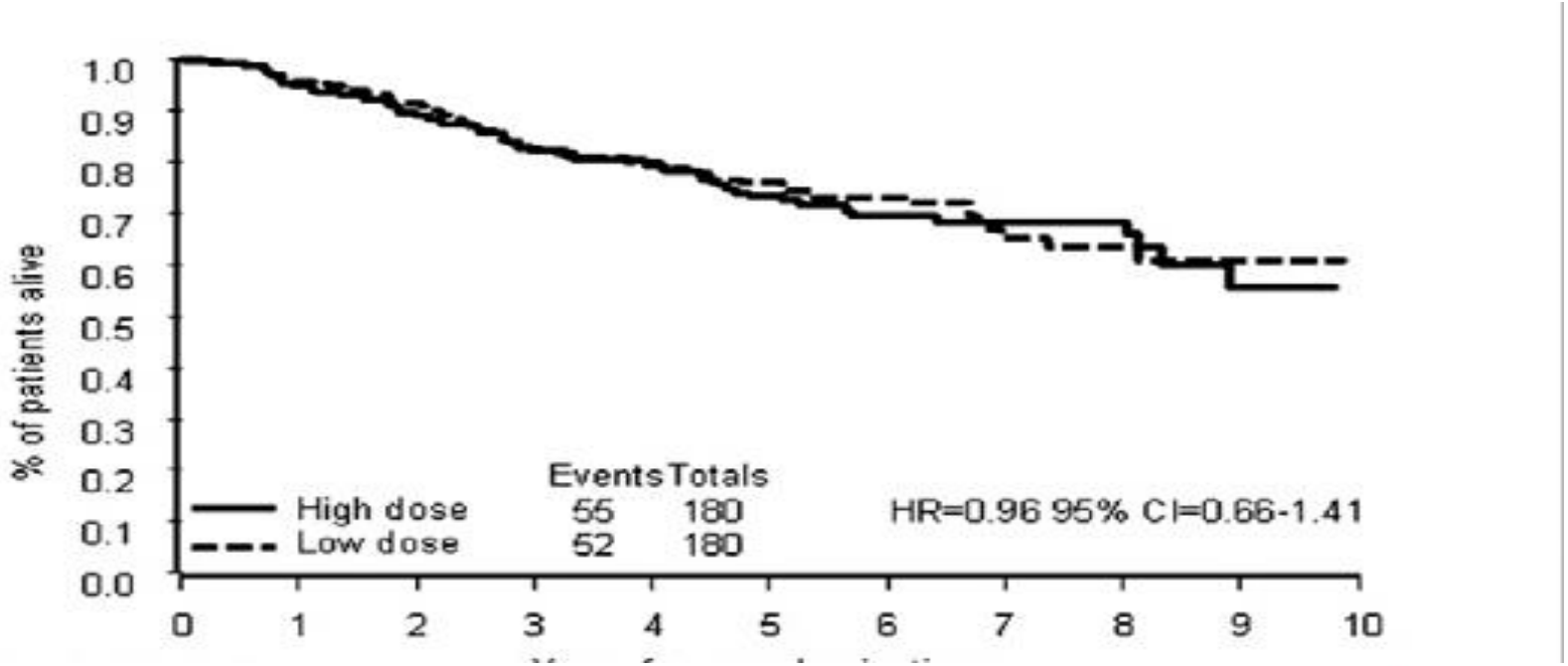
Lowry et al, Radiother Oncol, 2011

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

INDOLENT LYMPHOMAS:
Overall Survival



Lowry et al. 2011

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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

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

Haas RLM et al. J Clin Oncol 21, 2474-2480, 2003

- Haas et al: JCO 2003 of 109 pts with 304 sites
- **Overall RR 92%**
- CR in 67 patients (61%), PR in 34 patients (31%), SD in six patients (6%), and PD in two patients (2%)
- The median time to progression was 14 months
- The median time to local progression was 25 months
- The 67 patients with CR showed a median time to progression of 25 months and a median time to local progression of 42 months
- Minimal toxicity

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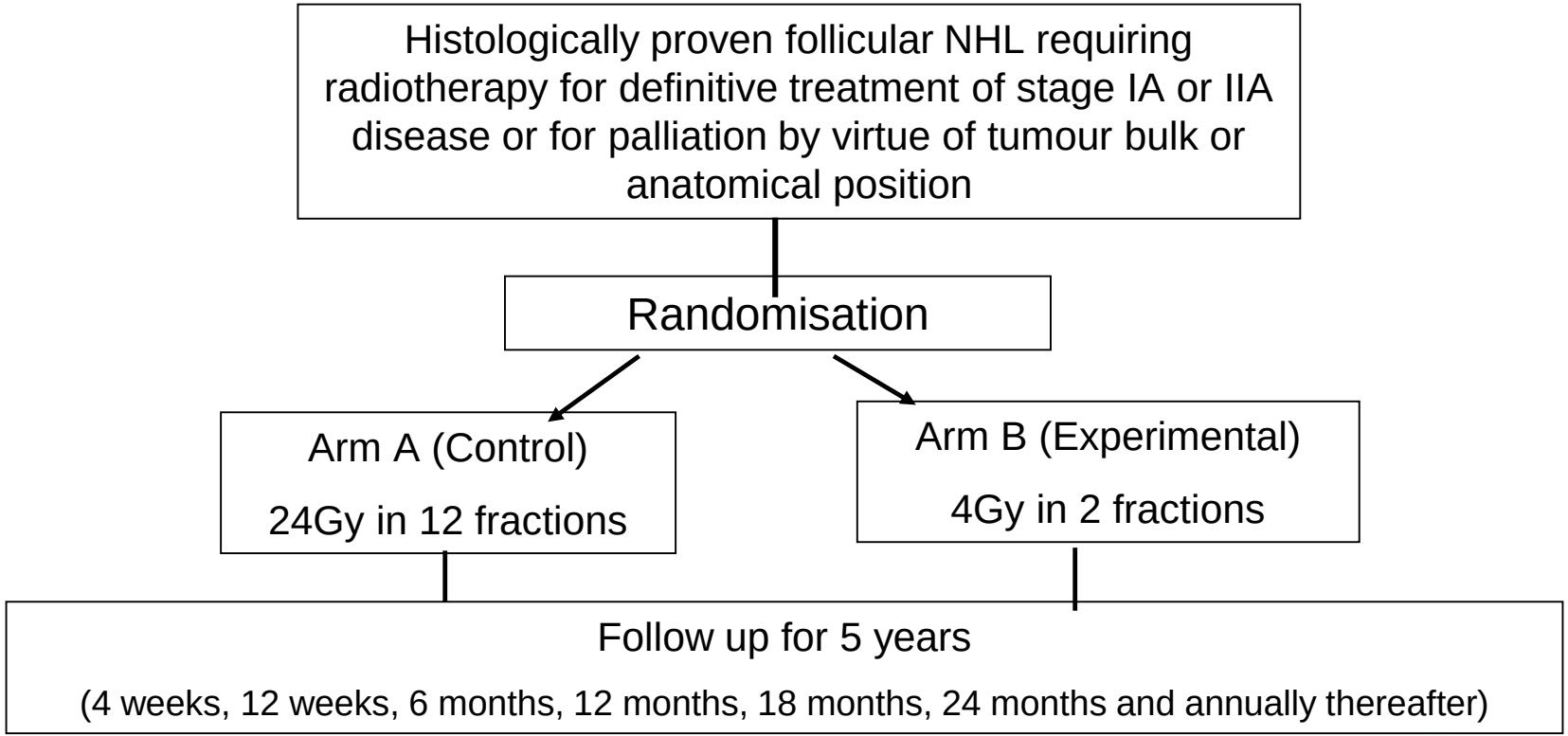
FoRT: Study design : A randomised trial of low dose radiotherapy for follicular lymphoma



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.

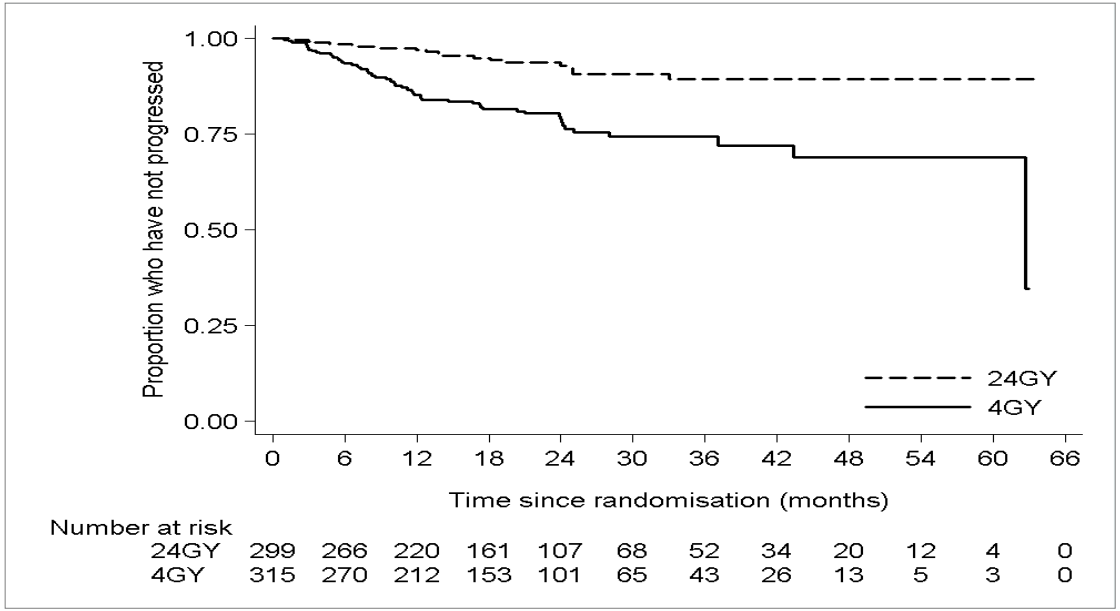
Table 3: **Response by subgroup**

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**



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,

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

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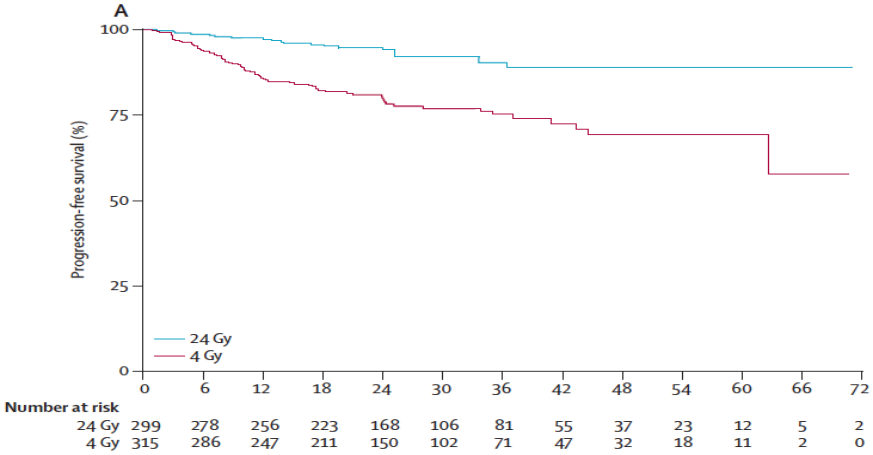
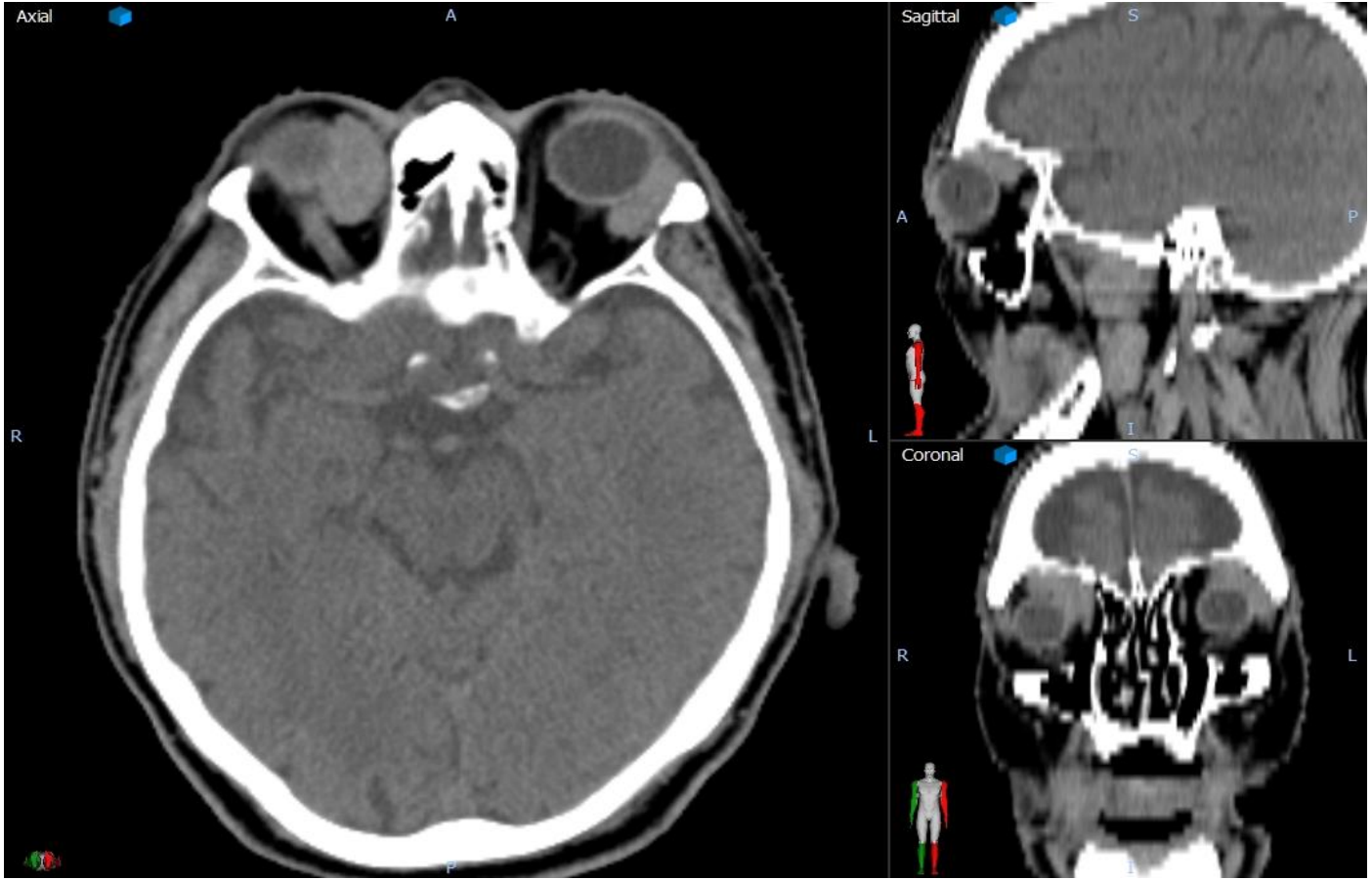
Lancet Oncol **2014; 15: 457–63**

	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.



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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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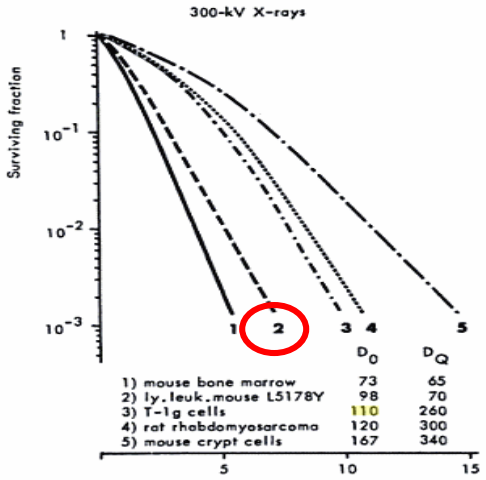
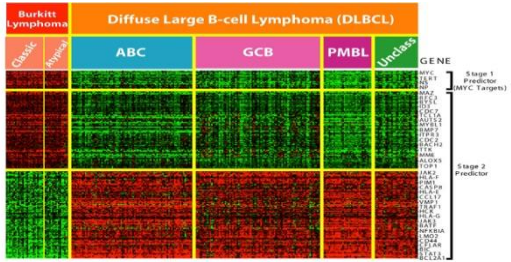
What Drives Radiation Sensitivity in Lymphoma?

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

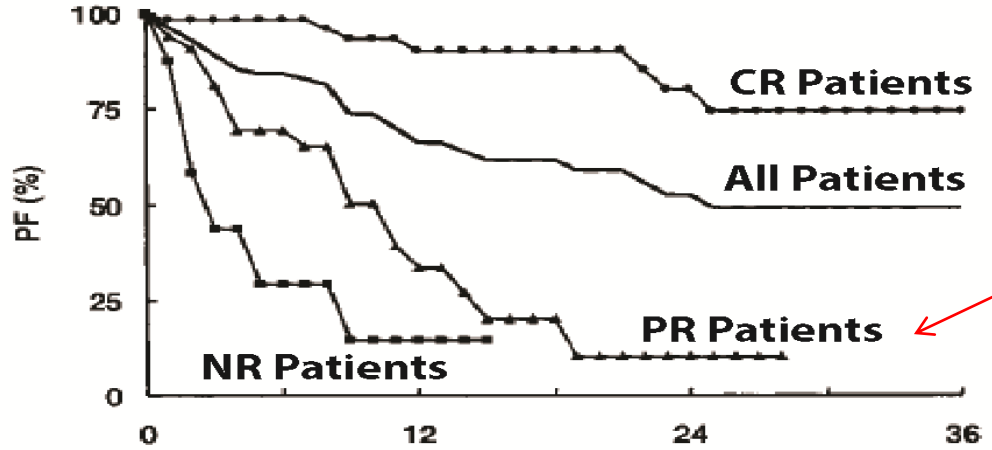
Wide spectrum of response to RT in lymphoma (4-40 Gy): Dramatic variations in radiosensitivity can be explained by molecular differences in the tumor

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

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?

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RT techniques

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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

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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)

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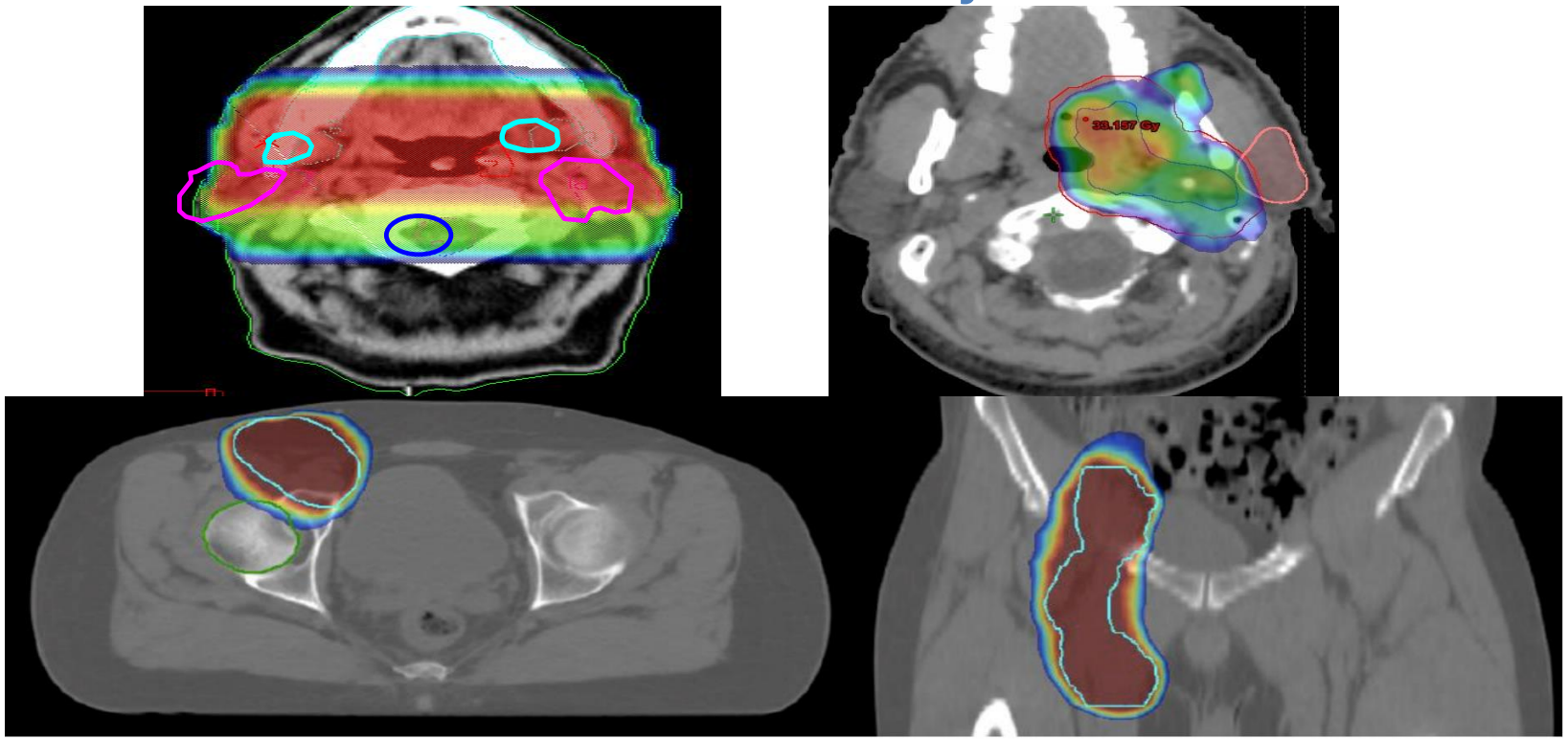
Conformal planning and precise delivery

Conventional RT

Intensity modulated RT



Conclusions

- RT remains treatment of choice for majority of stage I/II$_1$ indolent lymphomas, resulting in long term progression free survival and possible “cure” achievable with very low morbidity

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

James O. Armitage

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Modern RT in indolent nodal lymphoma

- Radiation therapy has changed dramatically over the last few decades in terms of both irradiated volumes and doses
- Smaller treatment volumes, lower radiation dose and advanced conformal radiotherapy can certainly allow a safer radiation delivery

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Deep inspiration breath hold in thoracic tumours: imaging and treatment

Marianne C Aznar

Dept. Of Oncology, Copenhagen University Hospital, Rigshospitalet

With the help of the Dept. of Clinical Physiology, Nuclear Medicine and PET

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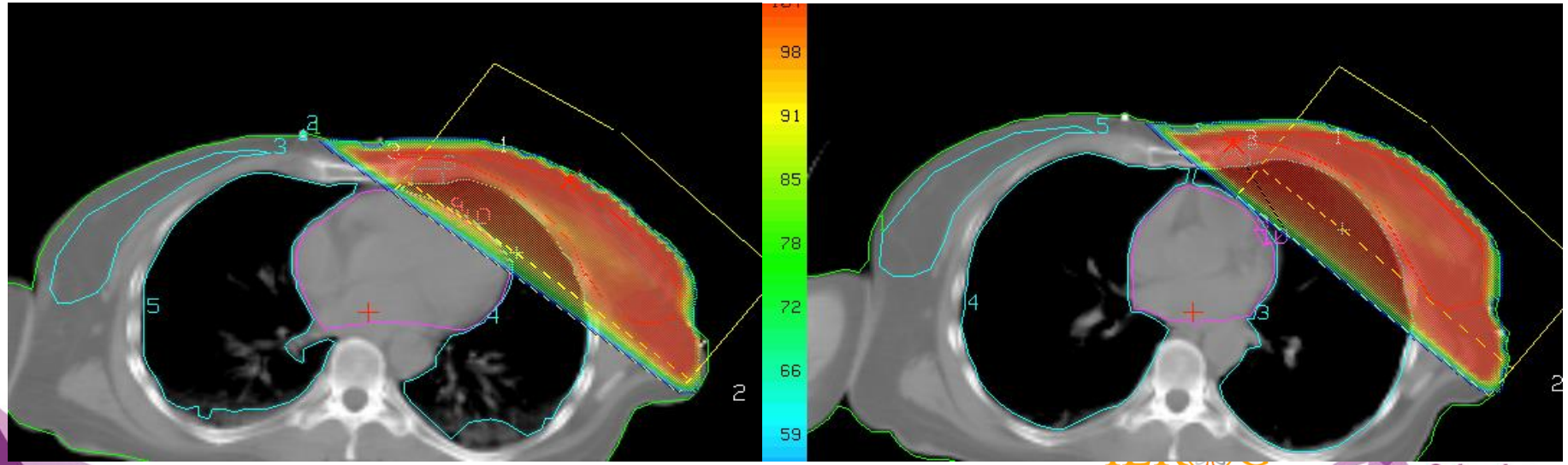
At Rigshospitalet

- Deep inspiration treatment since 2003 in left-sided breast cancer patients
- > 1000 patients



LYMPHOMA: A SPECIAL CASE

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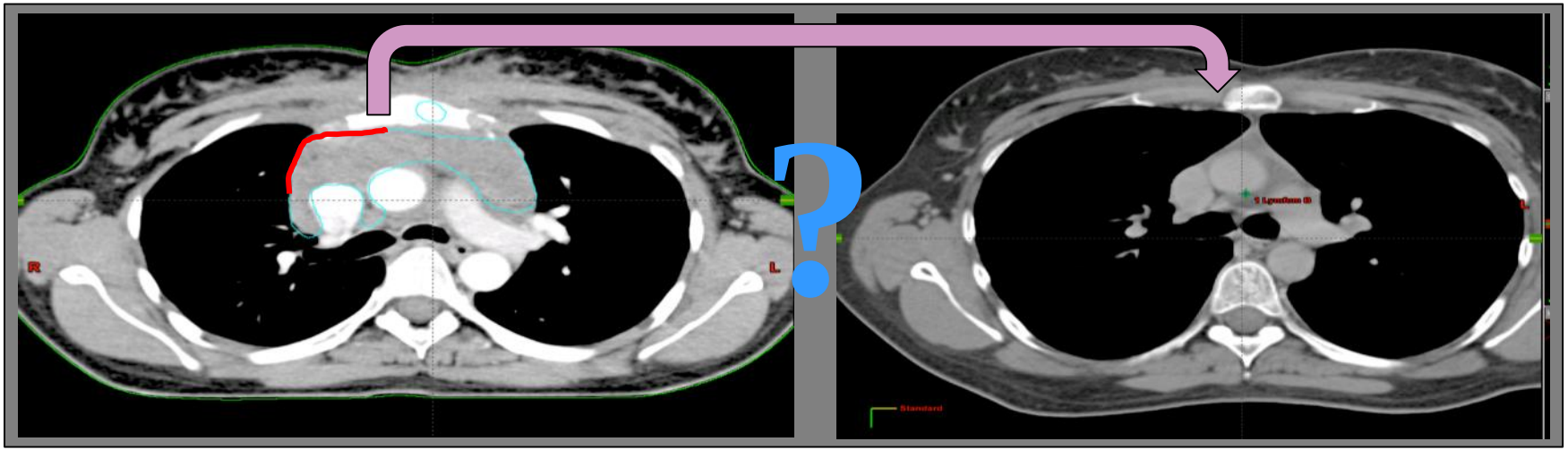
Fusing prechemo and planning images

Pre-chemo PET/CT

free breathing

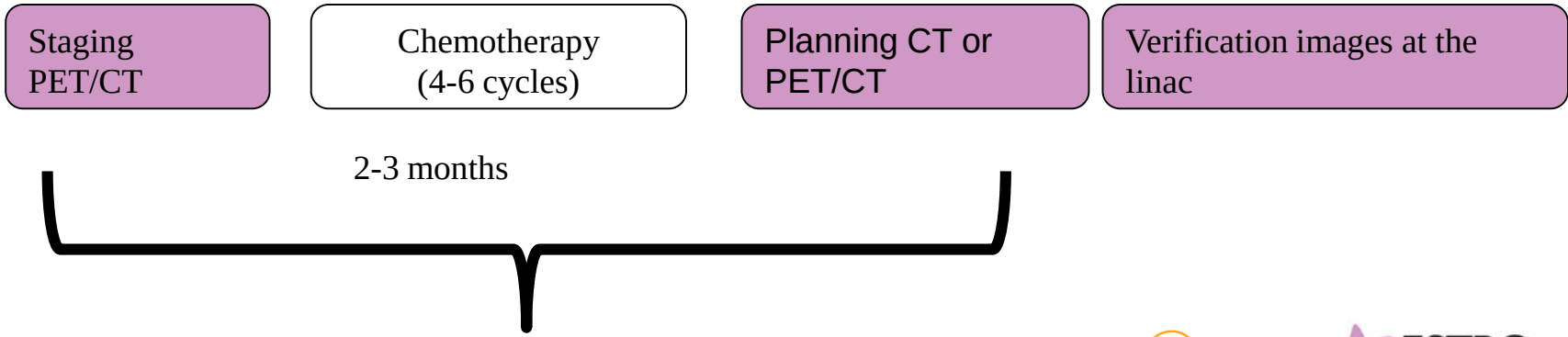
Planning CT

at deep inspiration



DIBH through the whole imaging chain

- All images in DIBH



Rigshospitalet (The Finsen Center)

- 3500 patients /year

- 2 dedicated CT scanners
- 1 dedicated MR scanner
- Joint facilities with Nuclear Medicine department
  - 4 PET/CT, one dedicated to RT planning
  - 1 PET/MR
  - Radiographers rotating between departments
  - 3 radiologist hired by both departments

- 11 linacs

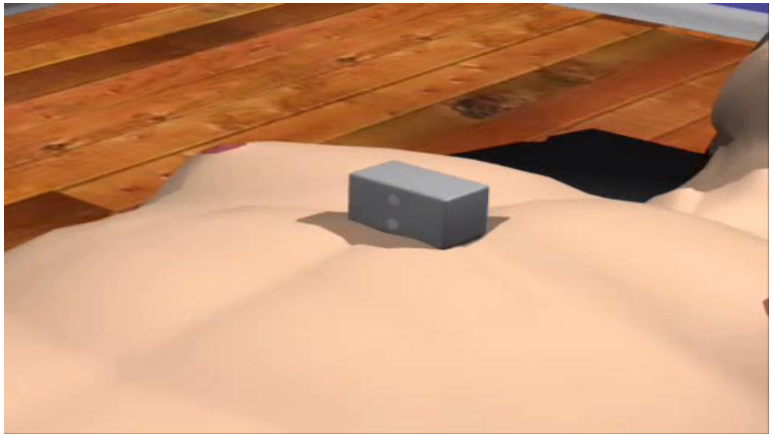
How to handle registration uncertainties ?

- 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!

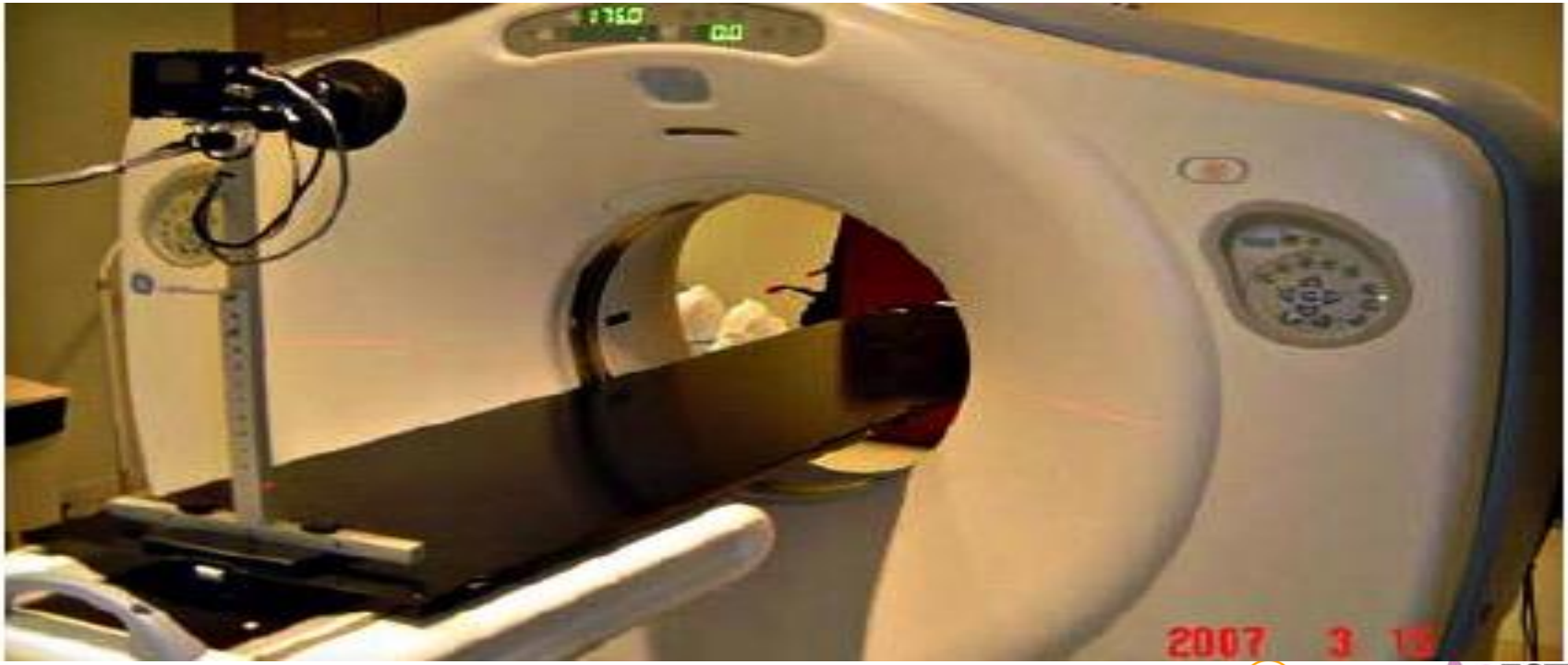
Respiration monitoring



<u>Varian RPM system:</u>
Deep inspiration breath hold
Gating
4D CT

On all linacs and scanners

CT + PET/CT



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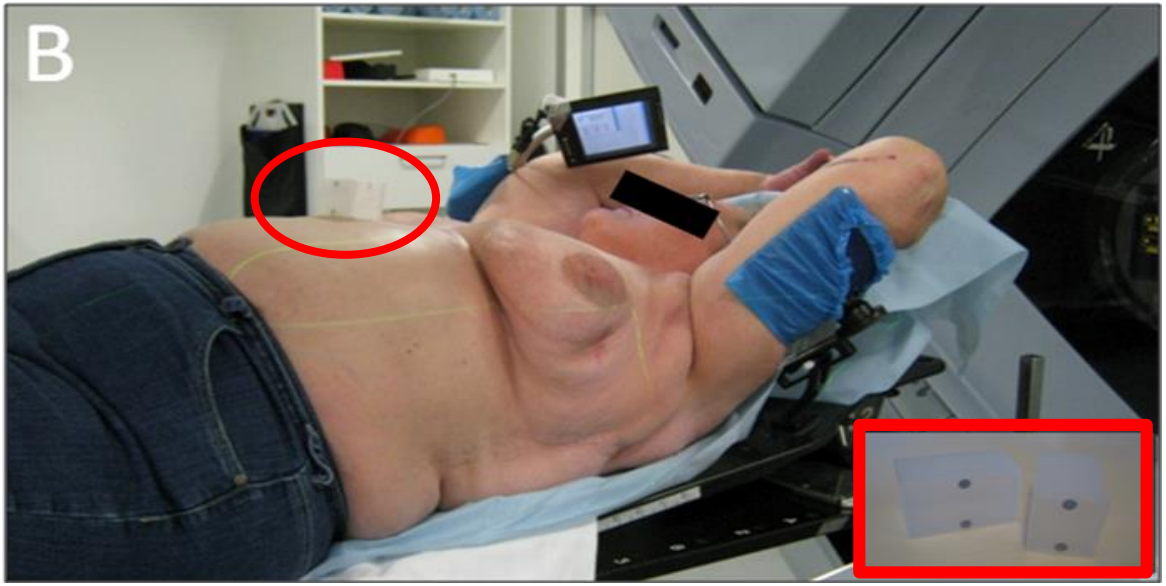
Equipment

Courtesy of Sidsel Damkjær, Copenhagen



At Rigshospitalet: RPM system from Varian + third part screens/goggles

Alternatives: ABC system from Elekta, VisionRT, C-RAD sentinel…

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 equipement, etc… plus extra acquisition) : 15-30 min
- Good communication with PET extremely valuable !

PET/CT acquisition in practice

•Pre chemo scan: FDG on Siemens Biograph 40 PET/CT

• Free breathing scan followed by one FOV scan in breath hold

•6 breath holds of 20 seconds each

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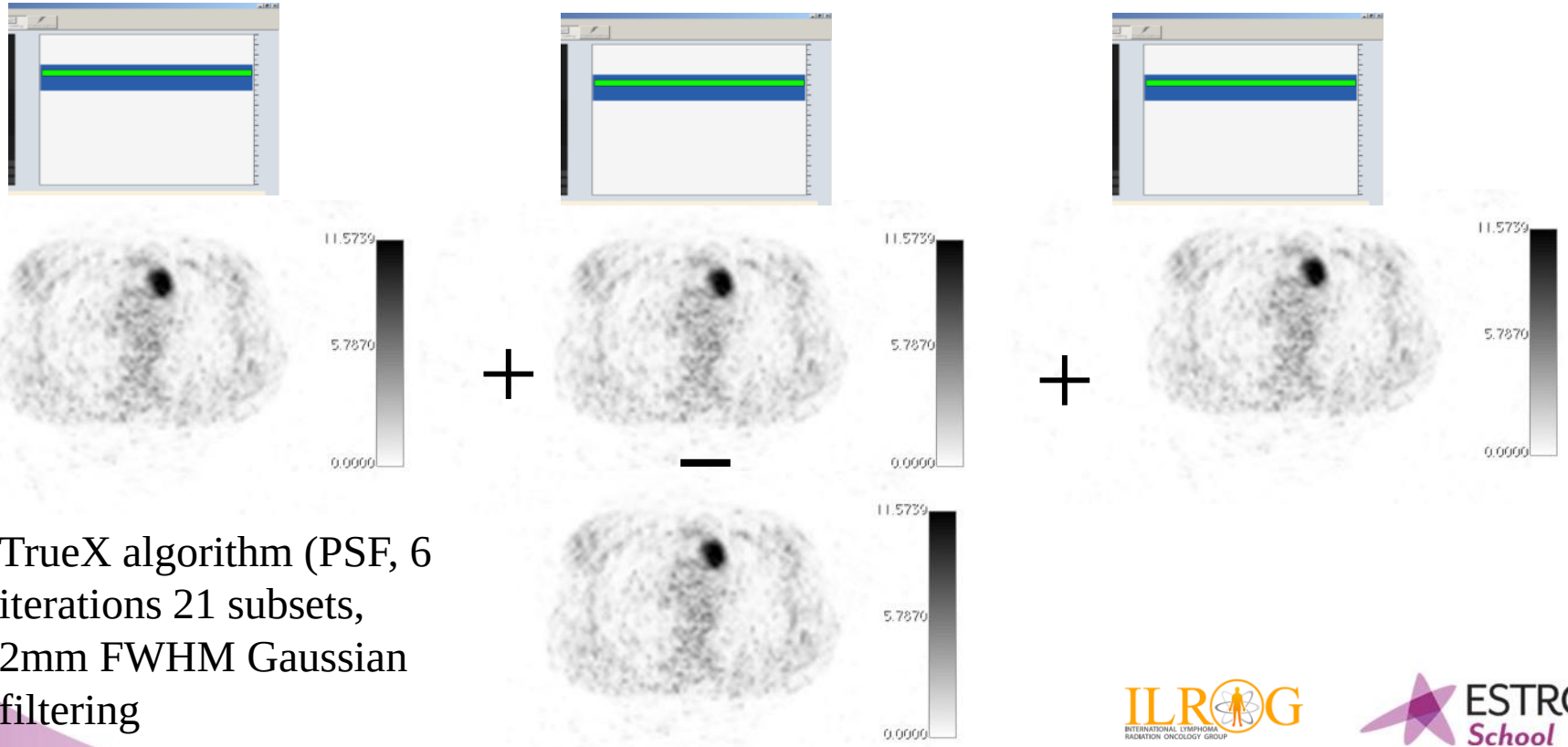
Methods: Image reconstruction



TrueX algorithm (PSF, 6 iterations 21 subsets, 2mm FWHM Gaussian filtering

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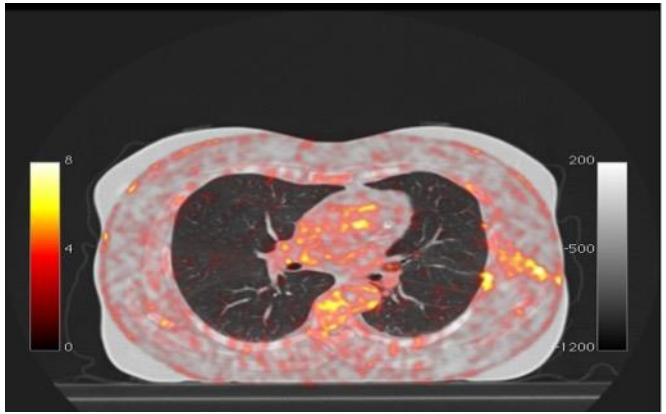
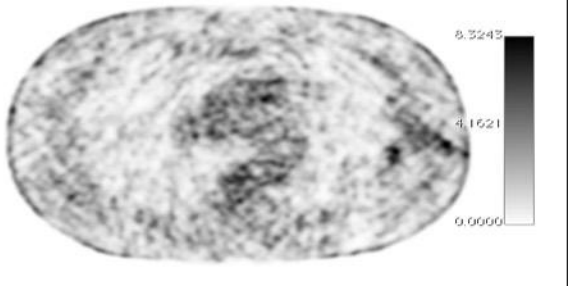
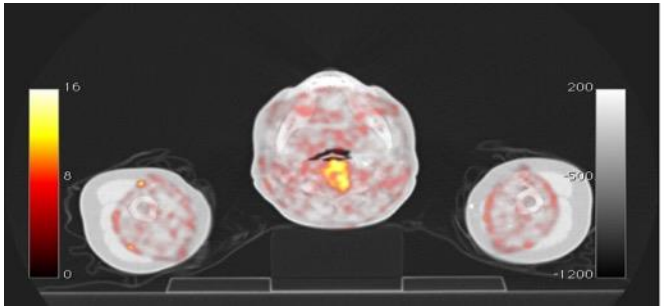
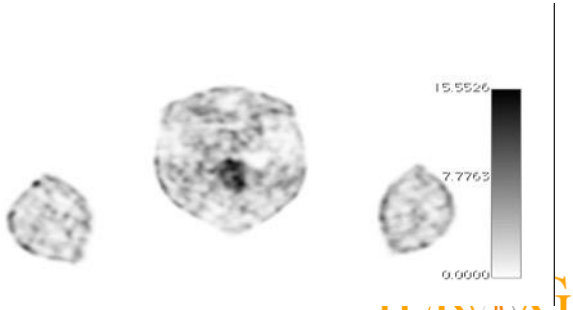
Some problems at start-up !!









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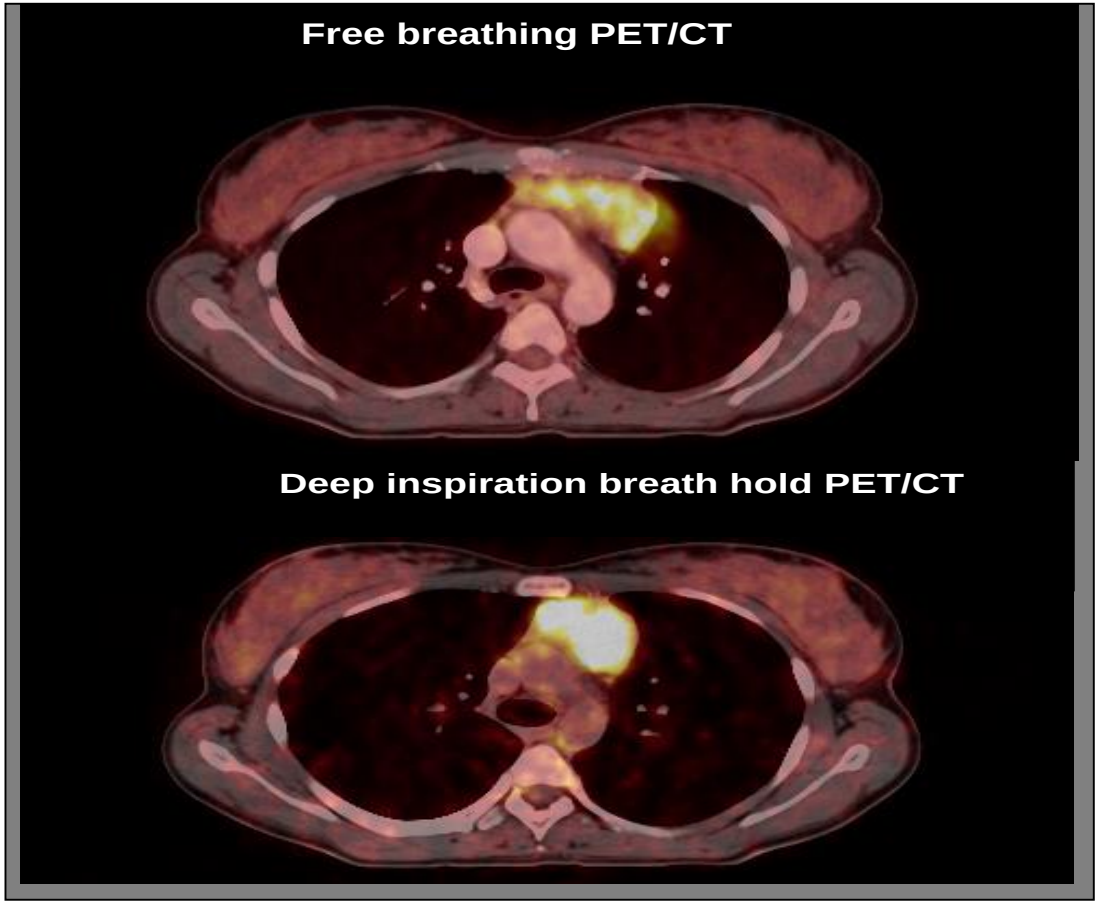
Results: reduced respiration artifacts



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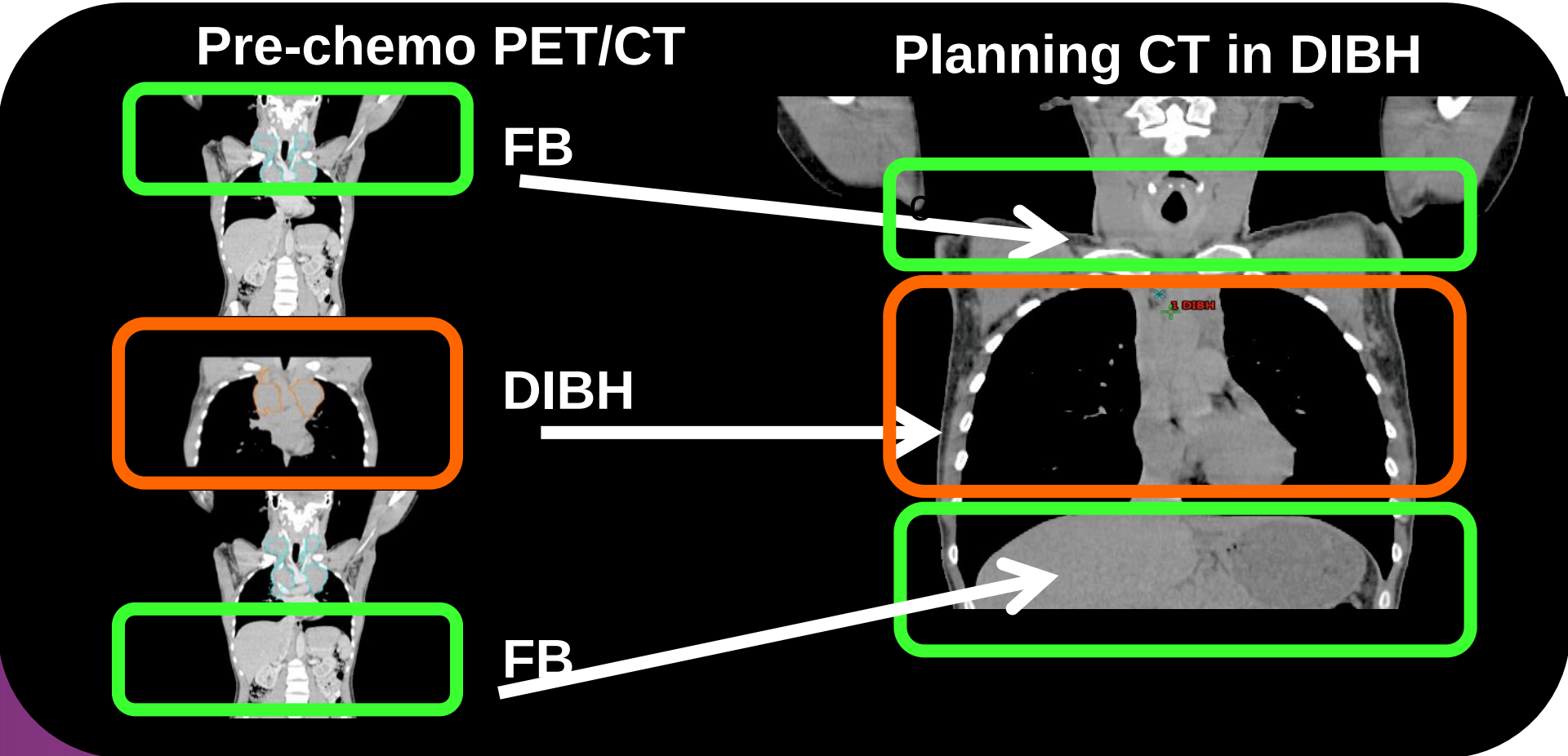
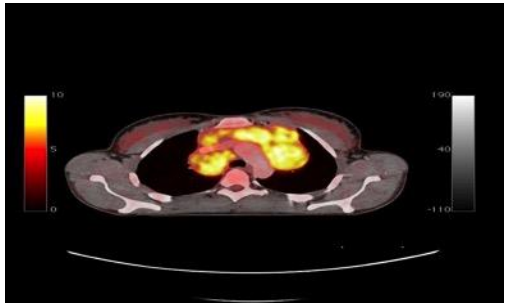
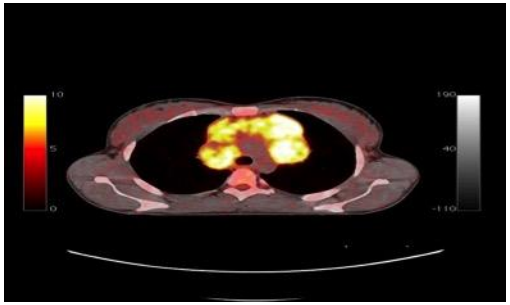
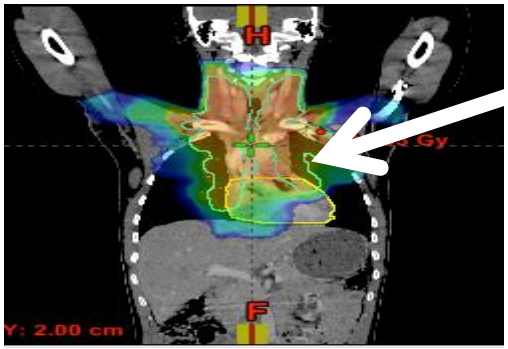
Registration for contouring



Dosimetric impact

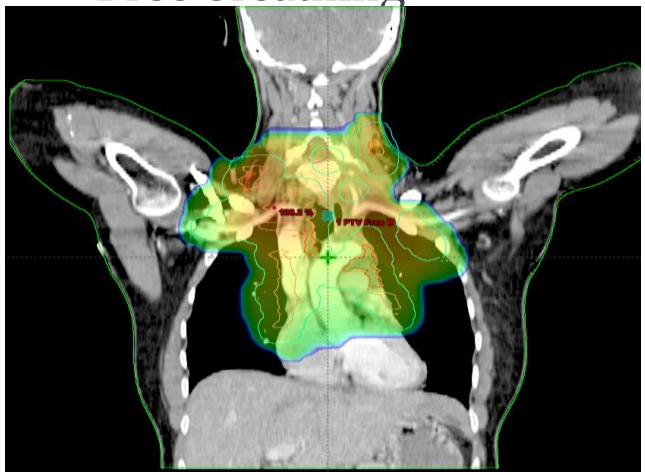




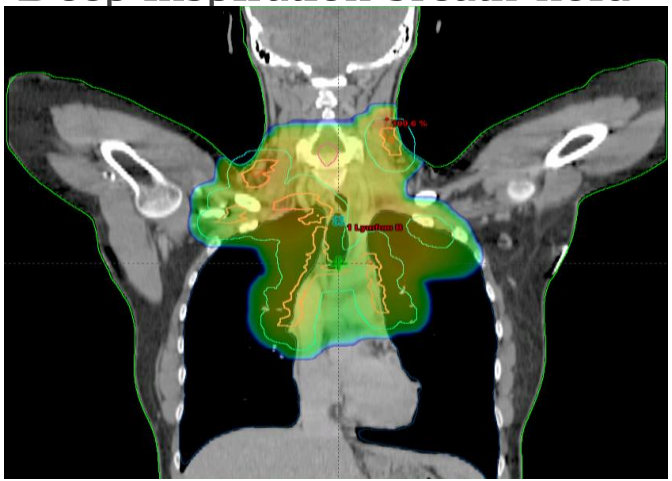


Breath hold decreases the exposure of healthy tissues

- Free breathing

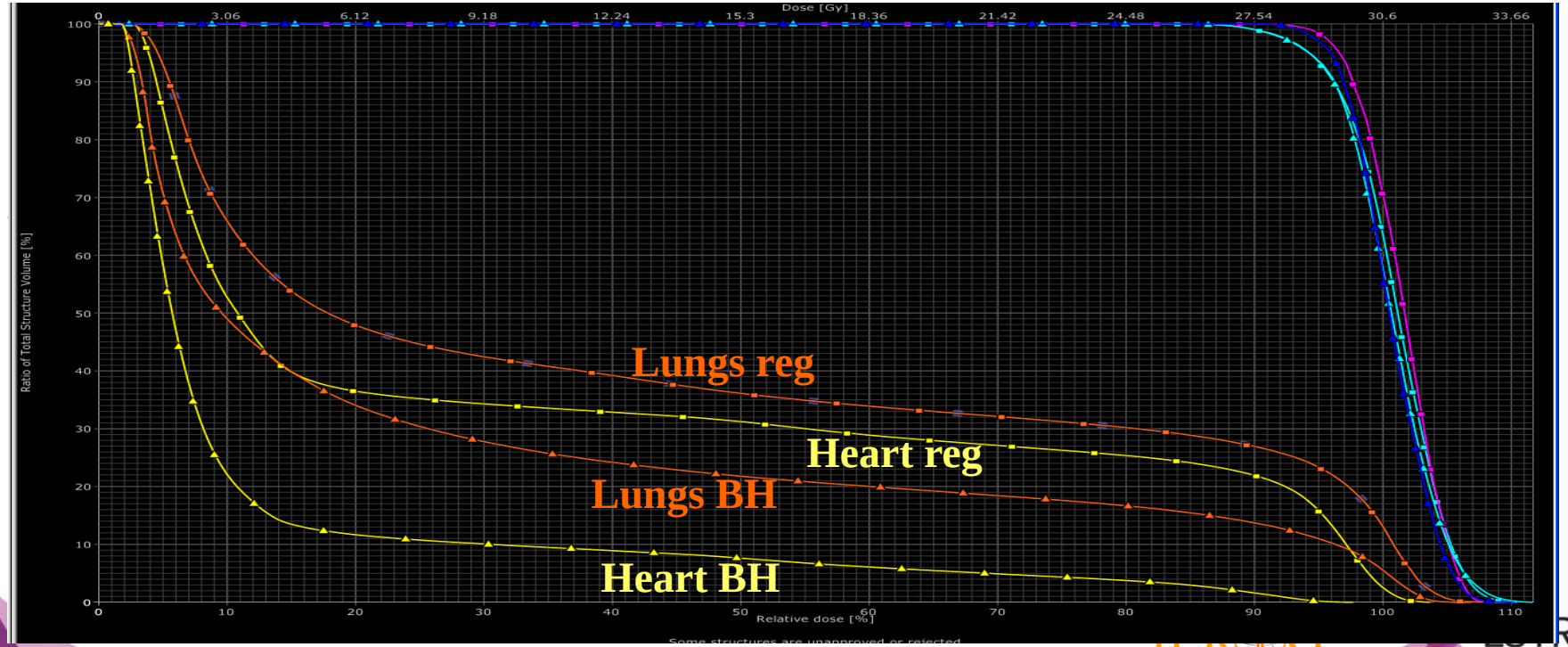


- Deep inspiration breath-hold

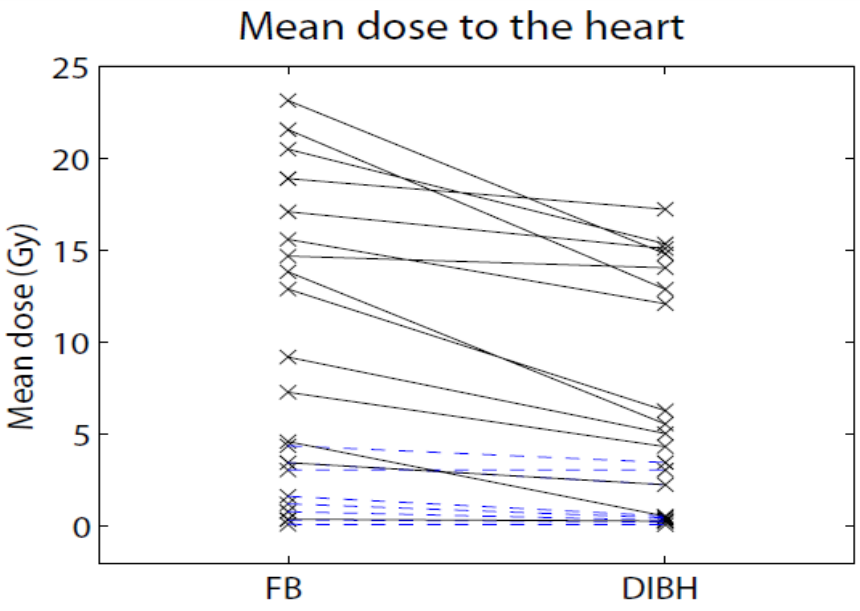


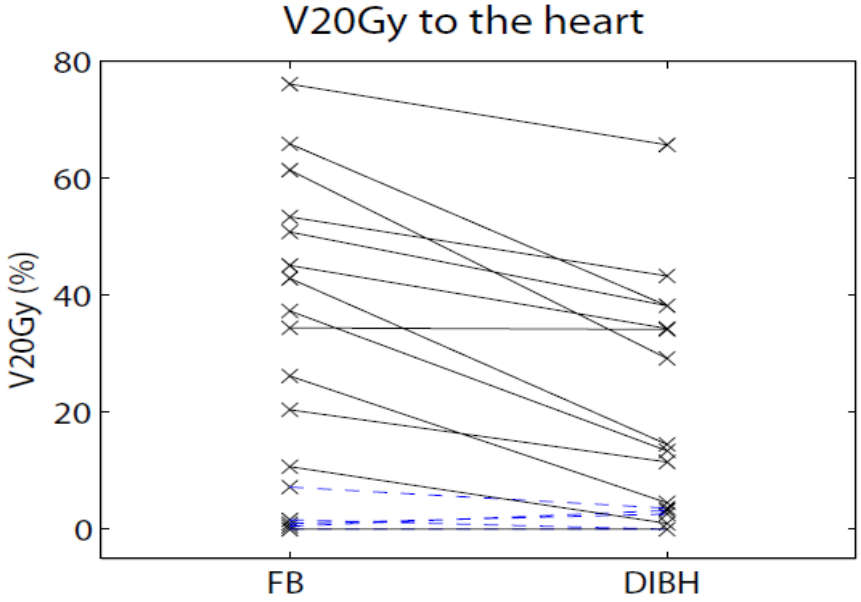
Notice lung volume and heart position

Mean dose to lungs: 8.5Gy vs 12.8 Gy



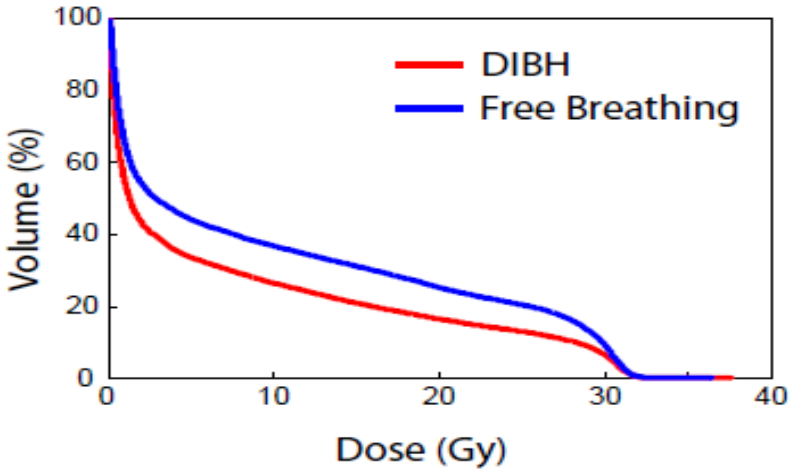
Benefit: inter-patient variation



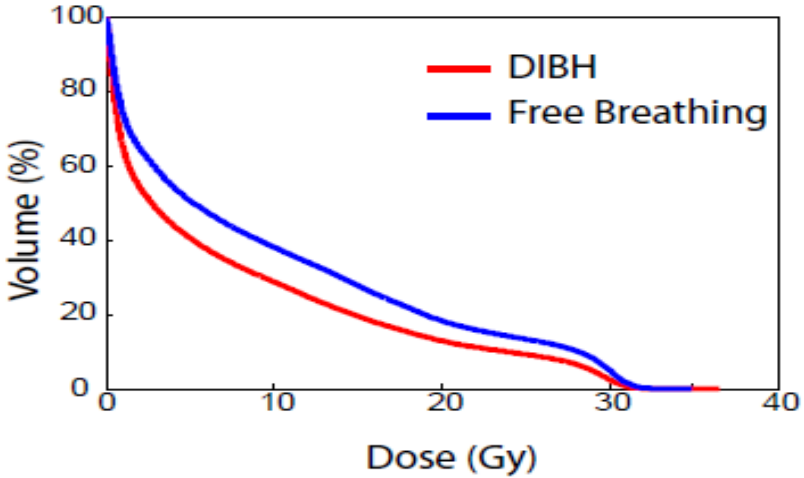


Benefit: over the whole group

Lung



Heart



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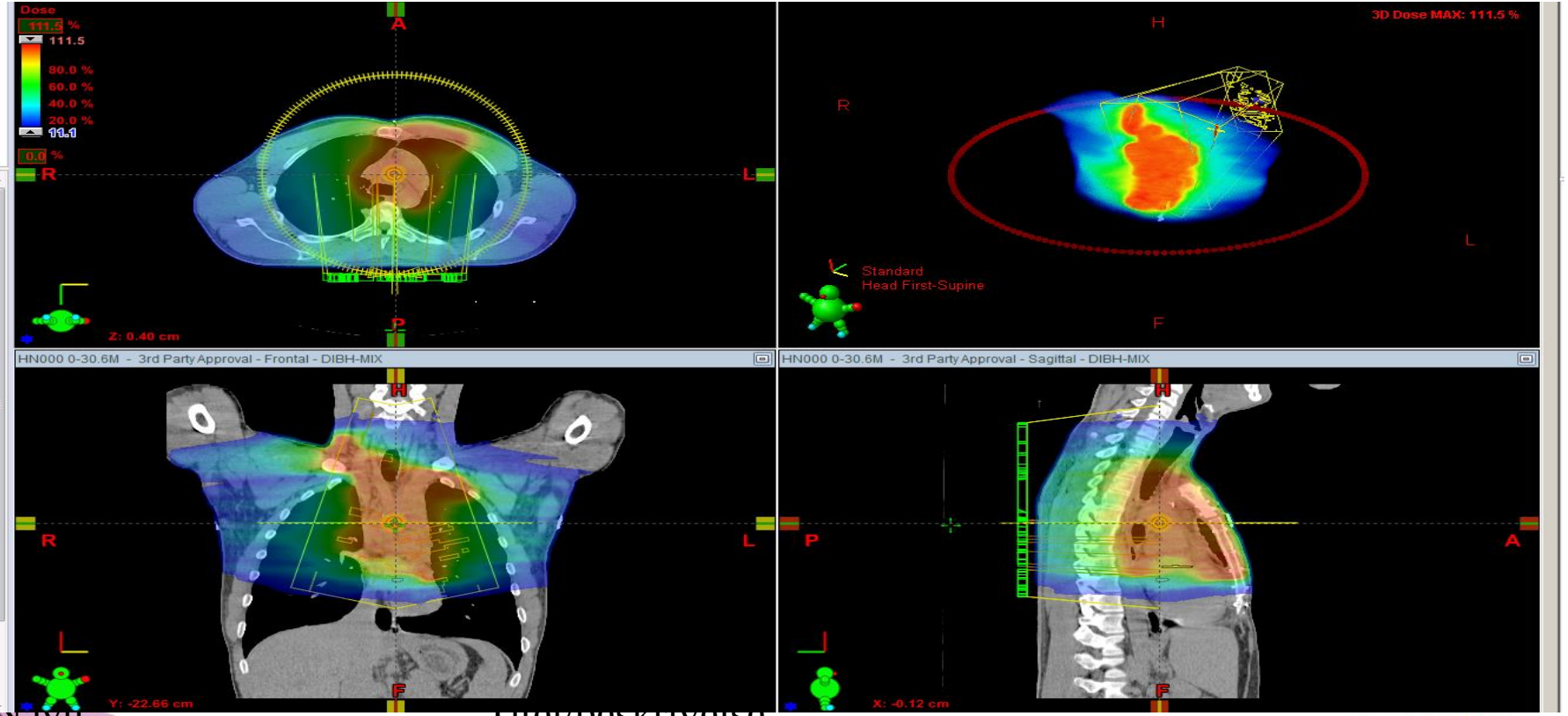
RPM integrated with linac
Beam switches on and off automatically

DIBH + VMAT/IMRT



Combining DIBH and VMAT

<u>At Rigshospitalet:</u>

For IGRT: 2 very short DIBHs (one per image)
For each 3D field: one DIBH
For each arc: 1 to 2 DIBHs

Total: <u>worst</u> case scenario 8-10 breath holds of 10 to 20 sec (patient catches her breath between fields)

Treatment time slot of 10-15 min

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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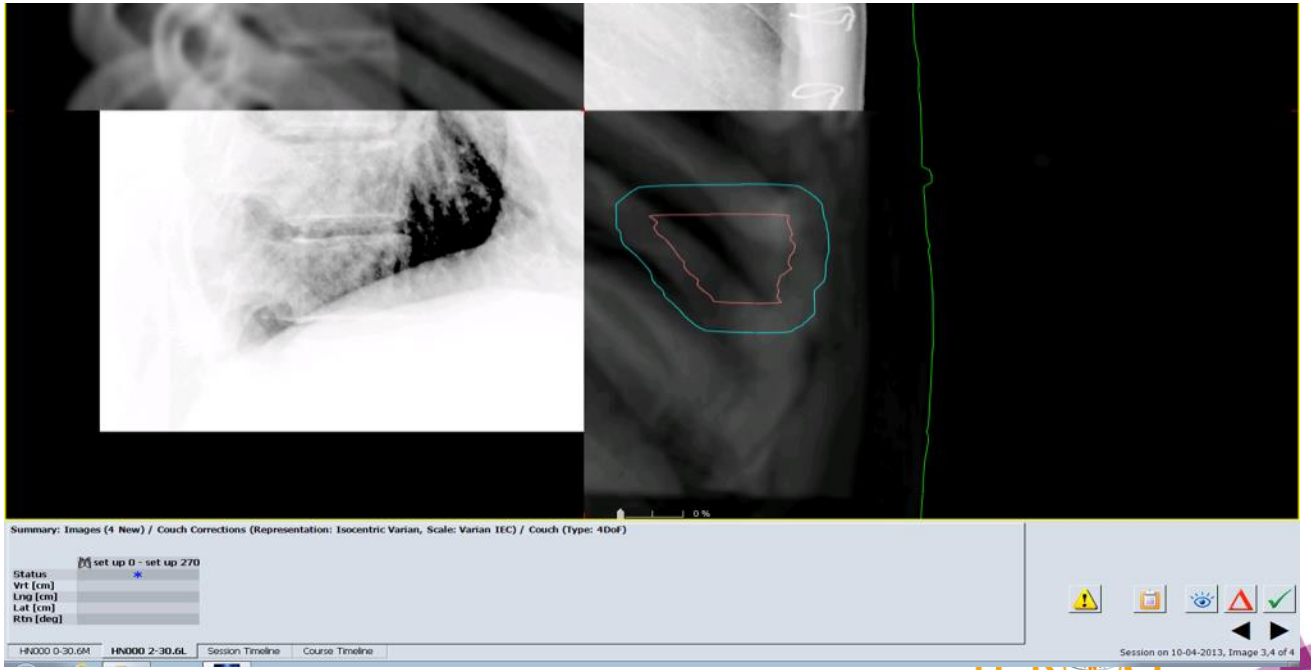
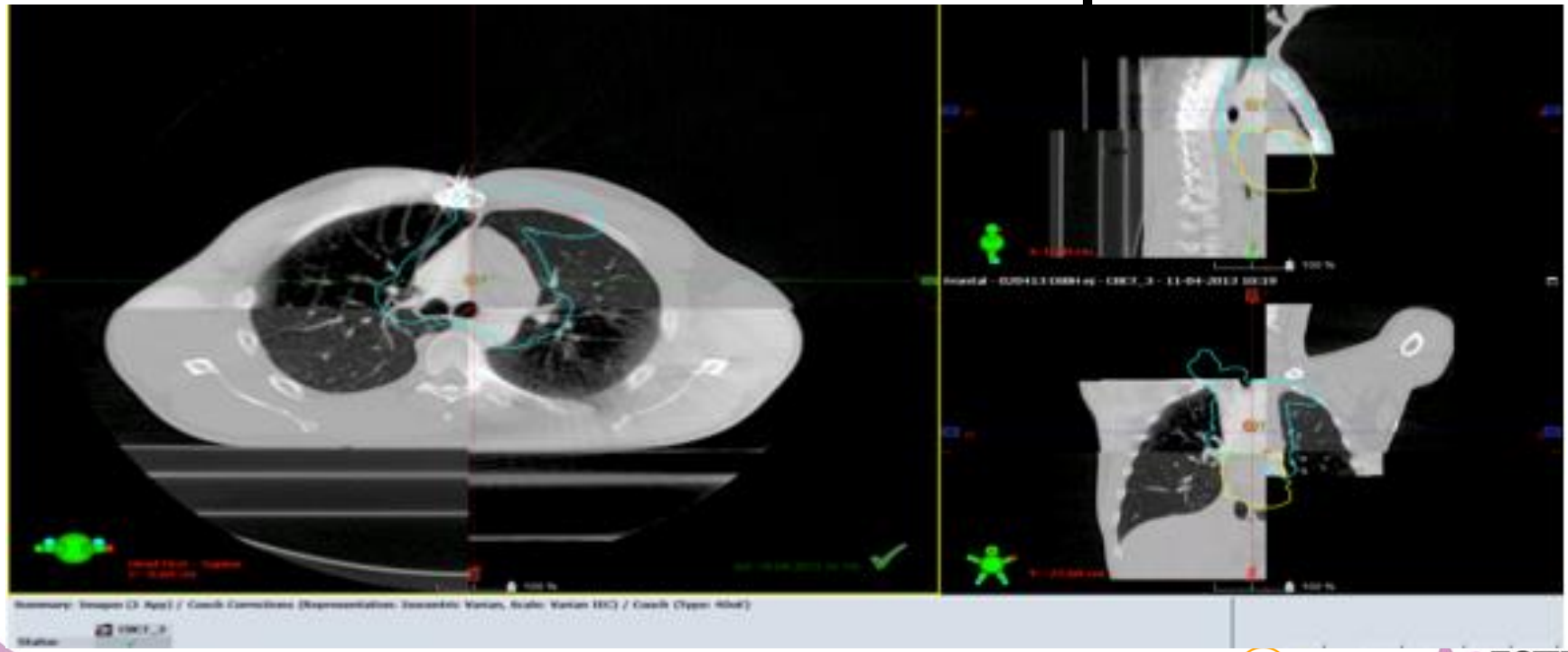
Daily 2D images: fuse on spine, check sternum



Can check heart position



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 !

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

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 !

NEXT FRONTIERS?

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DIBH and proton therapy?

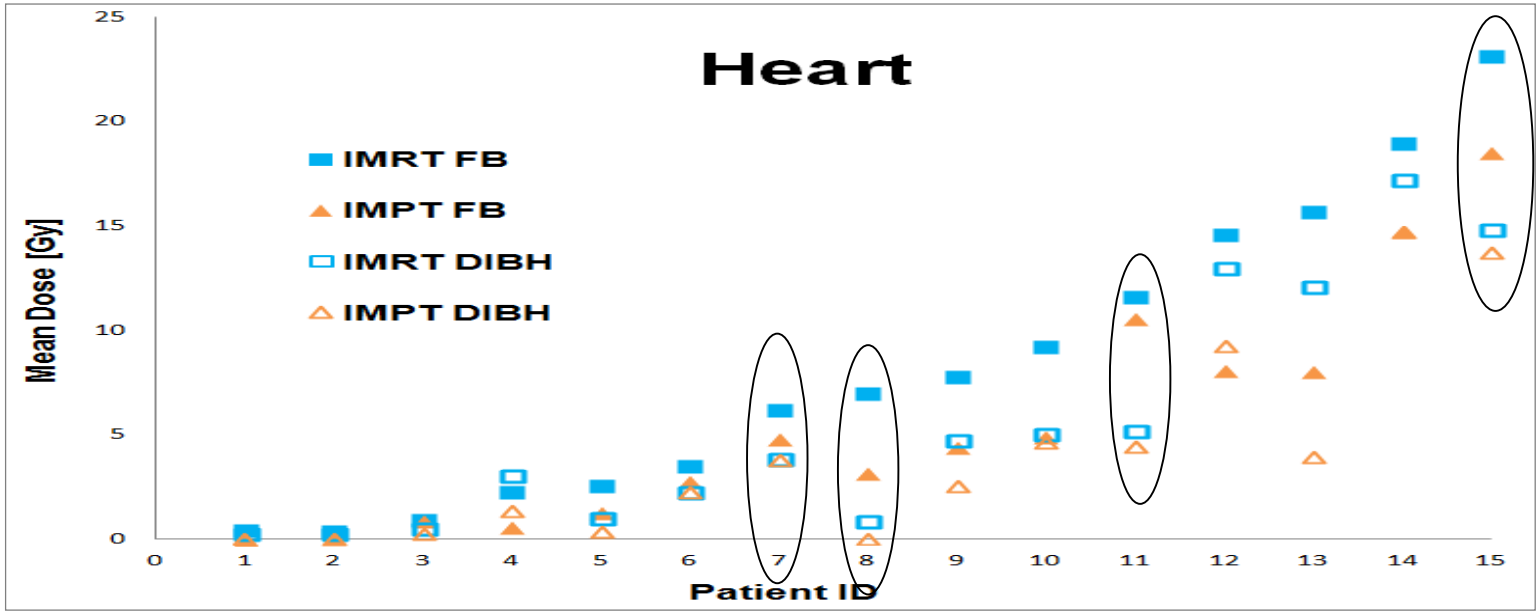
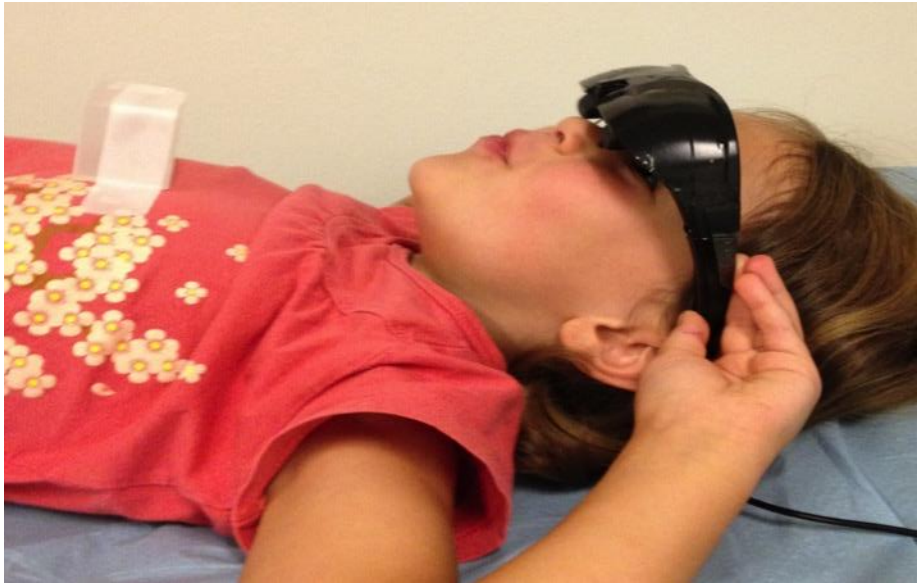


Figure 2. Mean dose to the heart for each modality for each patient (sorted by dose from IMRT FB). The difference in dose from each modality varied between patients.

TEDDI

- Pediatric phase II
- Multi national (DK, SE, FI)
- PI: Maja Maraldo MD PhD



- Compliance (reproducibility), dosimetric benefit, patient experience

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Acknowledgments

Department of radiation therapy, especially:

- Peter M Pedersen
- Maja Maraldo
- Lena Specht
- Ivan Vogelius
- Mirjana Josipovic
- Sidsel Damkjær
- Deborah Schut

Department of Clinical Physiology Nuclear Medicine and PET, especially:

- Anne Kiil Berthelsen
- Flemming Andersen
- Annika Loft
- Thomas Levin Klausen
- Marianne Federspiel

The principles of the use of systemic treatment in non-Hodgkin lymphomas

Andy Davies

Chair UK National Caner Research Institute High-Grade Lymphoma Sub-Group

ESTRO/ILROG COURSE:

HAEMATOLOGICAL MALIGNANCIES

September 2018

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

CANCER RESEARCH UK

UNIVERSITY OF Southampton

Conflicts of Interest

Celgene: Research funding; Advisory Board; Honorarium

Roche: Advisory Boards; Honorarium; Research support

Gilead: Advisory Boards; Honorarium; Research support

Takeda: Advisory Boards; Honorarium; Research support, Travel to scientific conferences

CTI: Advisory Boards; Honorarium; Travel to scientific conferences

Mundipharma: Advisory Boards; Honorarium; Travel to scientific conferences

GSK: Research support

Bayer: Research support

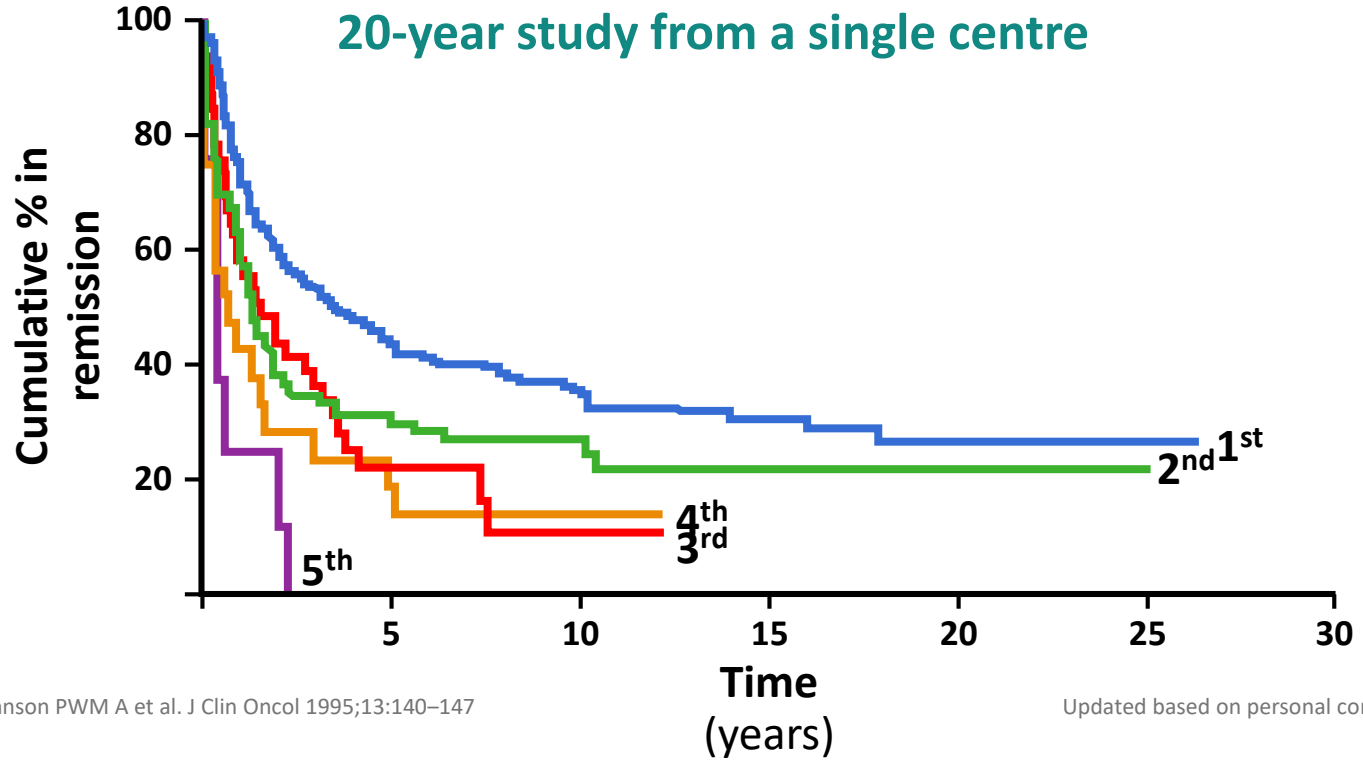
Janssen: Honorarium; Research support

Karyopharma: Advisory Board; Research support

Pfizer: Research support; Honorarium

FOLLICULAR LYMPHOMA: DURATION OF REMISSION

Outcome of treatment in patients with recurrent FL: 20-year study from a single centre

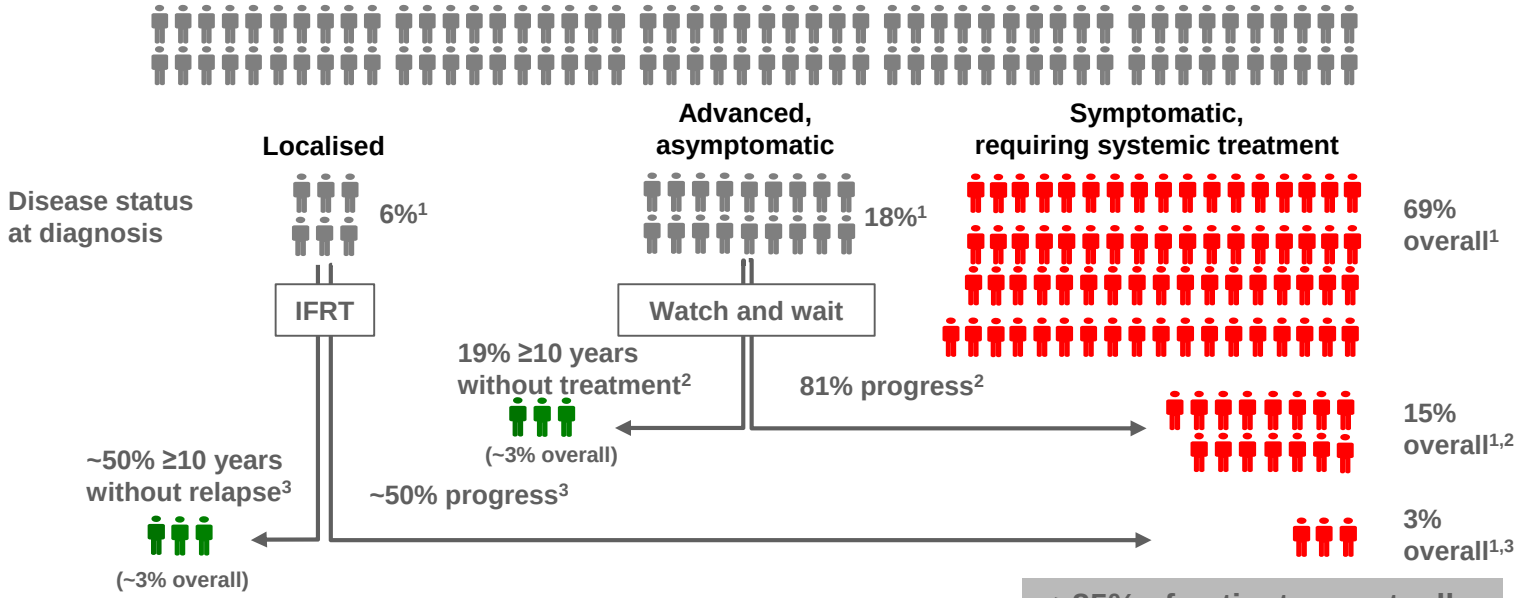


Adapted from Johnson PWM A et al. J Clin Oncol 1995;13:140–147

Updated based on personal communication to speaker

Estimating the need for treatment in FL

Considering 100 patients treated…



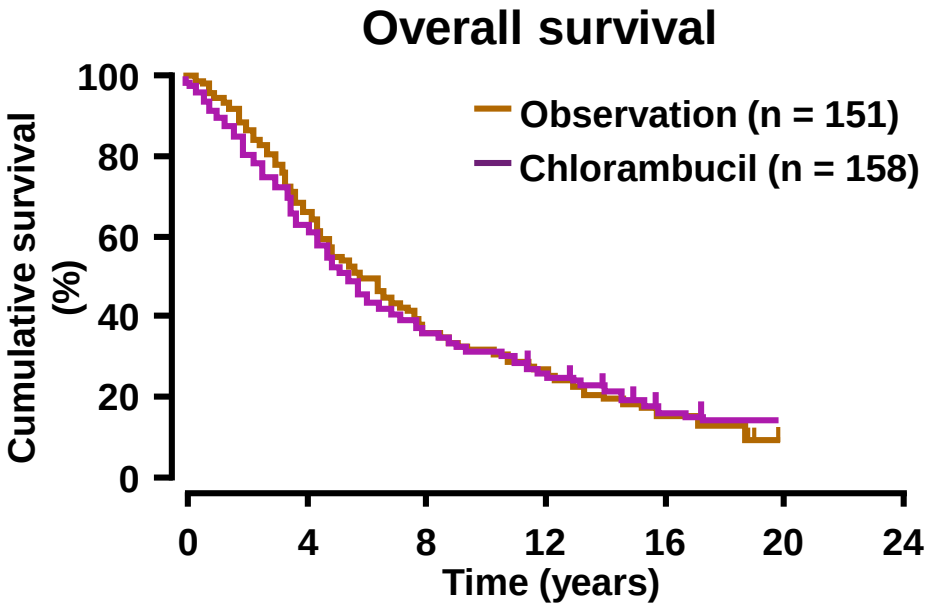
FL, follicular lymphoma; IFRT, involved-field radiotherapy

*All figures are **estimates** based on:*
1. Friedberg J, *et al. J Clin Oncol* 2009; 27:1202–1208;
2. Ardeshna KM, *et al. Lancet* 2003; 362:516–522;
3. Yahalm J. *Curr Treat Options Oncol* 2014; 15:262–268.

No survival benefit with immediate chemotherapy treatment vs watch and wait in patients with asymptomatic FL

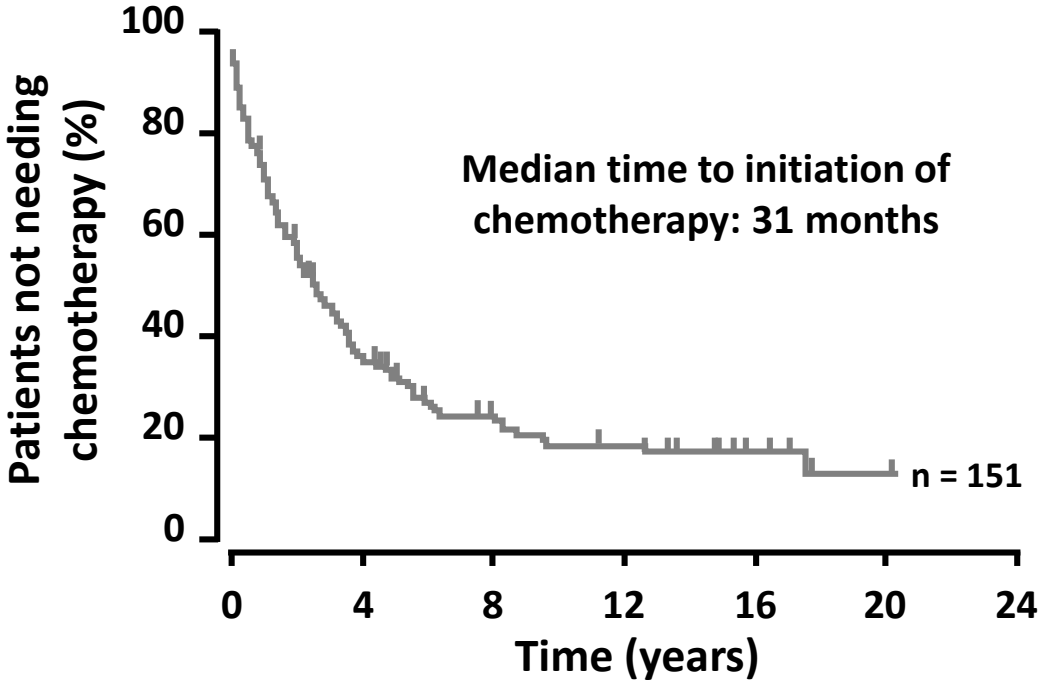
Advanced stage but clinically non-aggressive (BNLI) defined by absence of:

- Pruritis or B symptoms
- Rapid progression in last 3 months
- Life-threatening organ involvement
- Cytopenias secondary to bone marrow involvement
- Bone lesions
- Renal infiltration
- Macroscopic liver involvement

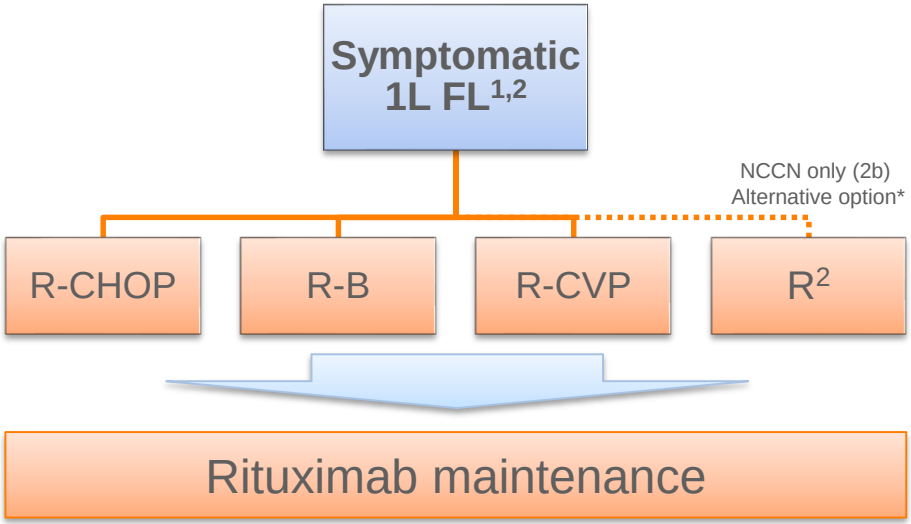


Ardeshna KM, *et al. Lancet* 2003; 362:516–522.

Watching and waiting: Low tumour burden asymptomatic



First-line treatment options recommended by NCCN or ESMO[1,2]

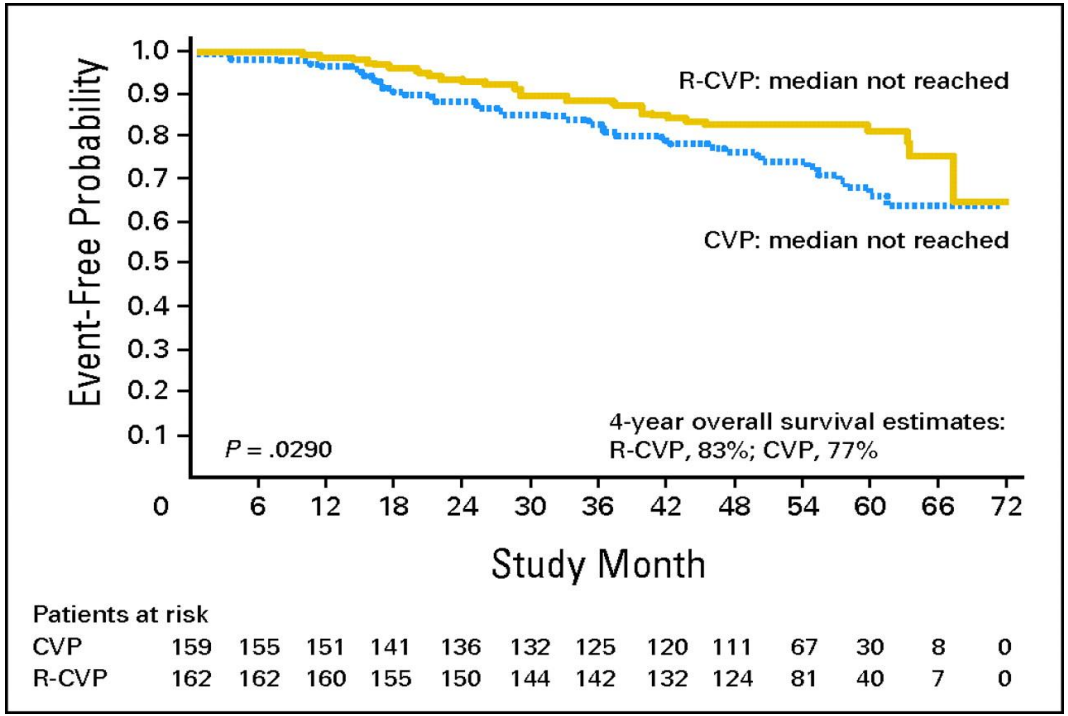


Phase 3 Study[3,4,5]	N	Median Follow up, mos (range)	Estimated 3-year PFS (%)
Hiddemann, 2005 (GLSG)			
CHOP	205	18 (1–38)	50
R-CHOP	223	18 (1–38)	75
Salles, 2011 (PRIMA)			
R-chemo + observation	513	36 (IQR 30–42)	58
R-chemo + R maintenance	505	36 (IQR 30–42)	75
Hochster, 2009 (ECOG1496)			
CVP + observation	113	44.4	33
CVP + R maintenance	115	44.4	64

*NCCN guideline recommendation only (category 2b); rituximab alone may be considered if low tumour burden[2]
1L, first line;; chemo, chemotherapy CHOP, cyclophosphamide, vincristine, doxorubicin and prednisone/prednisolone; CVP, cyclophosphamide, vincristine and prednisone/prednisolone; FL, follicular lymphoma; PFS, progression-free survival; R, rituximab

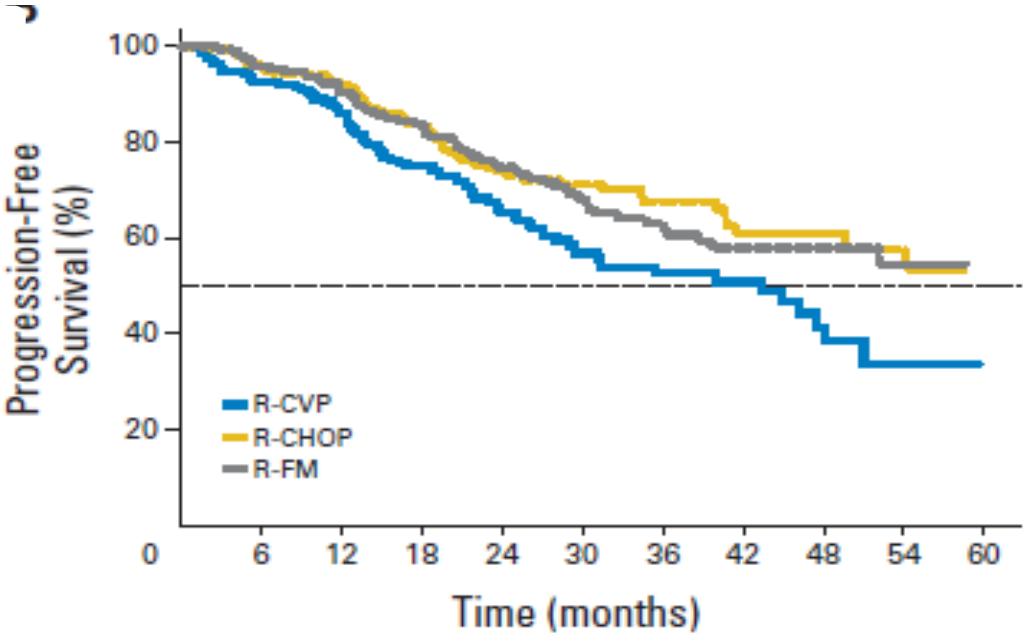
1. Dreyling M, *et al. Ann Oncol* 2016; 27(Suppl. 5):v83–v90;
2. NCCN Guidelines. B-cell Lymphomas. Version 2.2017;
3. Jacobson CA, Freedman AS. *Lancet* 2013; 381:1163–1165;

The Brits are known for their love of R-CVP…..



Marcus, R. et al. J Clin Oncol; 26:4579-4586 2008

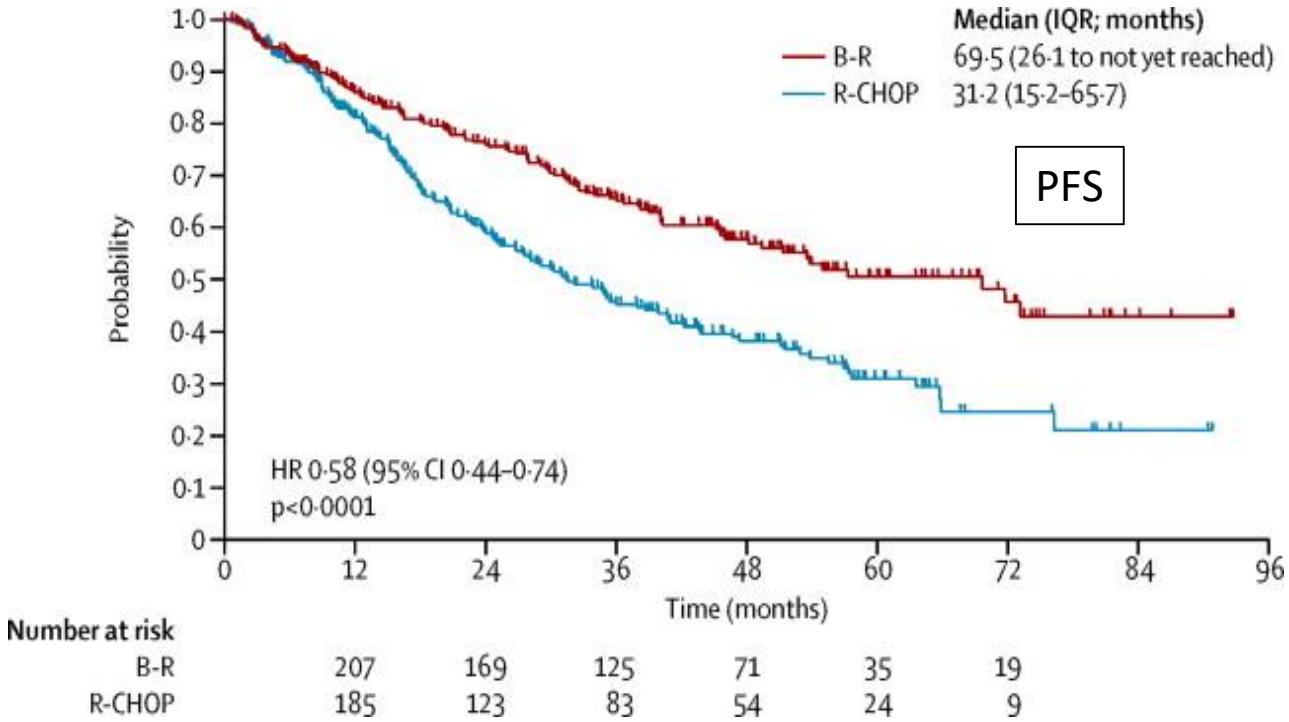
FOLL05 Trial. PFS



No. at risk											
R-CVP	168	154	136	108	85	60	41	27	14	6	1
R-CHOP	165	157	147	128	89	70	51	36	22	14	6
R-FM	171	163	151	130	101	73	55	36	23	14	5

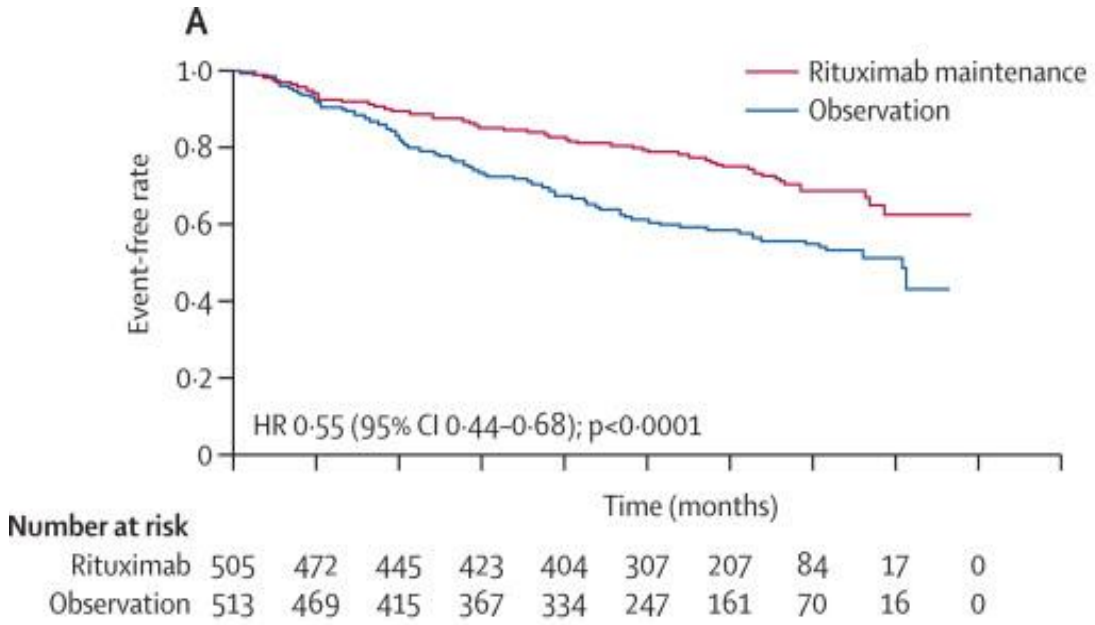
Federico et al JCO 2013

StiL Study



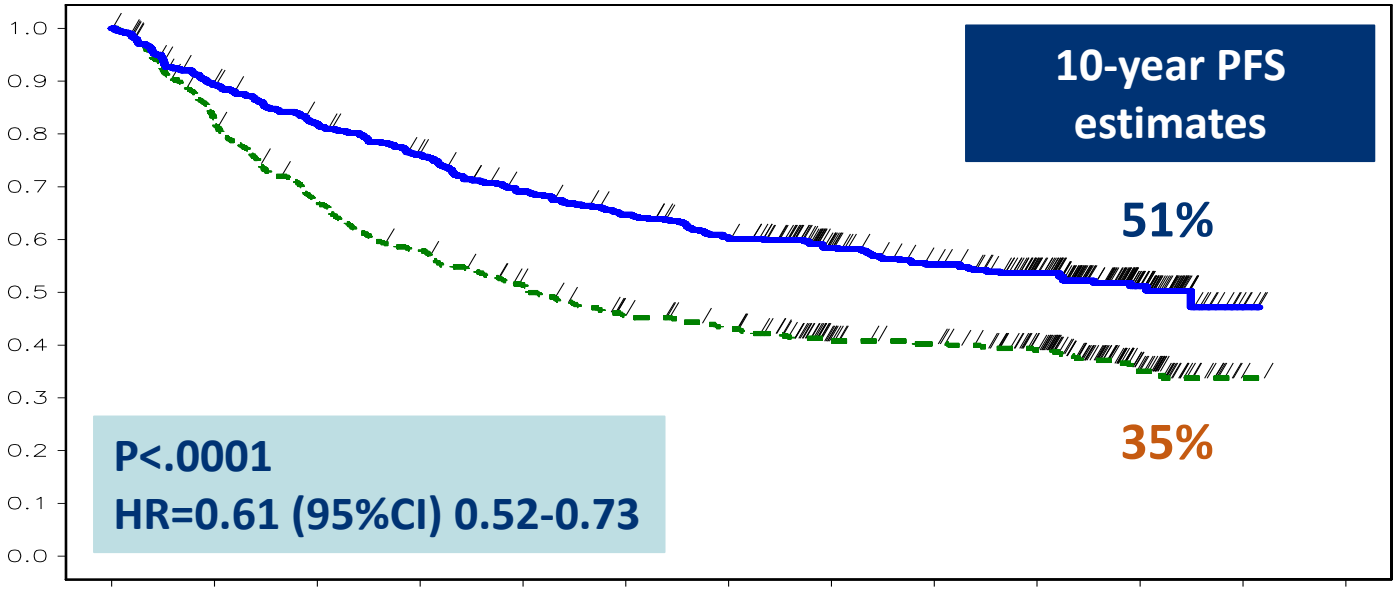
Rummel et al Lancet April 2013

PRIMA: Maintenance



Salles et al. Lancet 2010

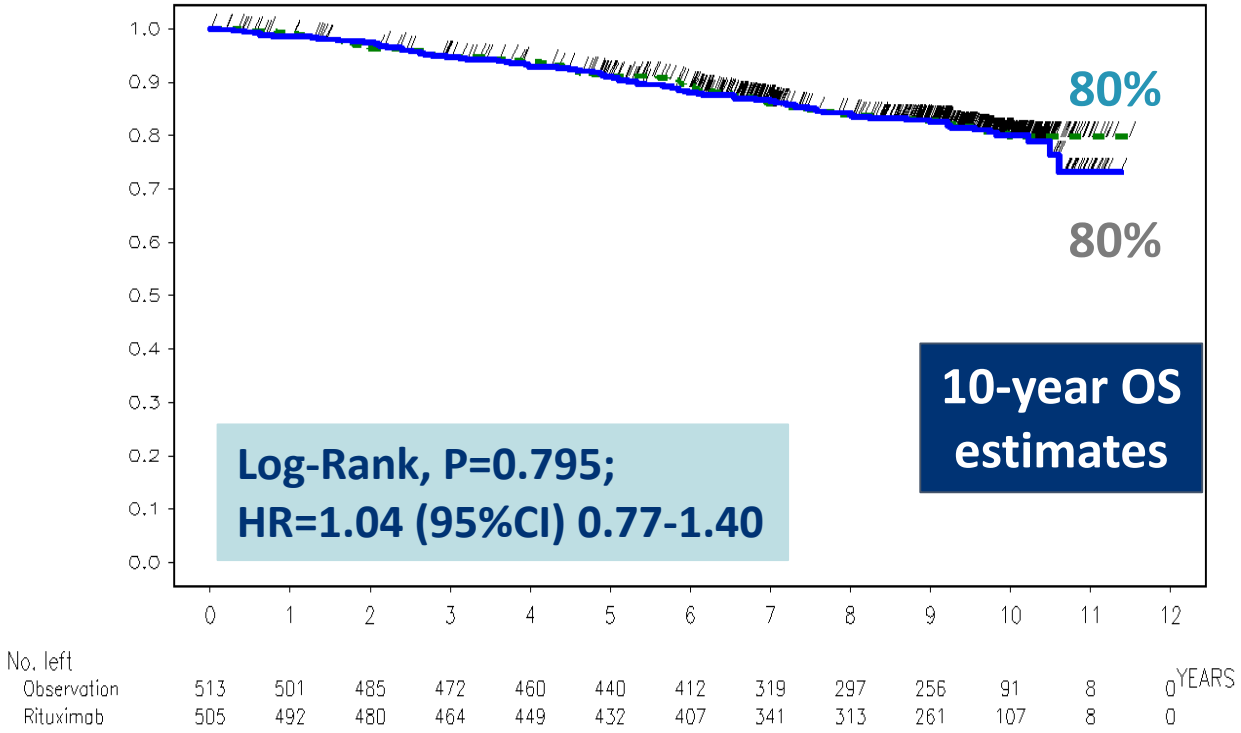
Effect of R maintenance on Progression Free Survival (PRIMA at 10 years)



No. left												
Observation	513	415	336	290	251	217	200	155	147	122	41	1
Rituximab	505	445	406	372	333	309	284	231	208	170	67	4

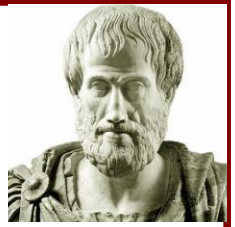
Salles et al, ASH 2017; Abstract #486

Effect of R maintenance on Overall Survival at 10 years (PRIMA at 10 years)

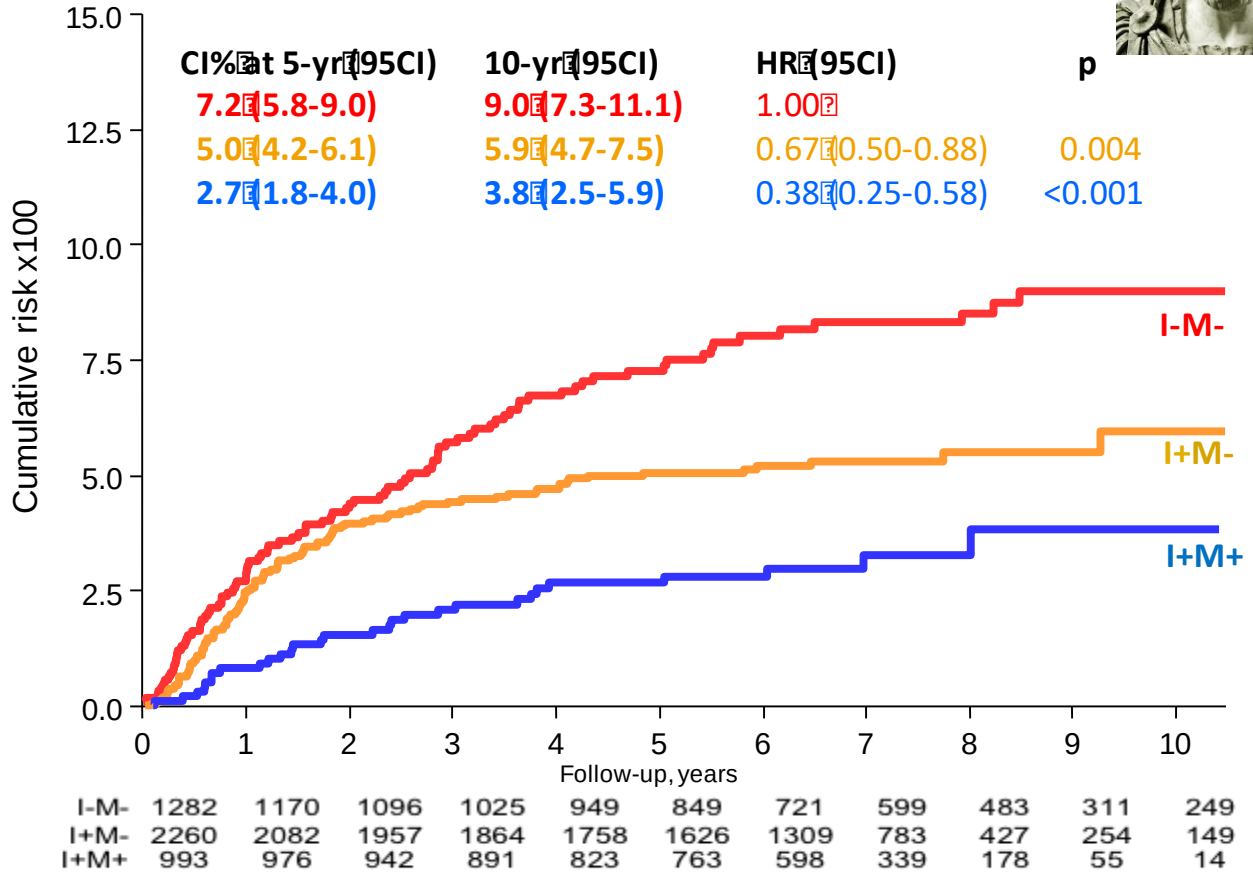


Salles et al, ASH 2017; Abstract #486

Cumulative Incidence by Rituximab exposure



CI% at 5-yr (95CI)	10-yr (95CI)	HR (95CI)	p
7.2 (5.8-9.0)	9.0 (7.3-11.1)	1.00	
5.0 (4.2-6.1)	5.9 (4.7-7.5)	0.67 (0.50-0.88)	0.004
2.7 (1.8-4.0)	3.8 (2.5-5.9)	0.38 (0.25-0.58)	<0.001

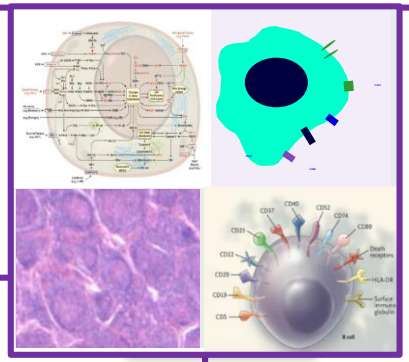


Microenvironment

- immunmodulators
- T-cell exhaustion

Actionable mutations

- EZH2
- CD79a/b



Pathways

- Proteosome inhibitors
- Bcl-2 family inhibitors
- Survivin inhibitors
- Syk inhibitors
- mTOR inhibitors
- PI3K inhibitors
- Btk inhibitors
- Hsp 90 inhibitors

Surface markers

- Anti CD20 moAb
- Anti CD40 moAb
- Other targets

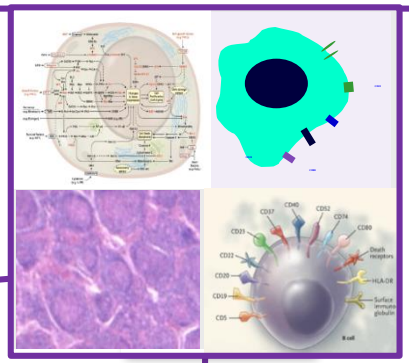
- HDAC inhibitors
- PKC inhibitors
- Aurora kinase inhibitors
- Nedd8-activating enzyme inhibitors

Microenvironment

- immunmodulators
- T-cell exhaustion

Actionable mutations

- EZH2
- CD79a/b



Surface markers

- Anti CD20 moAb
- Anti CD40 moAb
- Other targets

Pathways

- Proteosome inhibitors
- Bcl-2 family inhibitors
- Survivin inhibitors
- Syk inhibitors
- mTOR inhibitors
- PI3K inhibitors
- Btk inhibitors
- Hsp 90 inhibitors
- HDAC inhibitors
- PKC inhibitors
- Aurora kinase inhibitors
- Nedd8-activating enzyme inhibitors

Obinutuzumab: Putative mechanism(s) of action

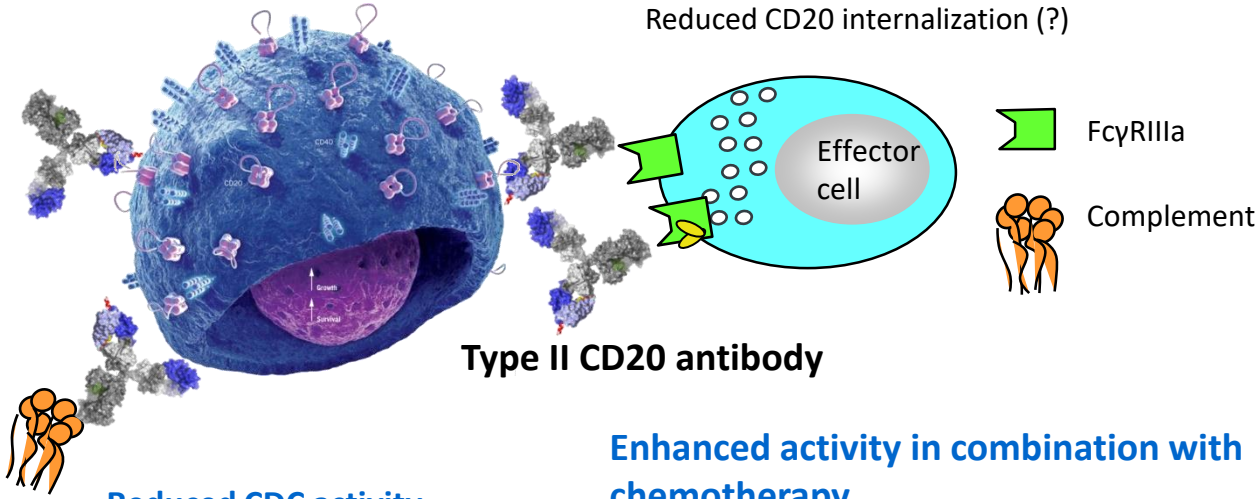
Increased direct cell death

Type II antibody & elbow-hinge modification

Increased ADCC

Higher affinity to the 'ADCC receptor' FcγRIIIa (GlycoMab TM technology) &

Reduced CD20 internalization (?)



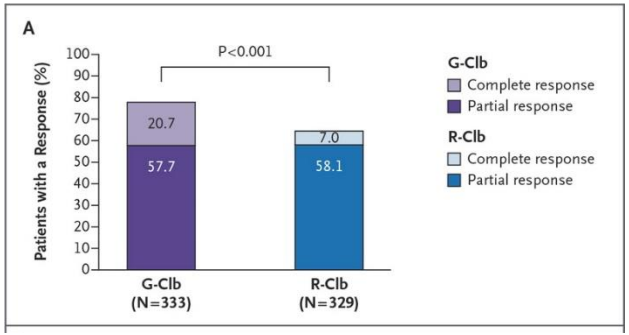
Reduced CDC activity

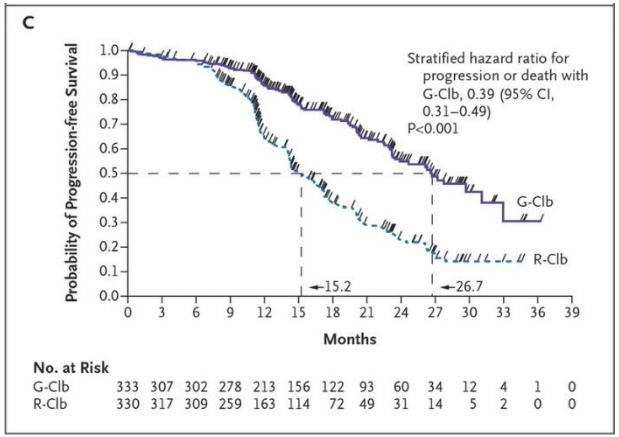
Type II antibody

Enhanced activity in combination with chemotherapy

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity

Response Rates and Progression-free Survival with Obinutuzumab–Chlorambucil versus Rituximab–Chlorambucil.

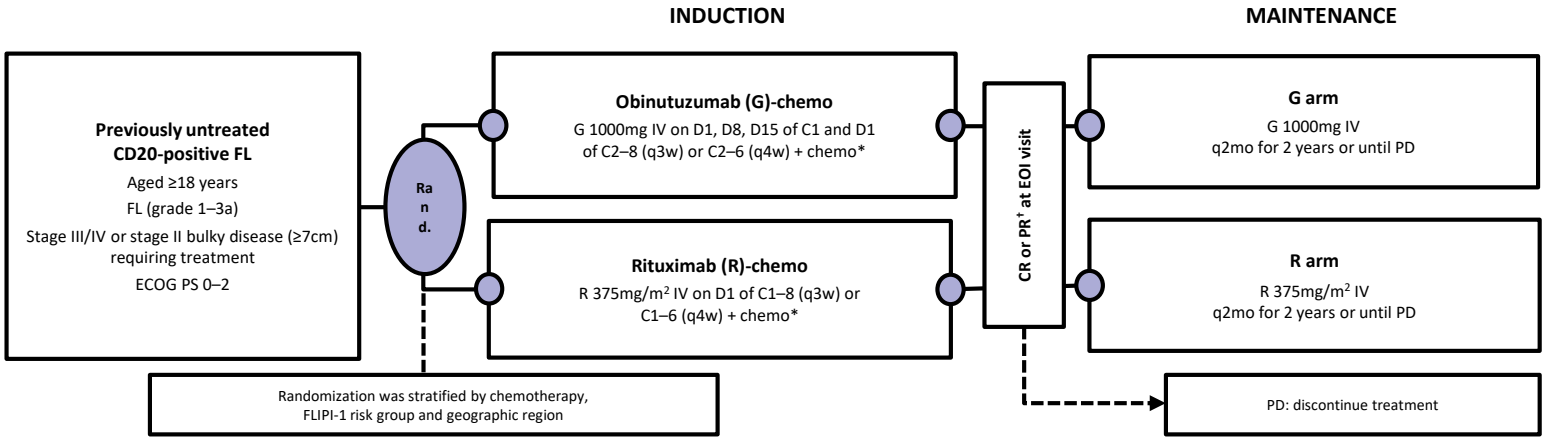




Goede V et al. N Engl J Med 2014;370:1101-1110.

GALLIUM study design (FL)

International, open-label, randomized Phase III study in 1L pts (NCT01332968)



Primary endpoint

- PFS (INV-assessed)

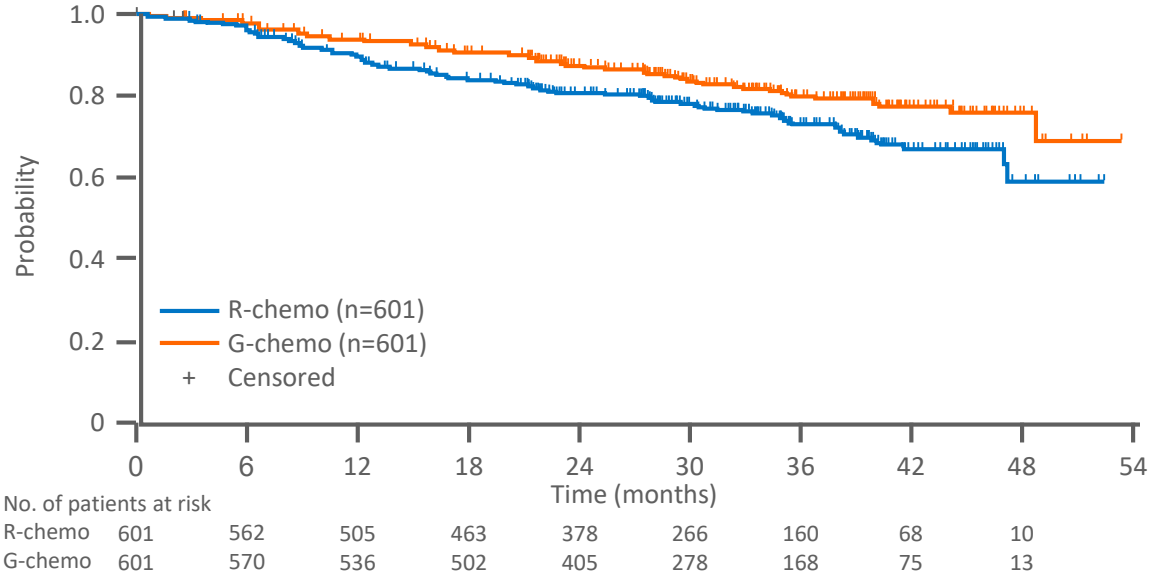
Secondary endpoints

- PFS (IRC-assessed)
- OS, EFS, DFS, DoR, TTNALT
- ORR/CR at EOI (+/– FDG-PET)
- Safety
- PROs

*CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; chemo regimen chosen by site prior to initiation and received by all FL pts at site; †Patients with SD at EOI entered observation for up to 2 years or until PD if earlier; EOI, end of induction; INV, investigator; IRC, Independent Review Committee; PRO, patient-reported outcome; TTNALT, time to next anti-lymphoma treatment

Marcus et al. N Engl J Med 2017; 377(14):1331-1344

Primary endpoint of investigator-assessed PFS



PFS by investigator	R-chemo (n=601)	G-chemo (n=601)
Events, n (%)	144 (24.0)	101 (16.8)
Median PFS, months (95% CI)	NE (47.1, NE)	NE (NE, NE)
Stratified HR (95% CI), p value	0.66 (0.51, 0.85), p=0.0012	
3-year PFS, % (95% CI)*	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)

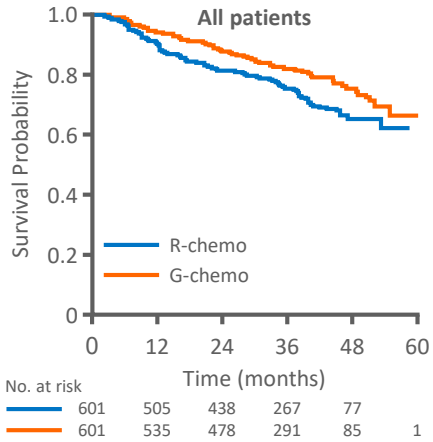
Median follow-up: 34.5 months

- GALLIUM met its primary endpoint demonstrating a 34% reduction in the risk or PD/relapse or death for G-chemo vs R-chemo in FL patients, a statistically significant and clinically meaningful difference

*7% difference in 3-year PFS between the two arms was as expected; both arms performed better than protocol assumptions
CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; NE, not estimable; PD, disease progression; PFS, progression-free survival

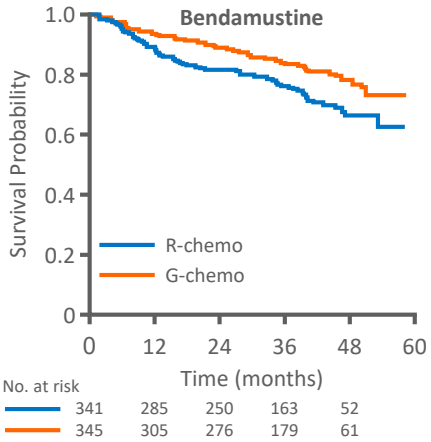
Marcus R, et al. N Engl J Med 2017;377:1331–44

INV-assessed PFS by chemotherapy backbone (10 September 2016 cut-off)



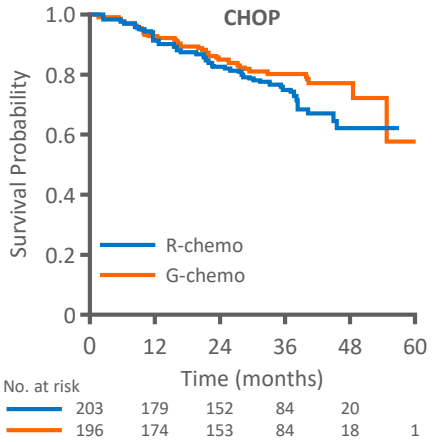
HR, 0.68 (95% CI: 0.54, 0.87); p=0.0016

3-year PFS:
81.5% for G-Chemo vs 75.0% for R-chemo



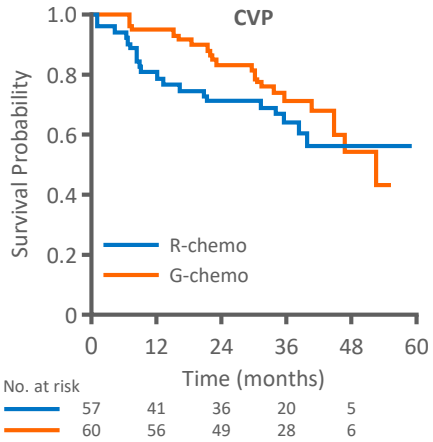
HR, 0.63 (95% CI: 0.46, 0.88); p=0.0062

3-year PFS:
84.1% for G-B vs 76.4% for R-B



HR, 0.72 (95% CI: 0.48, 1.10); p=0.1266

3-year PFS:
80.6% for G-CHOP vs 75.6% for R-CHOP



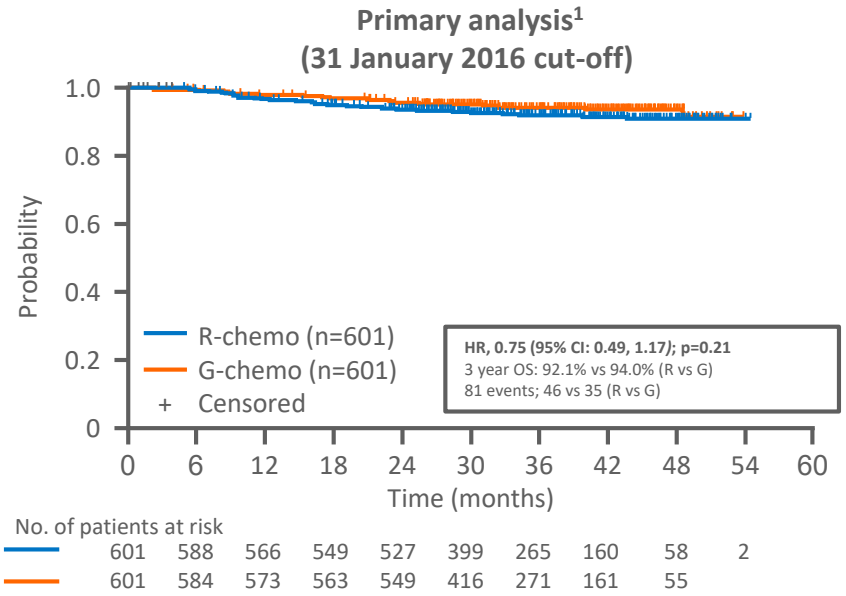
HR, 0.79 (95% CI: 0.42, 1.47); p=0.4560

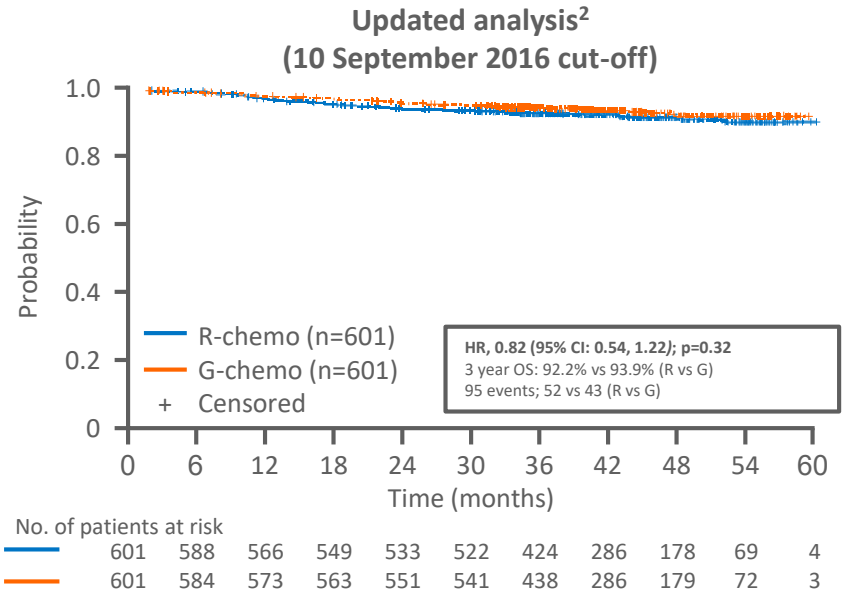
3-year PFS:
71.3% for G-CVP vs 64.2% for R-CVP

- PFS was superior with G-chemo relative to R-chemo with consistent effects across chemo regimens
- Study not designed or powered to compare differences between R-chemo and G-chemo within chemo groups

Hiddemann W, et al. ICML 2017 (Abstract 107)

OS



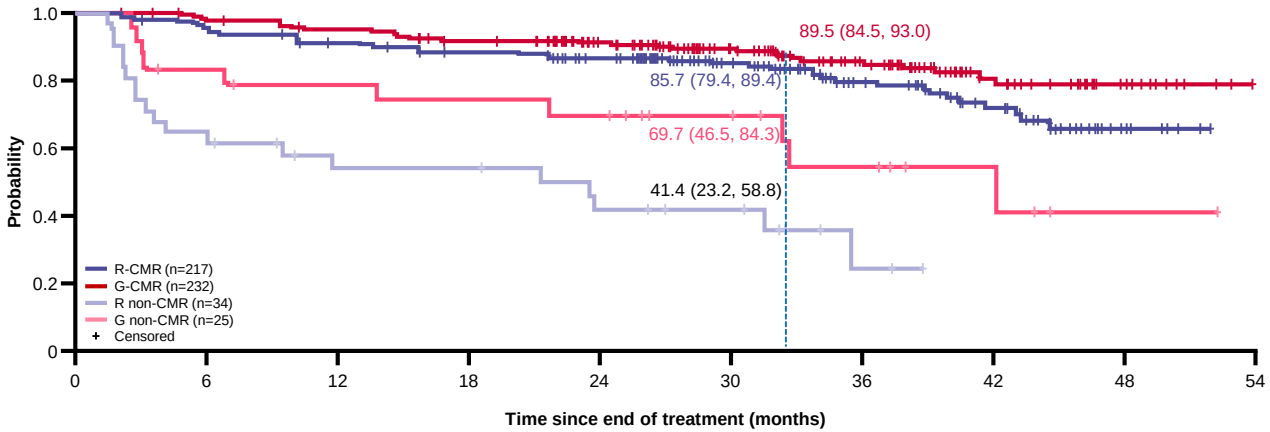


- OS analysis supportive of the primary endpoint (investigator-assessed PFS)
- From the updated analysis, OS still relatively immature. More deaths for any reason in R vs G arm (52 [8.7%] vs 43 [7.2%])
- GALLIUM not powered to detect differences in OS between treatment arms

1. Marcus R, et al. N Engl J Med 2017;377:1331–44
2. Hiddemann W, et al. ICML presentation 2017

Landmark (from EOI) PFS analysis: by antibody arm

PFS for non-CMR vs CMR status using Lugano 2014 criteria (N=508)

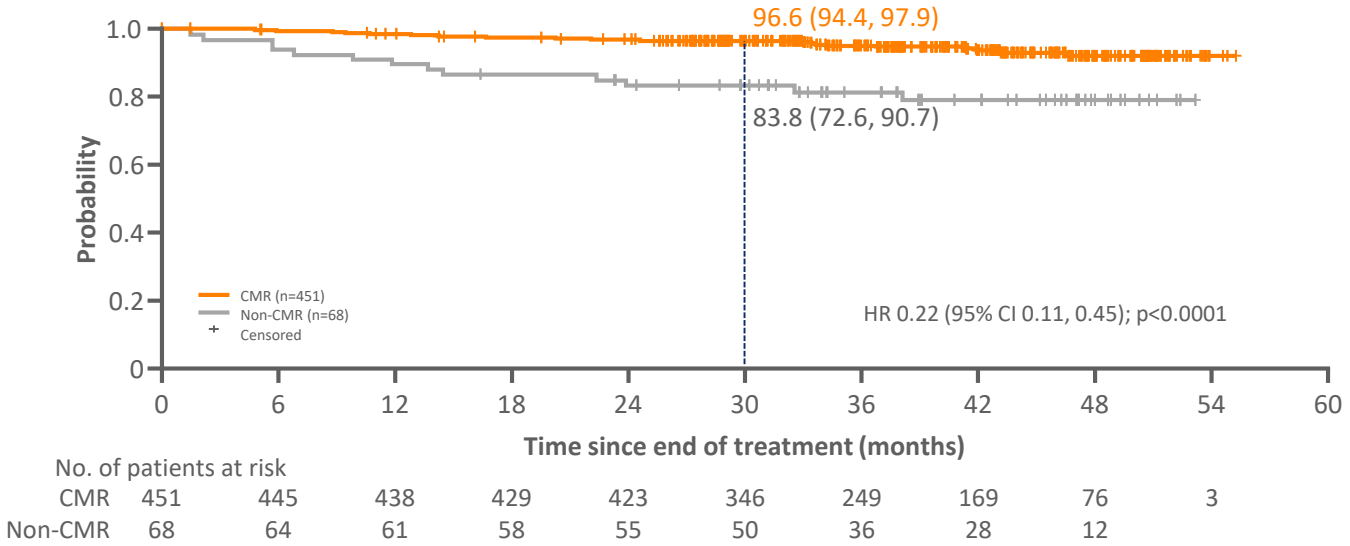


	R-CMR, n=217	*G-CMR, n=232*	*R non-CMR, n=34*	*G non-CMR, n=25*
2.5-year PFS from EOI, % (95% CI)	85.7 (79.4, 89.4)	89.5 (84.5, 93.0)	41.4 (23.2, 58.8)	69.7 (46.5, 84.3)
HR (95% CI)		**0.7 (0.4, 1.0); p=0.06**		**0.5 (0.2, 1.2); p=0.10**

Trotman J, et al. ICML 2017

Landmark (from EOI) OS analysis

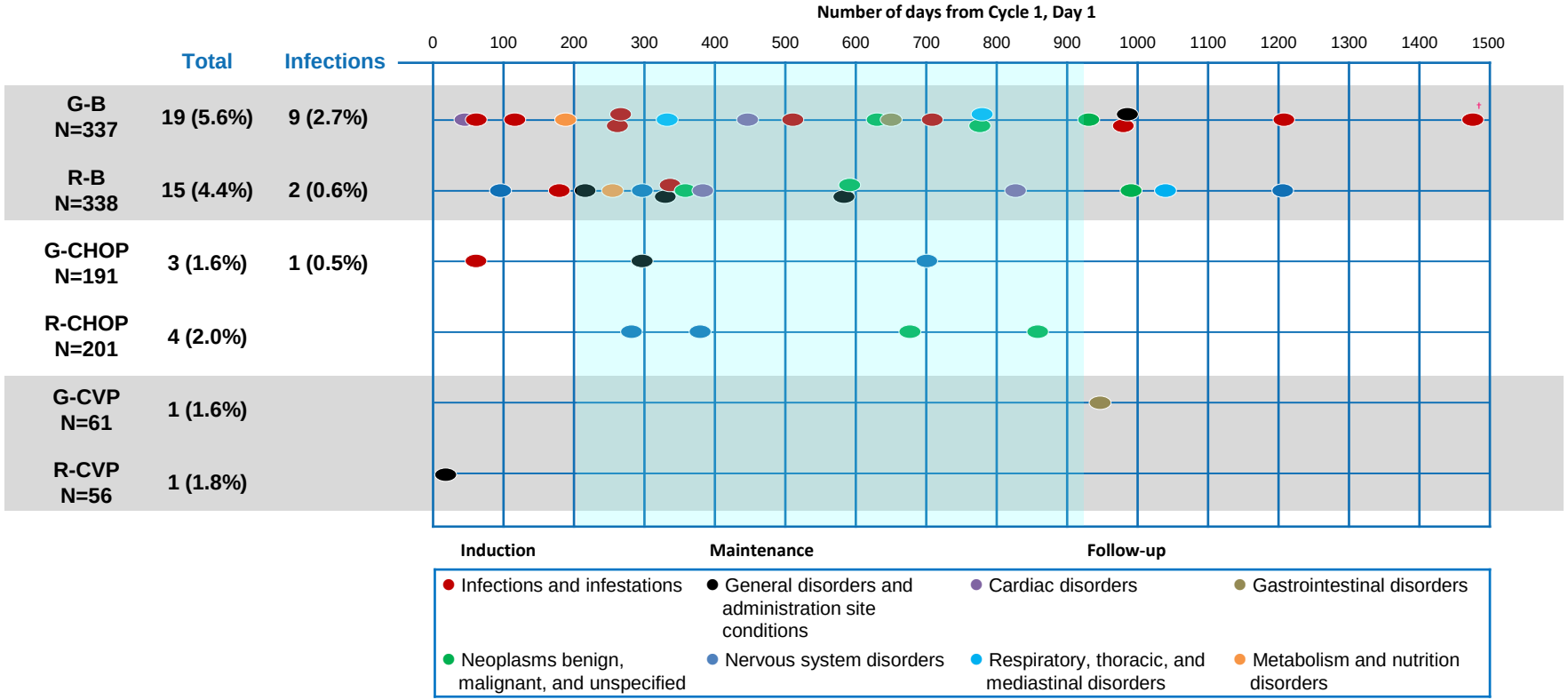
OS for non-CMR vs CMR status using Lugano 2014 criteria (N=519)*



*Patients who died or started a new anti-lymphoma treatment before EOI were excluded

Trotman J, et al. ICML 2017

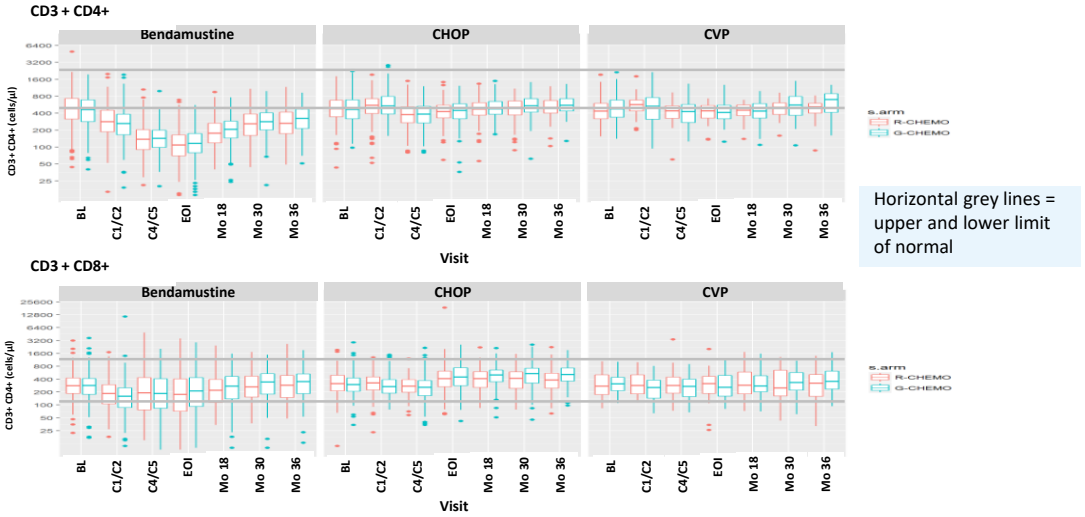
Grade 5 (fatal) AEs by treatment (FL)*



*Includes only pts who died before clinical cut-off date; †this patient (G-B group) was initially assigned three causes of death (*Clostridium difficile* colitis, prostate cancer, and myelodysplastic syndrome); *Clostridium difficile* colitis was the most acute, so the patient has been assigned to the 'Infections and infestations' category and the number of fatal AEs in G-B pts in neoplasms SOC reduced from 5 to 3

Hiddemann W, et al. ICML 2017

T-cell counts over time

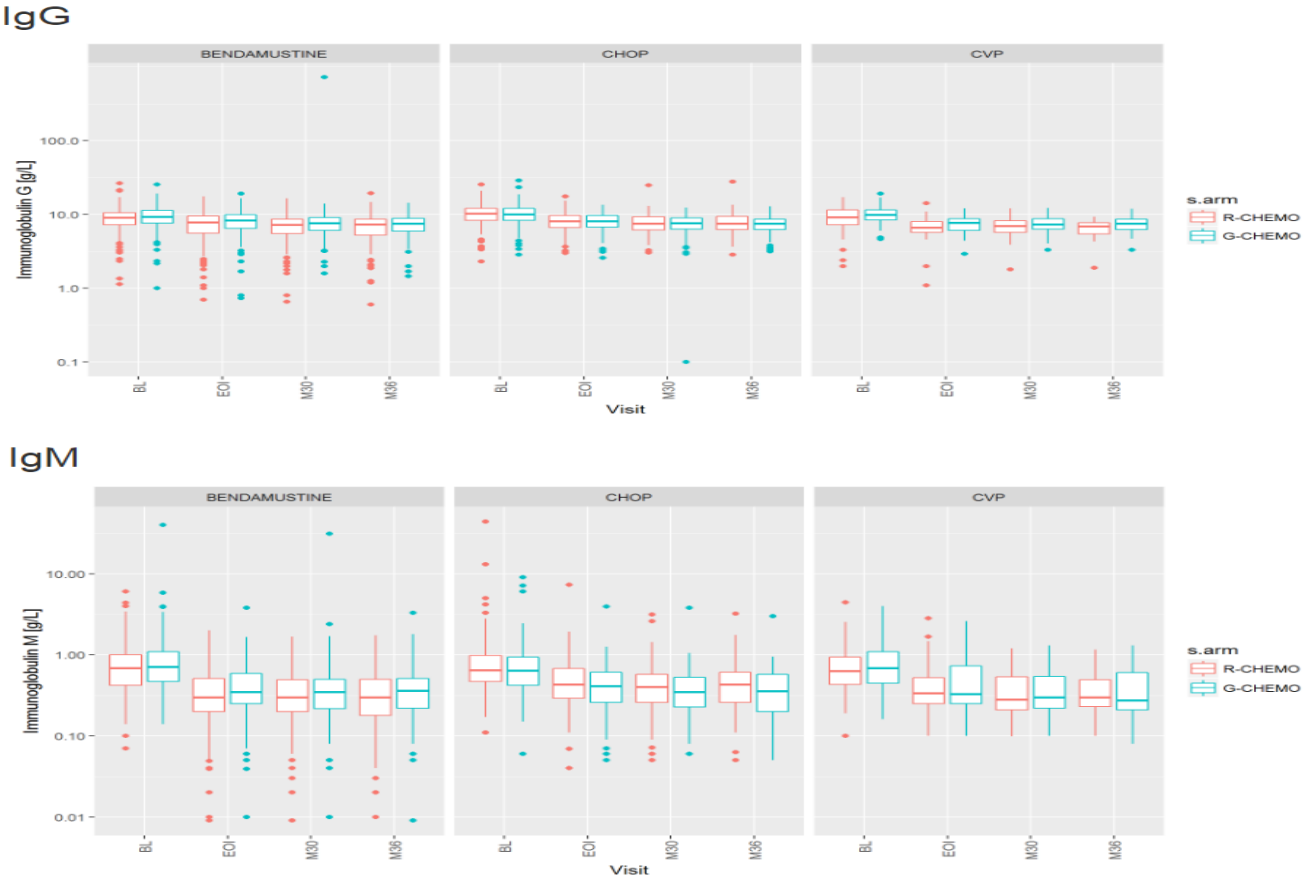


Horizontal grey lines = upper and lower limit of normal

Low T-cell count at baseline	*R-benda, n=341*	*G-benda, n=345*	*R-CHOP, n=203*	*G-CHOP, n=196*	*R-CVP, n=57*	*G-CVP, n=60*
CD3+/CD4+ cell count of ≤200/mm^3	36 (12.5%)	36 (11.4%)	12 (7.2%)	9 (5.1%)	2 (4.4%)	4 (7.4%)

Hiddemann W, *et al. Haematologica* 2017; 102:314. Abstract S775. Oral communication presented at EHA 2017

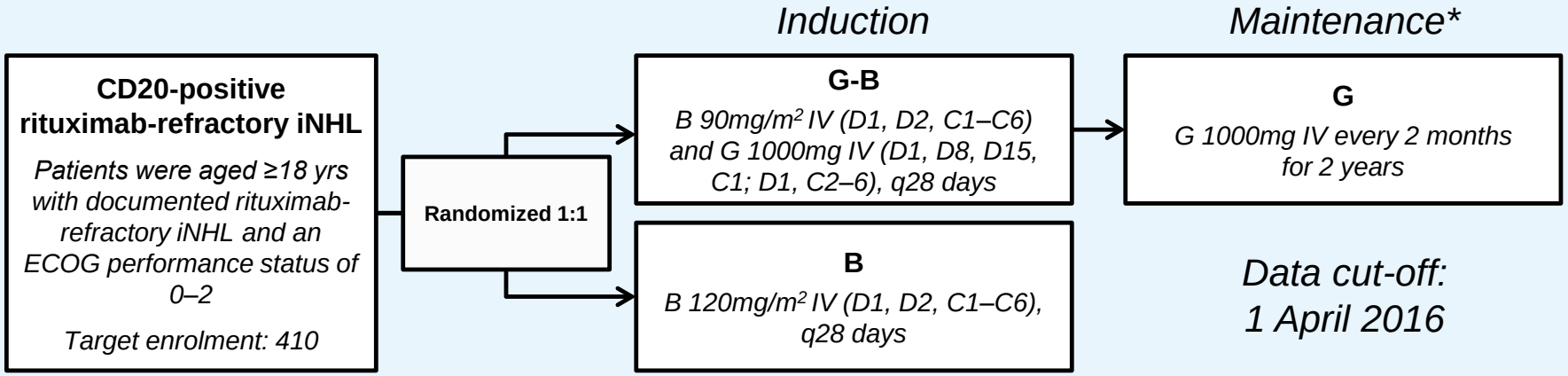
Immunoglobulin levels over time



Hiddemann W, *et al. Haematologica* 2017; 102:314. Abstract S775. Oral communication presented at EHA 2017

Gadolin:Study design (Cheson et al ASH 2016)

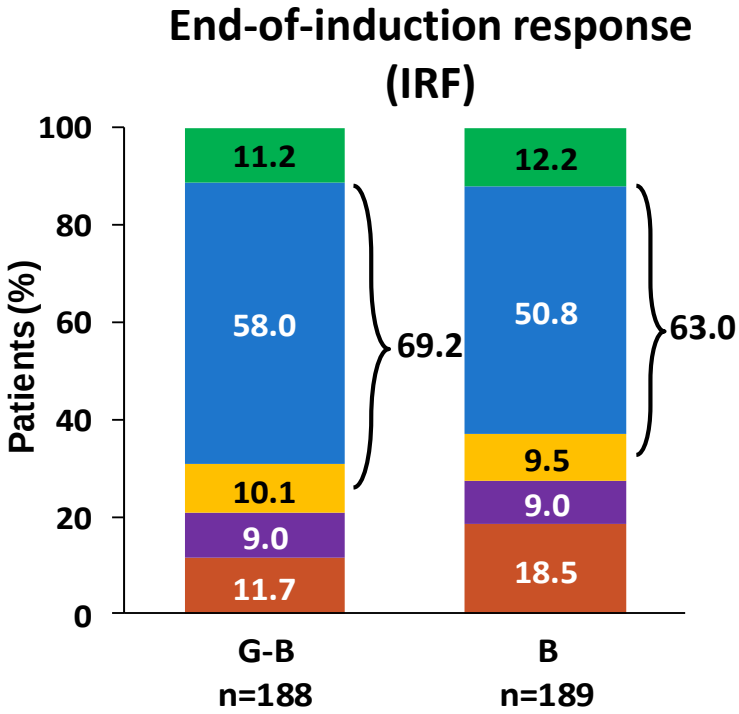
Open-label, multicenter, randomized, Phase III study in rituximab-refractory iNHL patients

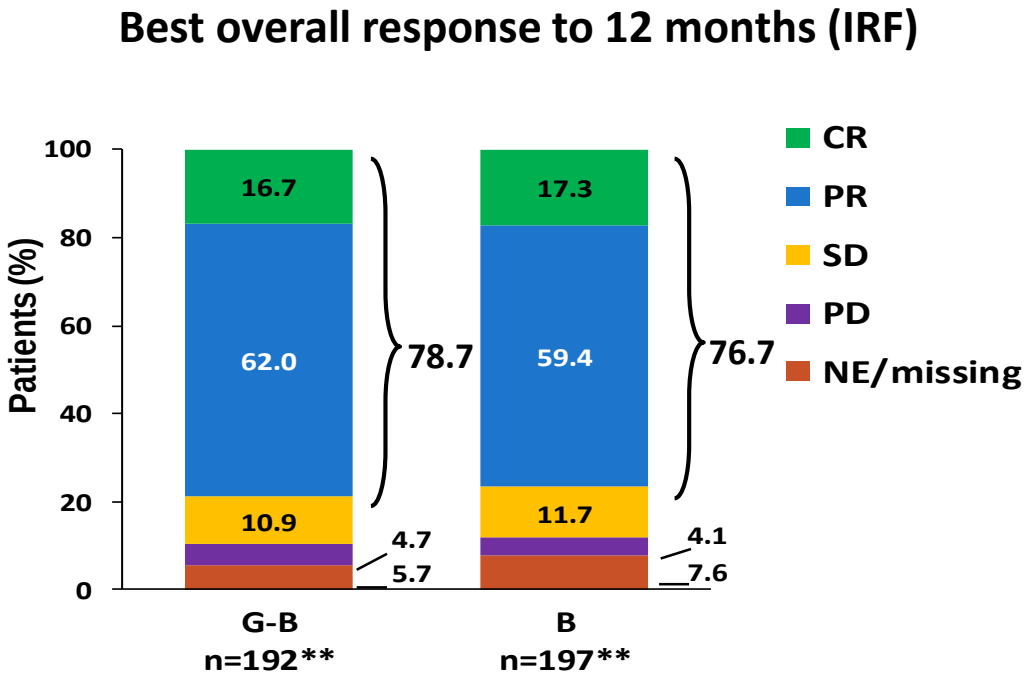


- **Rituximab-refractory definition:** Failure to respond to, or progression during any prior rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance settings
- **Endpoints considered in current analysis:** PFS (INV), OS, TTNT, safety

*Patients in the G-B arm without evidence of progression following induction received G maintenance

GADOLIN: Response to therapy





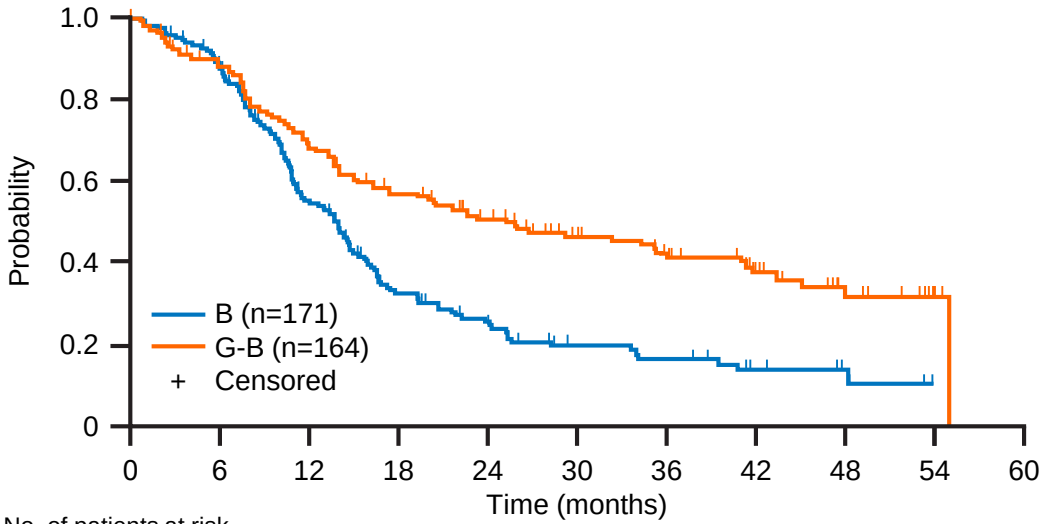
* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.

** Best overall response excludes ongoing patients who have not yet reached the first response assessment.

IRF, independent radiology facility

INV-assessed PFS in the FL population

Kaplan-Meier plot of INV-assessed PFS by treatment arm (FL)



No. of patients at risk

B	171	141	84	45	32	18	15	9	4	0	0
G-B	164	138	107	86	67	49	40	26	15	4	0

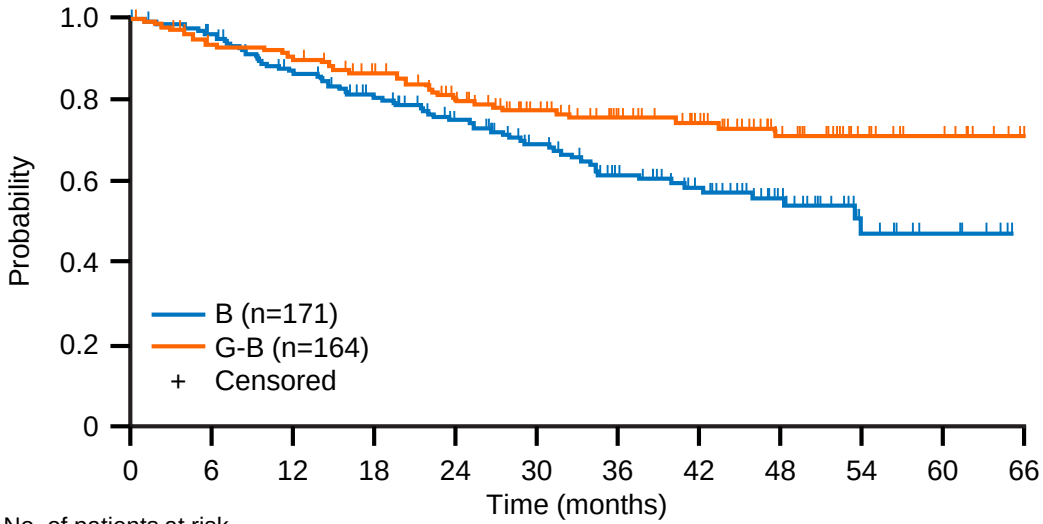
	G-B, n=164	B, n=171
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

OS in the FL population

Kaplan-Meier plot of OS by treatment arm (FL)



No. of patients at risk

B	171	159	137	122	103	84	65	49	32	13	7	0
G-B	164	147	141	129	111	90	71	56	38	20	12	0

	G-B, n=164	***B, n=171***
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

NR, not reached

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

Microenvironment

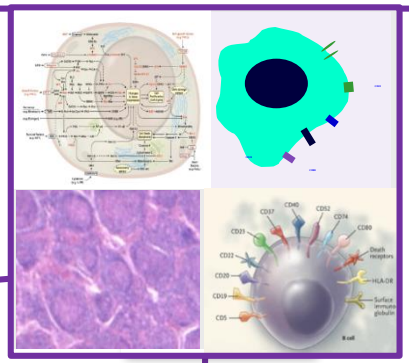
immunmodulators

T-cell exhaustion

Actionable mutations

EZH2

CD79a/b



Pathways

Surface markers

Anti CD20 moAb

Anti CD40 moAb

Other targets

Proteosome inhibitors

mTOR inhibitors

HDAC inhibitors

Bcl-2 family inhibitors

PI3K inhibitors

PKC inhibitors

Survivin inhibitors

Btk inhibitors

Aurora kinase inhibitors

Syk inhibitors

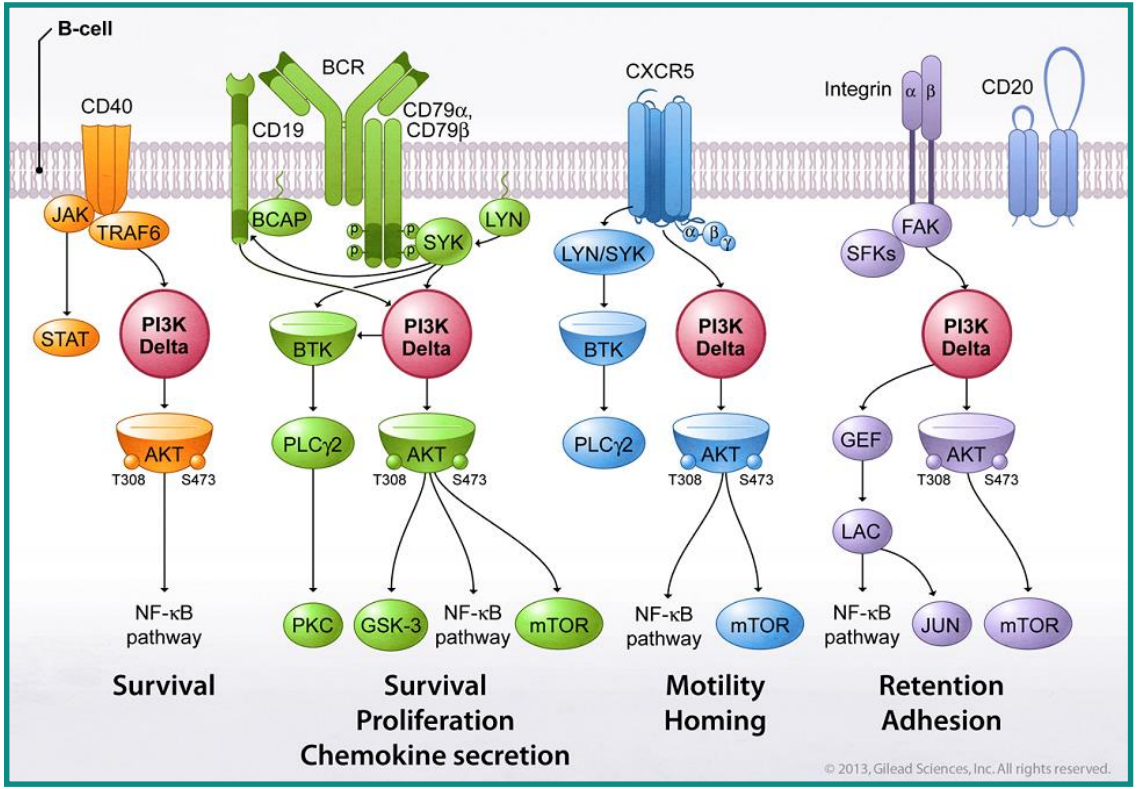
Hsp 90 inhibitors

Nedd8-activating enzyme inhibitors

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

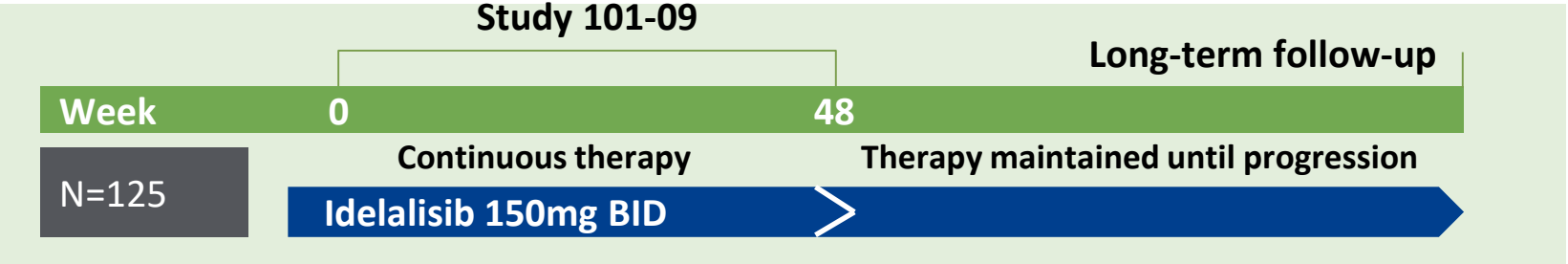
PI3Kδ INHIBITION IMPACTS MULTIPLE CRITICAL PATHWAYS IN INHL



Benson D *et al.* ASCO 2013, Abstract #8526

Idelalisib in Double-Refractory iNHL

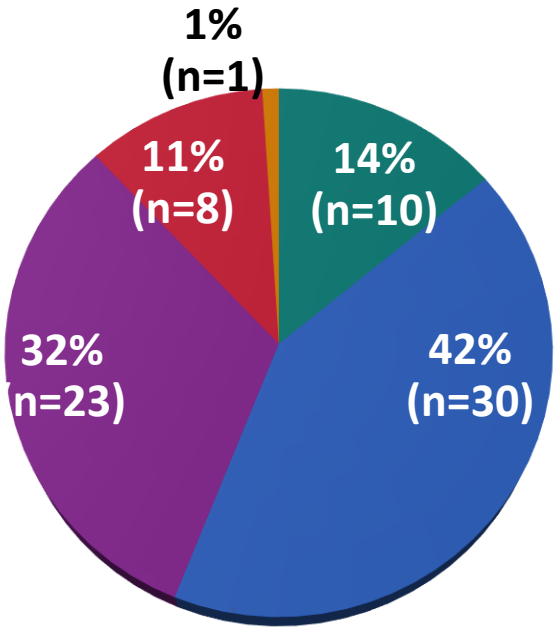
- **Phase II single-arm monotherapy study in patients with R/R iNHL**
- **Accrual completed October 2012**
- **Tumour assessments:**
  - Week 0, 8, 16, 24, 36 and 48, then every 12 weeks thereafter
  - Evaluated by independent review committee (IRC)
    - 2 radiologists with adjudication, if needed, and clinical review
- **Primary endpoint:** Overall response rate (ORR)
- **Secondary endpoints:** Duration of response (DOR), progression-free survival (PFS), safety



Gopal A *et al.* ASH 2014, Abstract #1708

OVERALL RESPONSE RATE (FL PATIENTS)

JUNE 2014



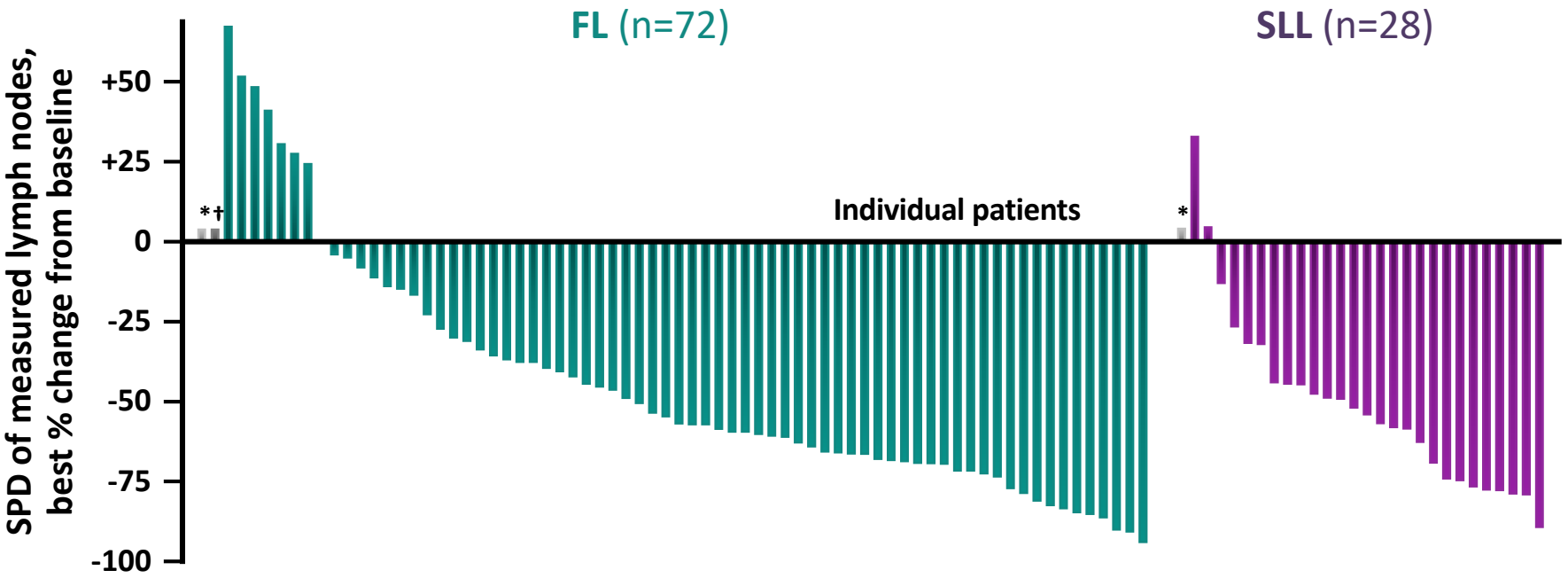
ORR (all FL patients)
55.6% (40/72)
95% CI, 43.4–67.3;
p<0.001

ORR (FL grade 3a)
66.7% (8/12)
95% CI, 34.9–90.1

- Complete response
- Partial response
- Minor response
- Stable disease
- Progressive disease
- Not evaluable

Gopal A *et al.* ASH 2014, Abstract #1708; Salles G *et al.* ASCO 2015, Abstract #346; Zinzani P *et al*. EHA 2015, Abstract #689

LYMPH NODE RESPONSE BY DISEASE SUBGROUP



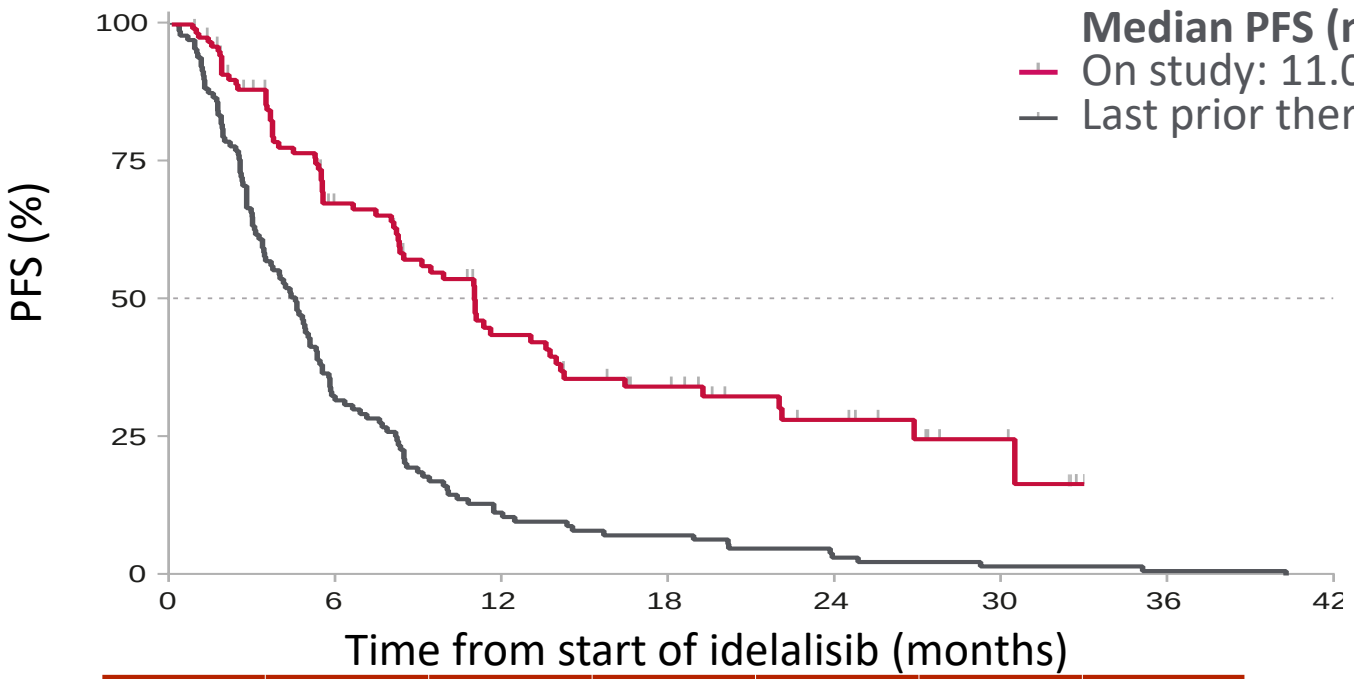
3 patients had no post baseline computed tomographic scan evaluation; *2 of these patients were not evaluable

†1 had progressive disease by lymph node biopsy.

‡Criterion for lymphadenopathy response (Cheson BD *et al. J Clin Oncol* 2007;25:579–86)

Gopal A *et al.* ASH 2014, Abstract #1708

PROGRESSION-FREE SURVIVAL (ALL INHL PATIENTS): ON STUDY VS. LAST PRIOR THERAPY



Patients at risk, n							
	125	60	33	22	12	4	
	125	40	14	9	5	2	1

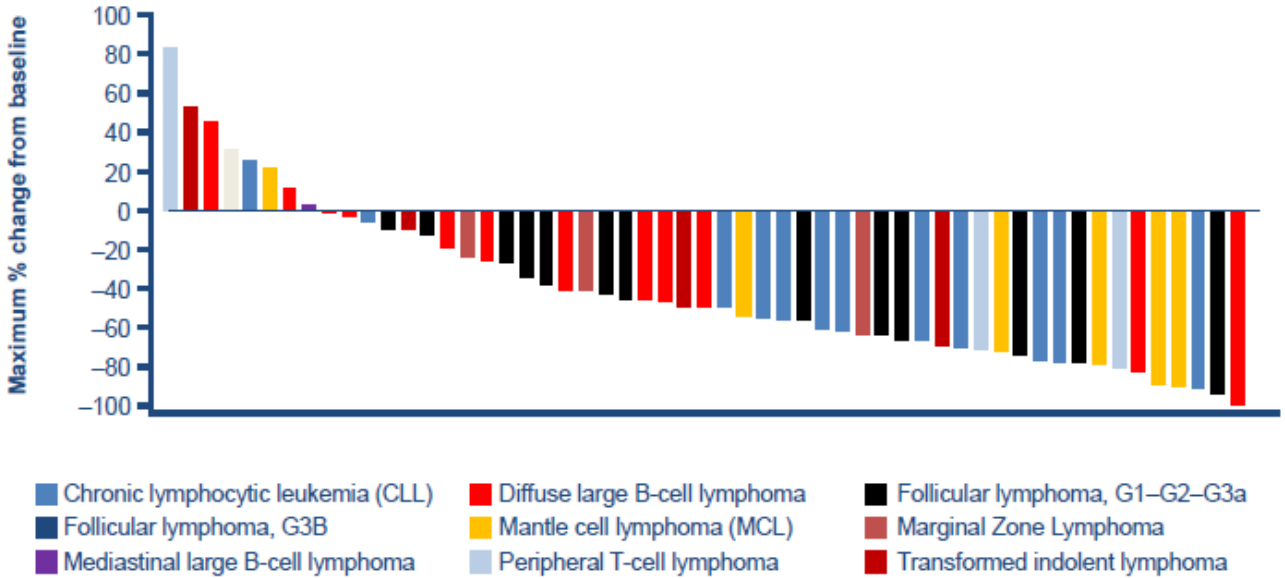
Gopal A *et al.* ASH 2014, Abstract #1708

ADVERSE EVENTS OCCURRING IN >12% OF PATIENTS (ALL INHL PATIENTS)

Adverse event, 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)

Gopal A *et al.* ASH 2014, Abstract #1708

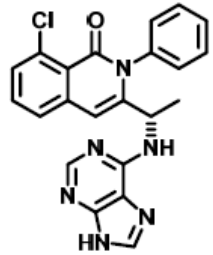
Copanlisib

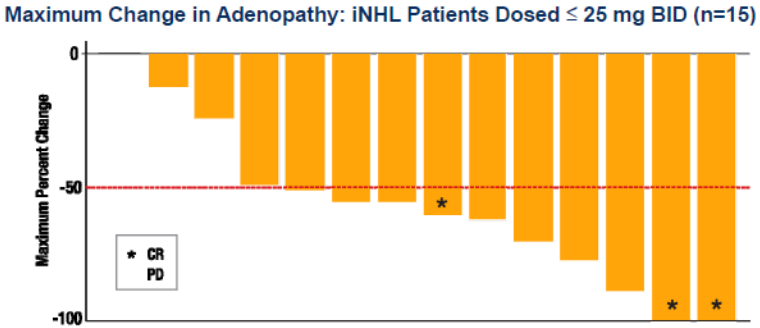


AEs ≥3. Neutropenia 24% ; hypertension 37%; hyperglycaemia 22%

Dreyling et al ASH 2014

Duvelisib





73% ORR includes one Waldenström Macroglobulinemia patient with a minor response (MR) without adenopathy (not shown above)

Douglas ASH 2013

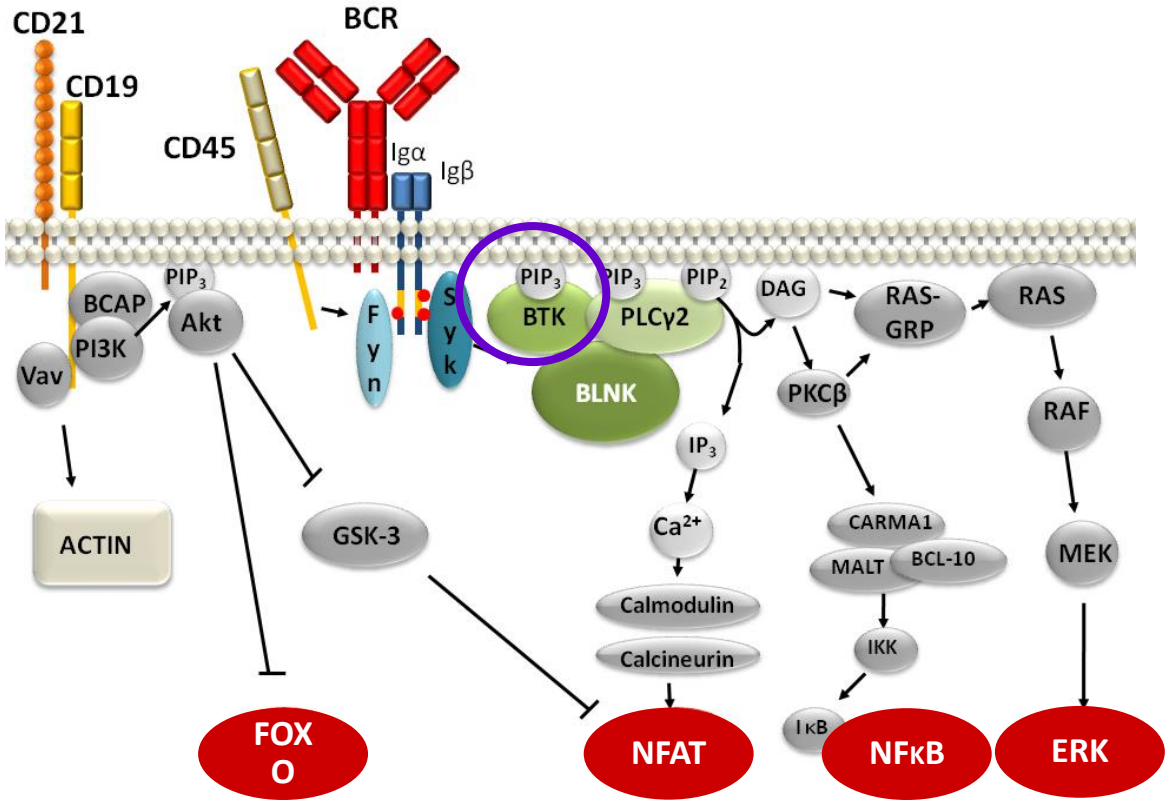
Optimal biological dose 25mg bd continuously

Expansion cohort (Flinn et al ASH 2014)(=31)

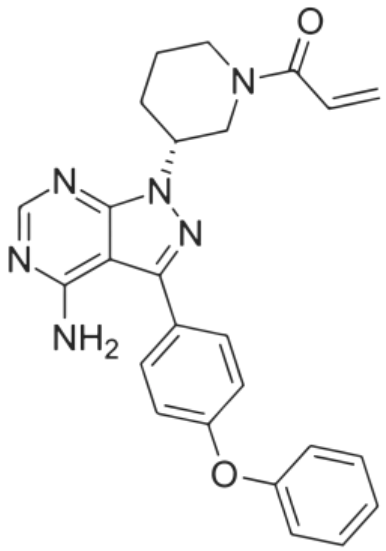
ORR 65%

5 complete responses, all follicular lymphoma

INHIBITING BTK…



Ibrutininb
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]

Through irreversible inhibition of BTK, ibrutinib is believed to disrupt key malignant processes and:[3,4]

- Induce apoptosis
- Inhibit adhesion (may lead to lymphocytosis)
- Inhibit migration and homing (prevents malignant cells from homing back to lymph organs)

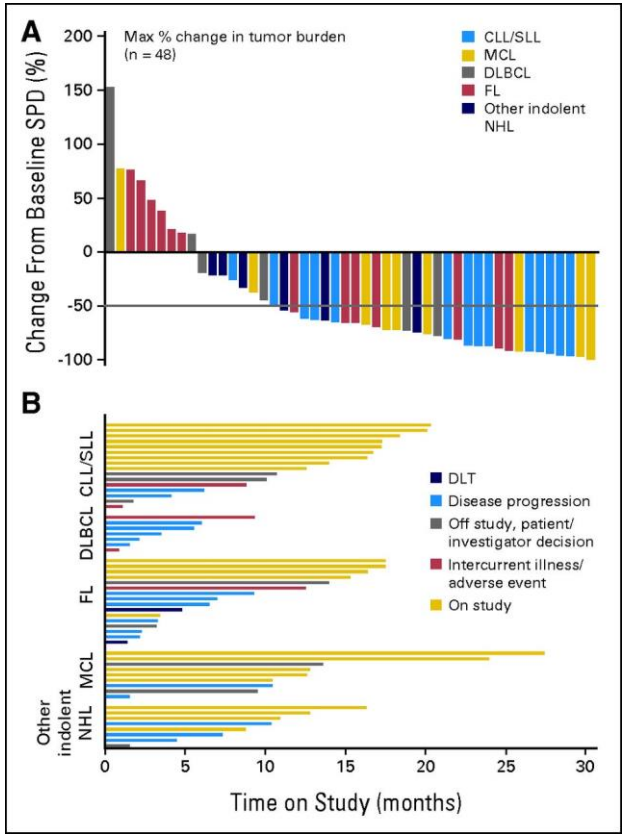
1. de Gorter DJJ, et al. Immunity 2007;26:93-104. **2.** Burger JA, et al. Blood 2009;114:3367-3375. **3.** Buggy J et al. Int Rev Immunol 2012; 31:119-132. **4.** Chavez J, et al. Core Evid 2013; 8:37-45.

IBRUTINIB IN B-CELL LYMPHOMA

56 patients with R/R NHL, CLL, or WM who had failed ≥ 1 previous therapy

	Responders (n/N)
Mantle cell	7/9
CLL/SLL	11/16
FL	6/16
DLBCL	2/7
WM	3/4
MZL	1/4
ORR	**60%**

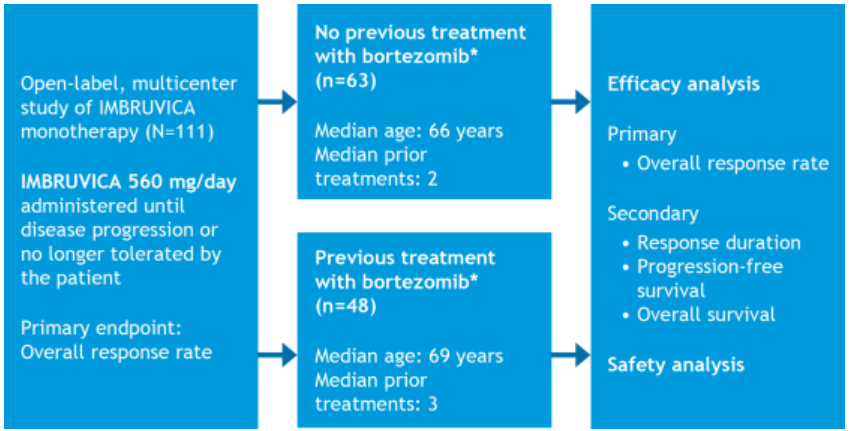
N=56. Median 3 (1–10) prior therapies



Advani RH *et al. J Clin Oncol* 2013;31:88–94

Phase II trial
Study design

Design of a phase II MCL study (PCYC-1104)[1]



* 63/111 patients had received treatment with bortezomib* (≥2 cycles) and 48/111 had not reached such treatment (<2 complete cycles or no prior therapy)
† Refractory disease was defined as a lack of at least a partial response to the last therapy before study entry. Advanced disease was defined as involvement of bone marrow, extranodal sites or both [1]

***Bortezomib is not approved for use in the treatment of MCL within the EU**

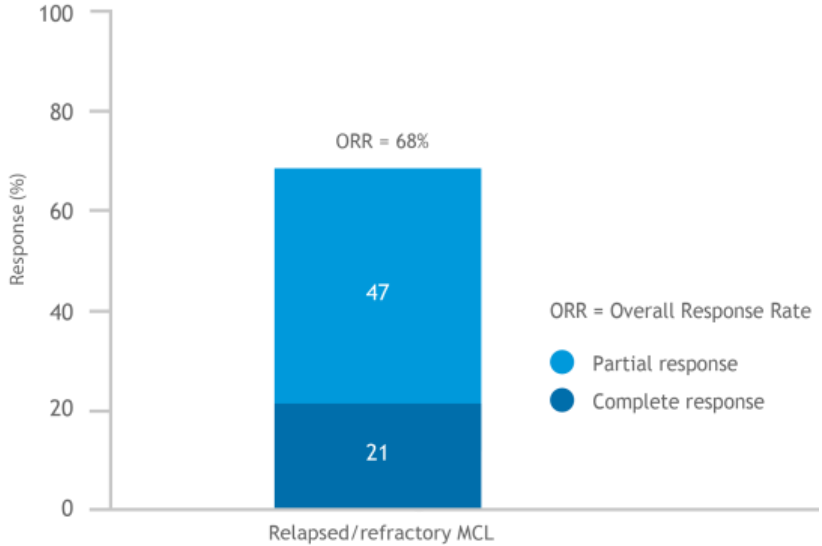
Ibrutinib monotherapy was studied in MCL patients (N=111) with a range of exposure to prior treatments in an open-label, multicentre, international, phase II trial.[1†]

- 72% of patients had advanced disease
- 45% of patients had refractory disease
- 55% of patients had received 3 or more prior regimens

EU: European Union; MCL: mantle cell lymphoma.
1. Wang M et al. N Engl J Med 2013; 369: 507-516

Phase II study
Response rates

High response rates in relapsed/refractory MCL[1]



Graph adapted from Wang M, et al. 2013.

Partial response: Regression of measurable disease and no new sites. [2]
Complete response: Disappearance of all evidence of disease. [2]
(Revised International Working Group Criteria for non-Hodgkin's lymphoma)

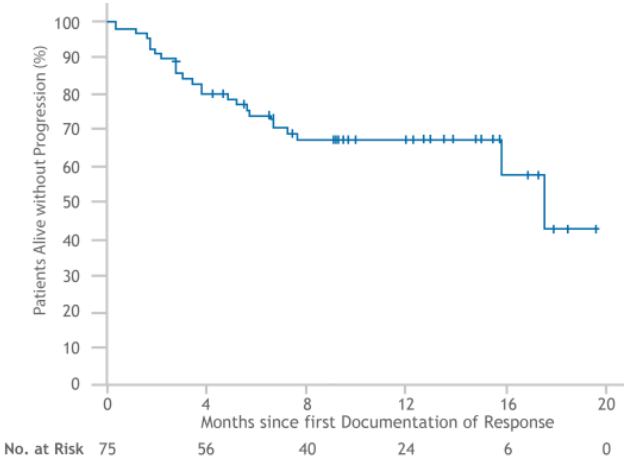
ibrutinib® delivered high response rates in relapsed/refractory MCL.[1]

- Responses were often seen early (median 1.9 months to initial response) and generally continued to improve over time[1]

MCL: mantle cell lymphoma.

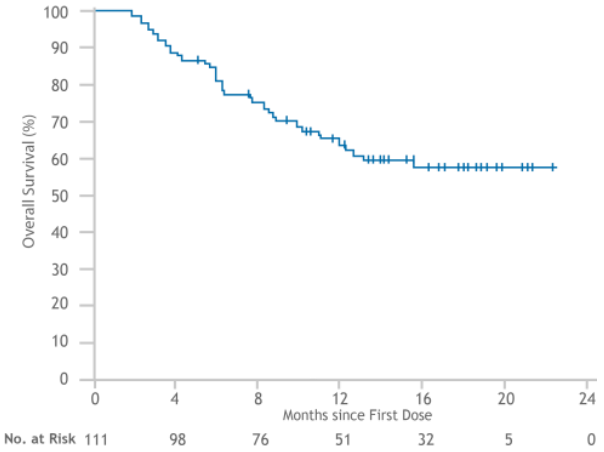
1. Wang M et al. N Engl J Med 2013; 369: 507-516.

Duration of response with ibrutinib



- 17.5 months estimated median response duration
- 13.9 months estimated median progression-free survival

Overall survival rate with ibrutinib



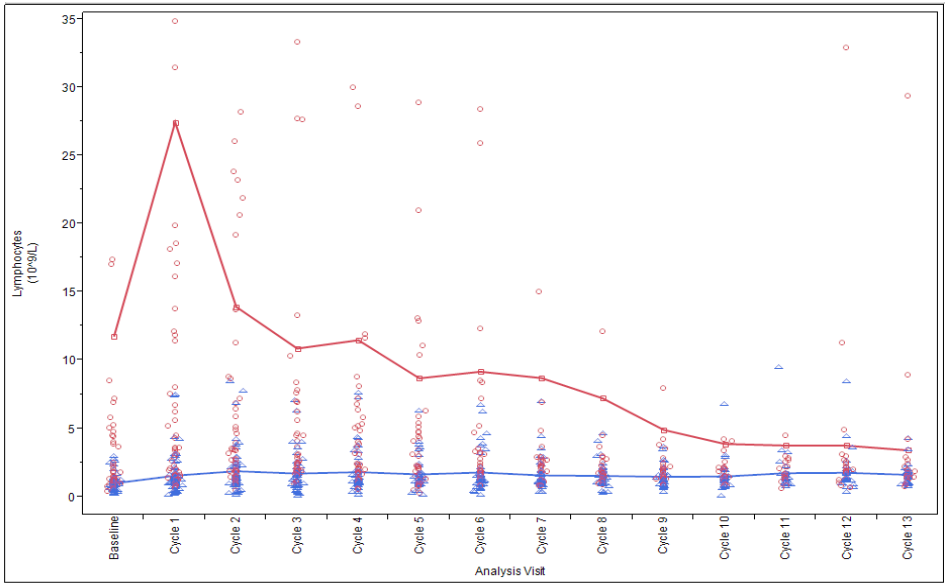
At the time of analysis (primary analysis of progression-free survival), the median overall survival had not been reached as 70 patients (63%) were still alive.[1]

- Estimated 58% overall survival at 18 months[1]

1. Wang M et al. N Engl J Med 2013; 369: 507-516.

Lymphocytosis and ibrutinib in MCL

Absolute lymphocyte count by analysis visit and bone marrow involvement[1]



Lymphocyte count remains largely unaffected in cases with no bone marrow involvement

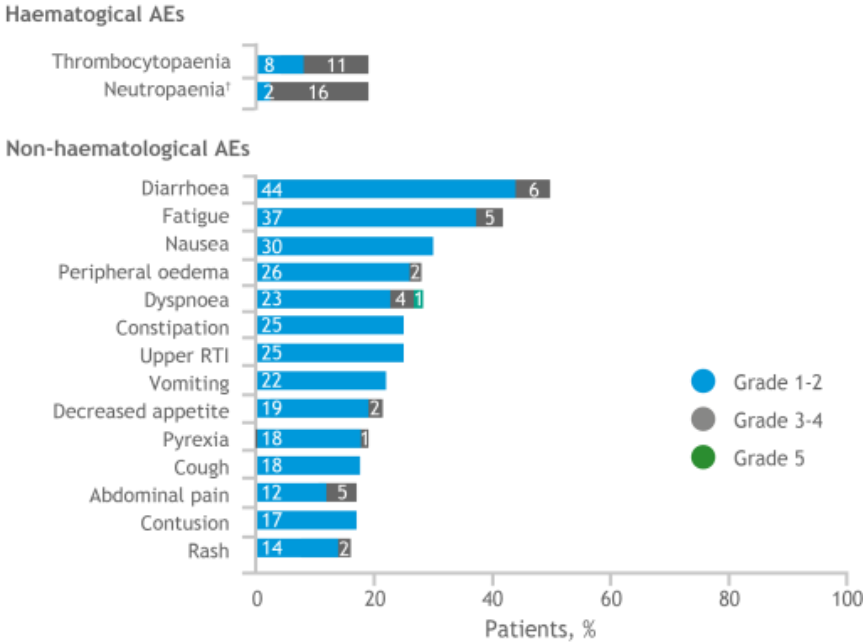
Red=bone marrow involvement; Blue=no bone marrow involvement

MCL: mantle cell lymphoma.

1. Furtado M et al. in press Br J Haematol

Phase II study
Adverse event profile

Adverse events (AEs) reported in ≥15% of MCL patients[1]



* Febrile neutropaenia 2.7%

Most AEs were grade 1 or 2.[1] There were low rates of grade 3 and 4 adverse events.[1]

- The rate of grade 3 bleeding events was 4.5%, there were no grade 4 or 5 events[1]
- The most common infection of grade ≥3 was pneumonia (6%)[1]

1. Wang M et al. N Engl J Med 2013; 369: 507-516.

IBRUTINIB MONOTHERAPY IN R/R FL: PHASE 2 CONSORTIUM (P2C) TRIAL

Relapsed/refractory FL, n=40
560mg OD until PD or unacceptable toxicity

Baseline characteristics	
FLIPI ≥3	55%
Rituximab refractory	45%
Previous stem cell transplant	20%
Refractory to last therapy	36%
Median number of prior therapies (range)	3 (1–11)

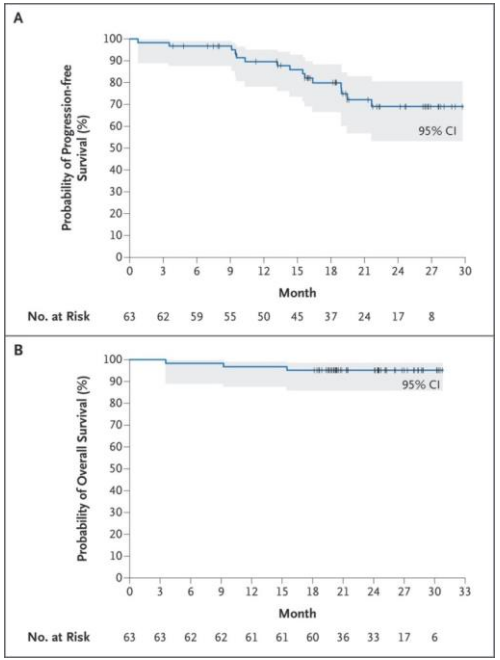
Summary of outcomes at median follow up of 6.5 months	
ORR	30% (1 CR)
Patients exhibiting tumour size reduction	65%
Median time to response (range)	2.4 months (1.8–12.9)
Response – Rituximab refractory – Rituximab sensitive	 2/18 (11%) 8/19 (42%) [p=0.06]
Median PFS (95% CI)	9.9 months (6–NR)

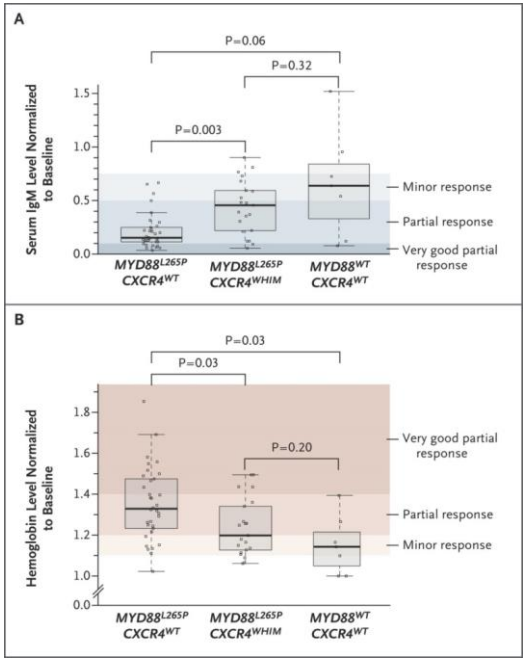
Bartlett NL *et al.* ASH 2014 Abstract #800

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

PFS

OS



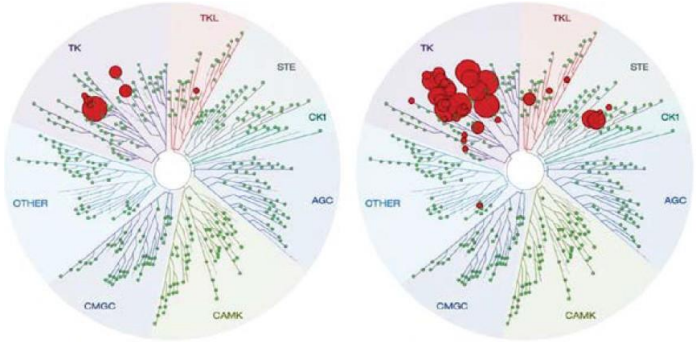


Treon SP et al. N Engl J Med 2015;372:1430-1440.

Acalabrutinib

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

Kinase Selectivity Profiling at 1 μM



Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126	10
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ERBB2	"1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

BLK = B lymphocyte kinase; BMX = bone marrow tyrosine kinase gene in chromosome X; BTK = Bruton tyrosine kinase; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase; ERBB4 = erb-b4 receptor tyrosine kinase; IC_{50} = inhibitory concentration of 50%; ITK = interleukin-2-inducible T-cell kinase; JAK3 = Janus kinase 3; TEC = tyrosine kinase expressed in hepatocellular carcinoma; TXK = T- and X-cell-expressed kinase.

Barf T, et al. *J Pharmacol Exp Ther*. 2017;363:240-252.

BCL-2 Inhibition

Bcl-2 highly expressed in FL

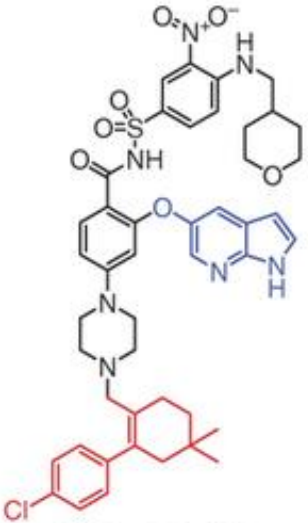
GDC-0199 oral active Bcl-2 inhibitor
Phase I dose escalation
200-900 mg cohorts
N=44 with NHL
FL =11 (26%)

Nausea (34%), diarrhoea (25%), fatigue (21%)

Tumour lysis in 1 patient each with DLBCL and MCL

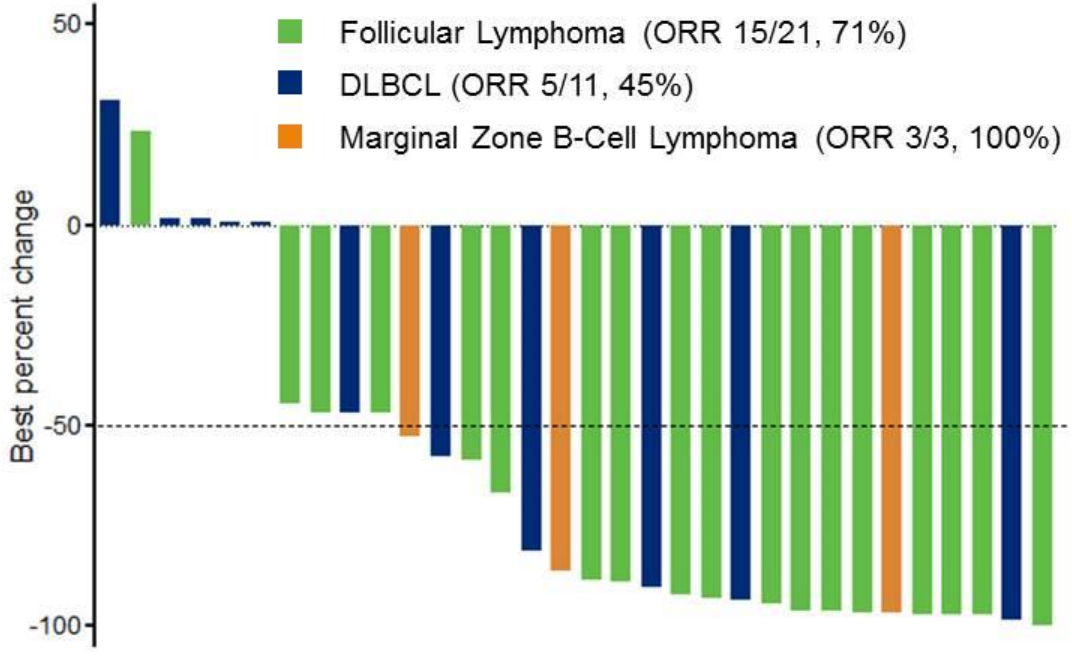
3/11 responses in FL

R2PD not yet established



GDC-0199

Best Percent Change from Baseline in Nodal Size



n=3 did not have post-baseline tumor assessment
As of January 9, 2015

Adapted from the de Vos presentation at European Hematology Association on 12 June 2015

Response to Venetoclax following failure BTKI (MCL)

- 20 patients evaluable for response assessment
- Median follow up from start of venetoclax: 5.1 months.
- ORR 60% (CR 20%, PR 40%)
- Median 3.75 x 28-day cycles (range 0.5-13).
- ORR according to prior BTKi response:
  - primary BTKi resistance (n = 9): ORR 44.4% *vs* response to prior BTKi (n = 11): ORR 72.7%

Treatment post Venetoclax	n (%)
Allogenic stem cell transplantation-> PEP-C	1
R-BAC	2[a]
R-Bendamustine	2
Lenalidomide-based+/-R	2
Ibrutinib	2
Nil	12

a) 1 patient R-BAC given with aim to bridge to allogenic SCT (developed secondary AML)

Blastoid (n = 4)

- Diagnosis to VEN (yrs): 2.1, 0.8, 0.9, 1.3
- Ki67%: 90%, 80%, 80%, 75%
- ORR: PD, PD, PD, CRu
- Cycles: 1.5, 1.5, 2, 1.25

Eyre et al EHA 2018

Microenvironment

immunmodulators

T-cell exhaustion

Actionable mutations

EZH2

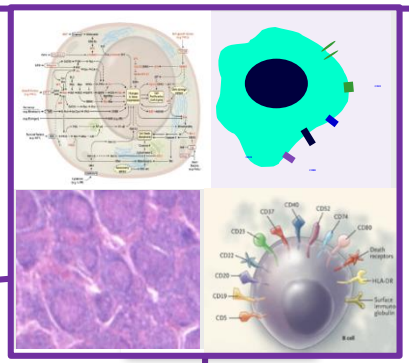
CD79a/b

Proteosome inhibitors

Bcl-2 family inhibitors

Survivin inhibitors

Syk inhibitors



Pathways

mTOR inhibitors

PI3K inhibitors

Btk inhibitors

Hsp 90 inhibitors

Surface markers

Anti CD20 moAb

Anti CD40 moAb

Other targets

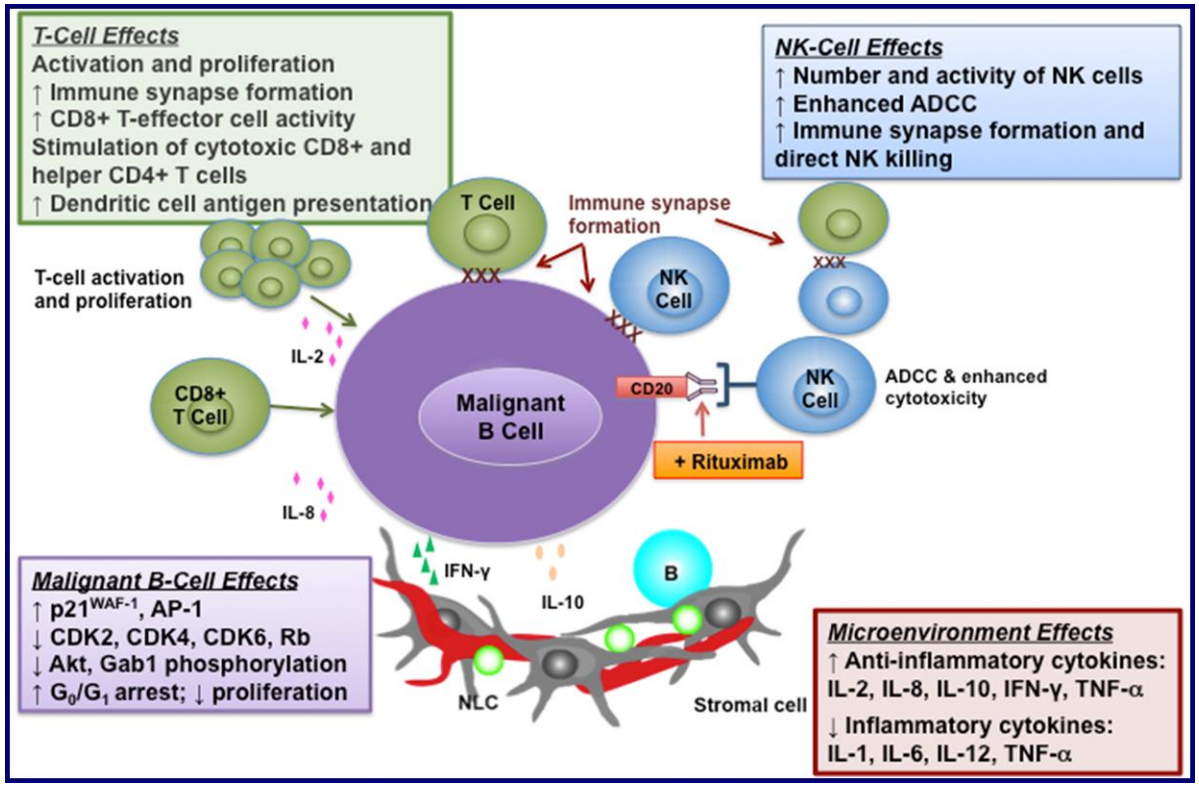
HDAC inhibitors

PKC inhibitors

Aurora kinase inhibitors

Nedd8-activating enzyme inhibitors

Proposed mechanism of action of lenalidomide + rituximab



Gribben JG, et al. JCO 2015; DOII:10.1200/JCO.2014.59.5363

The R^2 regimen

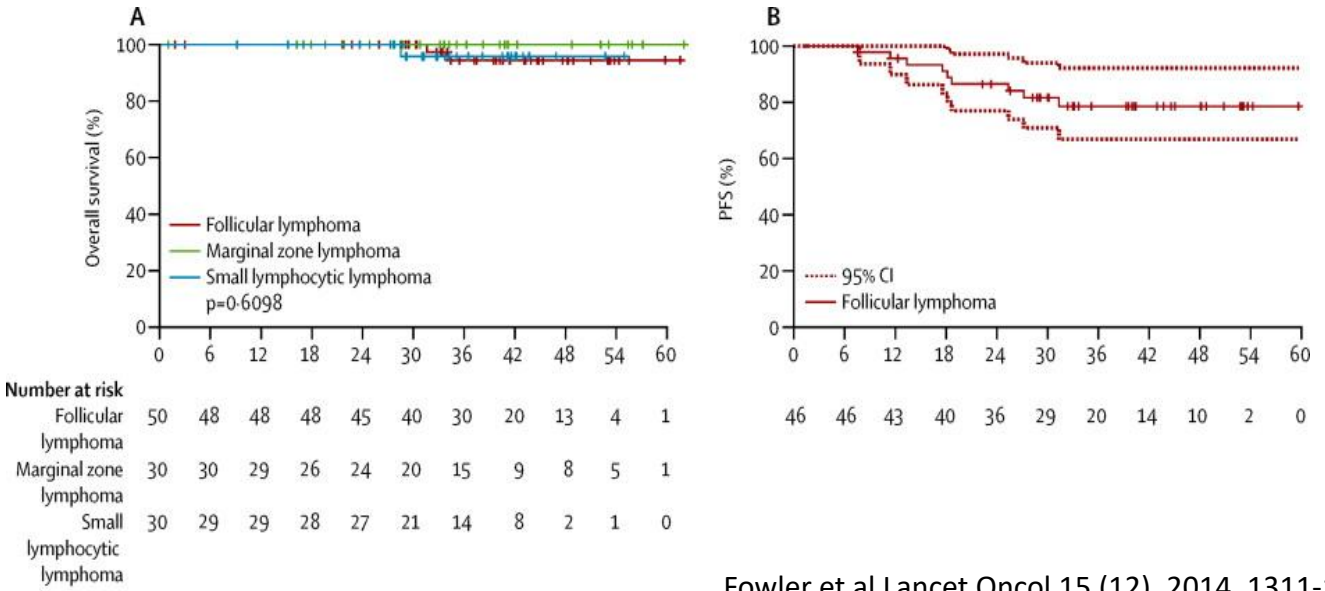
- Preclinical data suggests that lenalidomide may augment immune effector function and enhance rituximab mediated ADCC
- Previously untreated advanced stage 'indolent lymphoma'
- n=110 (103 pts. evaluable) 57% GELF criteria for high tumour burden

%	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 at al. Lancet Oncol 2014; 15(12):1311-8

Overall survival

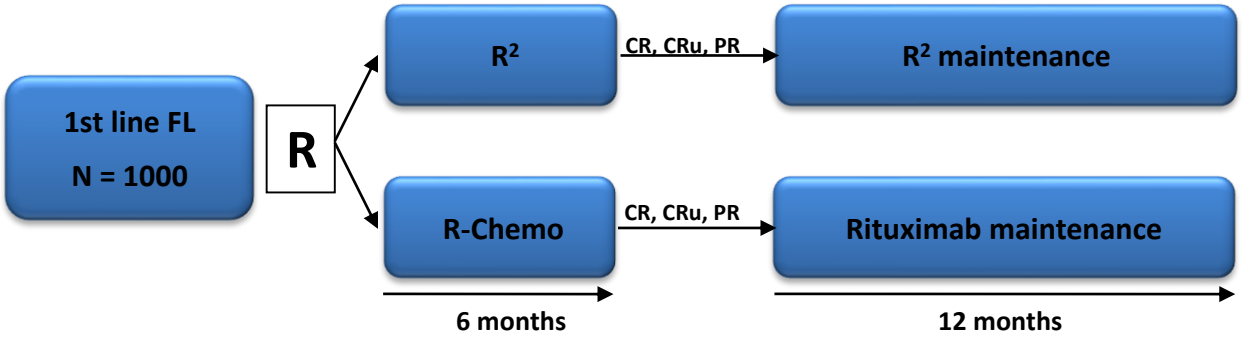
Progression-free survival: Follicular lymphoma



Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

RELEVANCE: A Lymphoma Study Association Trial

RELEVANCE is a prospective, randomized, phase 3 trial comparing the efficacy of the R^2 regimen versus R-CHEMO followed by rituximab maintenance in patients with treatment-naive FL



Co-primary endpoints: CR/CRu at 120 weeks and PFS

R-Chemo

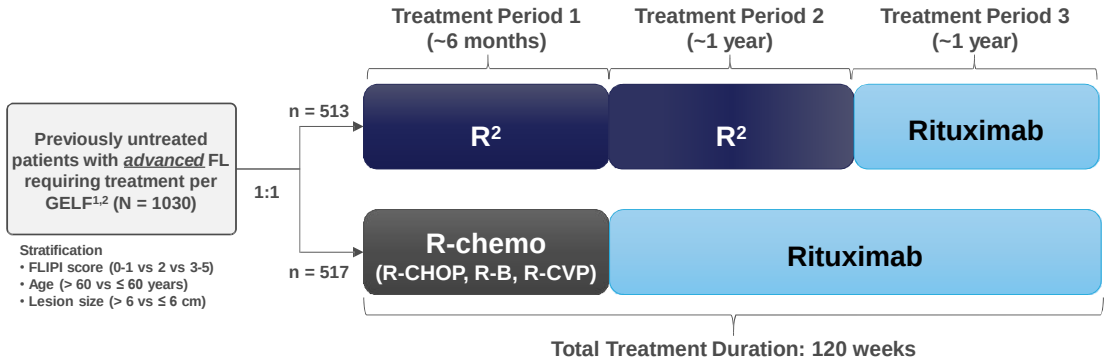
- Investigator choice of R-CHOP, R-CVP, R-B

R^2

- Lenalidomide 20-mg QD x 6 cycles (days 2-22 of 28-day cycle). If a CR is achieved at 6 months then 10-mg QD x 12 cycles; if PR, then additional 3-6 cycles of lenalidomide 20-mg
- Rituximab weekly x 4, then on day 1 of each cycle 2 to cycle 6, then every other cycle

ClinicalTrials.gov. http://www.clinicaltrials.gov/ct2/show/NCT01650701. Accessed October, 2015

RELEVANCE: STUDY DESIGN



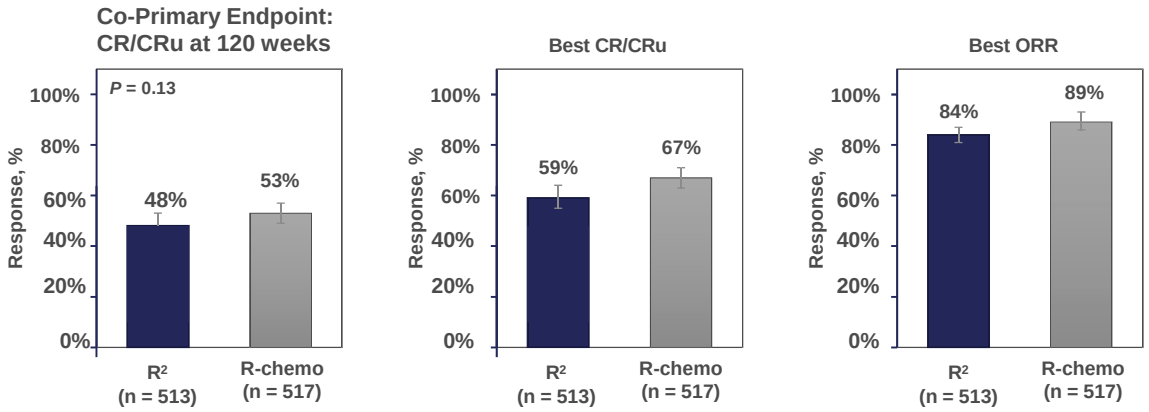
Co-primary endpoints (superiority)*

- CR/CRu at 120 weeks
- PFS

NCT01476787; NCT01650701; EUDRA 2011-002792-42. *Per central (IRC) review by 1999 IWG with CT.

1. Salles et al. *Lancet.* 2011;377:42-51. 2. Brice et al. *J Clin Oncol.* 1997;15:1110-1117. 3. Fowler et al. RELEVANCE: Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) Versus Chemotherapy Plus Rituximab, Followed by Rituximab Maintenance, in Patients With Previously Untreated Follicular Lymphoma. Oral presentation at: American Society of Clinical Oncology meeting. 2018; Jun 1-5; Chicago, IL. Abstract 7500.

RELEVANCE: RESPONSE BY IRC (ITT) (CO-PRIMARY ENDPOINT)

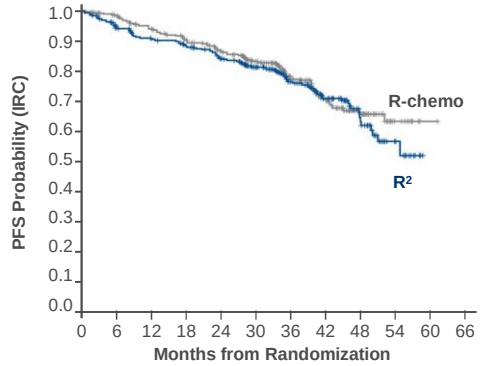


- 3-year DOR was 77% for R^2 vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC

Data cut-off 31May2017.

Fowler et al. RELEVANCE: Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) Versus Chemotherapy Plus Rituximab, Followed by Rituximab Maintenance, in Patients With Previously Untreated Follicular Lymphoma. Oral presentation at: American Society of Clinical Oncology meeting. 2018; Jun 1-5; Chicago, IL. Abstract 7500.

RELEVANCE: CO-PRIMARY ENDPOINT INTERIM PFS BY IRC (~50% EVENTS)



Number of Patients at Risk

R²	513	435	409	393	364	282	174	107	49	13	0
R-chemo	517	474	446	417	387	287	175	109	51	14	1	0

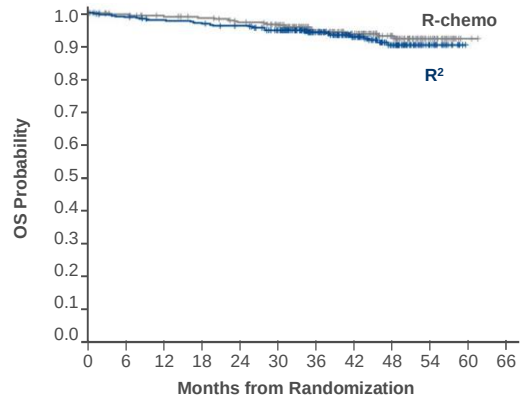
	R² (n = 513)	R-chemo (n = 517)
Events, n (%)	119 (23)	111 (21)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-82%)
HR (95% CI)	1.10 (0.85-1.43)	
P value	0.48	

- At a median follow-up of 37.9 months, interim PFS was similar in both arms

Data cut-off 31May2017.

Fowler et al. RELEVANCE: Phase III Randomized Study of Lenalidomide Plus Rituximab (R²) Versus Chemotherapy Plus Rituximab, Followed by Rituximab Maintenance, in Patients With Previously Untreated Follicular Lymphoma. Oral presentation at: American Society of Clinical Oncology meeting. 2018; Jun 1-5; Chicago, IL. Abstract 7500.

RELEVANCE: OVERALL SURVIVAL (IMMATURE; ITT)



Number of Patients at Risk

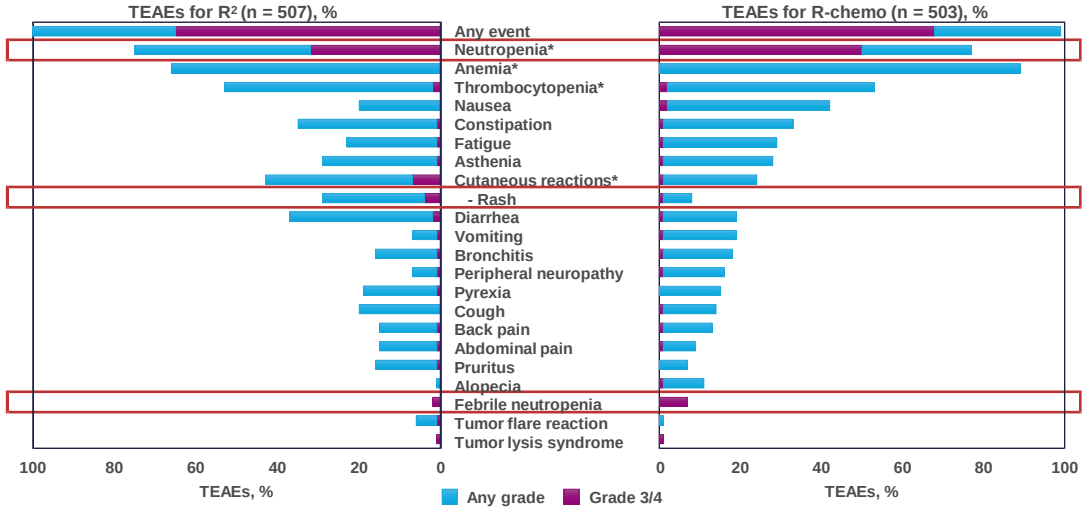
R²	513	499	491	486	479	459	312	194	105	24	0	
R-chemo	517	496	487	481	470	453	298	193	115	32	2	0

	R² (n = 513)	R-chemo (n= 517)
Events, n (%)	38 (7)	31 (6)
3-year OS (95% CI)	94% (91%-96%)	94% (91%-96%)
HR (95% CI)	1.16 (0.72-1.86)	

Data cut-off 31May2017.

Fowler et al. RELEVANCE: Phase III Randomized Study of Lenalidomide Plus Rituximab (R²) Versus Chemotherapy Plus Rituximab, Followed by Rituximab Maintenance, in Patients With Previously Untreated Follicular Lymphoma. Oral presentation at: American Society of Clinical Oncology meeting. 2018; Jun 1-5; Chicago, IL. Abstract 7500.

RELEVANCE: TREATMENT-EMERGENT ADVERSE EVENTS



Data cut-off 31May2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.
*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders.

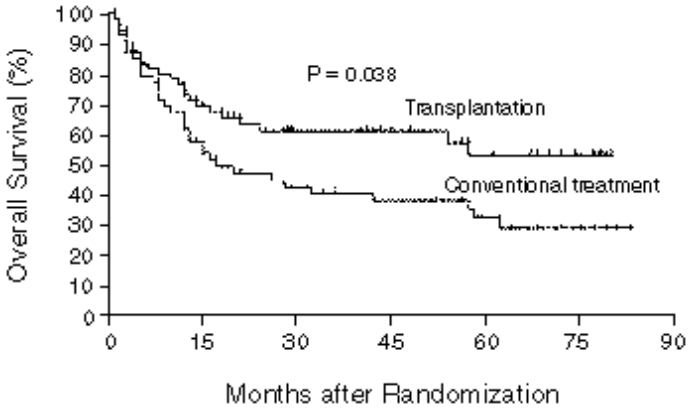
Fowler et al. RELEVANCE: Phase III Randomized Study of Lenalidomide Plus Rituximab (R²) Versus Chemotherapy Plus Rituximab, Followed by Rituximab Maintenance, in Patients With Previously Untreated Follicular Lymphoma. Oral presentation at: American Society of Clinical Oncology meeting. 2018; Jun 1-5; Chicago, IL. Abstract 7500.

Now back to some old fashioned thinking….

Dose intensification….

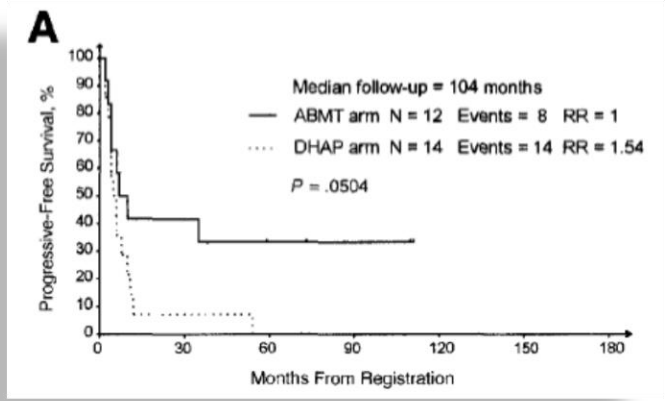
PARMA Trail (Phillip NEJM 1995)

- PARMA study (n=215 aggressive relapsed disease)
- 109 demonstrated chemosenstivity after DHAP x2: randomised DHAP x4 more or BEAC + ABMT
- OS 53 vs 32% at 5 years (*P*=0.038)
- Time to relapse (< or > 12 months most important prognostic factor, along with second line aaIPI and response to salvage PR vs CR



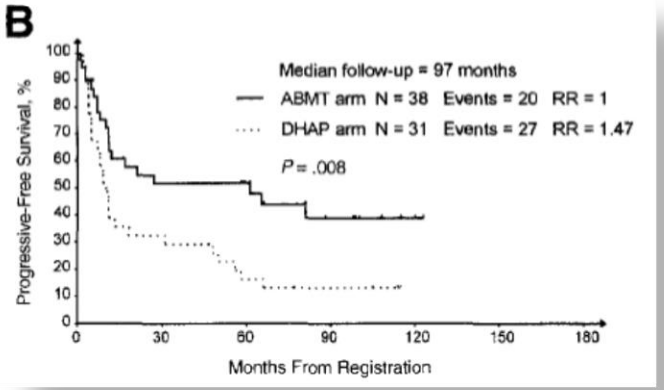
Guglielmi et al, JCO 1998

PARMA TRIAL: ABMT vs DHAP



(A) Actuarial PFS curves in responding early relapses (less than 12 months from initial diagnosis) according to treatment arm (ABMT versus DHAP).

(B) Actuarial PFS curves in responding late relapses (more than 12 months from initial diagnosis) according to treatment arm (ABMT versus DHAP)

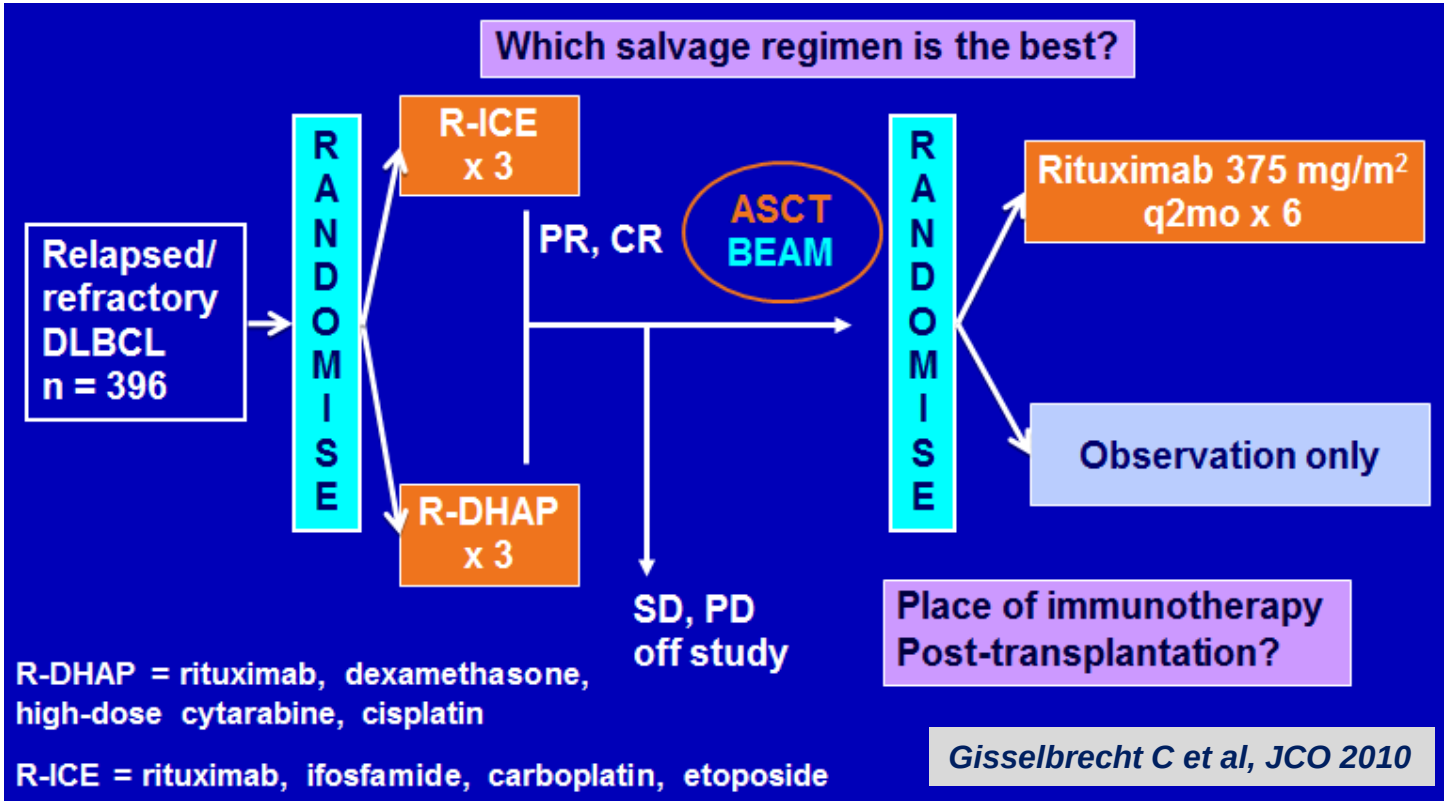


Guideline Recommendations for Treatment of Relapsed DLBCL

- Second-line therapy in candidates for high-dose therapy + ASCT
  - DHAP ± rituximab
  - ESHAP ± rituximab
  - GDP ± rituximab
  - GemOx ± rituximab
  - ICE ± rituximab
  - MINE ± rituximab
- Second-line therapy for patients who are not candidates for high-dose therapy
  - Clinical trial
  - Rituximab
  - CEPP ± rituximab
  - Lenalidomide
  - EPOCH ± rituximab

NCCN practice guidelines in oncology: non-Hodgkin's lymphomas V.1.2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf.

High Dose Chemotherapy plus ASCT: CORAL trial experience



Which Reinduction Strategy?

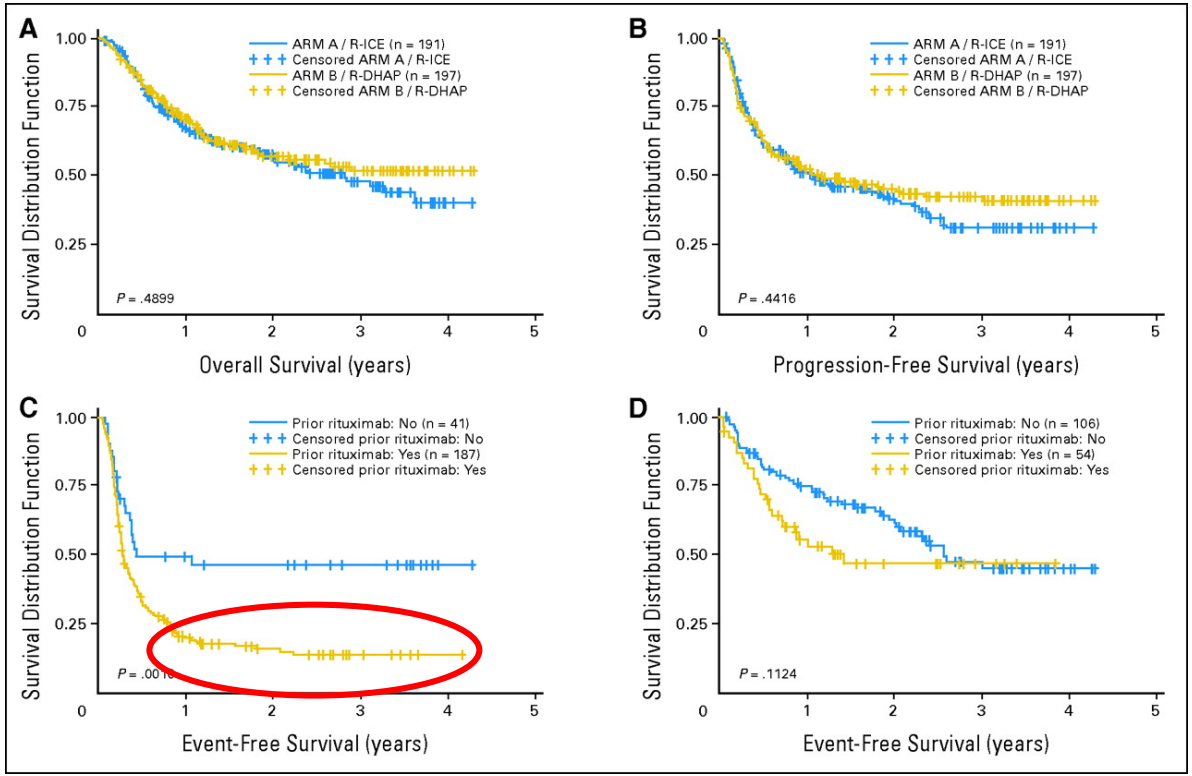
- DHAP, ESHAP, ICE, IVE , MIME *etc ?*
- Similar response rates
- CORAL study: n=396, median age 55 years.
  Similar response rates R-ICE 64%

  R-DHAP

  63%

Factors affecting response rates:

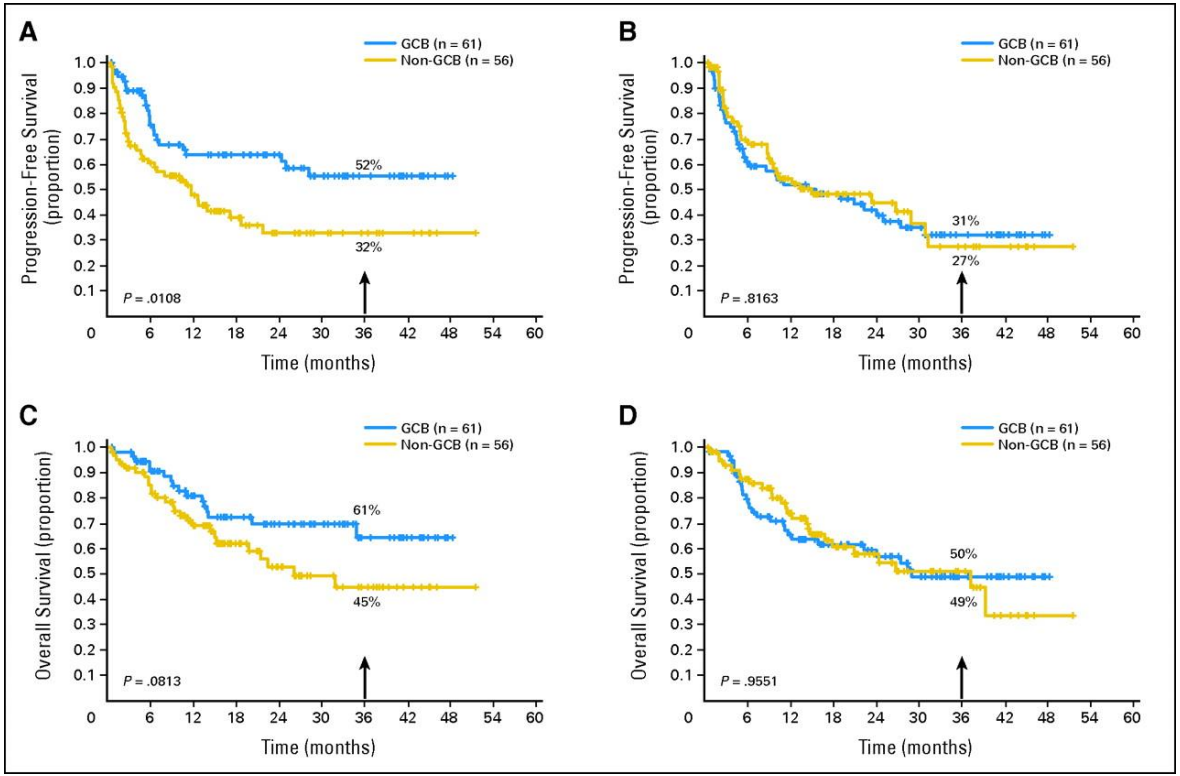
refractory disease
relapse less than 12 months after diagnosis
International Prognostic Index (IPI) >1 than 1
Prior rituximab treatment versus no (51% v 83%)



Gisselbrecht C et al. JCO 2010;28:4184-4190

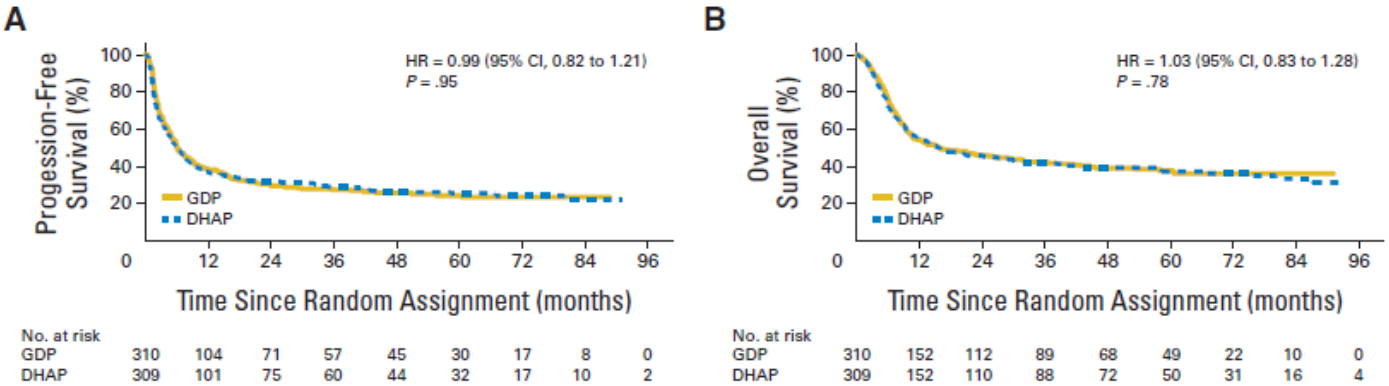
R-DHAP

R-ICE



Thieblemont C et al. JCO 2011;29:4079-4087

GDP…outpatient regimen



Crump et al. JCO 2014

Toxicity….

Table 3. Most Serious Adverse Events

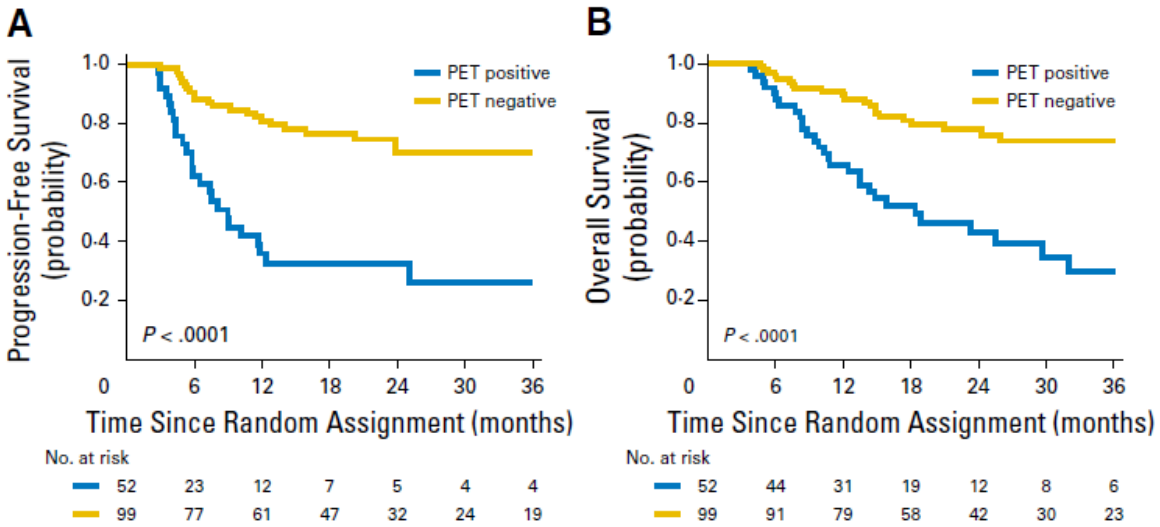
Adverse Event	GDP (n = 306) No.	GDP (n = 306) %	DHAP (n = 304) No.	DHAP (n = 304) %	*P*
Thrombosis/embolism	18	6	18	6	NS
Fatigue	30	10	28	9	NS
Nausea	13	4	25	8	.04
Vomiting	22	7	21	7	NS
Infection					
With grade 3 to 4 neutropenia	18	6	28	9	NS
Without neutropenia	21	7	22	7	NS
Febrile neutropenia	28	9	70	23	< .001
Syncope	7	2	16	5	
Worst overall	143	47	186	61	< .001

NOTE. Comparison of most frequently occurring serious adverse events, occurring in at least 5% of patients who received at least one dose of protocol therapy, at grade 3 or 4 (National Cancer Institute Common Toxicity Criteria version 2.0).

Abbreviations: DHAP, dexamethasone, cytarabine, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin; NS, not significant.

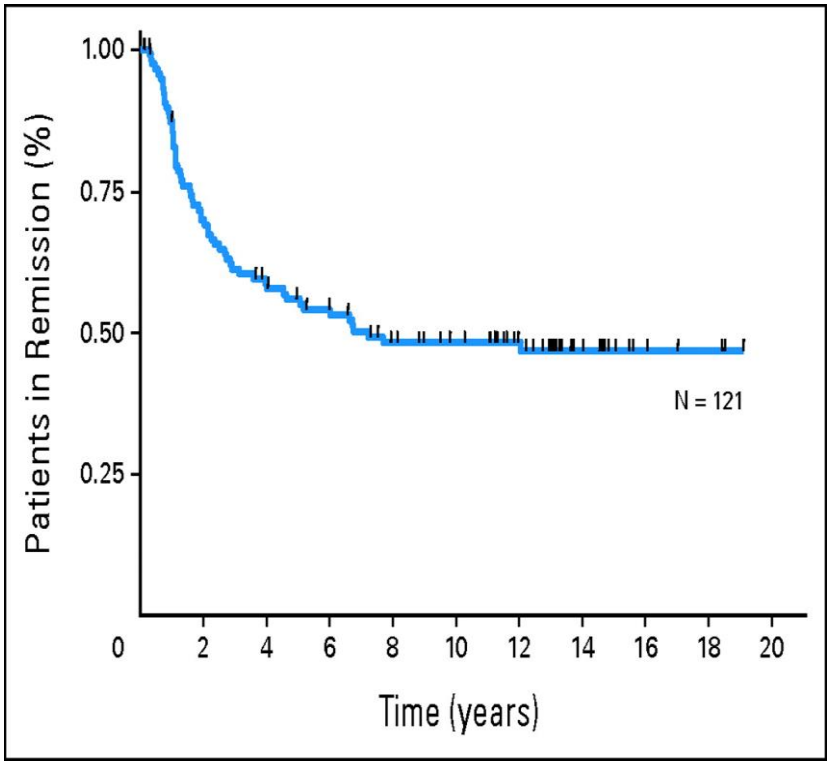
Crump et al. 2014

Value of pre-auto PET



Van Imhoff et al JCO 2016

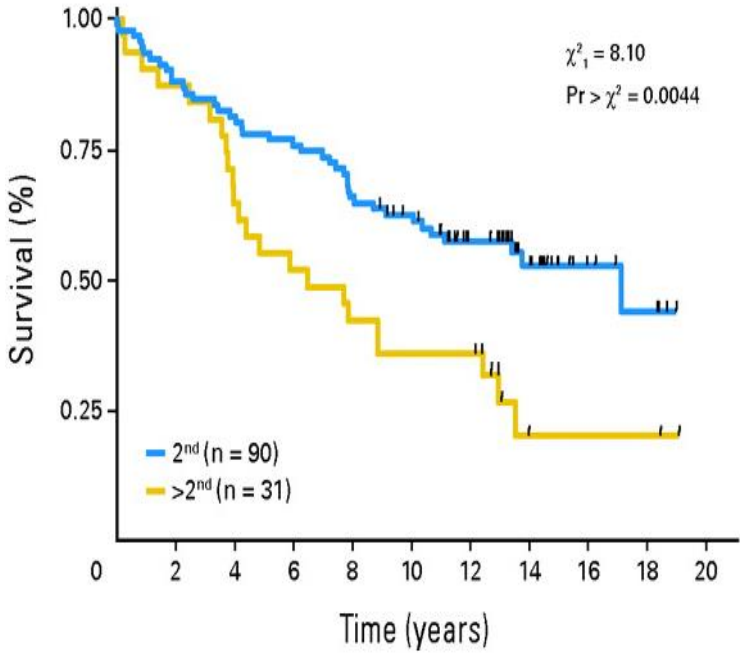
Auto in follicular lymphoma: Remission duration



Rohatiner et al. JCO 2007

Probably should do early in disease course…

Overall survival by remission number

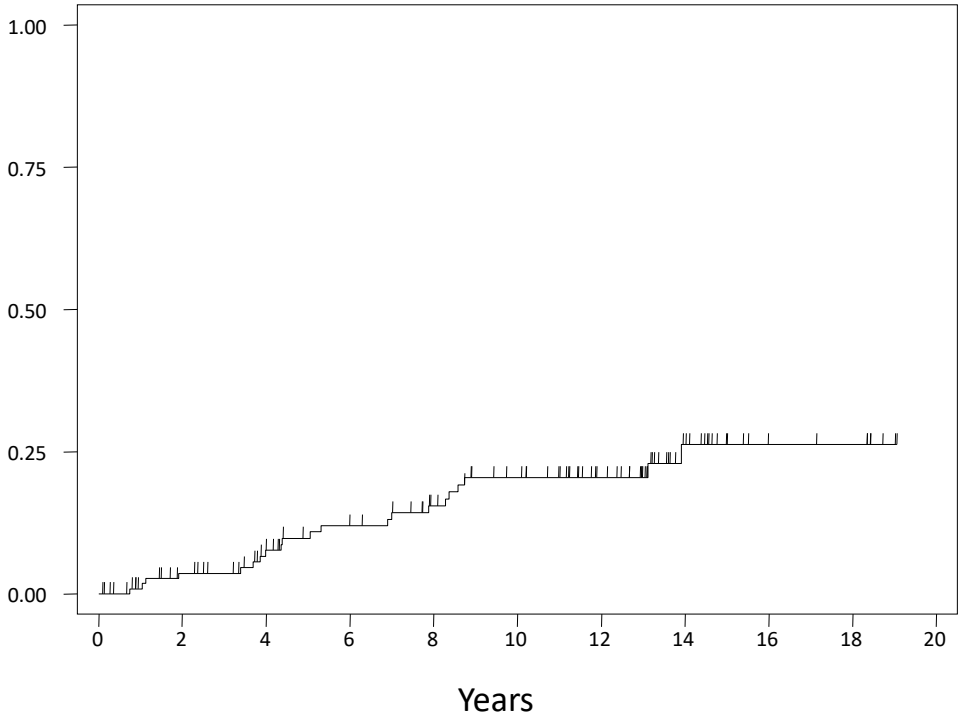


Ama Z.S. Rohatiner et al. JCO 2007;25:2554-2559

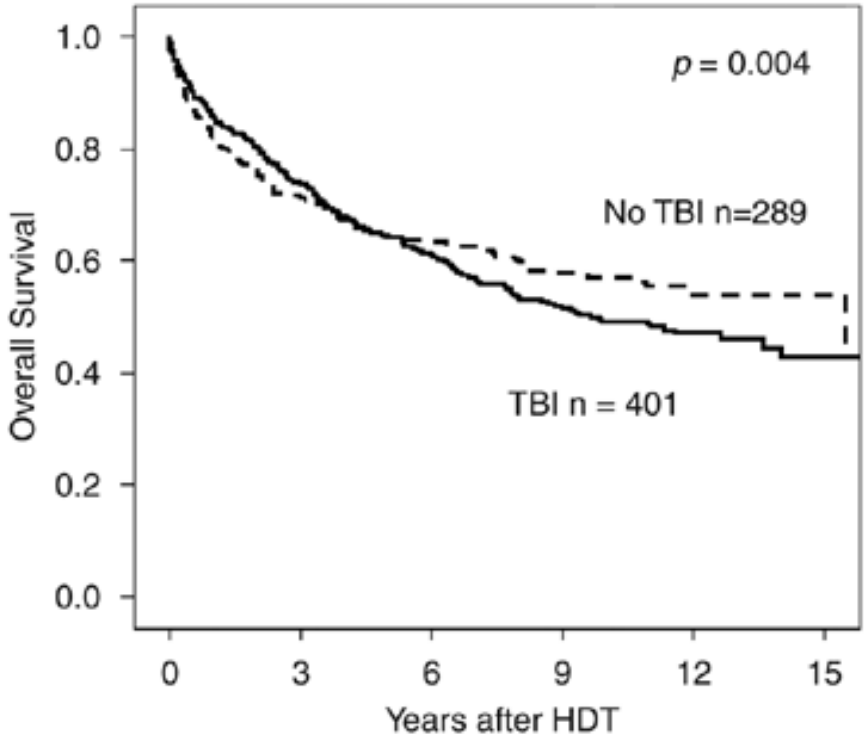
INCIDENCE OF tMDS/tAML

21 patients (17%) have developed tMDS/tAML at median of 5 years (range 0.7-14 years) post HDT

9 patients (10%) in second remission

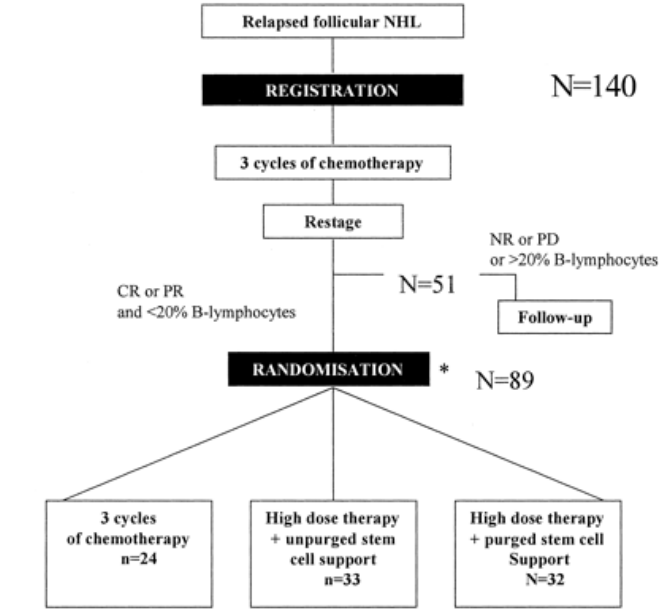


TBI based regimens can be avoided…..

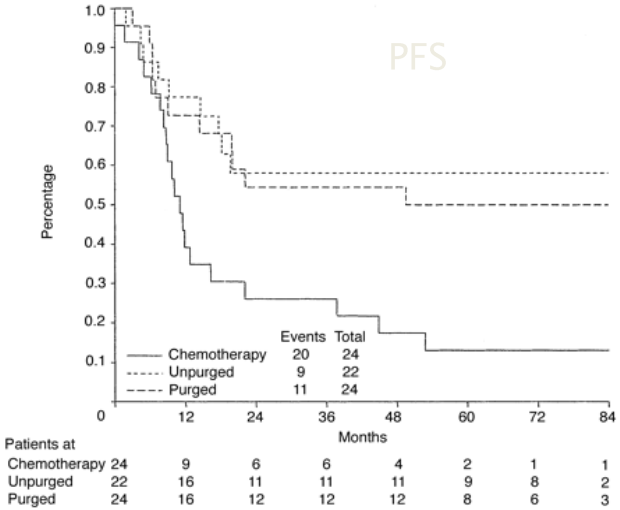


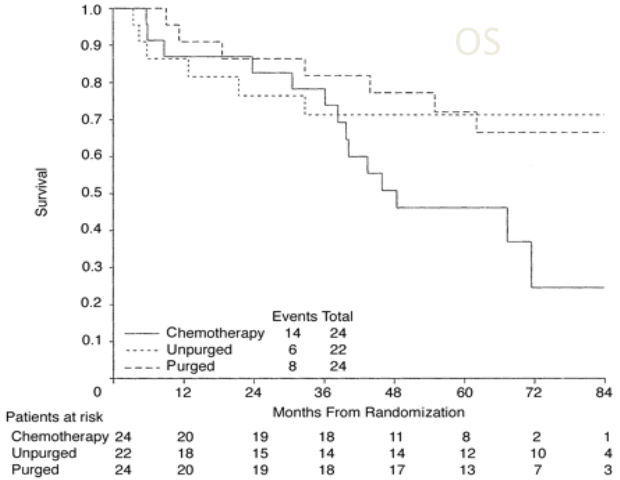
Montoto et al Leukemia 2007

THE CUP TRIAL



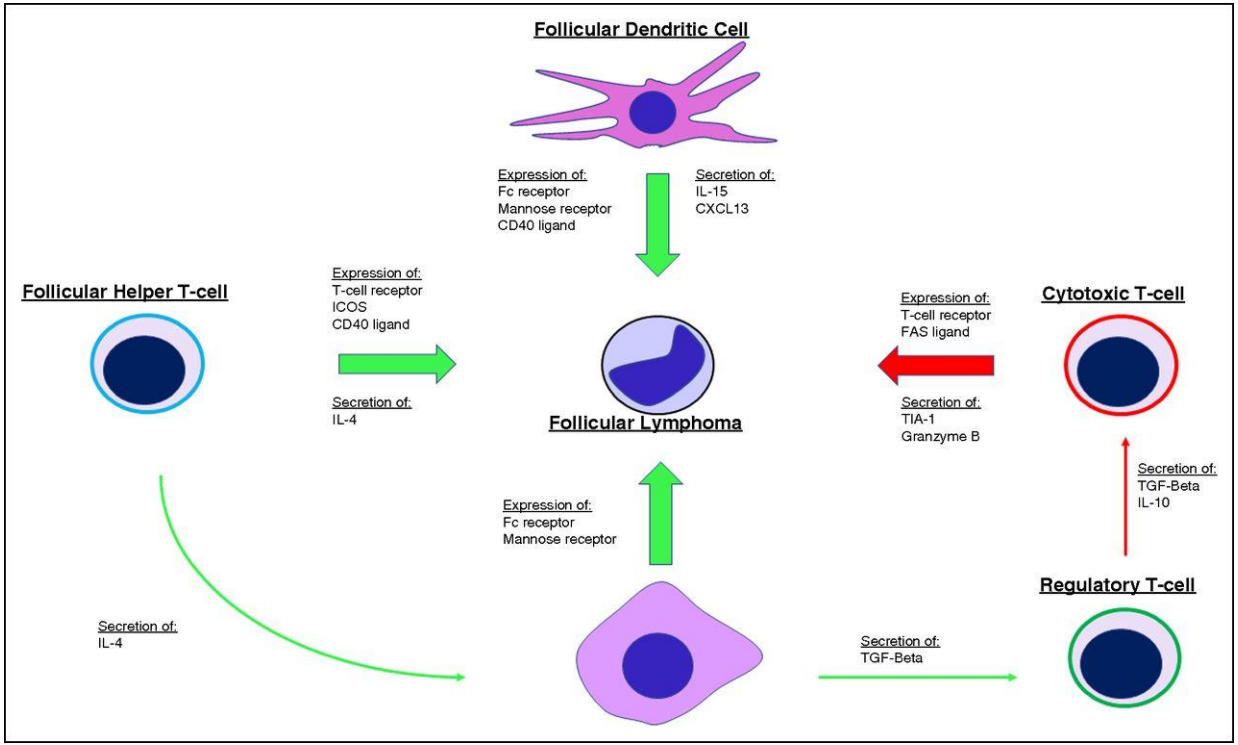
* Prior to randomisation clinicians must decide whether bone marrow or peripheral blood will be used as stem cell support





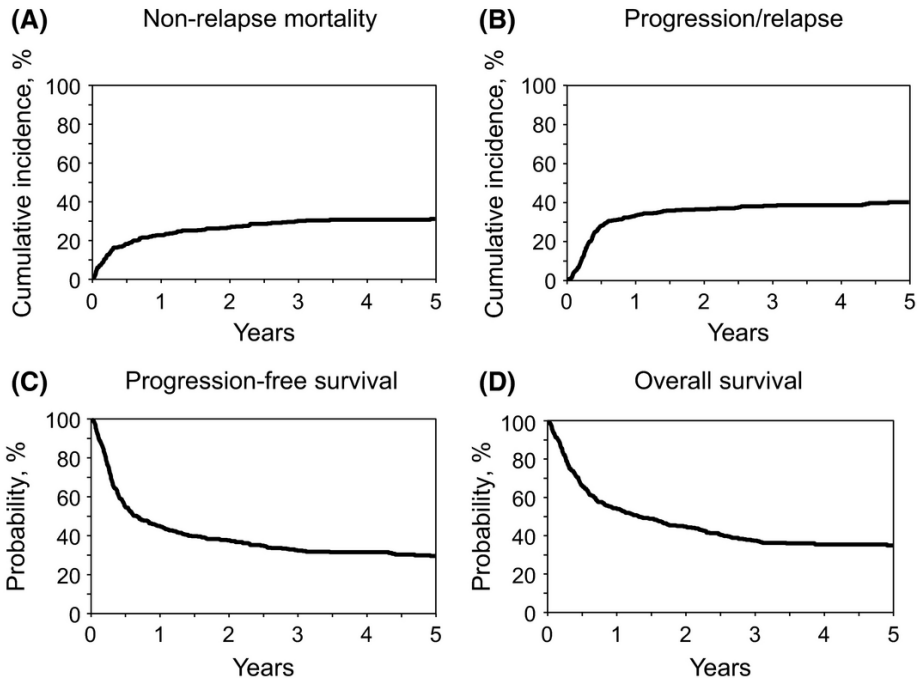
Schouten et al JCO 2003

Way too naïve to think that simple chemotherapy dose-response is way forward



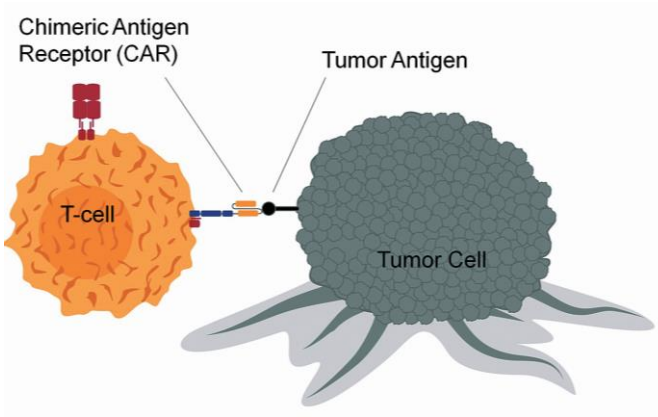
Brad S. Kahl, and David T. Yang Blood 2016;127:2055-2063

Allogeneic transplantation provides durable remission in a **subset** of DLBCL patients relapsing after autologous transplantation.. Fenske et al. BJH 2016

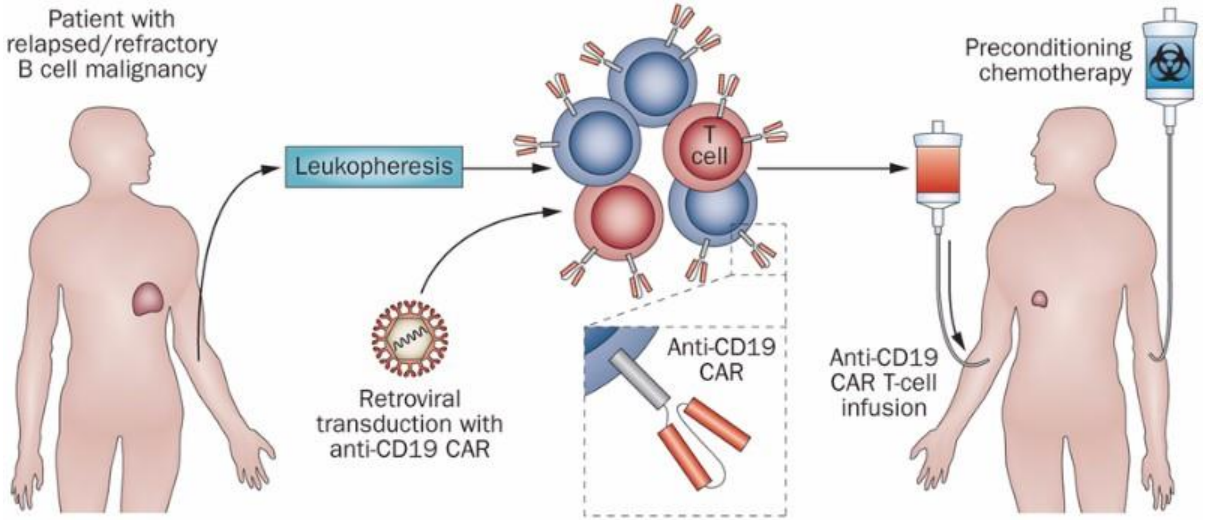


n=503
Median age 51

CAR-T

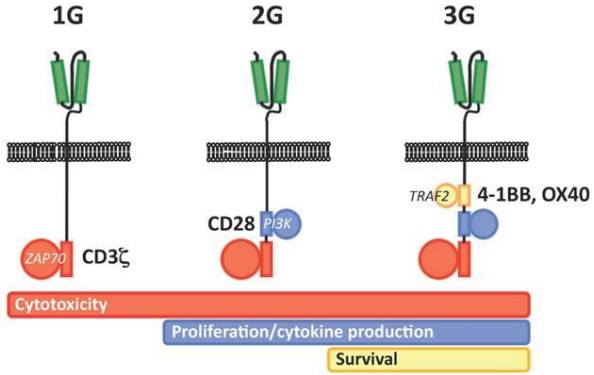

Chimeric Antigen
Receptor (CAR)
Tumor Antigen
T-cell
Tumor Cell

CAR-T cell manufacturing process



Strange and difficult names…

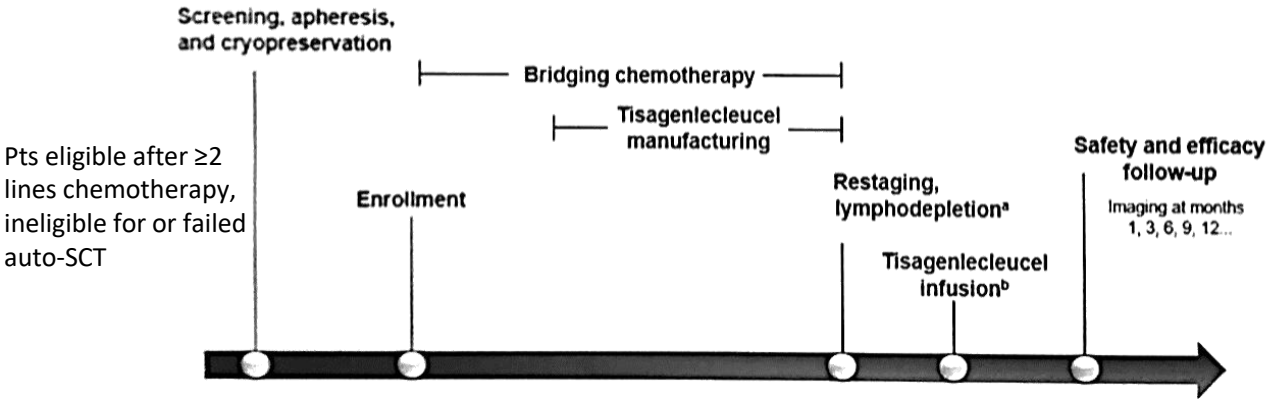
Name	Company	Abstract	Trial	Specifiction
Axibcabtagene Ciloleucel	Gilead	No. S801 Oluwole *et al*	ZUMA-1	CD28 signal
Tisagenlecleucel	Novartis	No. S799 Borchmann *et al*	JULIET	Lentiviral transduction 41BB signal
Lisocabtagene Maraleucel	Juno / Celgene	No. S800 Abramson *et al*	TRANSCEND NHL-001	41BB signal



JULIET: Study design (Novartis)

CD19 4-1BB, first approved CAR-T (child +TYA) B-ALL

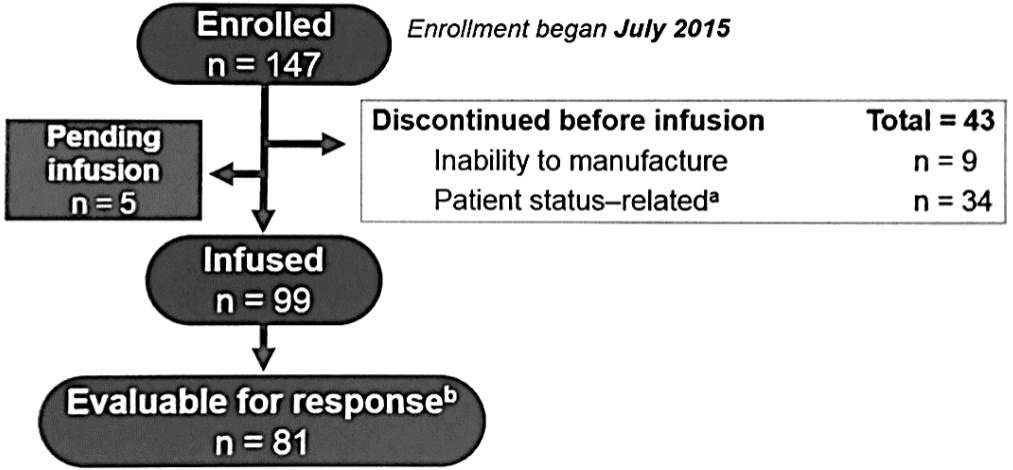
- Single-arm global pivotal trial of tisagenlecleucel in patients with r/r DLBCL (NCT02445248)



A longer than expected period between enrolment and infusion occurred due to manufacturing delays

[a]To be completed 2 to 14 days prior to tisagenlecleucel infusion
[b]Infusion conducted on an in- or outpatient basis at investigator discretion

JULIET: Study status (data cut March 2017)



[a]Death (n=16), physician decision (n=12), patient decision (n=3), adverse event (n2), protocol deviation (n=1)
[b]Patients who had ≥3 months of follow-ups or earlier progression of disease

JULIET: Patient characteristics

Baseline characteristics (N=99)	
Median time from infusion to DCO, months	5.6
Median age, years ≥65 years, %	56 (range, 22–76) 23
ECOG PS 0/1, %	55/45
Stage III or IV disease, %	77
Double/triplet hits in *CMYC*/*BCL2*/*BCL6* genes, %	15
Lymphodepleting chemo prior to infusion, %*	93
Median prior lines antineoplastic therapy, n (range)	3 (1–6) (95% ≥2; 51% ≥3 prior lines therapy)
Bridging therapy, %	90
Prior auto-SCT, %	47
Median dose	3.1 × 10 (range, 0.1–6.0 × 10) CTL019 transduced cells

*Prior to infusion, patients underwent restaging, 93% received lymphodepleting chemotherapy (73% received fludarabine 25 mg/m^2 /cyclophosphamide 250 mg/m^2/day × 3 days and 19% received bendamustine 90 mg/m^2/day × 2 days).

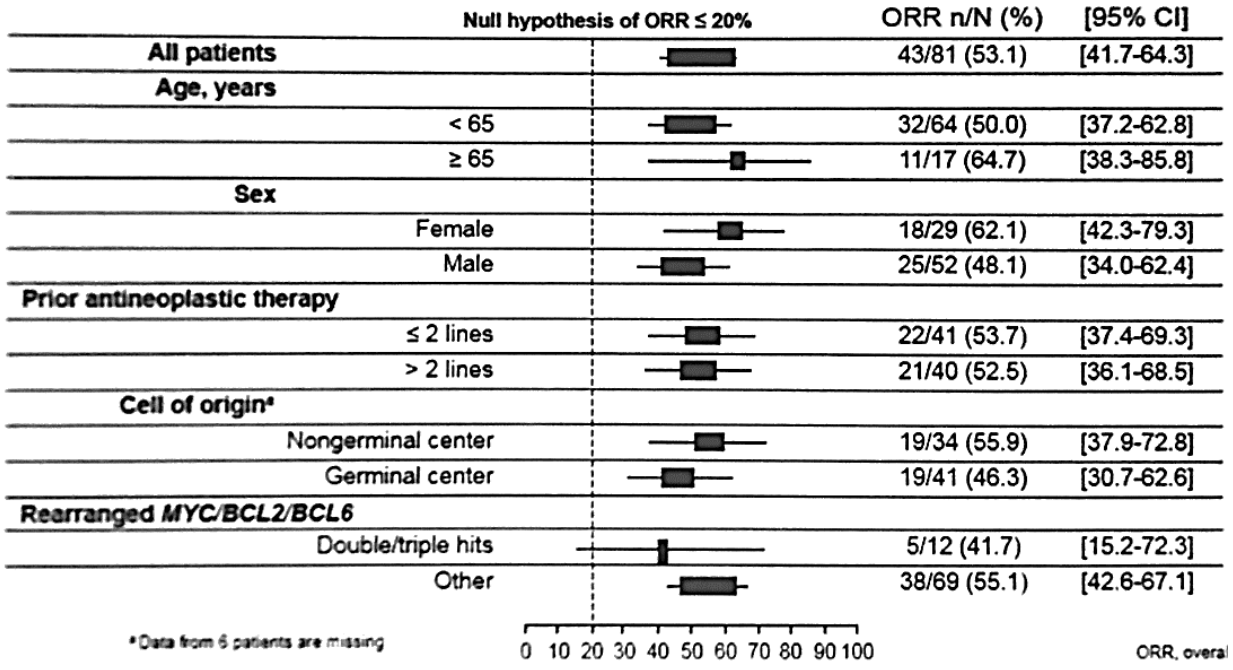
JULIET: Response rates

Response rate, %	Best overall response rate (N=81)	Response at 3 months (n=81)	Response at 6 months (n=46)
ORR (CR + PR)	53*	38	37
CR	40	32	30
PR	14	6	7

**P*<0.0001 (95% CI, 42-64%). Null hypothesis of ORR ≤20%

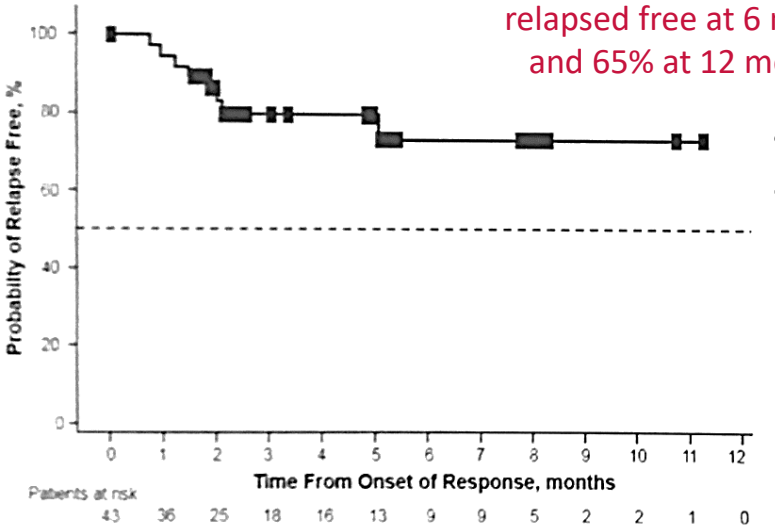
- Durability of responses is shown by the stability between 3 and 6 month response rates
- Response at 3 months is indicative of the long term benefit of this treatment

JULIET: Response rates across subgroups



JULIET: Duration of response

74% of patients were
relapsed free at 6 months
and 65% at 12 months



- **Median DOR and OS not reached**
- Almost all patients in CR at month 3 remained in CR
- No patients proceeded to transplant while in response

JULIET: Safety (N=99)

AESI	All grades, %	Grade 3, %	Grade 4, %
CRS	58	15	8
Neurological events	21	8	4
Prolonged cytopenia	36	15	12
Infections	34	18	2
Febrile neutropenia	13	11	2

Cytokine release syndrome	Pts
Time to onset, median (range) days	3 (1-9)
Duration, median (range) days	7 (2-30)
Hypotension requiring intervention, % High-dose vasopressors	28 6
Intubated, %	8
Anticytokine therapy, % Tocilizumab Corticosteroids	16 15 11

- No deaths due to tisagenlecleucel, CRS or cerebral oedema
- 26 patients (26%) were infused as outpatients
- 20/26 patients (77%) remained outpatient for ≥3 days after infusion

JULIET: Authors' conclusions

CONCLUSIONS

- Tisagenlecleucel produced a high percentage of durable responses in patients with r/r DLBCL
- Analysis confirms durable clinical benefit previously observed in the single-center University of Pennsylvania trial[1]
- JULIET shows feasibility of global distribution of CAR T-cell therapy using cryopreserved apheresis and centralized manufacturing

FUTURE PLANS

- These data served as the basis for global regulatory submissions
- Sponsor prepared for large scale production of tisagenlecleucel for r/r DLBCL in 2018
- Target 22-day manufacturing time has been achieved in the commercial setting

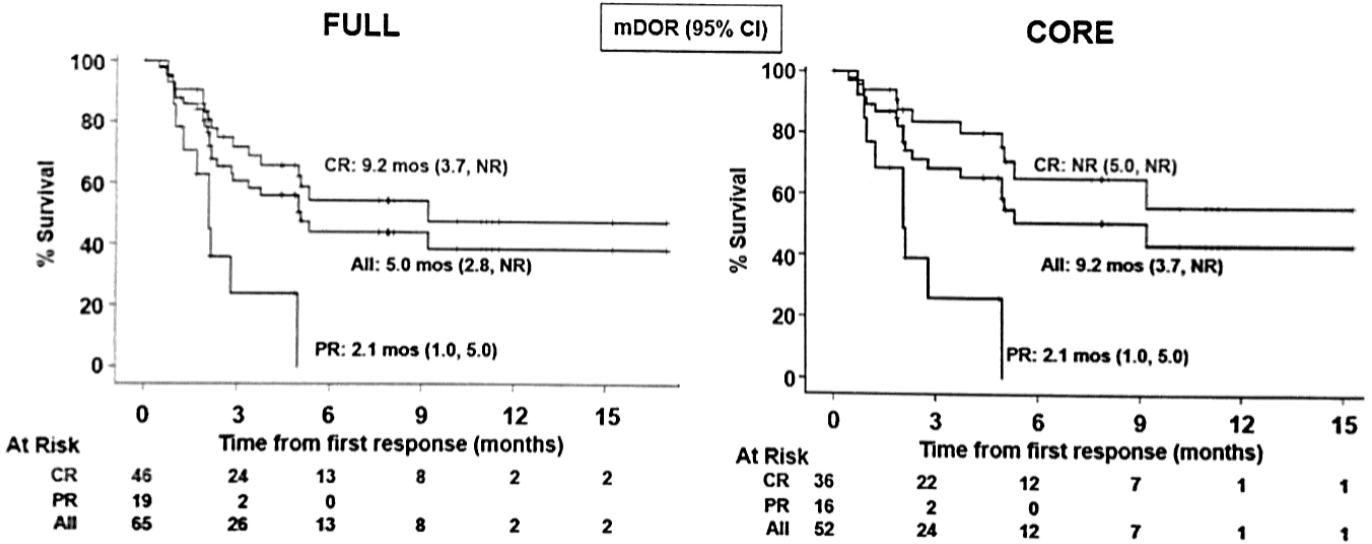
TRANSCEND: Response rates

	FULL	By B-NHL Subtype			
		DLBCL, NOS	tFL	tCLL/MZL	FL3B/PMBCL
BOR, n[a]	88	57	19	10	2
ORR, % (95% CI)	74 (63, 83)	74 (60, 85)	84 (60, 97)	50 (19, 81)	100 (16, 100)
CR, % (95% CI)	52 (41, 63)	51 (37, 64)	63 (38, 84)	30 (7, 65)	100 (16, 100)
≥ 3-mo f/u, n[b]	72	46	15	9	2
3-mo ORR, % (95% CI)	53 (41, 65)	54 (39, 69)	67 (38, 88)	22 (3, 60)	50 (1, 99)
3-mo CR, % (95% CI)	44 (33, 57)	43 (29, 59)	60 (32, 84)	22 (3, 60)	50 (1, 99)
≥ 6-mo f/u, n[c]	54	37	10	6	2
6-mo ORR, % (95% CI)	35 (23, 49)	35 (20, 53)	50 (19, 81)	0 (0, 46)	50 (1, 99)
6-mo CR, % (95% CI)	31 (20, 46)	32 (18, 50)	40 (12, 74)	0 (0, 46)	50 (1, 99)

BOR, best overall response; NOS, not otherwise specified

Homogeneous CORE patient population identified and will move forward in pivotal trial

TRANSCEND: Duration of response



In CORE population, 80% (16/20) of patients with CR at 3 months stay in CR at 6 months; 92% (11/12) of patients in response at 6 months stay in response for a longer-term

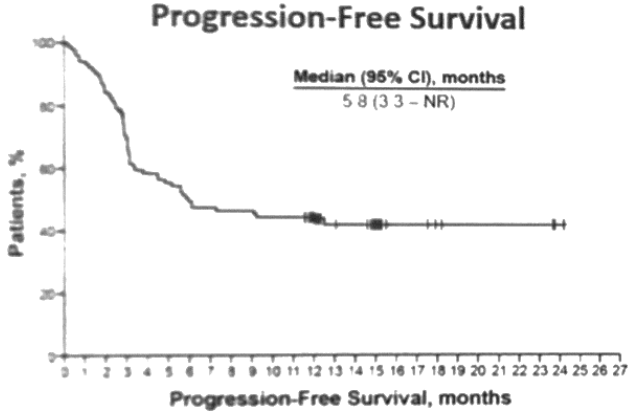
ZUMA-1: Response rates

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, mo	8.7		15.4	
	ORR	**CR**	**ORR**	**CR**
Best objective response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49 – 424) days

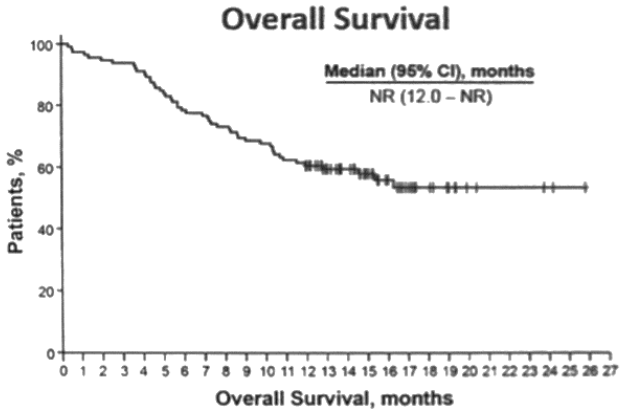
ORR 2-3 lines 94% (CR 65%); ≥4 67% (CR 53%)

ZUMA-1: Progression free and overall survival



Patients at Risk

Landmark	PFS
6-month	49
12-month	44
18-month	41



Patients at Risk

Landmark	OS
6-month	78
12-month	59
18-month	52

Immune effector cell team

- Disease specific team (lymphoma, myeloma, leukaemia, solid malignancies)
- Stem cell lab
- Apheresis team
- Neurology, infectious diseases, ICU, immunology, radiology
- Nursing team
- Pharmacy

Long term problems

- B cell aplasia
  - IVIG replacement
  - Infection monitoring
  - B cell counts
- Cytopenias beyond 28 days
- Complications of prior therapies

Potential

- Second malignancies:
  - Insertional mutagenesis
  - B cell aplasia: Immune dysregulation

Conclusions

- Immunochemotherapy has changed the clinical course of NHL
- Although there is much interest in chemotherapy free options, these are not without toxicity…chemotherapy is not dead
- Dose intensified therapies continue to have a role
- Allogeneic transplantation has only a limited role in NHL
- Much excitement about CAR-T, but minimal data…limited applicability

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WWW.ESTRO.ORG/SCHOOL

Aggressive nodal non Hodgkin lymphoma
The role of radiation therapy: Early Stage

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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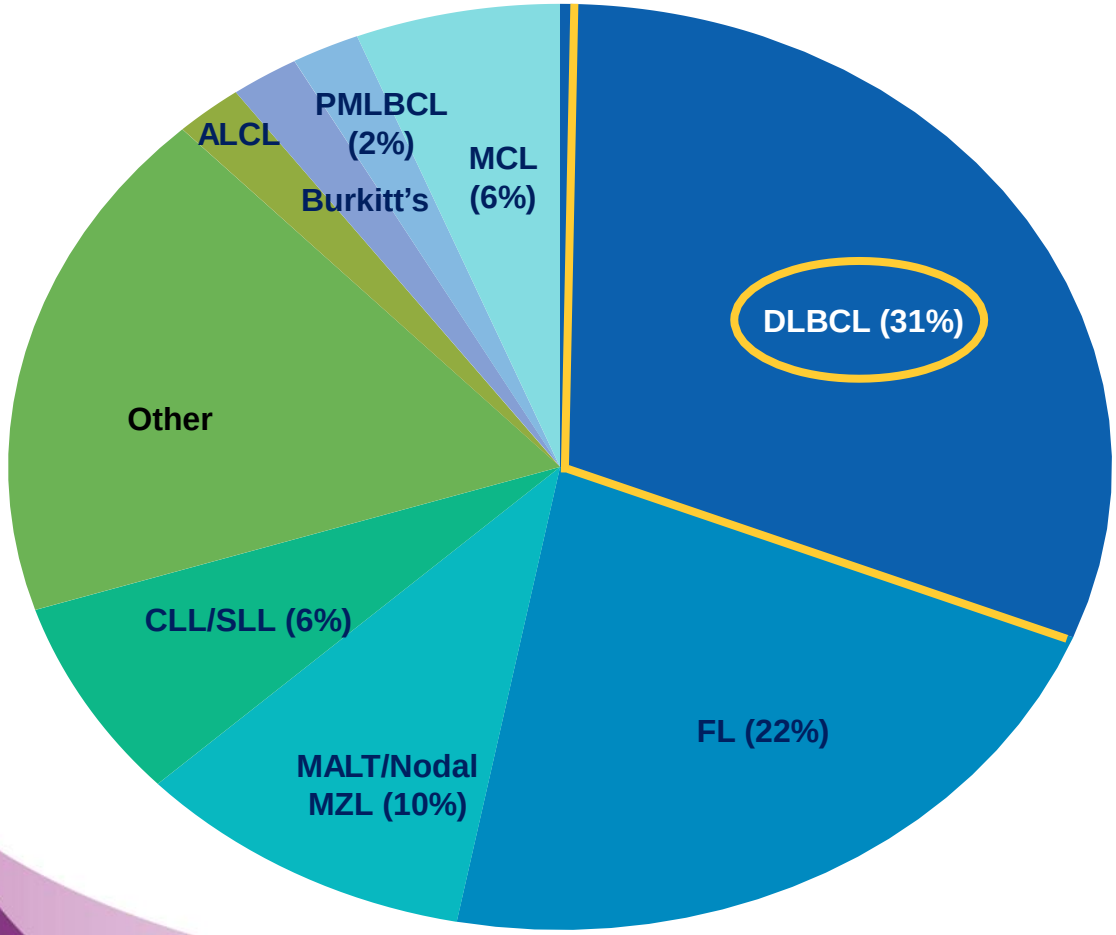
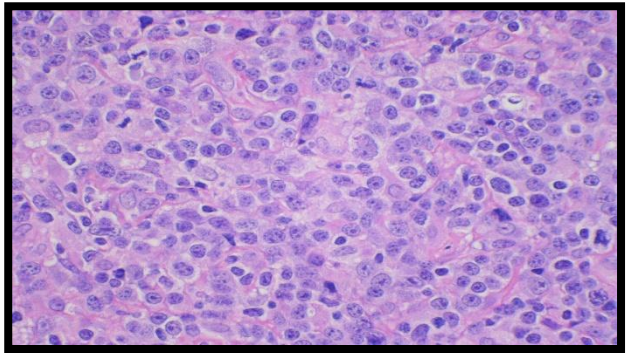
NHL: A Heterogeneous Disease



- 75% of aggressive NHL
- 40%: localized disease
- 40-50%: extranodal disease



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- CMT has been the standard (with CHOP)

- Recent changes:
  - Rituximab improved PFS & OS
  - PET response assessment
  - Omitting RT in HL

- Need to revaluate role of RT in DLBCL

DLBCL is different from HL

- Prognosis:
  - HL is highly curable
  - DLBCL is curable in 60-65% in **population-based** studies
  - **Salvage** is more successful in HL > DLBCL (especially >RCHOP)

- Age: median age 60-65

- Late effects:
  - No evidence of increased risk of **2nd malignancy** in NHL
  - Explanation:
    - 2nd malignancy risk is small > age 45
    - Competing causes of death: disease-related, co-morbidities

The main concern in DLBCL is curing the disease

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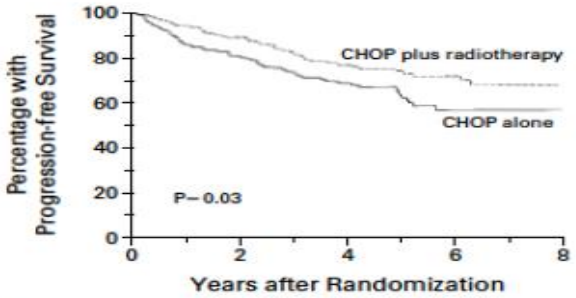
SWOG 8736

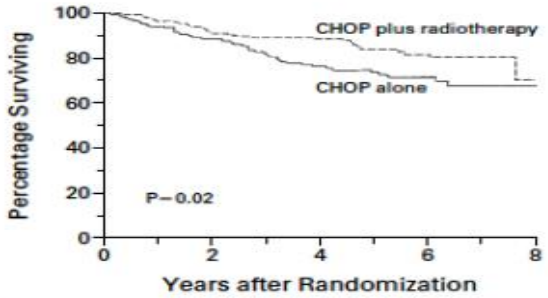
CHOP x 8 vs. CHOP x 3 + IFRT in Stage I/II DLBCL



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

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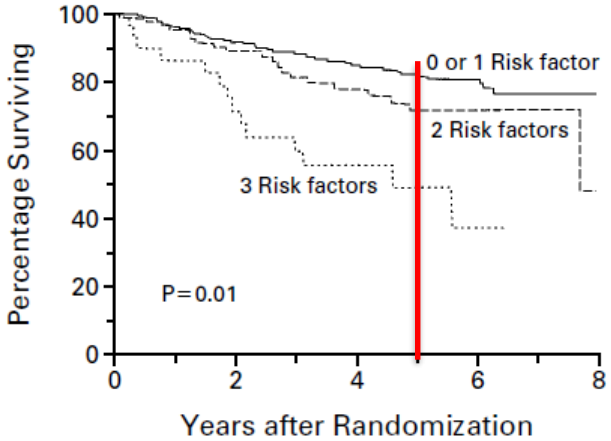
SWOG Contributions: Limited Stage DLBCL

- SWOG 8736
  - Established CHOP x 3+RT as standard of care
  - Introduced the stage-adjusted IPI:

Risk Factors
Age >60
Increased LDH
Stage II or IIE
ECOG Performance Status ≥ 2

Estimated 5-yr OS in S8736 By Risk Factors		
0-1	82%	(95%CI 77-87%)
2	71%	(95%CI 60-83%)
3	48%	(95%CI 22-69%)
4	0%	



(Miller, NEJM 1998)

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v116–v125, 2015
doi:10.1093/annonc/mdv304

Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

H. Tilly[1], M. Gomes da Silva[2], U. Vitolo[3], A. Jack[4], M. Meignan[5], A. Lopez-Guillermo[6], J. Walewski[7], M. André[8], P. W. Johnson[9], M. Pfreundschuh[10] & M. Ladetto[11], on behalf of the ESMO Guidelines Committee*

Table 2. International prognostic index (IPI)

International prognostic index (IPI)			Estimated 3-year overall survival [26–29] (95% CI)
Risk factors	Age >60 years Serum LDH > normal Stage III–IV Performance status 2–4 Extranodal sites >1		
Risk categories	Low	0–1	91 (89–94)
	Low intermediate	2	81 (73–86)
	High intermediate	3	65 (58–73)
	High	4–5	59 (49–69)
Age-adjusted international prognostic index (aaIPI) in patients ≤60 years			
Risk factors	Serum LDH > normal Stage III–IV Performance status 2–4		
Risk categories	Low	0	98 (96–100)
	Low intermediate	1	92 (87–95)
	High intermediate	2	75 (66–82)
	High	3	

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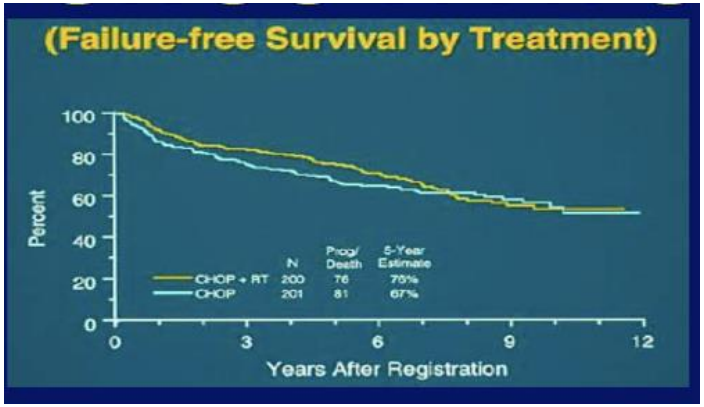
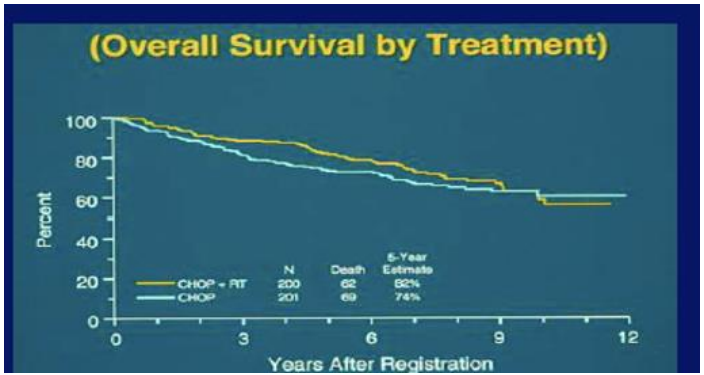
SWOG 8736:Updated Results





- Median f/u = 8.2 yrs
- FFS curves overlap at 7 yrs
- OS curves overlap at 9 years
- Late relapses and lymphoma deats in CMT arm

(Miller et al. ASH, 2001)

SWOG 8736:Updated Results

Cause Of Death S8736	CHOP8 (n = 92)	CHOP3+RT (n = 89)	Total (n = 181)
Relapse NHL	33	30	63
Cardiovascular	15	8	23
Congestive Heart Failure	7	1	8
Myocardial Infarction	3	1	4
Stroke	4	3	7
Other*	1	3	4
Secondary Malignancies	4	10	14
Lung	1	5	6
GI	2	3	5
Breast	1	0	1
Prostate	0	1	1
Melanoma	0	1	1
Infection	8	7	15
Miscellaneous**	10	14	24
Unknown	22	20	42

*AAA Rupture (1); Cardiac Arhythmia (2); PE (1)
**ALS (1); Alzheimers (2); COPD (2); Diabetes (2); Gastric Outlet Obstruction (1); Lewy Body Dementia (1); Liver Failure (1); Malnutrition (2); Parkinsons (2); Renal Failure (2); Respiratory Failure (3); Suicide (1); Surgical Complication (1); Trauma (3)

(Miller et al. ASH, 2001)

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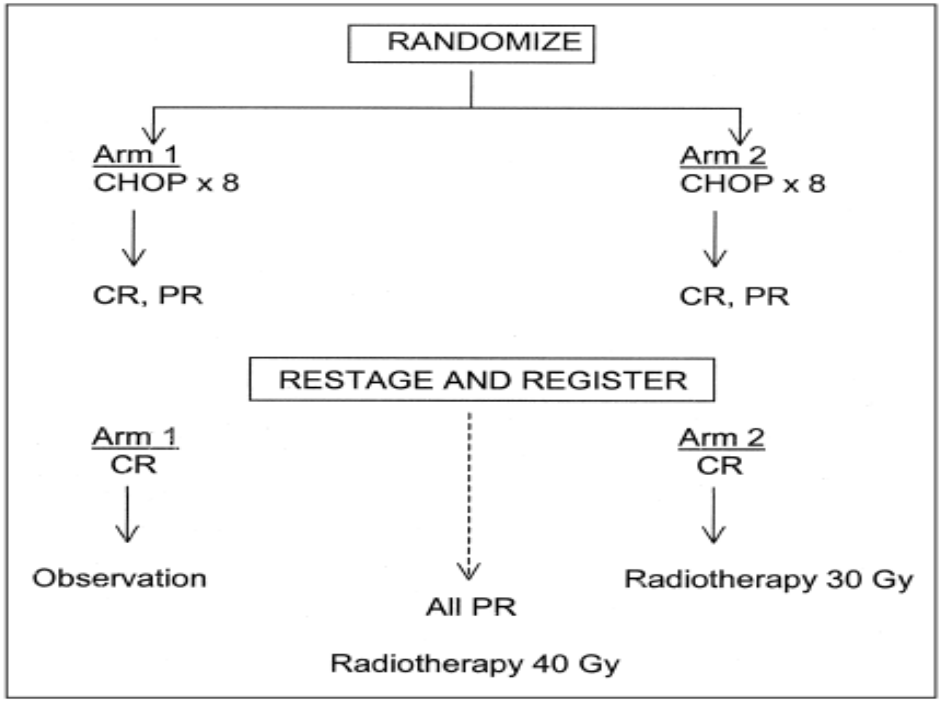
Chemotherapy With or Without Radiotherapy in Limited-Stage Diffuse Aggressive Non-Hodgkin's Lymphoma: Eastern Cooperative Oncology Group Study 1484

Sandra J. Horning, Edie Weller, KyungMann Kim, John D. Earle, Michael J. O'Connell, Thomas M. Habermann, and John H. Glick

JOURNAL OF CLINICAL ONCOLOGY

VOLUME 22 · NUMBER 15 · AUGUST 1 2004



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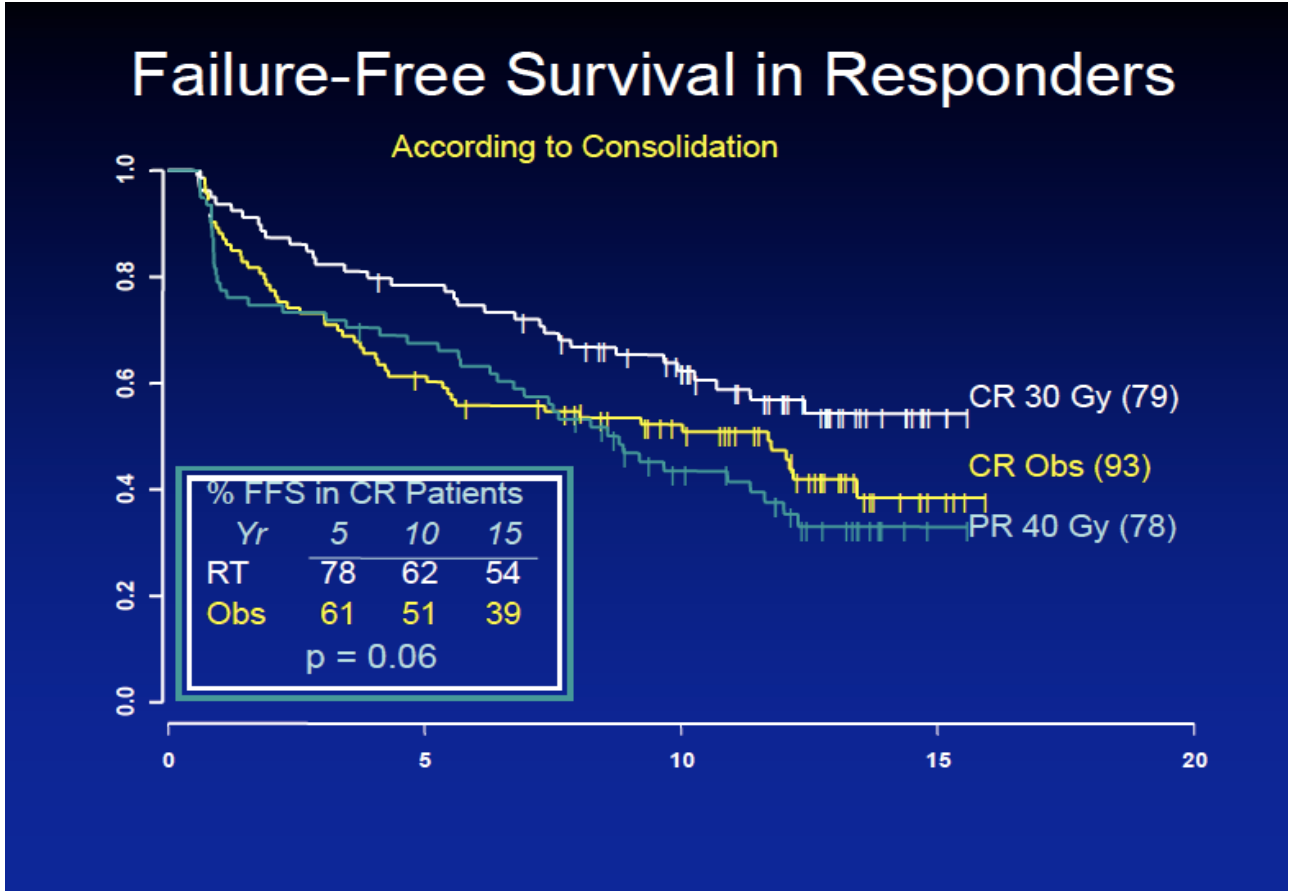
Failure-Free Survival in Responders



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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 < 60, stage I-II, IPI 0

R
647 pts

ACVBP
318

3 x CHOP 21
+ IFRT (40 Gy)
329

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The NEW ENGLAND JOURNAL of MEDICINE

ACVBP versus CHOP plus Radiotherapy for Localized Aggressive Lymphoma

N Engl J Med 2005;352:1197-205.

ACVBP vs CHOP + RT in Stage I/II aggressive Lymphoma

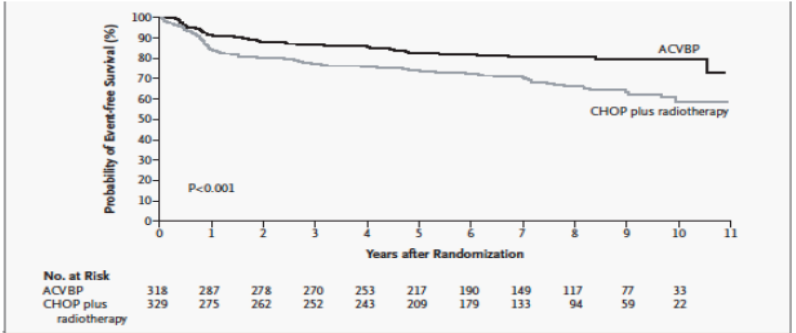

Figure 1. Event-free Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

Overall Survival

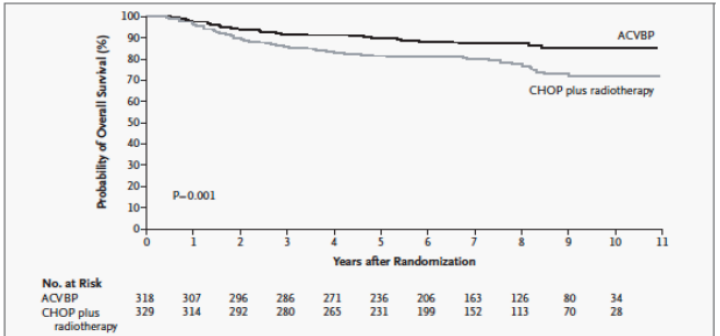

Figure 3. Overall Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

11% acute severe toxicity

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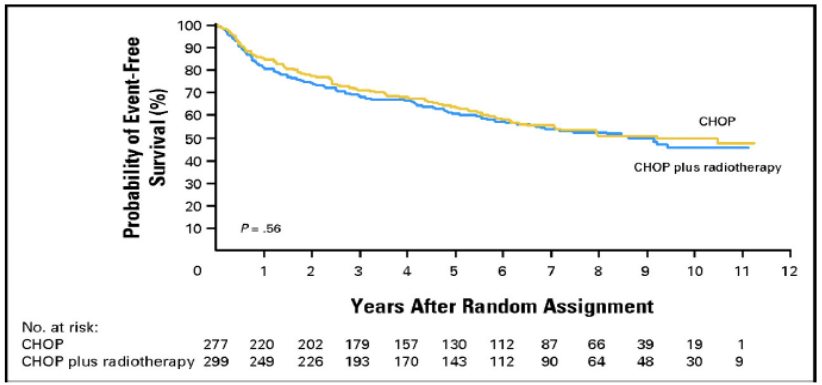
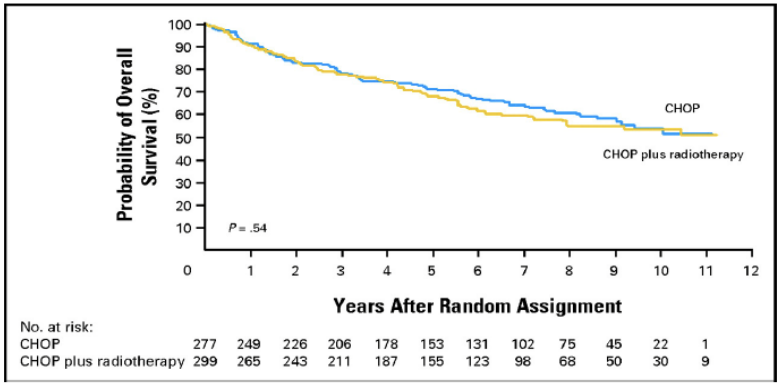
CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

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



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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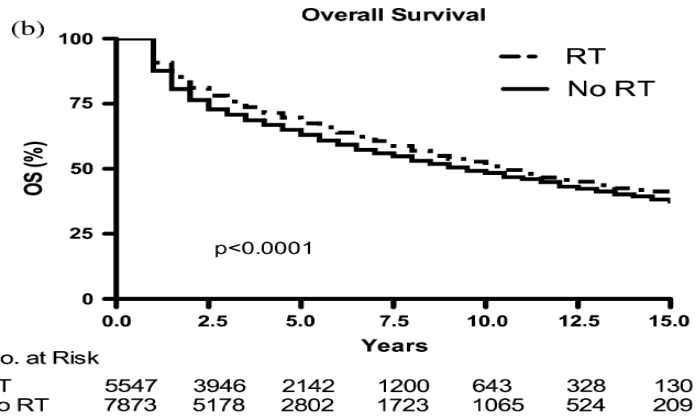
- Combined modality therapy has been the standard of care for most patients with localized diffuse large B-cell lymphoma (DLBCL), particularly those with limited stage low risk disease or bulky sites.

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	$p^{\dagger}$
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



- In the modern era the selection of appropriate patients for combined modality therapy has become increasingly complex over the last decade with the transition to:

➢ **immunochemotherapy (Rituximab);**

➢ **emergence of functional imaging for response evaluation.**

Is there (still) a role for Radiation Therapy in DLCL?

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VOLUME 34 · NUMBER 13 · MAY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Re-Examining the Role of Radiation Therapy for Diffuse Large B-Cell Lymphoma in the Modern Era

Andrea K. Ng, *Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
Bouthaina Shbib Dabaja, *The University of Texas MD Anderson Cancer Center, Houston, TX*
Richard T. Hoppe, *Stanford University School of Medicine, Stanford, CA*
Timothy Illidge, *University of Manchester, Manchester Academic Health Sciences Centre, The Christie National Health Service Foundation Trust, Manchester, United Kingdom*
Joachim Yahalom, *Memorial Sloan Kettering Cancer Center, New York, NY*

International Journal of Radiation Oncology biology • physics

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Radiation Therapy for Diffuse Large B-Cell Lymphoma: Indications, Outcomes, and Controversies

By Chelsea C. Pinnix, MD, PhD, *Associate Editor*

Received Dec 10, 2015. Accepted for publication Dec 15, 2015

Will Rituximab markedly change the results of CHOP+RT?

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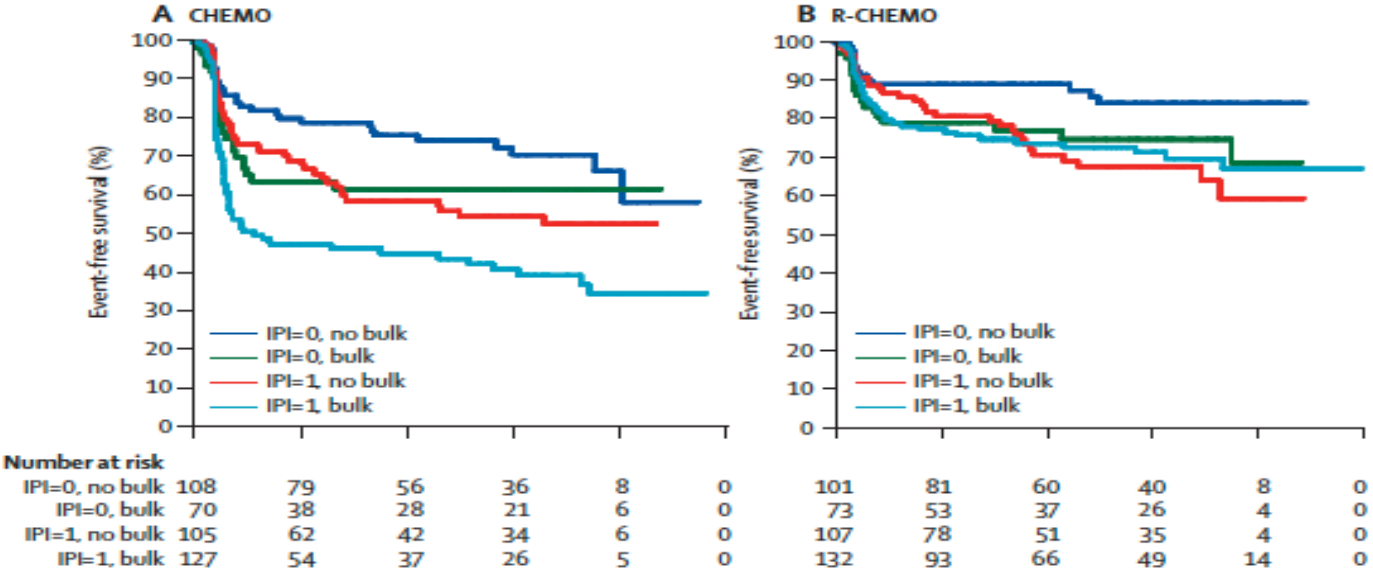
CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group

*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**



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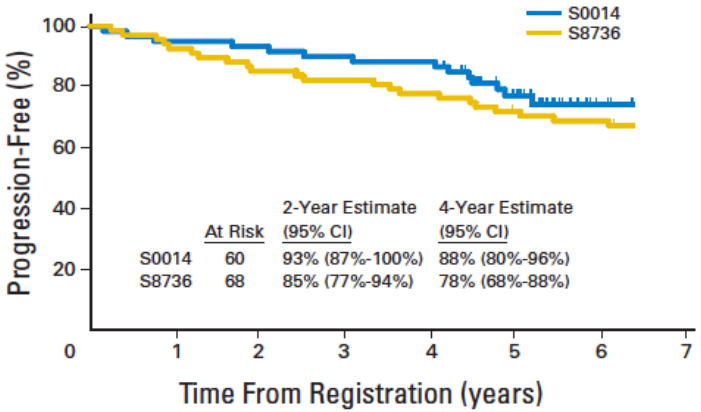
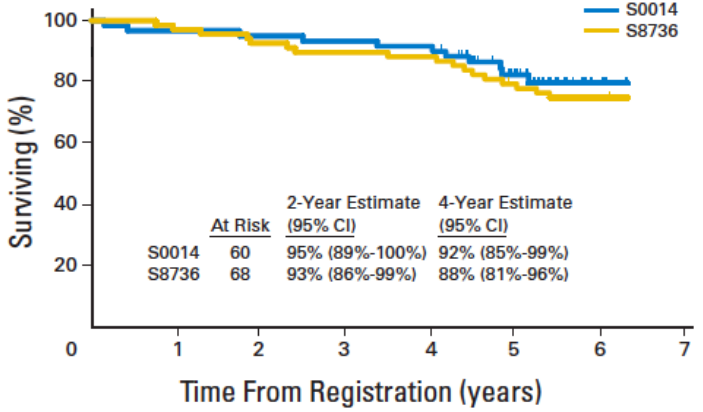
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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 GC in 75% of cases (demonstrated lower benefit of R)

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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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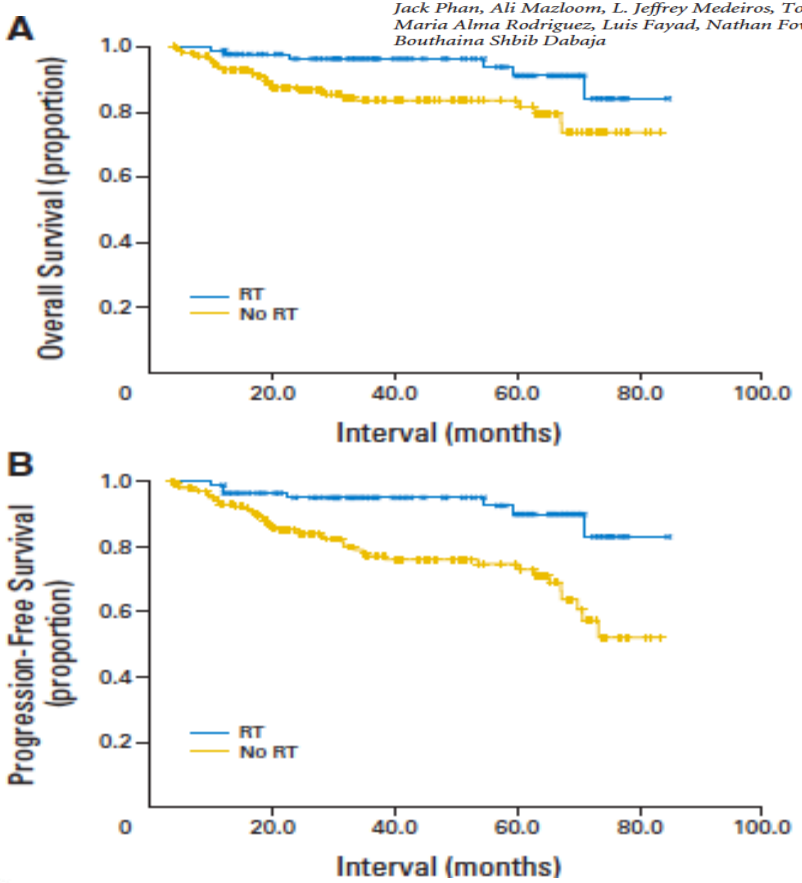

Table 5. Multivariate Analysis of Overall and Progression-Free Survival for All Patients

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

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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

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

Lancet Oncol 2008; 9: 435–44

- Linear prognostic effect of tumor diameter on OS, which is decreased (but not eliminated) by the addition of rituximab

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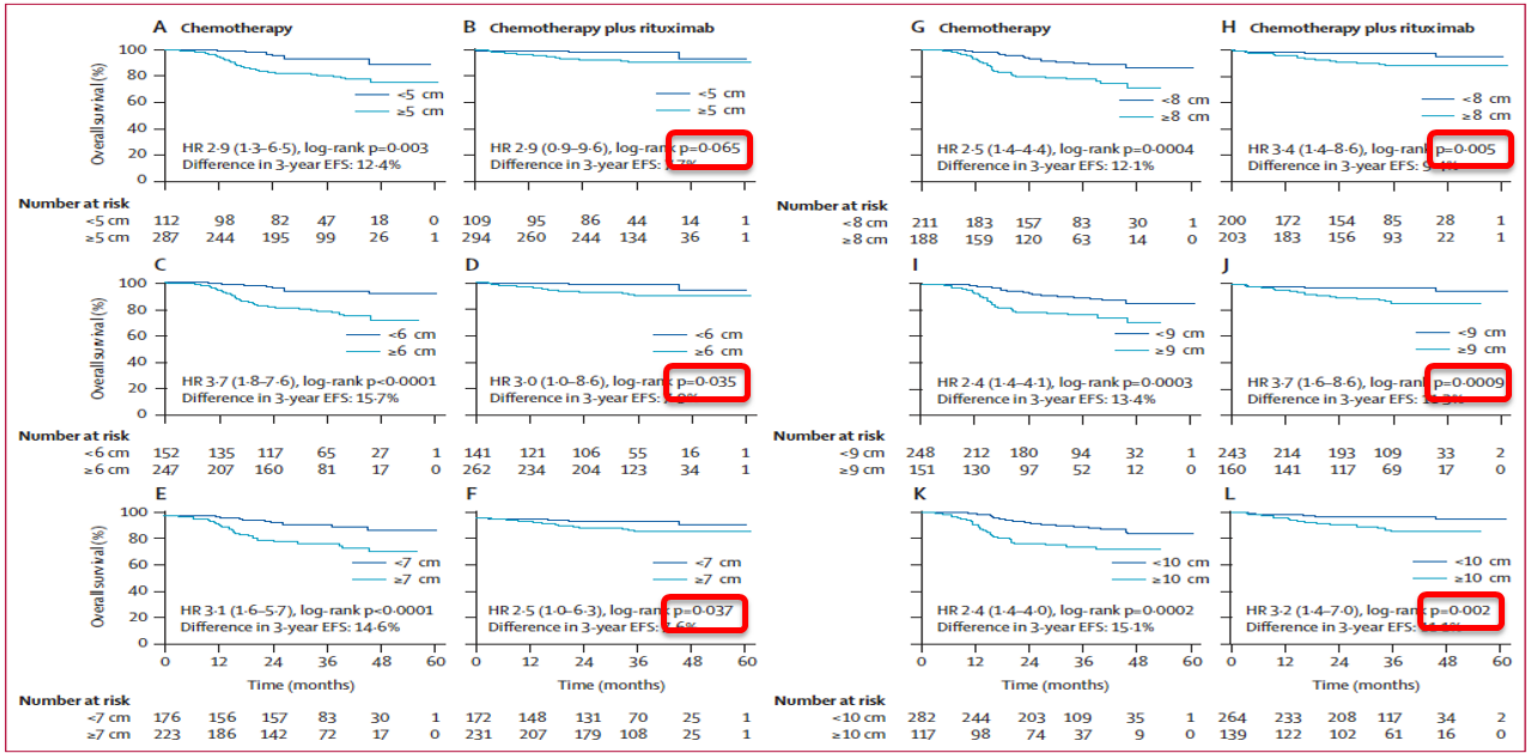
Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study



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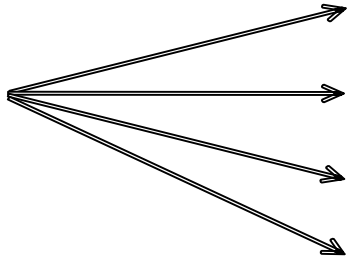
Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma (n=1,222)

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 (RICOVER-noRT)

(Held et al, JCO 2014 Pfreundschuh. Lancet Oncol, 2008)

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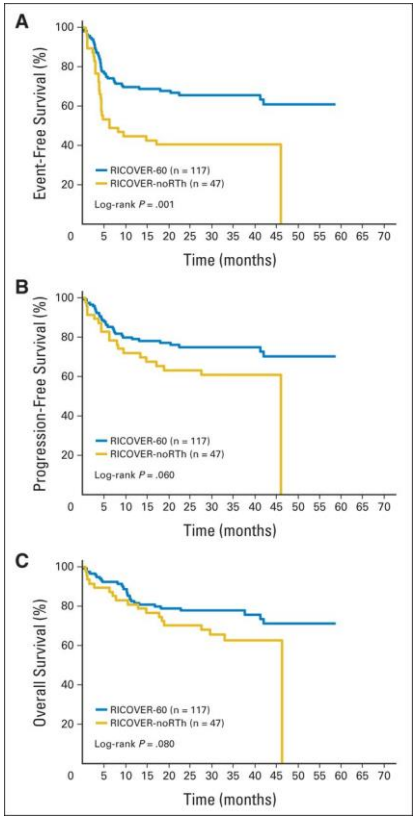
Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Intent-To-Treat Analysis:

EFS

PFS

OS

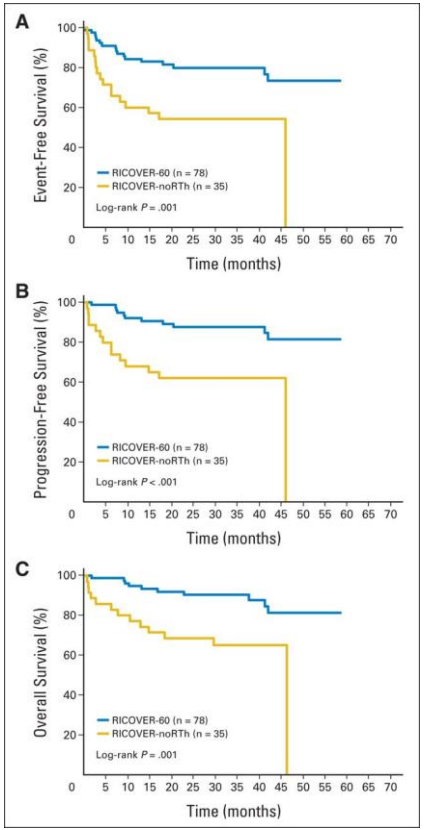


Per-Protocol Analysis:

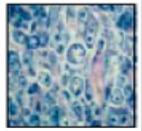
EFS

PFS

OS

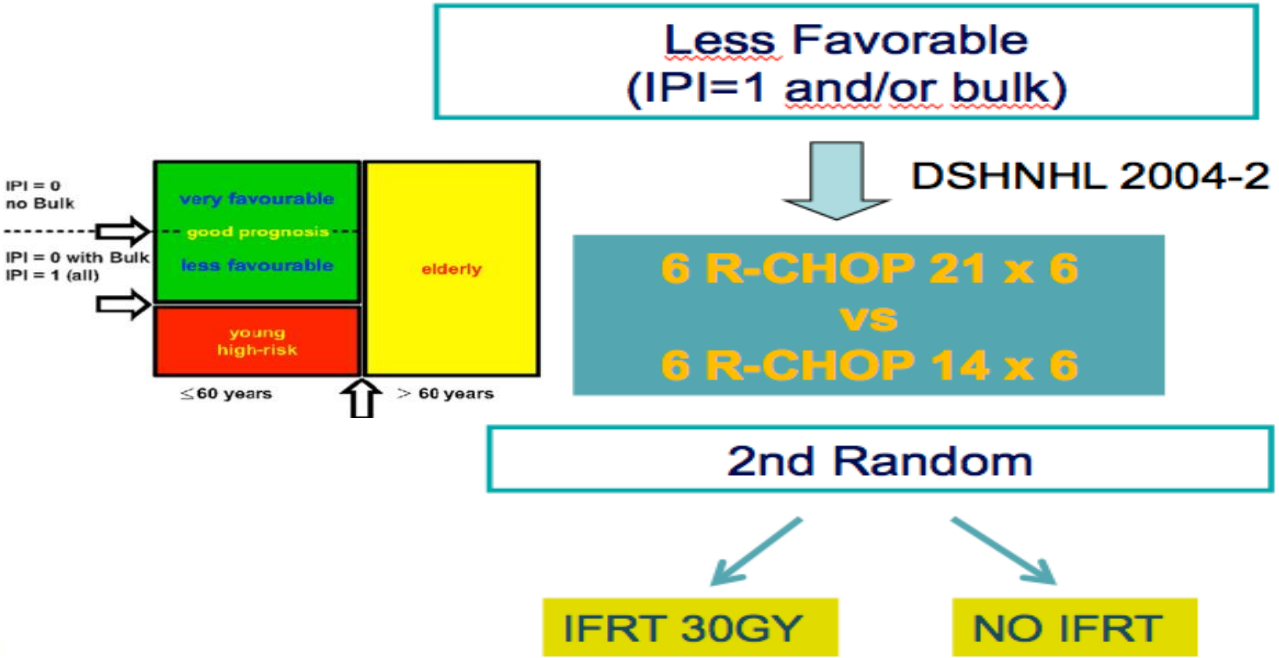


(Held et al, JCO 2014)



GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP*

* (supported by Deutsche Krebshilfe)



Patients with extranodal and/or bulky disease (>7.5 cm) were eligible for the RT randomization

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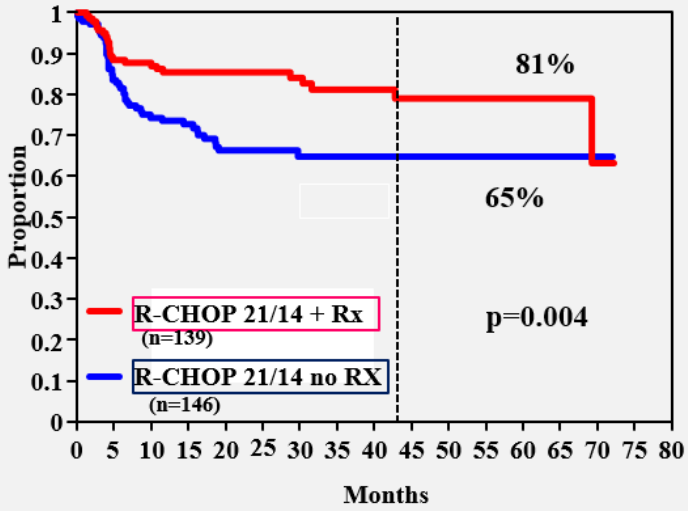
UNFOLDER phase 3 study: preliminary results

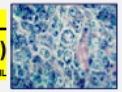
Patients 18- 60 years, aaIPI=0 with bulk or aaIPI=1, ITT (n=443)

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*

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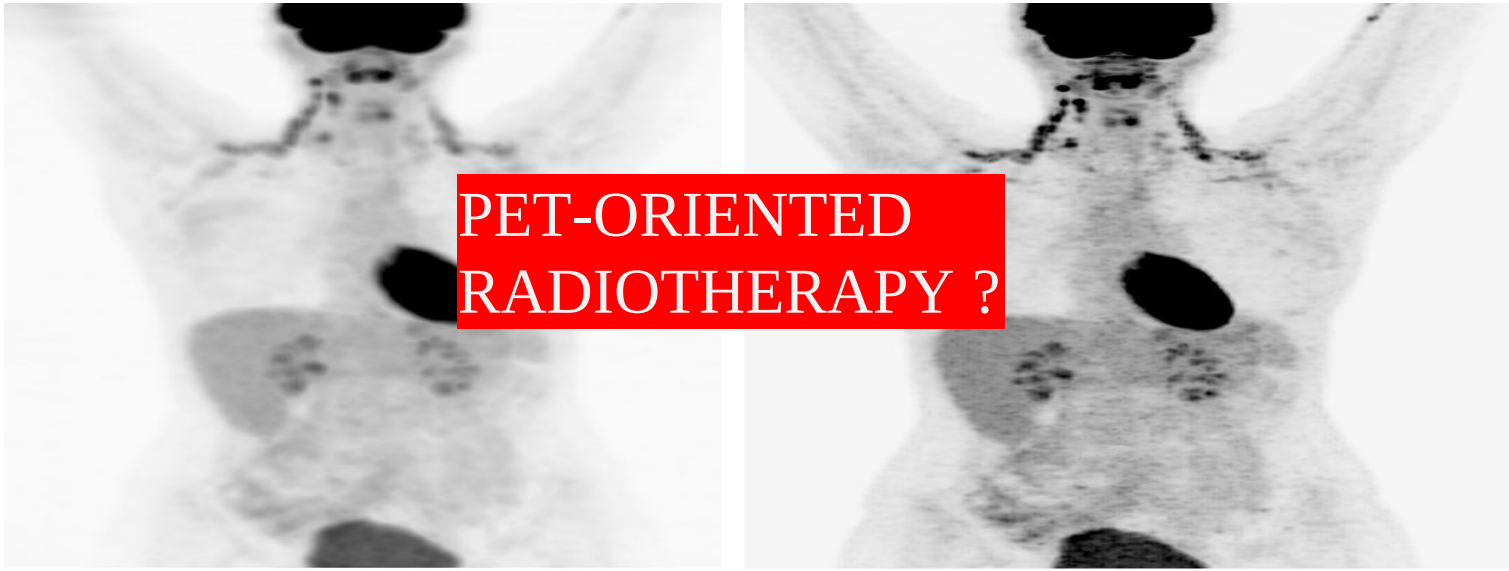
To irradiate or not to irradiate ?



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PET-oriented RT: BCCA experience

N=50 ; stage I-II ; no B symptoms; mass < 10 cm

Median FU 17 months

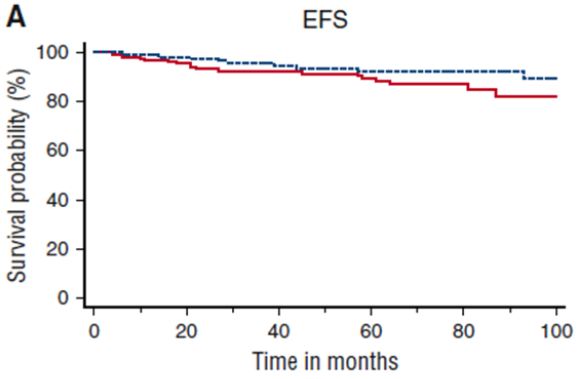
R-CHOP 21 x 3 → PET

	N		Terapia	Recidive	2yFFP	*p*
PET neg →	37	→	CHOP x 1	1	97%	
						.09
PET pos →	13	→	IFRT	3	75%	

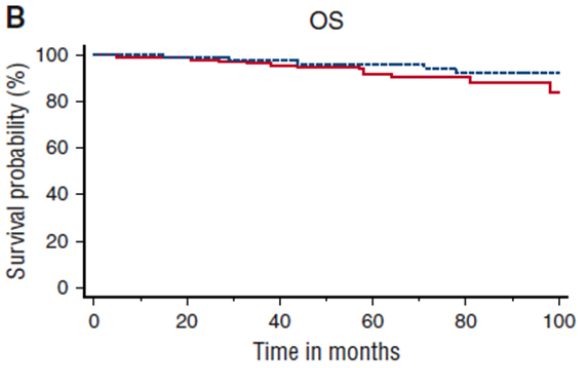
(Sehn, ASH 2007)

R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma

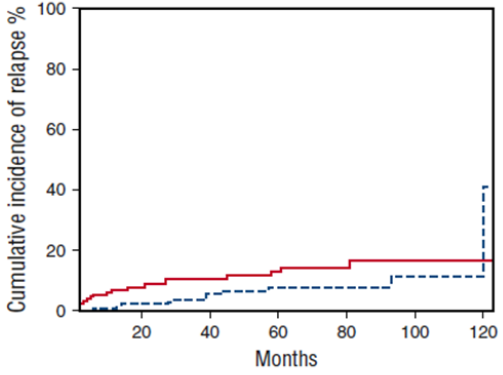
R-CHOP alone (159 pts) vs. R-CHOP + 40 Gy IFRT (160 pts)



89% in R-CHOP arm vs.
92% in R-CHOP + RT arm
(p 0.18)



92% in R-CHOP arm vs.
96% in R-CHOP + RT arm
(p not significant)



Median time to relapse was 21 months, with no difference between the 2 arms

R-CHOP alone is not inferior to R-CHOP followed by RT in patients with nonbulky limited-stage DLBCL

(Lamy et al., *Blood*, Aug 2018)

- Patients with residual fluorodeoxyglucose-avid disease after four cycles of R-CHOP were recommended RT regardless of randomization

- These patients achieved similarly favorable outcome to those with a PET CR after R-CHOP with or without RT, suggesting a role for RT in patients who achieve only a PR to chemotherapy

R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma

blood

- Issues:
- 300'sh
- Outcome is not better than the 0014 SWOG with 3 RCHOP RT
- giving more chemo to older > 60 of age
- 40 Gy of radiation
- IFRT
- Old news!, we want to see same outcome with less toxicity

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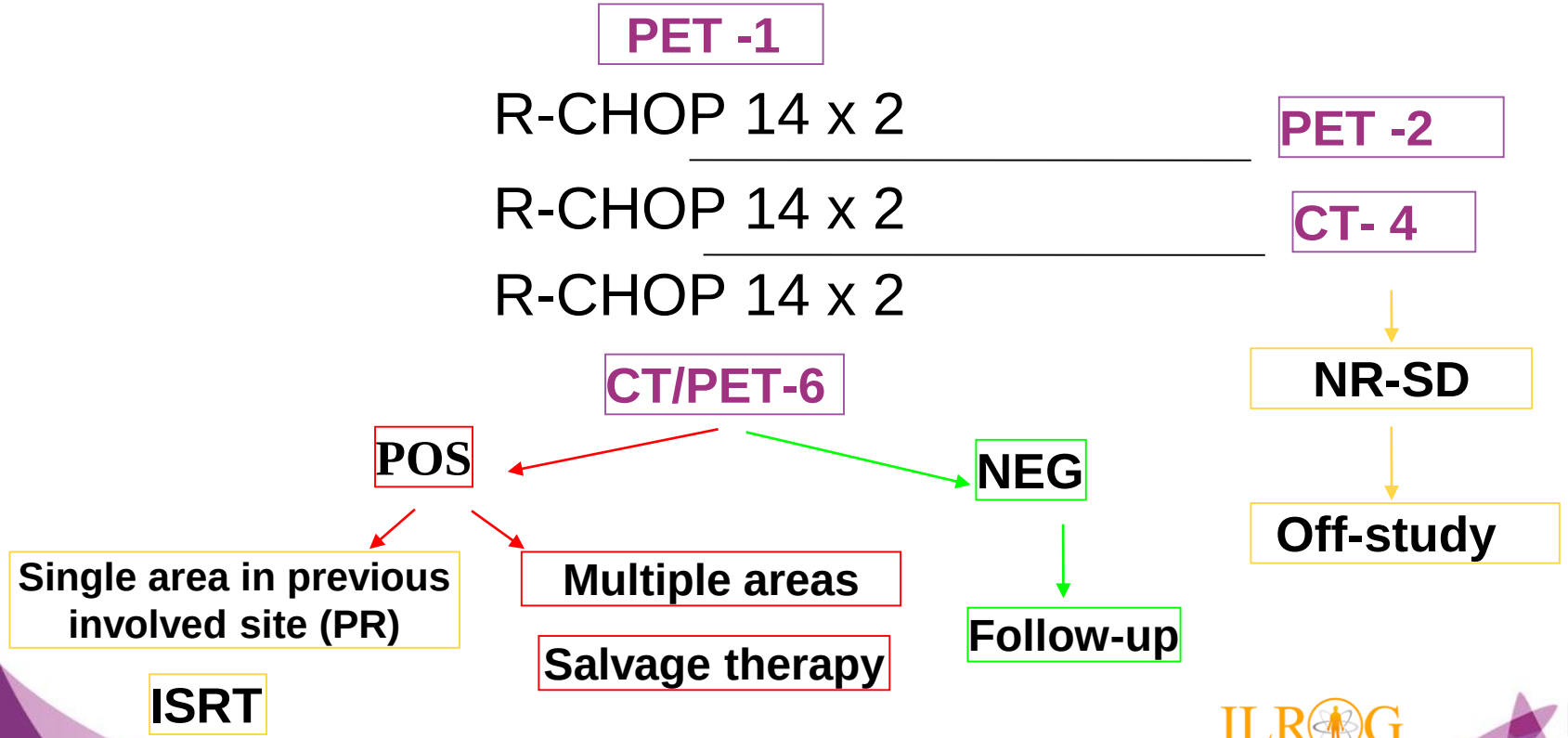
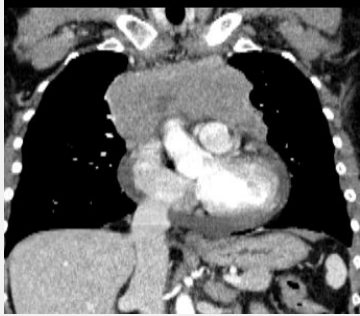
DLCL 10 IPI = 0 bulk, 1 and/or bulk (7.5 cm) (less favourable according MInT)



IELSG 37: trial design



PMBCL diagnosis
basal PET-CT 1

Standard therapy
R-Chemo

*RCHOP 14-21; R-V/MACOP-B
DA-EPOCH-R; R-ACVBP;
R-CHO(E)P like

PET-CT 2
Central review

5-6 wks after R-Chemo

Positive not randomised pts will be followed for response, PFS and OS analysis of the chosen salvage strategy .

Positive

Negative

Random 1:1

8 wks after R-Chemo

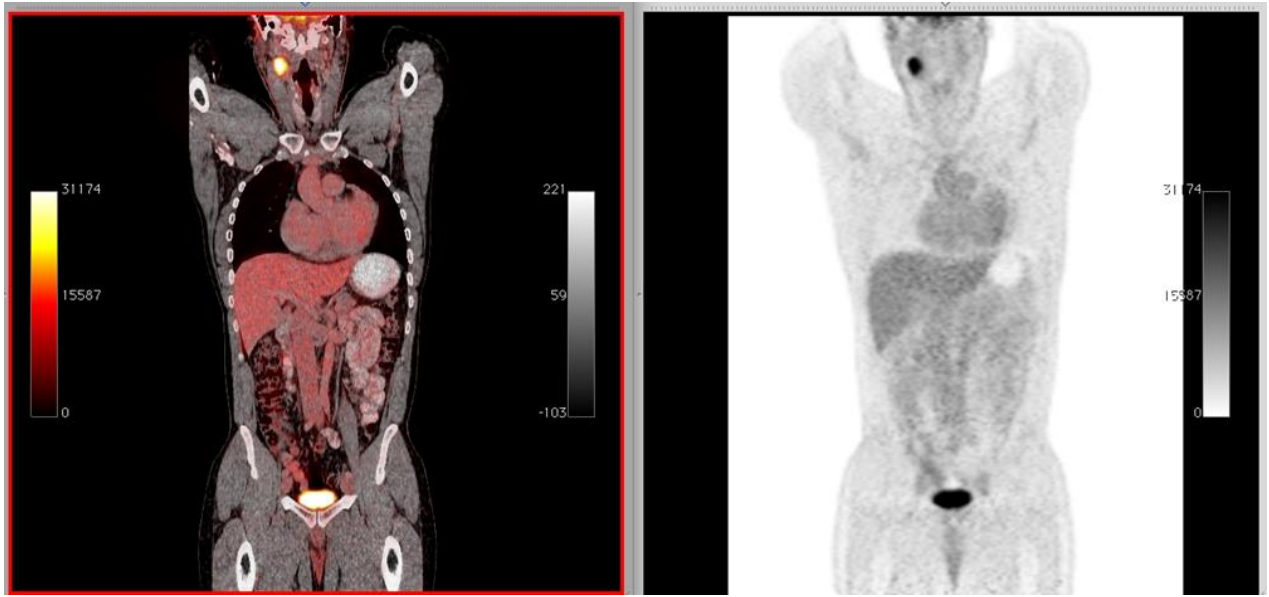
376 pts to randomize

Mediastinal RT
30 Gy

Observation

INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

Combined modality OR chemotherapy alone in early stage DLCL



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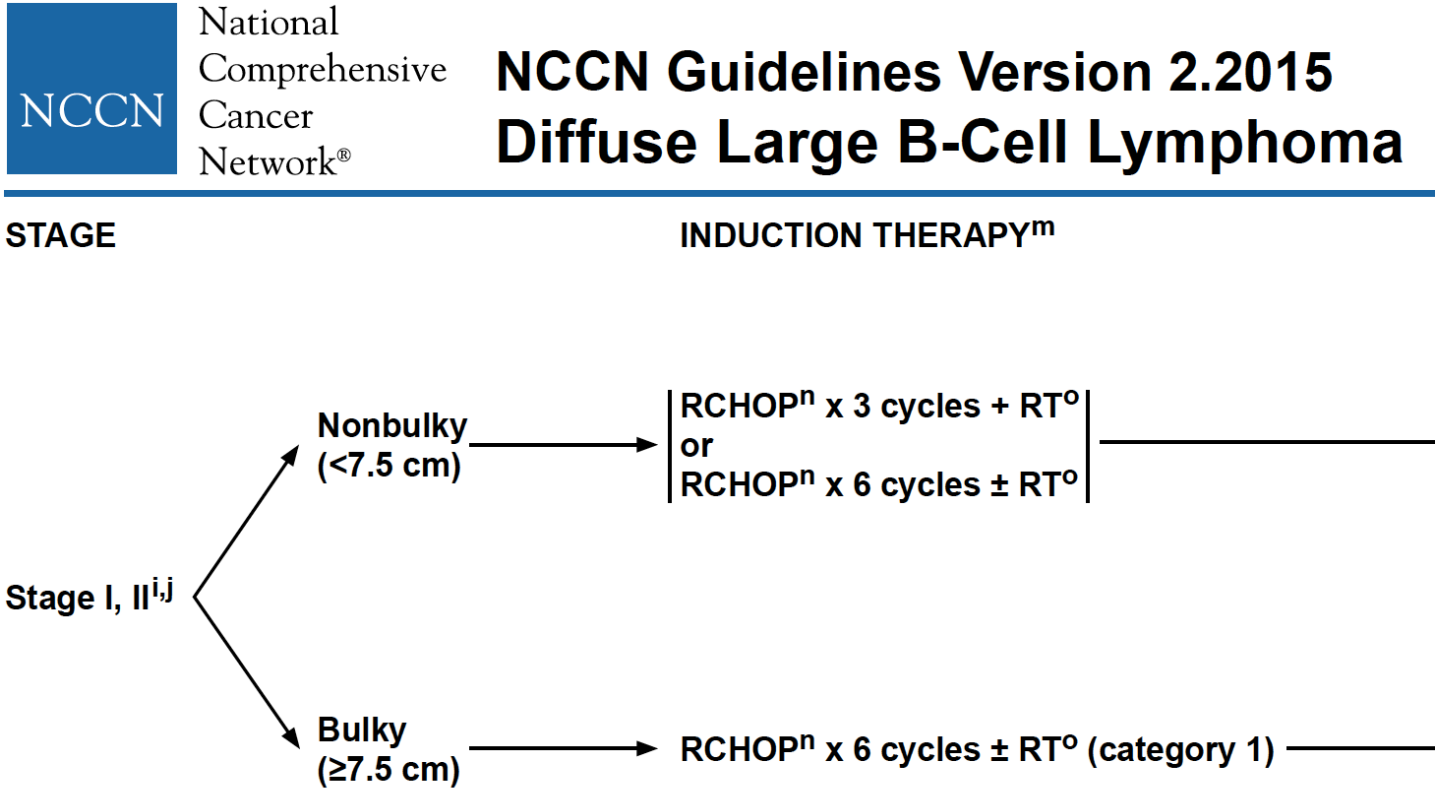
Which is the current Treatment Strategy?



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Radiation Therapy After R-CHOP for Diffuse Large B-Cell Lymphoma: The Gain Remains

Joachim Yahalom, *Memorial Sloan-Kettering Cancer Center, New York, NY*

- 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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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.61.7654

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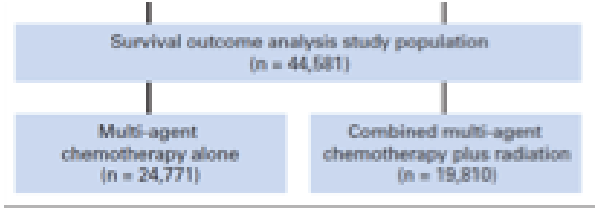
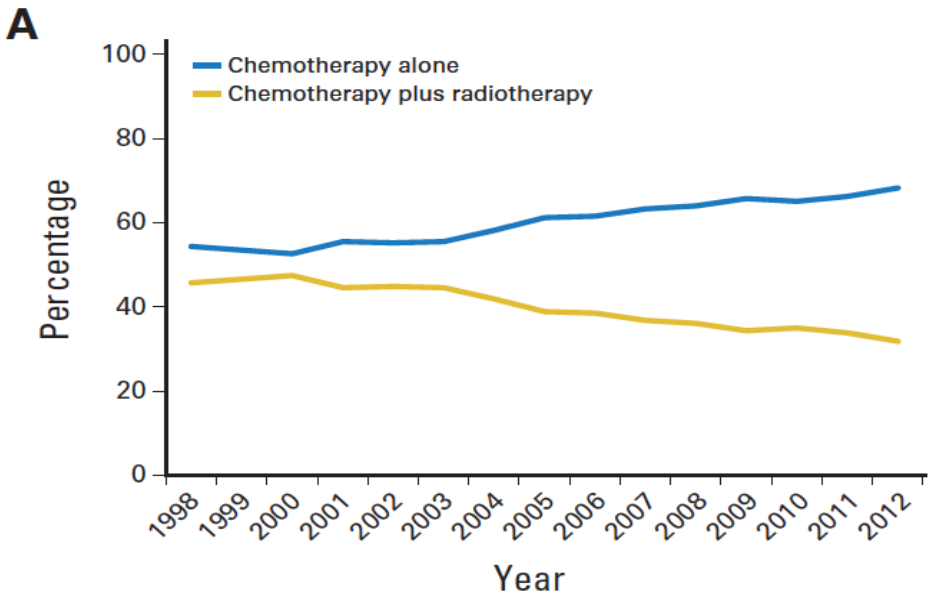
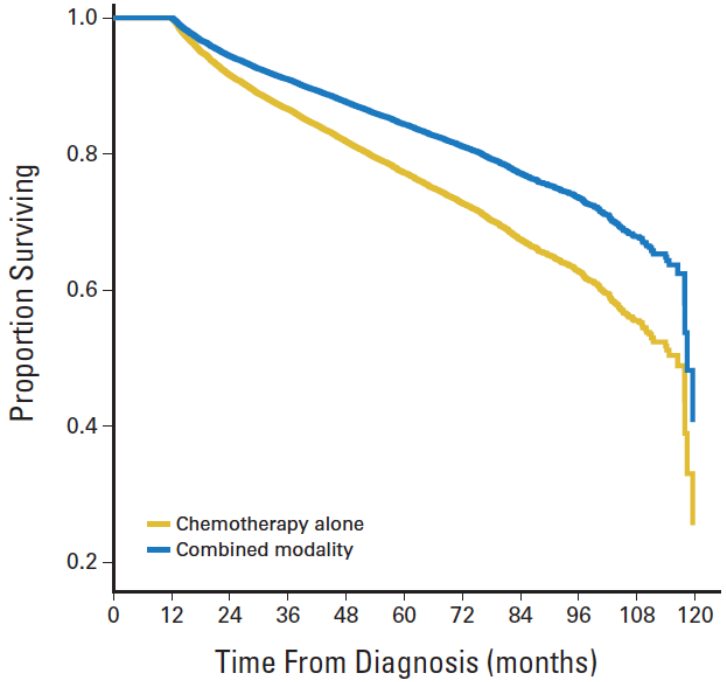


Treatment Selection and Survival Outcomes in Early-Stage Diffuse Large B-Cell Lymphoma: Do We Still Need Consolidative Radiotherapy?

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

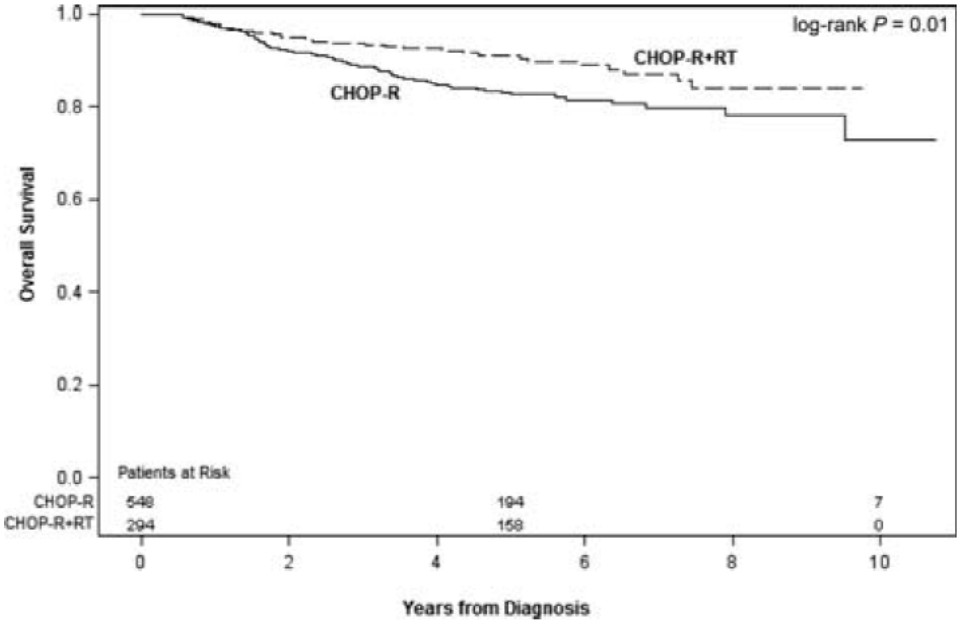




Radiation for Diffuse Large B-Cell Lymphoma in the Rituximab Era: Analysis of the National Comprehensive Cancer Network Lymphoma Outcomes Project

TABLE 2. Causes of Death

Coded Cause of Death	Treatment Group		
	All	R-CHOP	R-CHOP+RT
All deaths, n (%)	119	88 (73.9)	31 (26.0)
Missing, n (%)	3 (2.5)	2 (2.3)	1 (3.2)
Unknown, n (%)	22 (18.5)	17 (19.3)	5 (16.1)
Other, n (%)	18 (15.1)	14 (15.9)	4 (12.9)
Progressive disease, n (%)	66 (55.5)	49 (55.7)	17 (54.8)
Excessive toxicity, n (%)	3 (2.5)	2 (2.3)	1 (3.2)
Secondary malignancy, n (%)	6 (5.0)	3 (3.4)	3 (9.7)
Accidental death, n (%)	1 (0.8)	1 (0.8)	0



(Dabaja B. et al Cancer 2014;121:1031-1039)

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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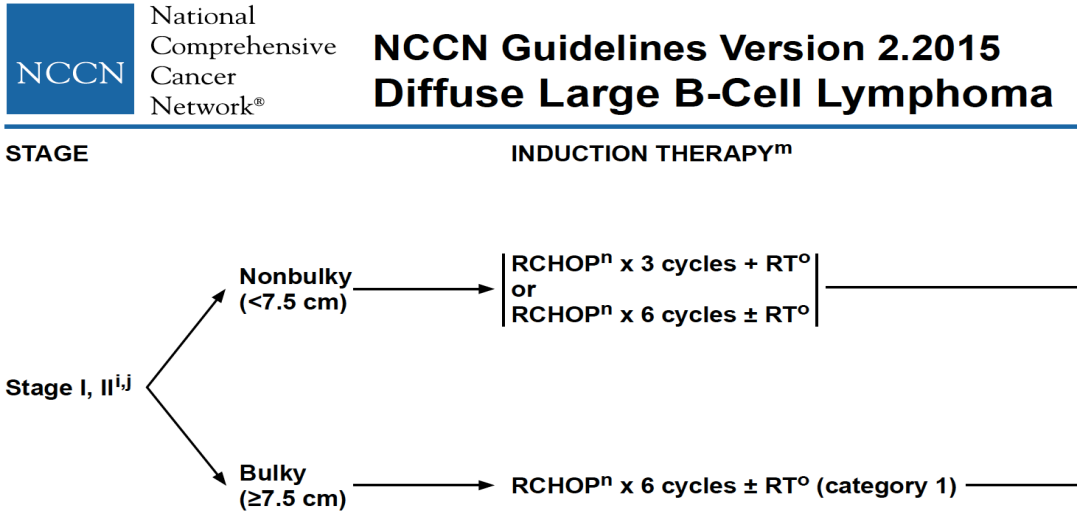
MODERN, BETTER TARGETED, SAFER, AND LOWER-DOSAGE, CONSOLIDATIVE RT

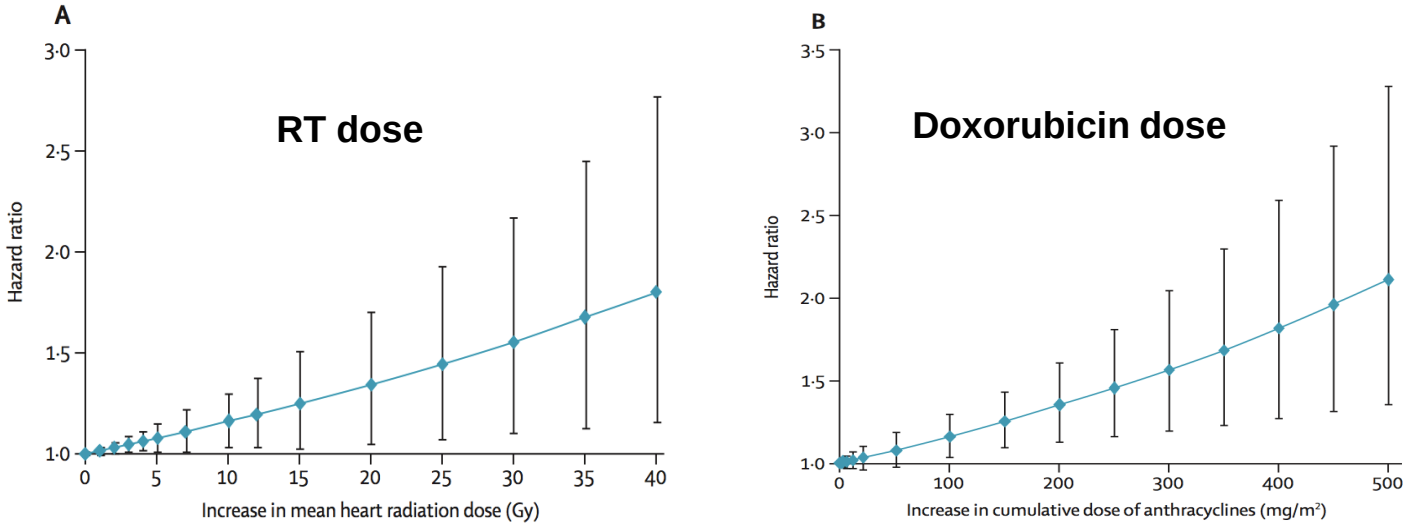
Therapeutic burden:

R-CHOP x 3 cycles followed by 30 Gy IS-RT probably better than R-CHOP x 6 cycles



Why not to give more chemotherapy to avoid RT…

Estimated HR for cardiovascular events according to mean heart RT dose and cumulative dose of anthracyclines



Example: an increase in **mean heart dose of 5 Gy** yields the **same excess risk** of cardiac events as an increase in cumulative **anthracycline dose of 50 mg/m2** (≈1 cycle of ABVD or R-CHOP)

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

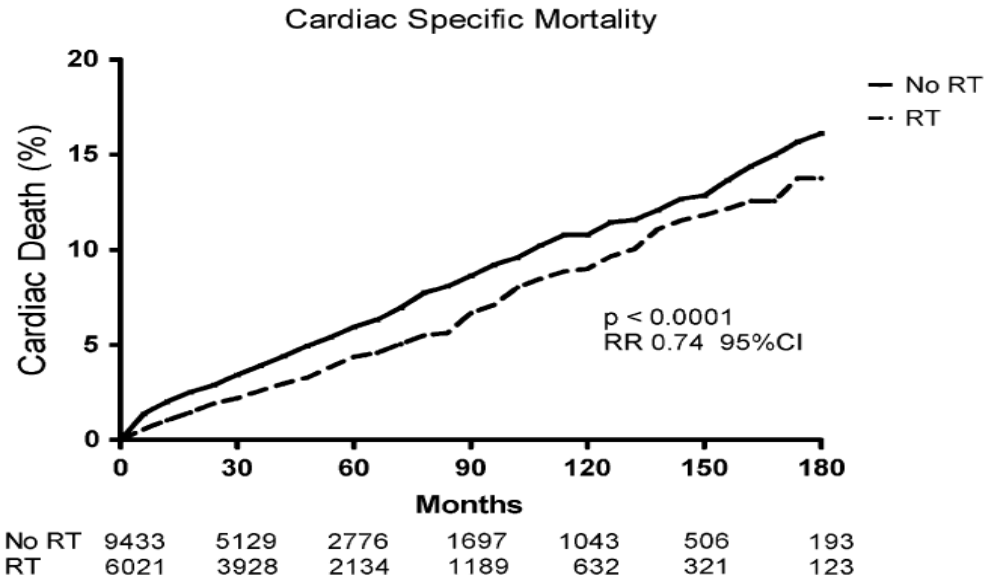


Fig. 1. Cardiac death in patients with stage I–II DLBCL. A comparison between patients treated with and without RT.

Increased Cardiac Death in Patients Treated without RT

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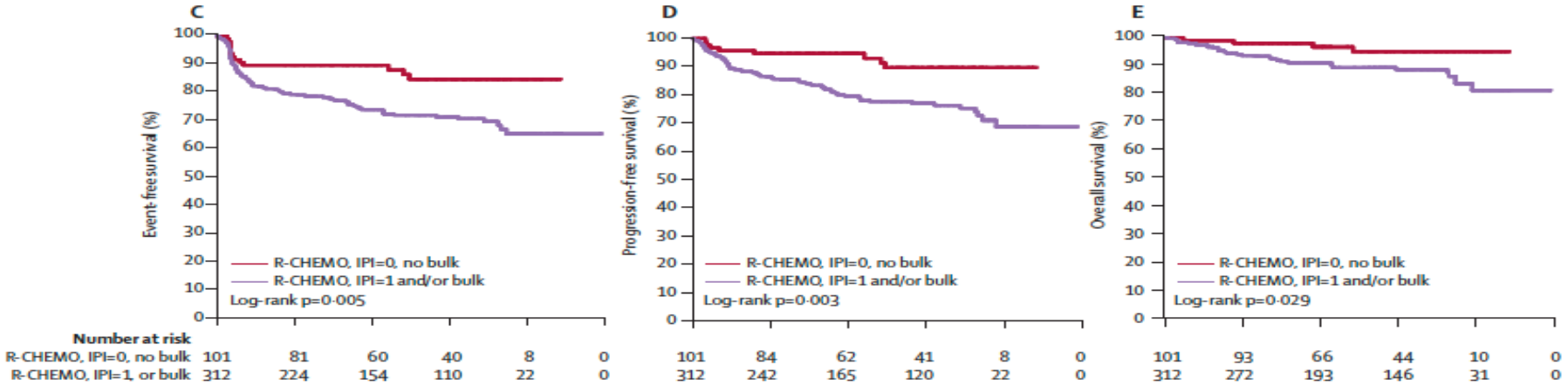
- Given the favorable toxicity profile of RT to 30 Gy administered with modern RT techniques to involved sites, coupled with the suboptimal outcomes for patients with DLBCL, it is difficult to justify withholding a treatment that can positively influence PFS and possibly OS.



- Late Effects of RT: Distinct Considerations for DLBCL.

- General suggestions that RT no longer has a role in treating early-stage lymphomas should thus be reexamined carefully

Patients with low risk disease may also benefit from abbreviated chemotherapy and RT instead of prolonged chemotherapy

Annals of Oncology 26 (Supplement 5): v116–v125, 2015
doi:10.1093/annonc/mdv304

Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

H. Tilly[1], M. Gomes da Silva[2], U. Vitolo[3], A. Jack[4], M. Meignan[5], A. Lopez-Guillermo[6], J. Walewski[7], M. André[8], P. W. Johnson[9], M. Pfreundschuh[10] & M. Ladetto[11], on behalf of the ESMO Guidelines Committee*

Table 3. Recommended treatment strategies in diffuse large B-cell lymphoma

Patients ≤60 years		
IPI low risk (aaIPI = 0) and no bulk	IPI low risk (aaIPI = 0) with bulk or IPI low-intermediate risk (aaIPI = 1)	IPI intermediate-high risk or IPI high risk (aaIPI = 2, 3)
R-CHOP21 × 6	R-ACVBP and sequential consolidation or R-CHOP21 × 6 + IF-RT on bulk	R-CHOP21 × 6–8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens in selected patients: R-CHOEP14 × 6 or R-CHOP or R-ACVBP plus HDCT with ASCT
Consider CNS prophylaxis in patients at risk for CNS progression		
Elderly >60 years		
Fit, 60–80 years	>80 years without cardiac dysfunction	Unfit or frail or >60 years with cardiac dysfunction
R-CHOP21 × 6–8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R	Attenuated regimens: R-miniCHOP21 × 6	Doxorubicin substitution with gemcitabine, etoposide or liposomal doxorubicin or others: R-C(X)OP21 × 6 or palliative care
Consider CNS prophylaxis in patients at risk		

Guidelines for the management of diffuse large B-cell lymphoma

Sridhar Chaganti,[1] Tim Illidge,[2] Sally Barrington,[3] Pam Mckay,[4] Kim Linton,[5] Kate Cwynarski,[6] Andrew McMillan,[7] Andy Davies,[8] Simon Stern,[9] Karl Peggs[10] and on behalf of the British Committee for Standards in Haematology

bjh guideline

Recommendations

- It is recommended that patients with non-bulky (<7·5 cm) stage IA DLBCL presenting at sites associated with low morbidity for radiotherapy (e.g. groin, neck or axilla), be treated with 3–4 cycles of R-CHOP chemotherapy followed by ISRT of 30 Gy (1B). Six cycles of R-CHOP is an alternative and should be the preferred option if disease involves a site where the acute and late complications of RT are better avoided (1A).
- Patients with non-bulky stage IIA DLBCL should be treated with 6 cycles of R-CHOP (1A).
- Patients with bulky stage IA/IIA DLBCL should be treated with 6 cycles of R-CHOP followed by ISRT of 30 Gy to initial sites of bulk (1B).

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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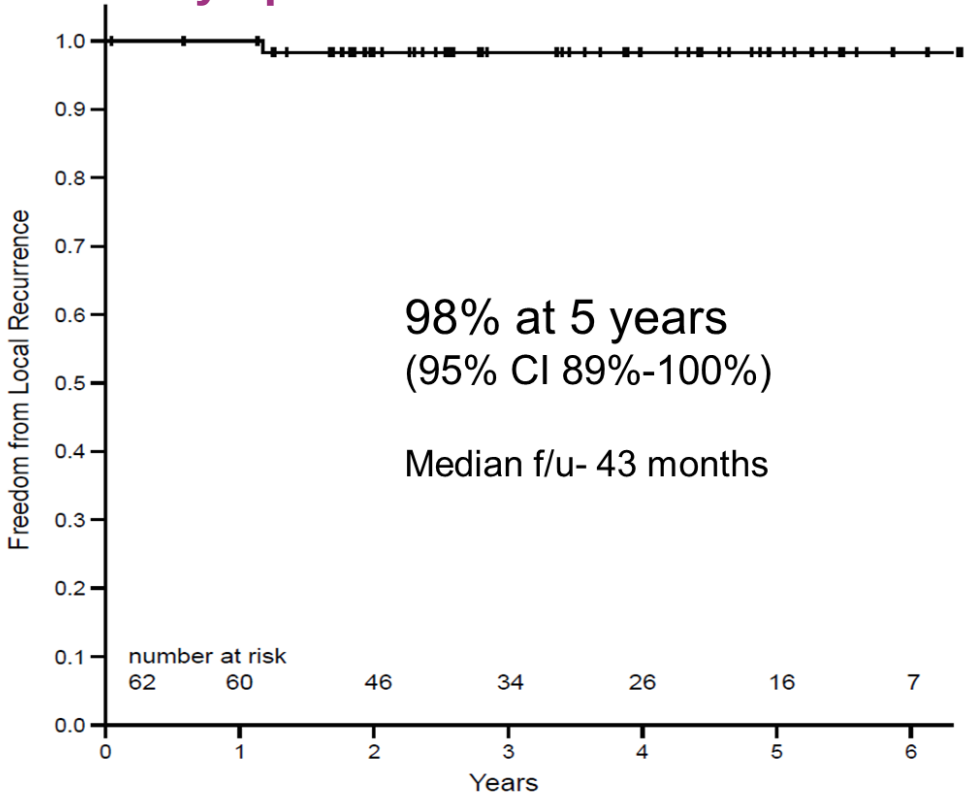
Phase II Study of Dose-Reduced Consolidation Radiation Therapy in Patients with Diffuse Large B-Cell Lymphoma

- N=62 (2010-2016)
- DLBCL NOS: n=50 (81%); Primary mediastinal B-cell lymphoma: n=12 (19%)
- Stage: I- 39%; II- 40%; III- 6%; IV- 15%
- Median tumor size: 5.7 cm
  - Bulky (≥ 7.5 cm): n=23 (40%)
  - Bulky (≥ 10 cm): n=16 (28%)
- Chemotherapy
  - R-CHOP: 58 (94%)
  - R-EPOCH: 4 (6%)
- 4 cycles: 21 (34%); 5 cycles: 2 (3%); 6 cycles: 39 (63%)



Courtesy of Dr. Kelsey C.

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

The treatment of patients with DLBCL requires multidisciplinary collaboration to ensure optimal outcome

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

Aggressive nodal non Hodgkin lymphoma: Advanced stage and relapsed/refractory disease

Andy Davies

Chair UK National Caner Research Institute High-Grade Lymphoma Sub-Group

ESTRO/ILROG COURSE:

HAEMATOLOGICAL MALIGNANCIES

September 2018

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

CANCER RESEARCH UK

UNIVERSITY OF Southampton

Conflicts of Interest

Celgene: Research funding; Advisory Board; Honorarium

Roche: Advisory Boards; Honorarium; Research support

Gilead: Advisory Boards; Honorarium; Research support

Takeda: Advisory Boards; Honorarium; Research support, Travel to scientific conferences

CTI: Advisory Boards; Honorarium; Travel to scientific conferences

Mundipharma: Advisory Boards; Honorarium; Travel to scientific conferences

GSK: Research support

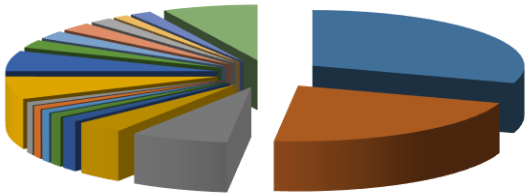
Bayer: Research support

Janssen: Honorarium; Research support

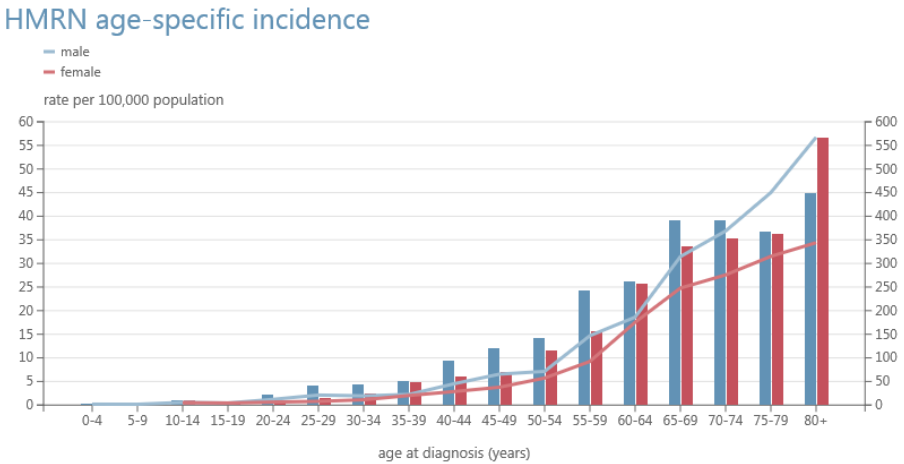
Karyopharma: Advisory Board; Research support

Pfizer: Research support; Honorarium

DLBCL



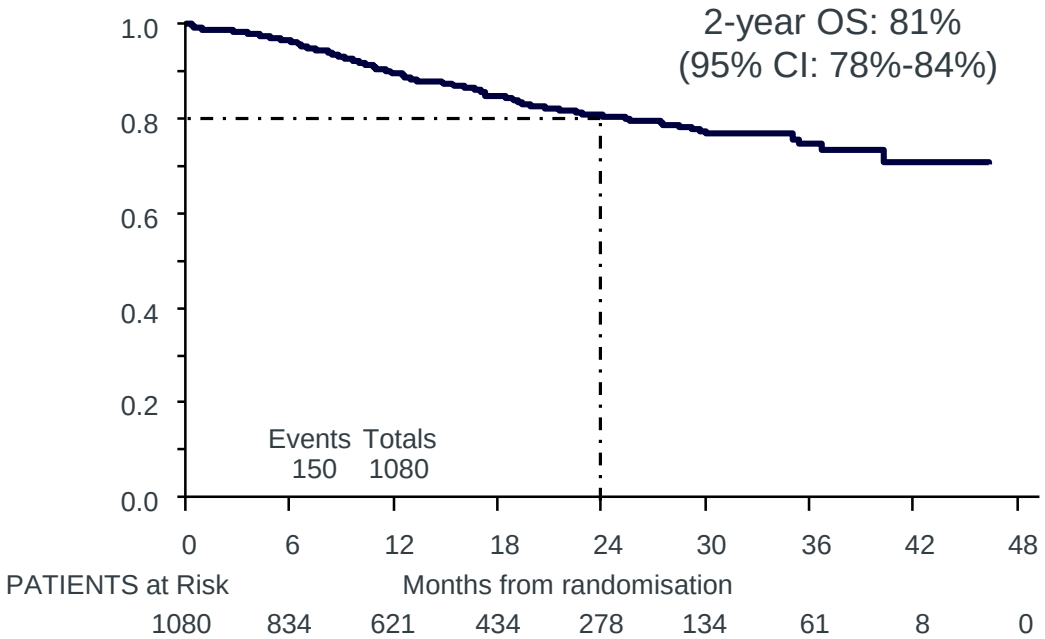
- LBLC
- FOLLICULAR
- EXTRA NODAL MARGINAL ZONE
- PERIPHERAL T NOS
- NASAL NK/T
- ANCIOIMMUNOBLASTIC
- ENTEROPATHY ASSOCIATED
- HEPATOSPLENIC
- ATLL
- CLL
- MANTLE CELL
- MEDIASTINAL LARGE B CELL
- ANAPLASTIC LARGE CELL



Haematological Malignancies Research Network 2017

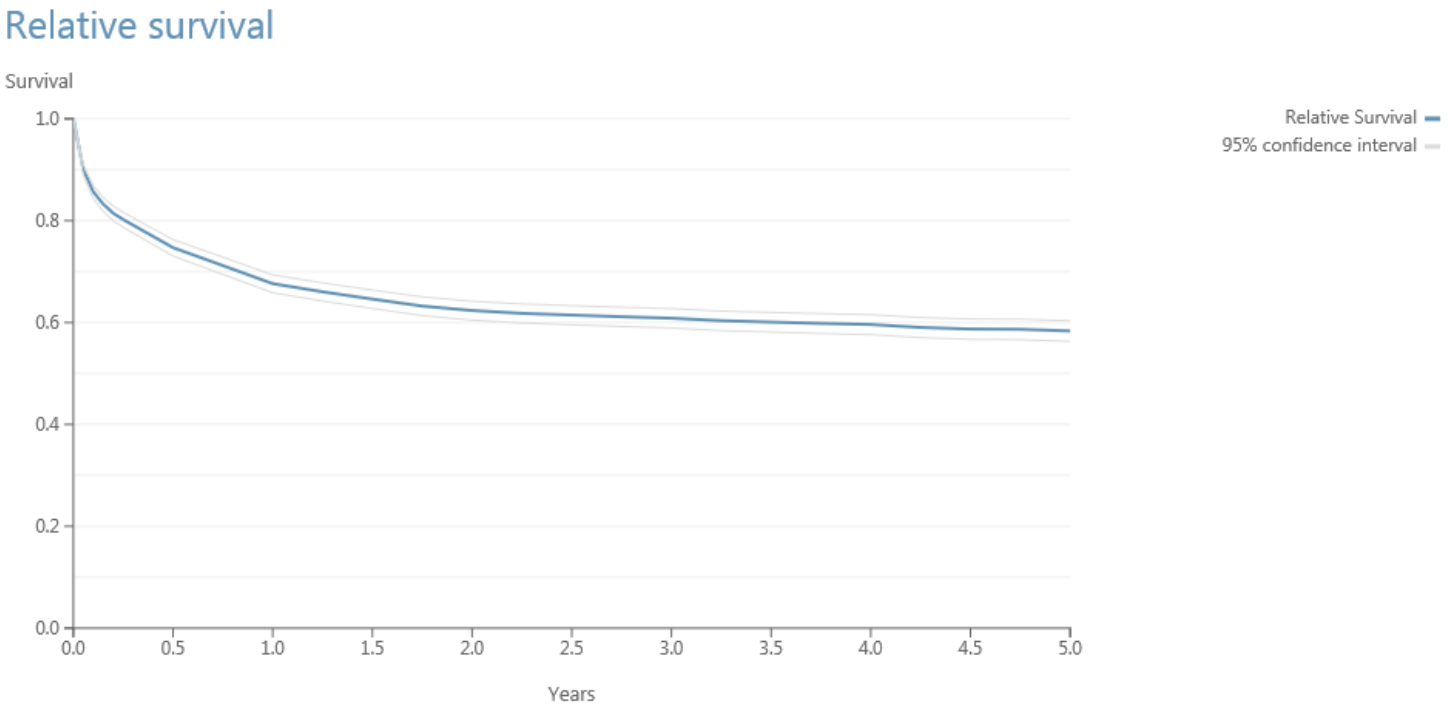
DLBCL is a curable disease

Overall survival: UK R-CHOP 14 vs 21



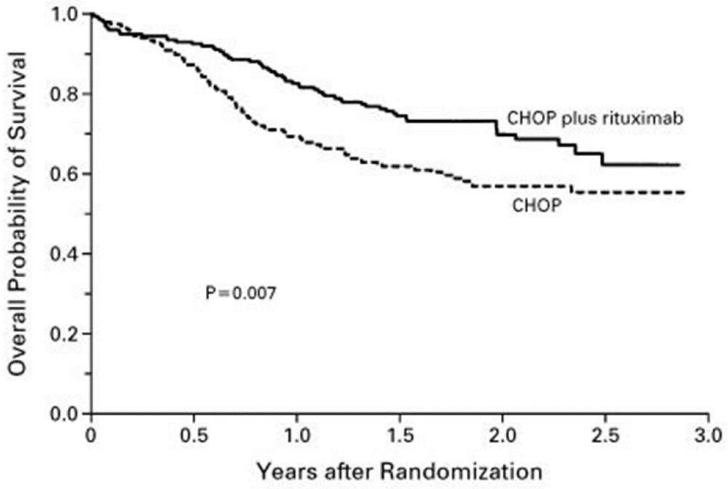
Cunningham, J Clin Oncol (2009) 27:15s,

Real World Data



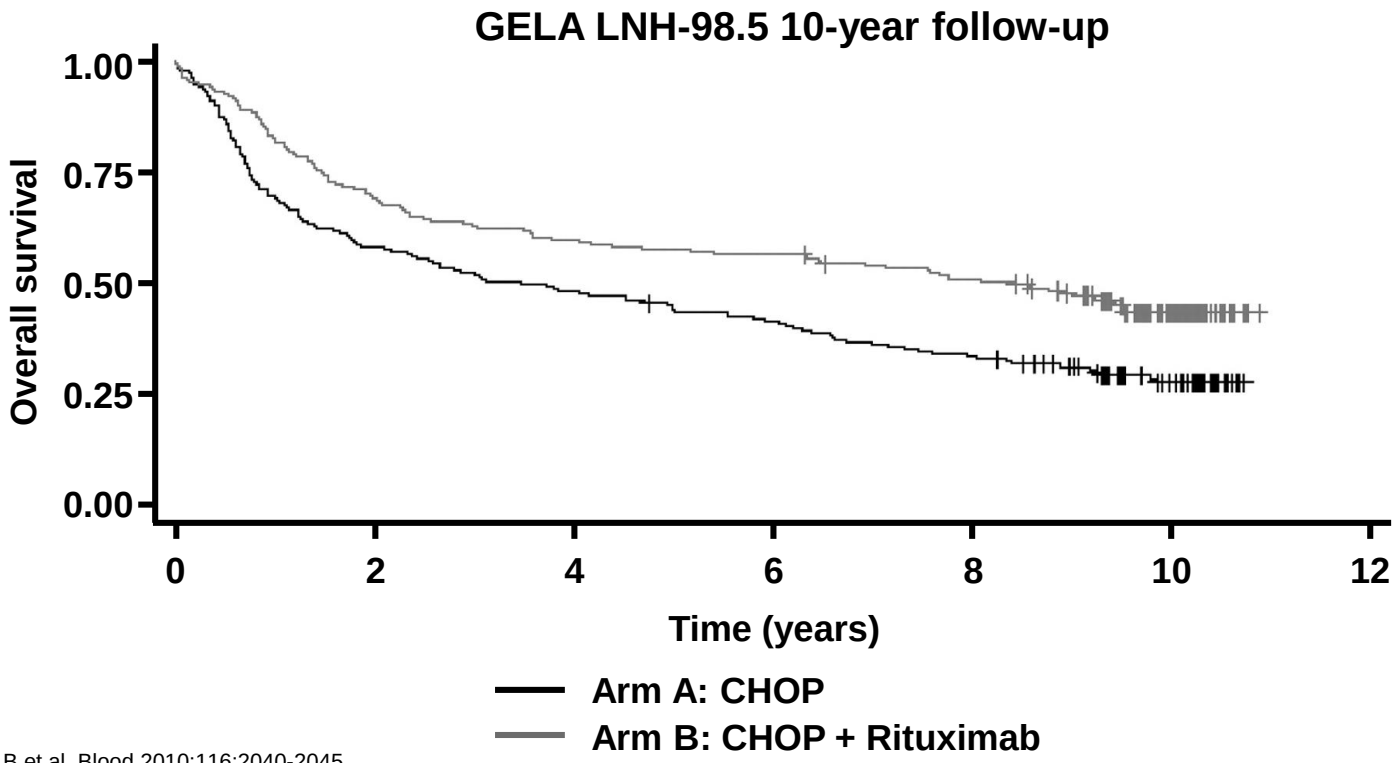
CHOP CHEMOTHERAPY PLUS RITUXIMAB COMPARED WITH CHOP ALONE IN ELDERLY PATIENTS WITH DIFFUSE LARGE-B-CELL LYMPHOMA

Bertrand Coiffier, M.D., Eric Lepage, M.D., Ph.D., Josette Brière, M.D., Raoul Herbrecht, M.D., Hervé Tilly, M.D., Reda Bouabdallah, M.D., Pierre Morel, M.D., Eric Van Den Neste, M.D., Gilles Salles, M.D., Ph.D., Philippe Gaulard, M.D., Felix Reyes, M.D., and Christian Gisselbrecht, M.D.



No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

The benefit of rituximab is maintained over time



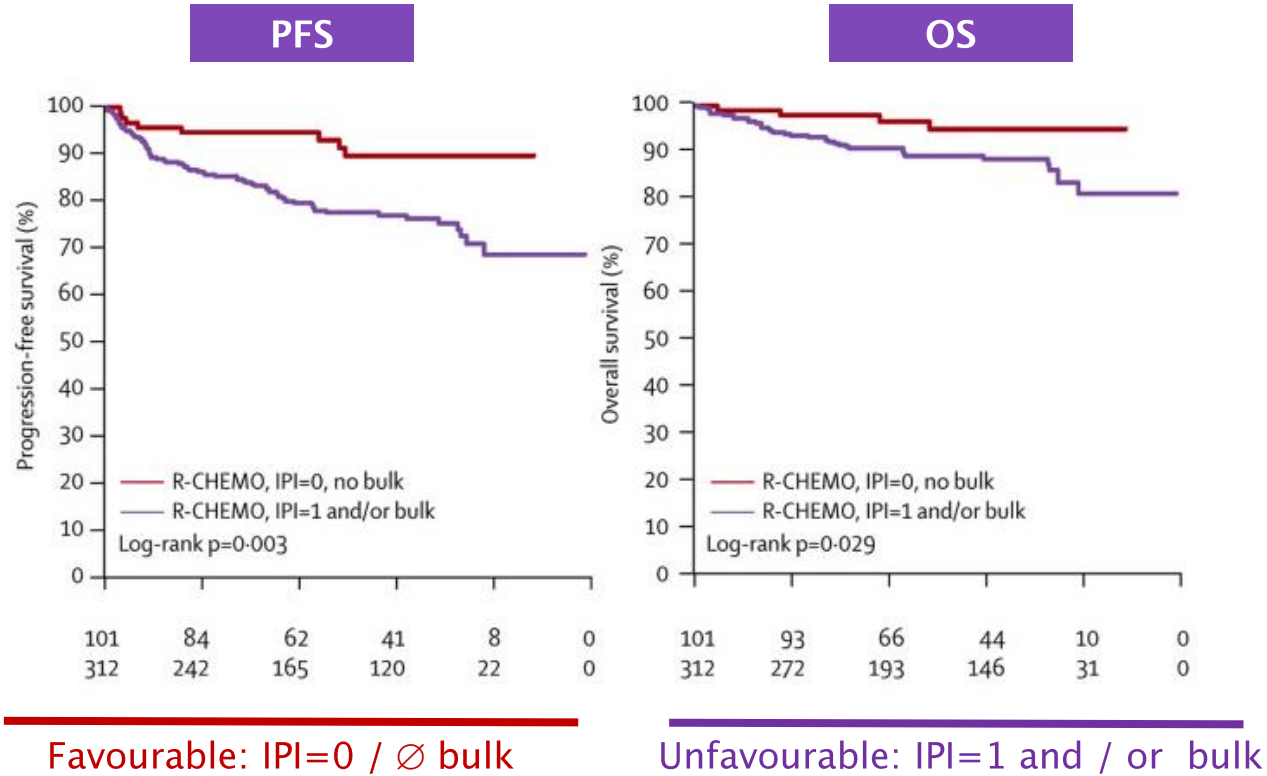
Coiffier B et al. Blood 2010;116:2040-2045

Revision to WHO classification 2016

Diffuse large B-cell (NOS)	
	Germinal Centre B-cell type
	Activated B-cell type
T-cell/histiocyte rich large B-cell	
Primary DLBCL of central nervous system	
Primary cutaneous DLBCL leg type	
EBV+ DLBCL, NOS	
	EBV+ mucocutaneous ulcer
Primary mediastinal lymphoma	
Intravascular large B-cell lymphoma	
Primary effusion lymphoma	
Plasmablastic lymphoma	
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement	

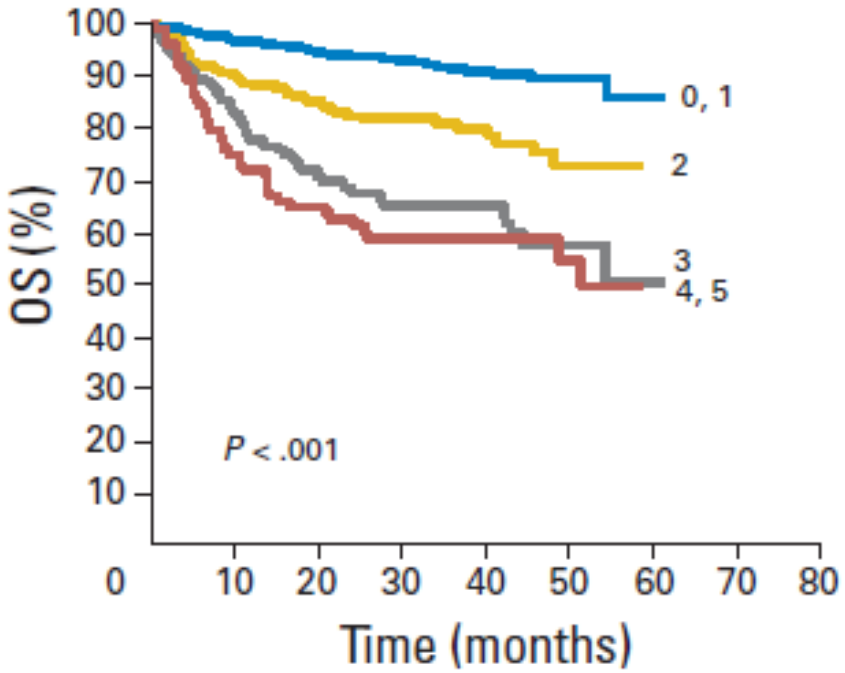
Swerdlow et al. Blood 2016

There are groups with excellent outcomes…MInT



Pfreundschuh et al Lancet Oncol 2011

There is clear heterogeneity in clinical outcomes



IPI

Age greater than 60 years
Stage III or IV disease
Elevated serum LDH
ECOG $\geq$ 2
More than 1 extranodal site

Age adjusted IPI

Stage
LDH
Performance status

Ziepert at al. J Clin Oncol 28:2373-2380.

ESMO Guidelines

Young (age <61)

aaIPI=0 no bulk	aaIPI=1/aaIPI=0 +bulk	aaIPI≥2
R-CHOP 21 x6	R-ACVBP + consolid.	R-CHOP 21 x8
	R-CHOP 21 x6 + IFRT (to bulk)	R-CHOP 14 x6 +Rx2
		R-CHEOP14 x6
		R-ACVBP + HDT
		R-CHOP14 +HDT
		Clinical trial

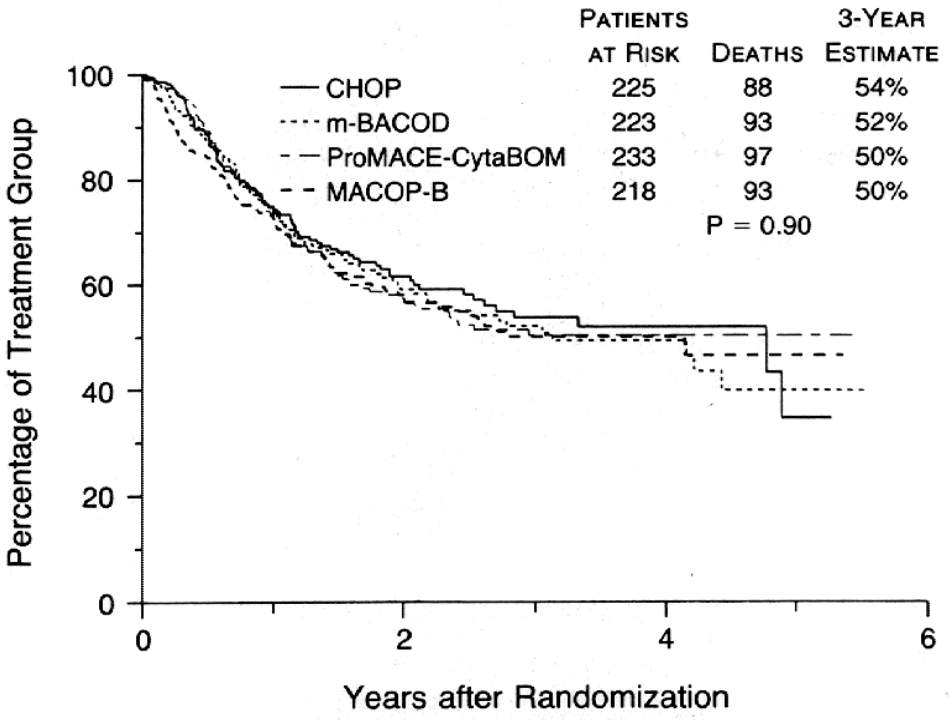
Tilly et al. 2015 Annals of Oncol, 26,116–125

No clear standard in this group

Is there much yet to be achieved with conventional chemotherapy

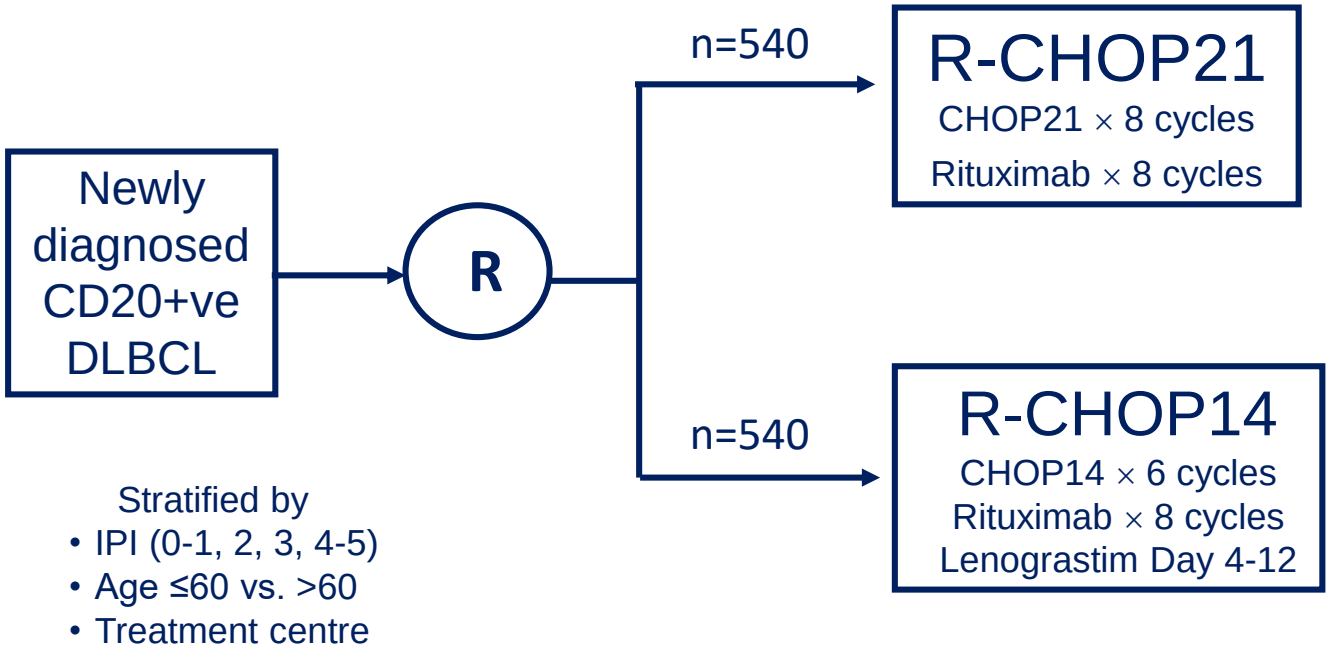
Probably not…..

Intensified regimens…might they hold the answer?



Fisher RI, et al . N Engl J Med1993; 328:1002– 006.

Dose Density: UK R-CHOP14 vs. 21

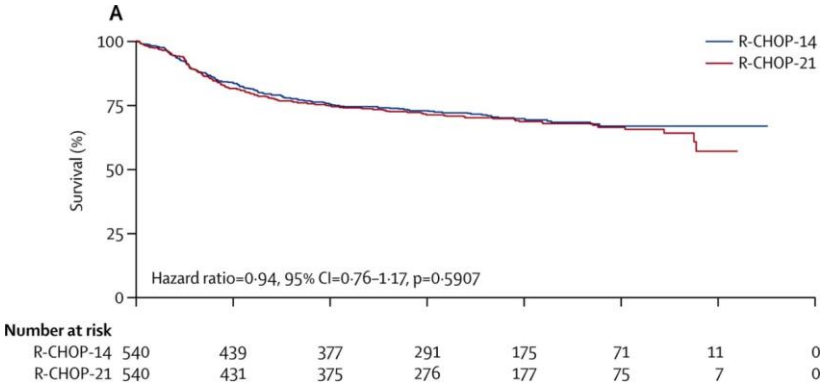


1080 patients; 119 sites
Recruitment March 2005 - Nov 2008

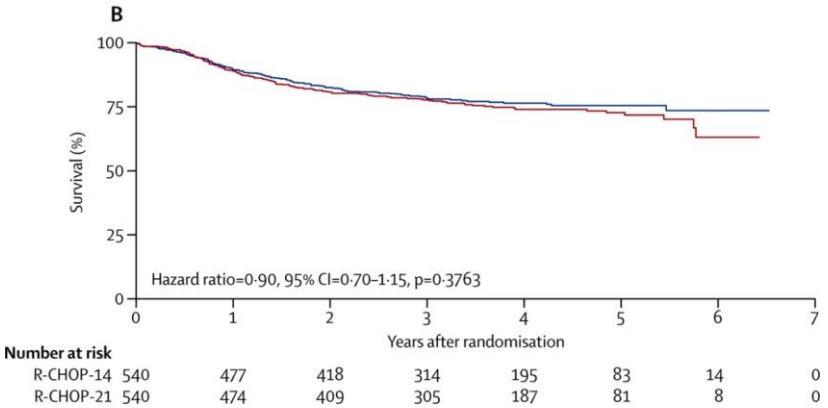
Cunningham, D, *et al. Lance*t 2013; 381:1817–1826.

R-CHOP14 vs 21: no difference in outcome

Progression -free survival

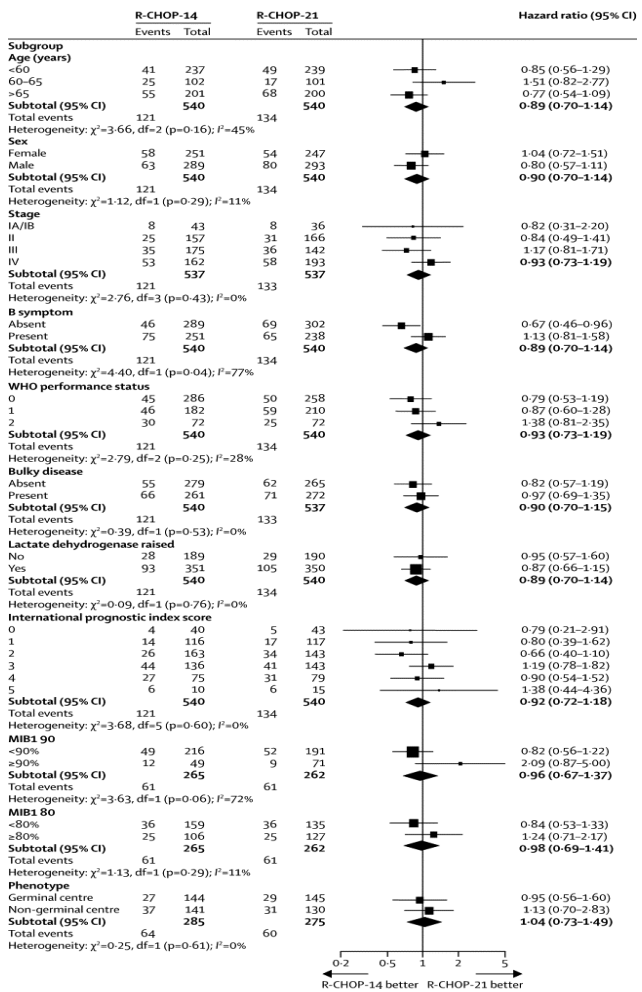


Overall survival



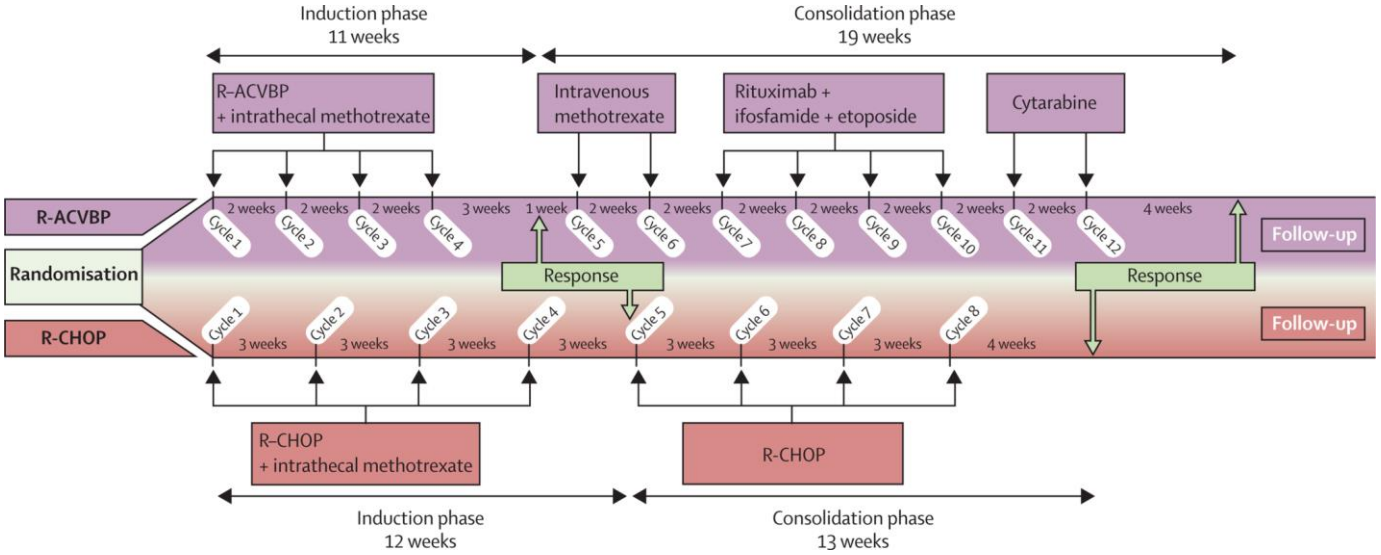
Cunningham, D, *et al. Lancet* 2013; 381:1817–1826.

R-CHOP14 vs 21: no subgroup could be identified



Cunningham, D, *et al. Lancet* 2013; 381:1817–1826.

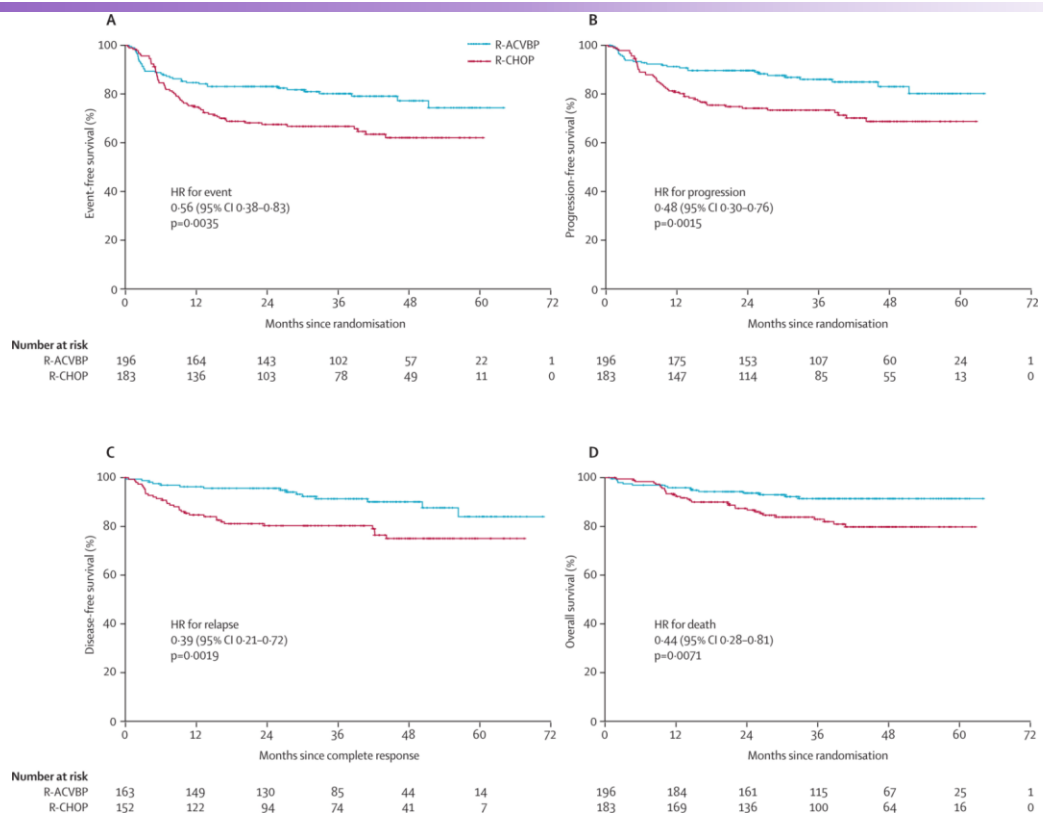
Other ways of improving dose intensity: GELA LNH03-2B



Young (age 18-59) aa IPI 1
n=380
Median age 47
55% stage III/IV, 44% bulk

Recher C, *et al Lancet* 2011: 378:1858-18676.

Improved outcome in R-ACVBP arm



Recher C, *et al Lancet* 2011: 378:1858-18676.

- Improvement in EFS, PFS and OS
- Outcome of R-CHOP x 8 arm inferior to those observed in MInT with R-CHOP x 6
- Excess utilisation of healthcare resource
- Excess of toxicity

	R-ACVBP	R-CHOP
Toxicity (grade ≥3)		
Neutropenia	78%	64%
Anemia	35%	5%
Thrombocytopenia	30%	3%
Febrile neutropenia	38%	9%
Toxic deaths (n)	3	2

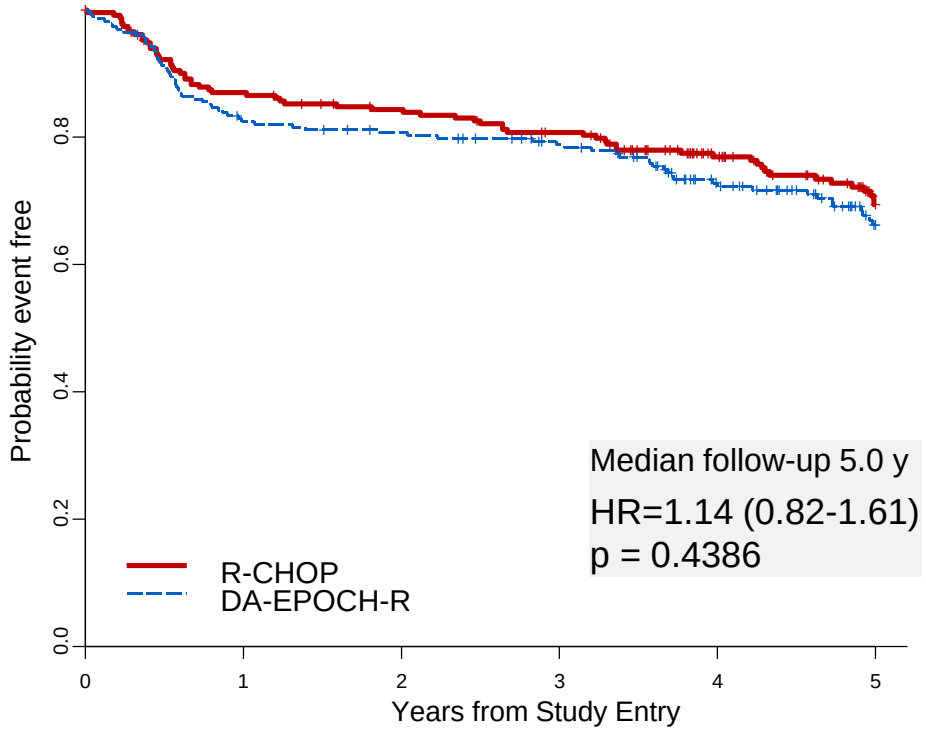
Recher C, *et al Lancet* 2011: 378:1858-1867.

Phase III Randomized Study of R-CHOP vs. DA-EPOCH-R and Molecular Analysis of Untreated Large B-Cell Lymphoma: CALGB/Alliance 50303

Wyndham H. Wilson, Sin-Ho Jung, Brandelyn N. Pitcher, Eric D.Hsi, Jonathan Friedberg, Bruce Cheson, **Nancy L. Bartlett**, Scott Smith, Nina Wagner-Johnston, Brad S. Kahl, Louis M. Staudt, Kristie A. Blum, Jeremy Abramson, Oliver W. Press, Richard I. Fisher, Kristy L. Richards, Heiko Schoder, Julie E. Chang, Andrew D. Zelenetz, John P. Leonard

Abstract 469, American Society of Hematology, Dec 4, 2016

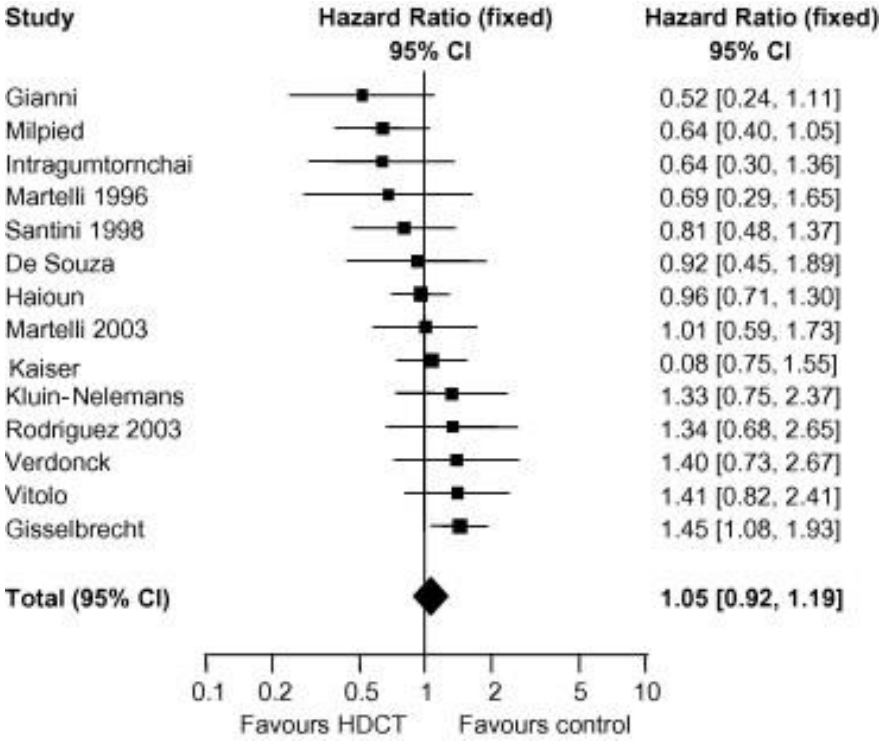
50303 Event Free Survival



Arm	N	Events	3 Y (95% CI)	5 Y (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Increasing dose intensity…High dose therapy

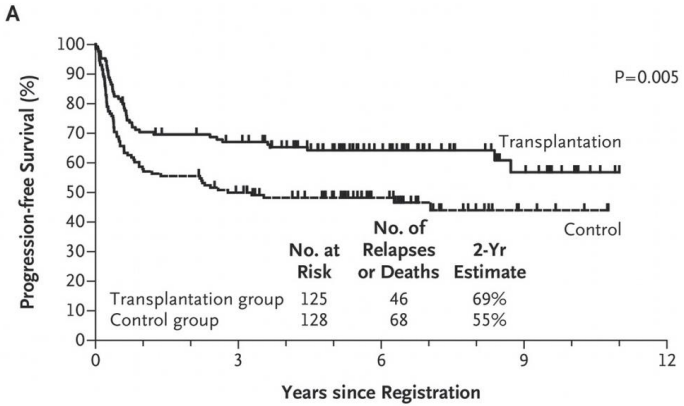


Greb A, *et al. Cancer Treat Rev* 2007; 33: 338–346

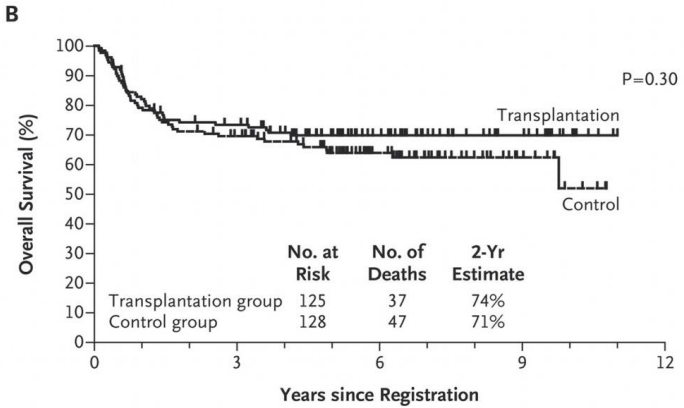
…may improve PFS for poorer prognosis patients (not OS)

All patients high or high-intermediate IPI

PFS



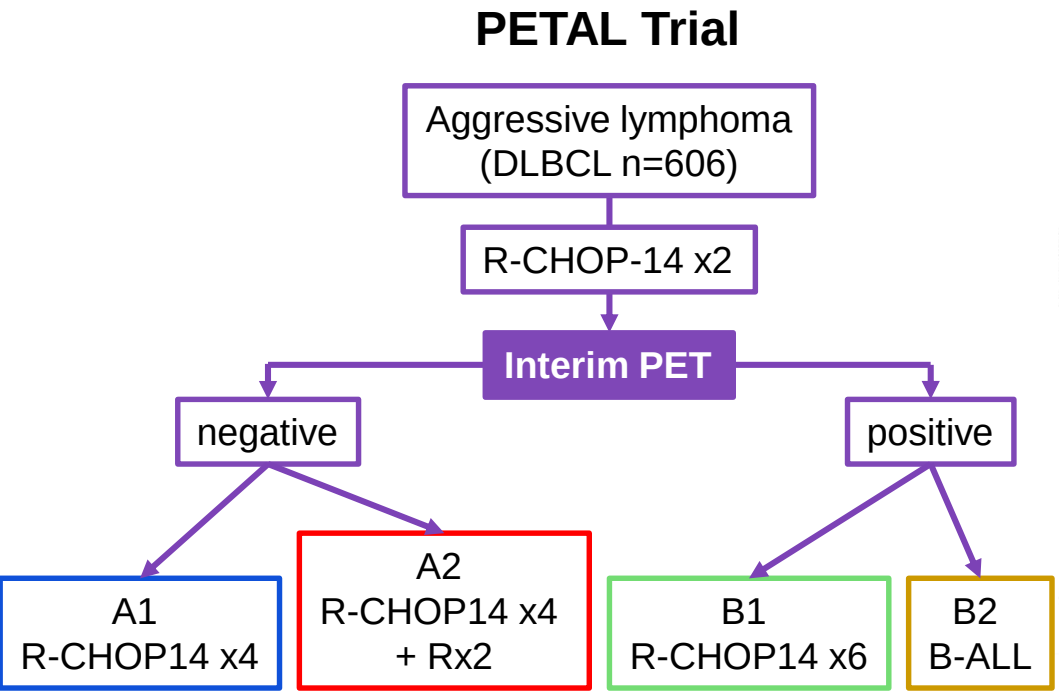
OS

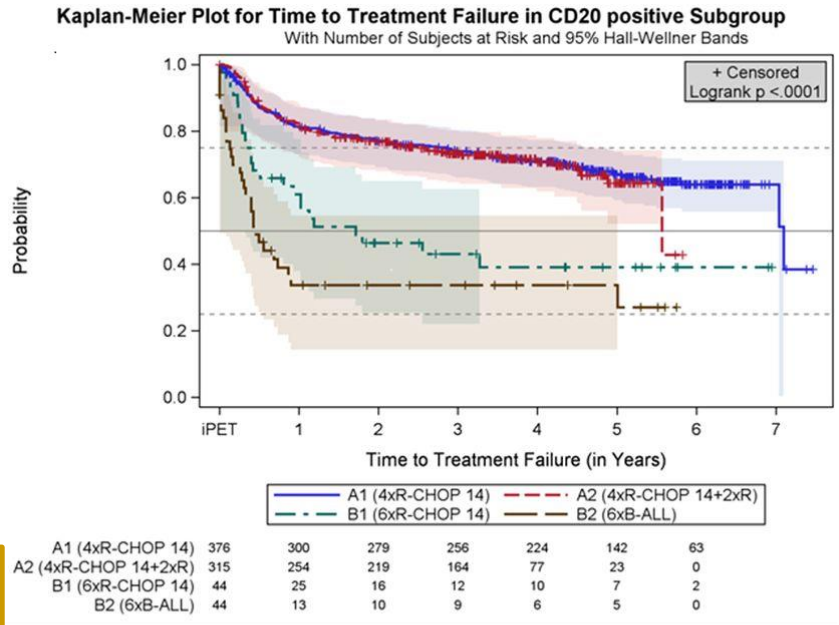


Similar findings in Italian DLCL04 Study Chiappella Lancet Oncol 2017

Stiff PJ et al. N Engl J Med 2013;369:1681-1690

Intensification of therapy based in interim PET…

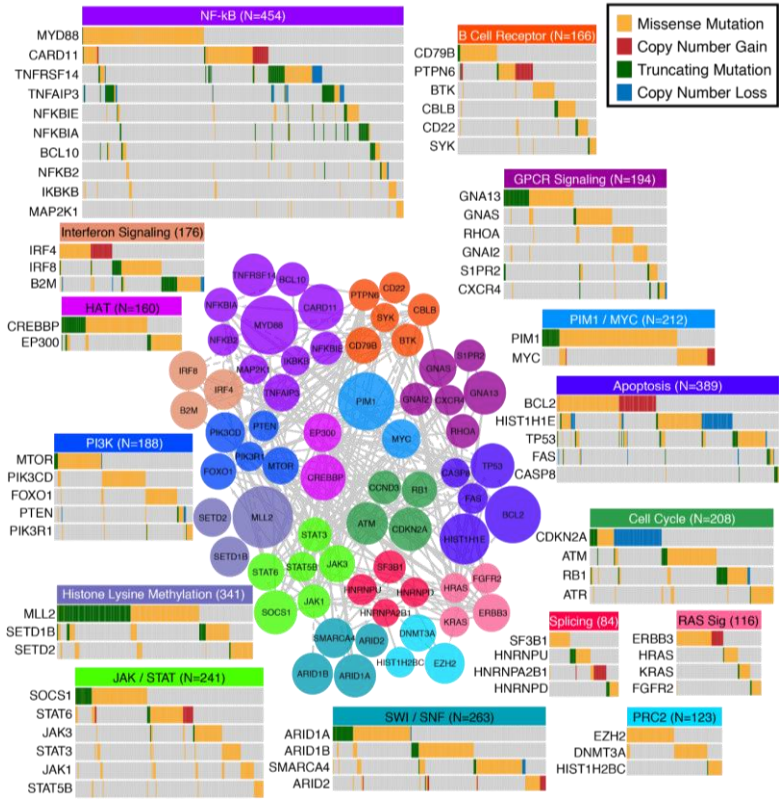




Duehrsen et al. Blood 128:1857

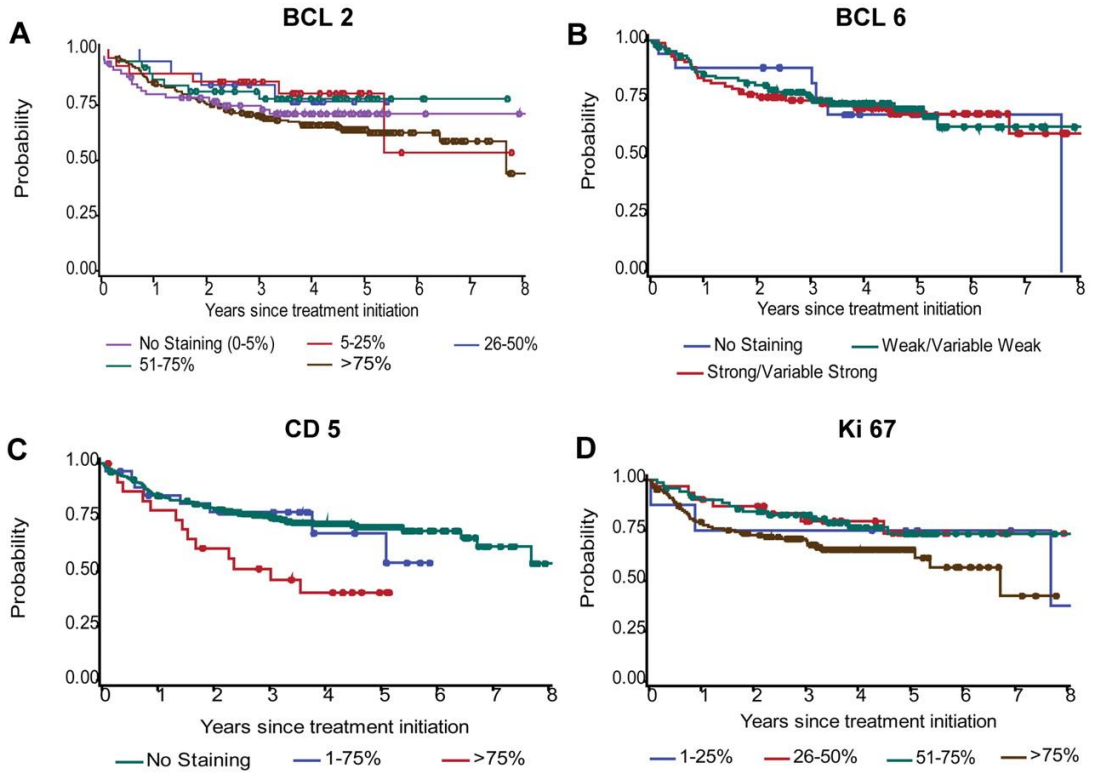
We should be capitalising on biological insights

Integrative Genetic and Clinical Analysis through Whole Exome Sequencing in 1001 Diffuse Large B Cell Lymphoma (DLBCL) Patients Reveals Novel Disease Drivers and Risk Groups



Zhang et al ASH 2016 and Reddy Cell 2017

Overall survival of R-CHOP-treated patients in Lunenburg analysis



Salles G et al. Blood 2011;117:7070-7078

CD5 Positive DLBCL

Comprises 5-10% of DLBCL cases

Older women, advanced stage, high LDH and extranodal sites

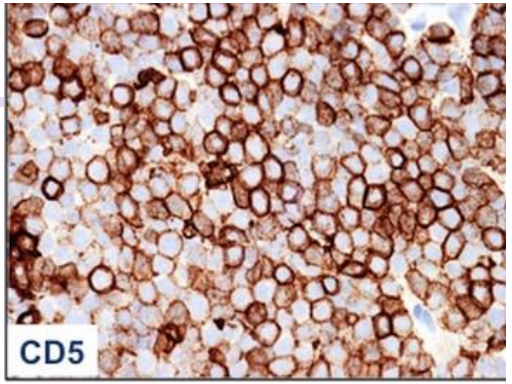
Most cases of are of the non-GCB type

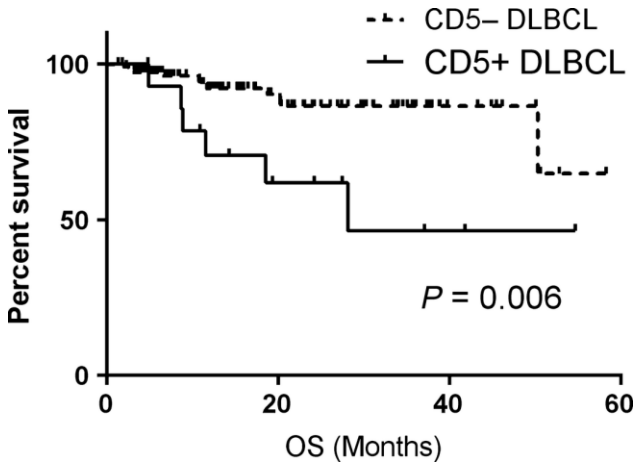
Rule of Richter's transformation of CLL and blastoid type mantle cell lymphoma

Clinical course of de novo CD5+ DLBCL is recognised as more aggressive than that associated with CD5-DLBCL

Frequent CNS involvement

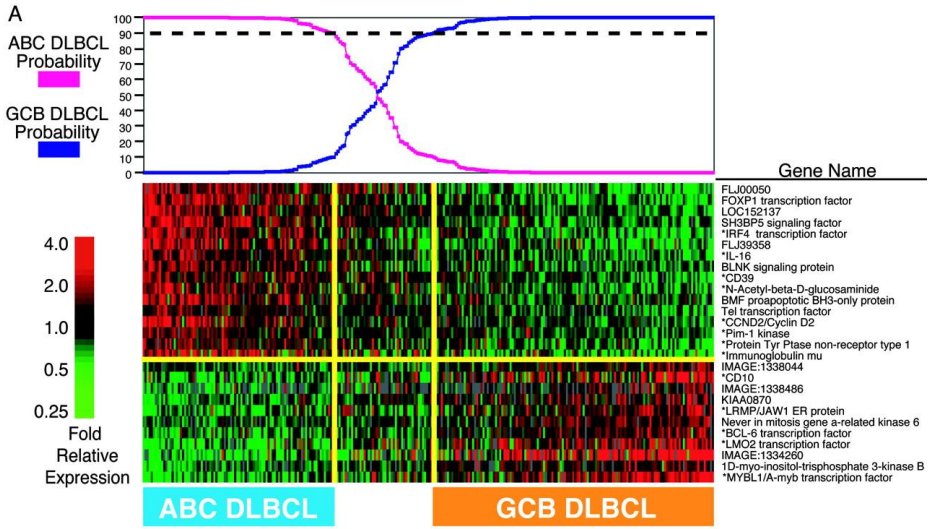
Using DA-EPOCH-R does not overcome poor prognosis





Thakra et al Eur Journal Haematology 2017

Application of complex models of biological heterogeneity



B

Model Prediction

DLBCL Subgroup by Hierarchical Clustering

	ABC	GCB	Other
ABC	37	1	4
GCB	1	58	8

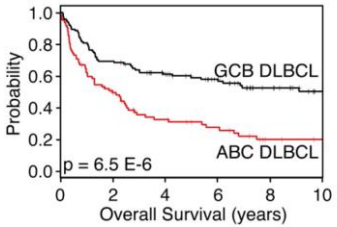
Training Set

	ABC	GCB	Other
ABC	38	1	2
GCB	2	57	8
Type 3	14	18	25

Validation Set

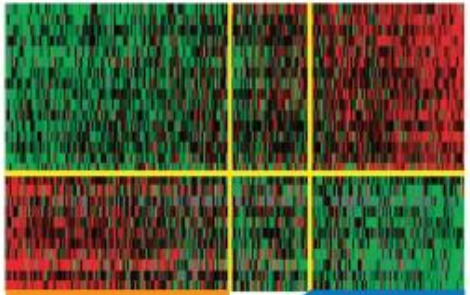
	ABC	GCB	Other
ABC	75	2	6
GCB	3	115	16
Type 3	14	18	25

All Samples



Wright, George et al. (2003) Proc. Natl. Acad. Sci. USA 100, 9991-9996

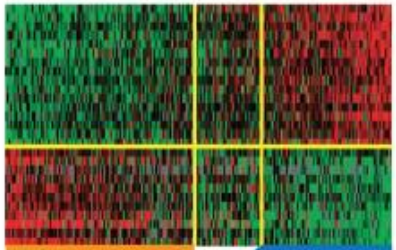
Translocations and Copy Number Changes



	GCB	ABC
BCL6 translocation	11%	22%
MYC translocation	14%	9%
BCL2 translocation	45%	0%
PTEN deletion	11%	0%
REL amplification	26%	5%
BCL2 amplification	1%	11%
CDKN2A/B deletion	4%	30%
PRDM1 deletion	0%	26%
SPIB amplification	3%	26%

Lenz et al Proc Natl Acad Sci USA 2008

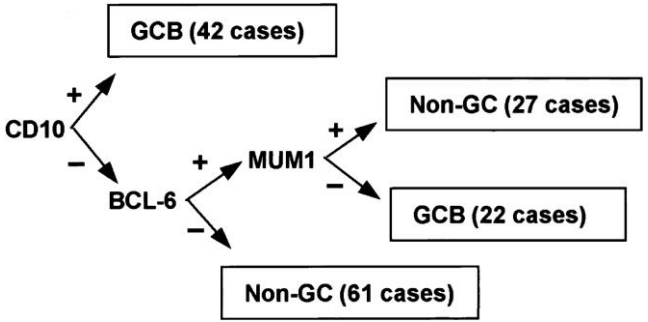
Recurrent Gene Mutations

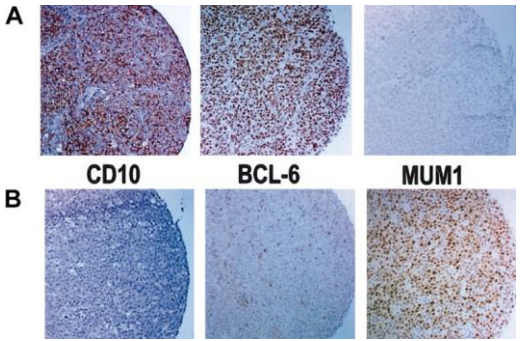


	GCB	ABC
CREBBP	32%	9%
FOXO1	11%	8%
MLL2	27%	21%
TP53	26%	18%
EZH2	22%	0%
GNA13	29%	0%
MEF2B	22%	0%
SGK1	24%	0%
TNFRSF14	13%	0%
CARD11	4%	10%
CD79B	2%	21%
MYD88	2%	29%
PRDM1	0%	27%

Morin et al Nat Genet 2010
Davis et al Nature 2010
Ngo et al Nature 2011
Morin et al Nature 2011
Pasqualucci et al Nat Genet 2011

But how to distinguish phenotype?

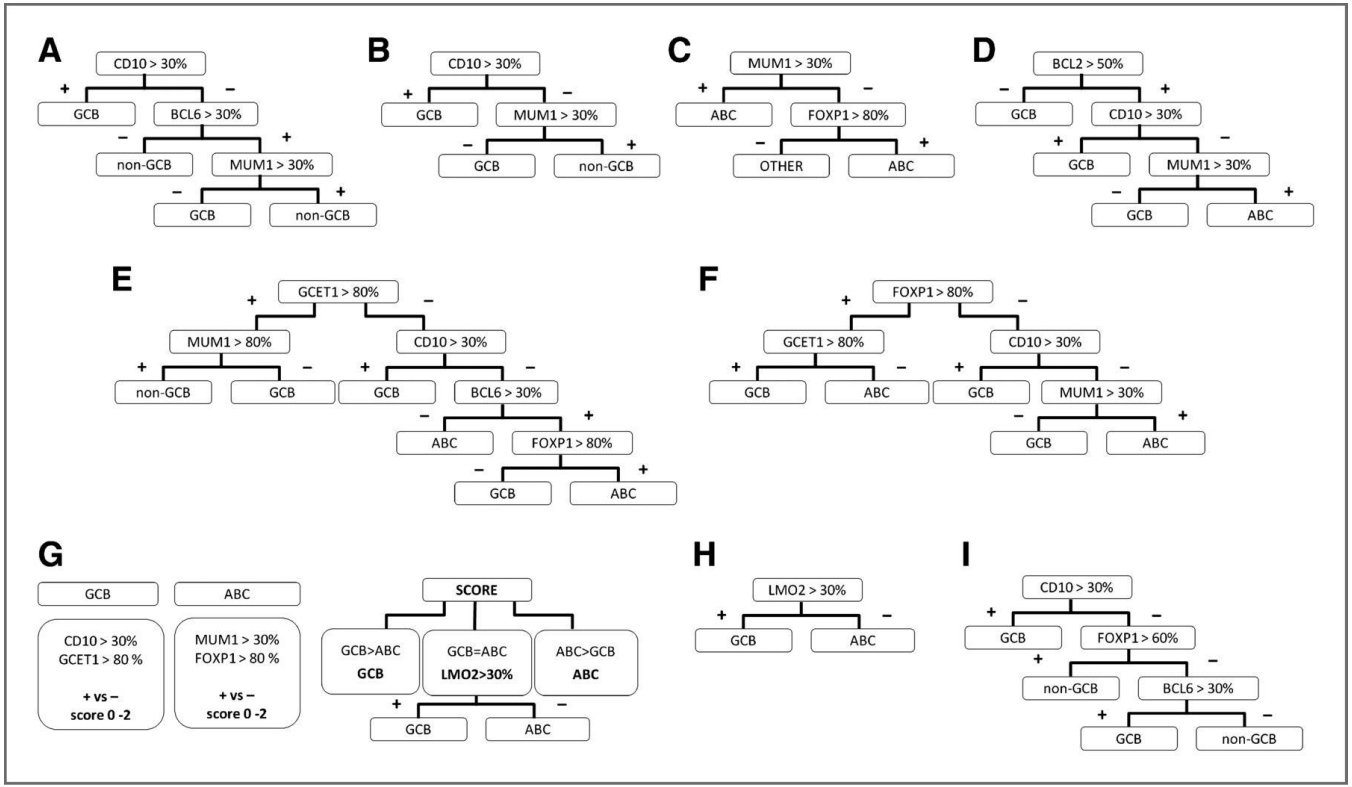




- Getting it right is important when looking prospectively at therapy, not prognosis
- The immunophenotype is not that good:
  - CD10+ (about 1/3), Mum-1-: Almost all GCB
  - CD10- (2/3) hard to distinguish ABC from GCB on immuno's
  - Bcl-6 is a difficult stain
  - Discordance with mRNA (~20%)
- Conflicting IHC datasets
- Lunenberg project demonstrates poor correlation between centres (technical and interpretative)

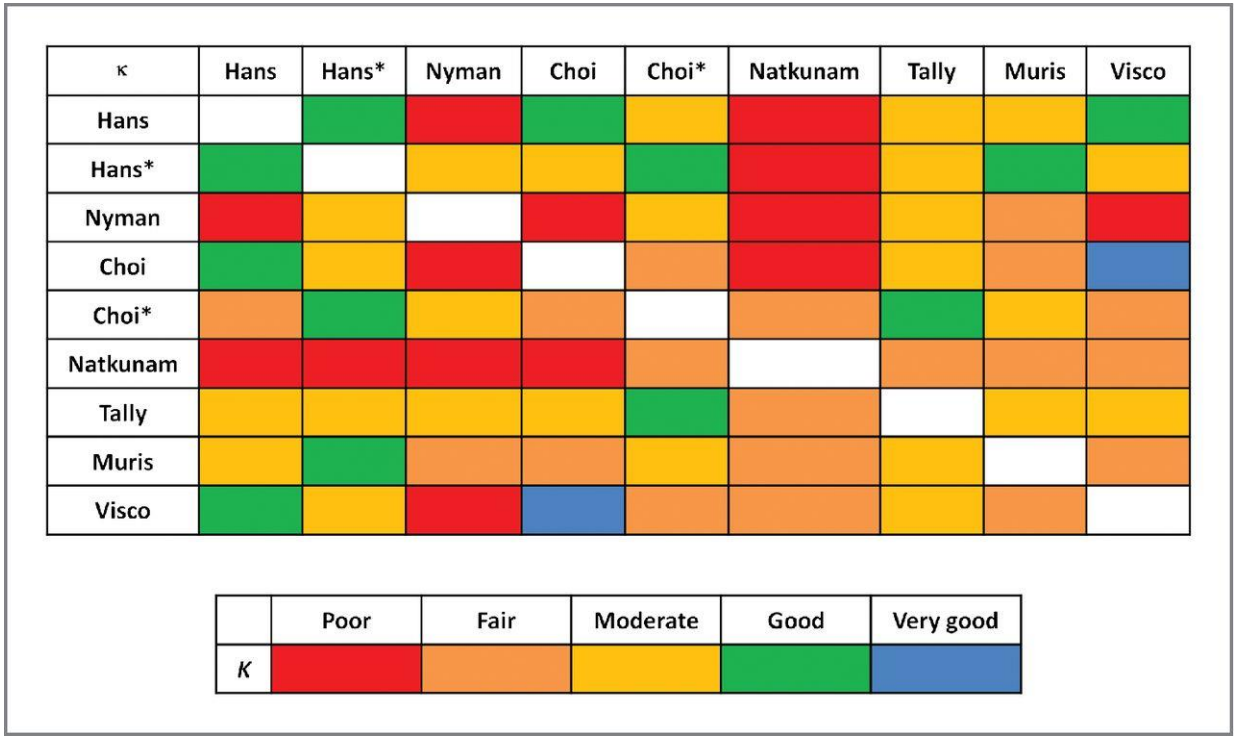
Hans, C. P. et al. Blood 2004;103:275-282

Lots of different IHC Algorithms…



Rita Coutinho et al. Clin Cancer Res 2013;19:6686-6695

But correlation is poor….

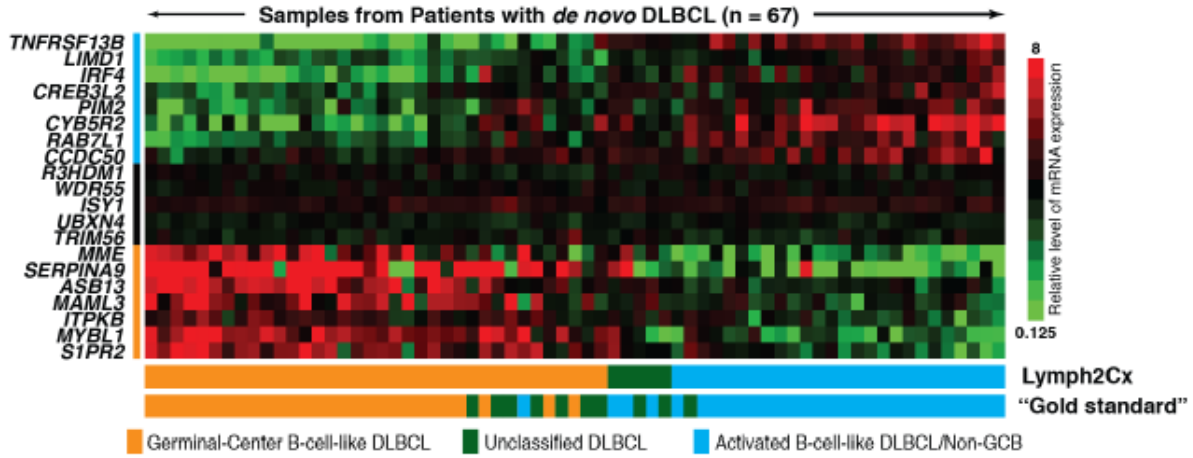


Rita Coutinho et al. Clin Cancer Res 2013;19:6686-6695

Pairwise agreement according to κ statistics. *, Modified.

Reliable tools in formalin-fixed paraffin-embedded tissue

- **NanoString Technology**

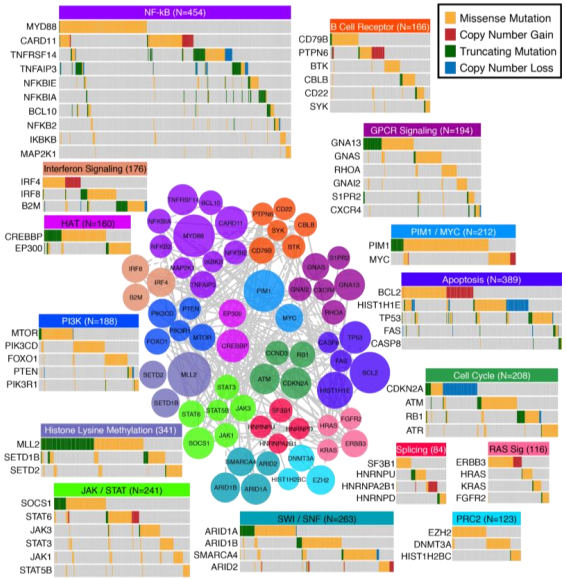


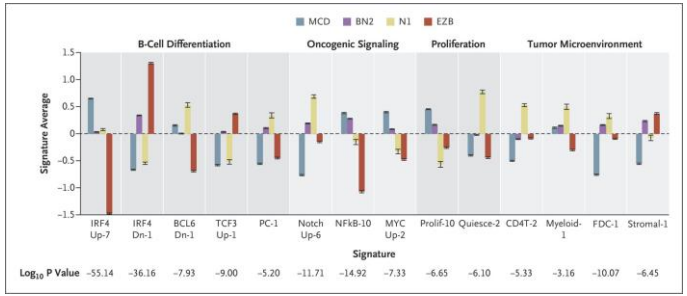
2% misclassification of ABC/GCB compared with GEP on fresh frozen tissue

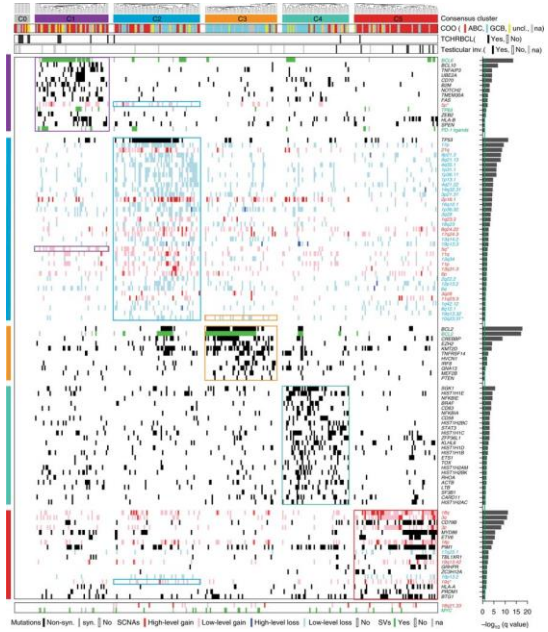
Other emerging platforms

Scott et al, Blood 2014

Deeper biological insights





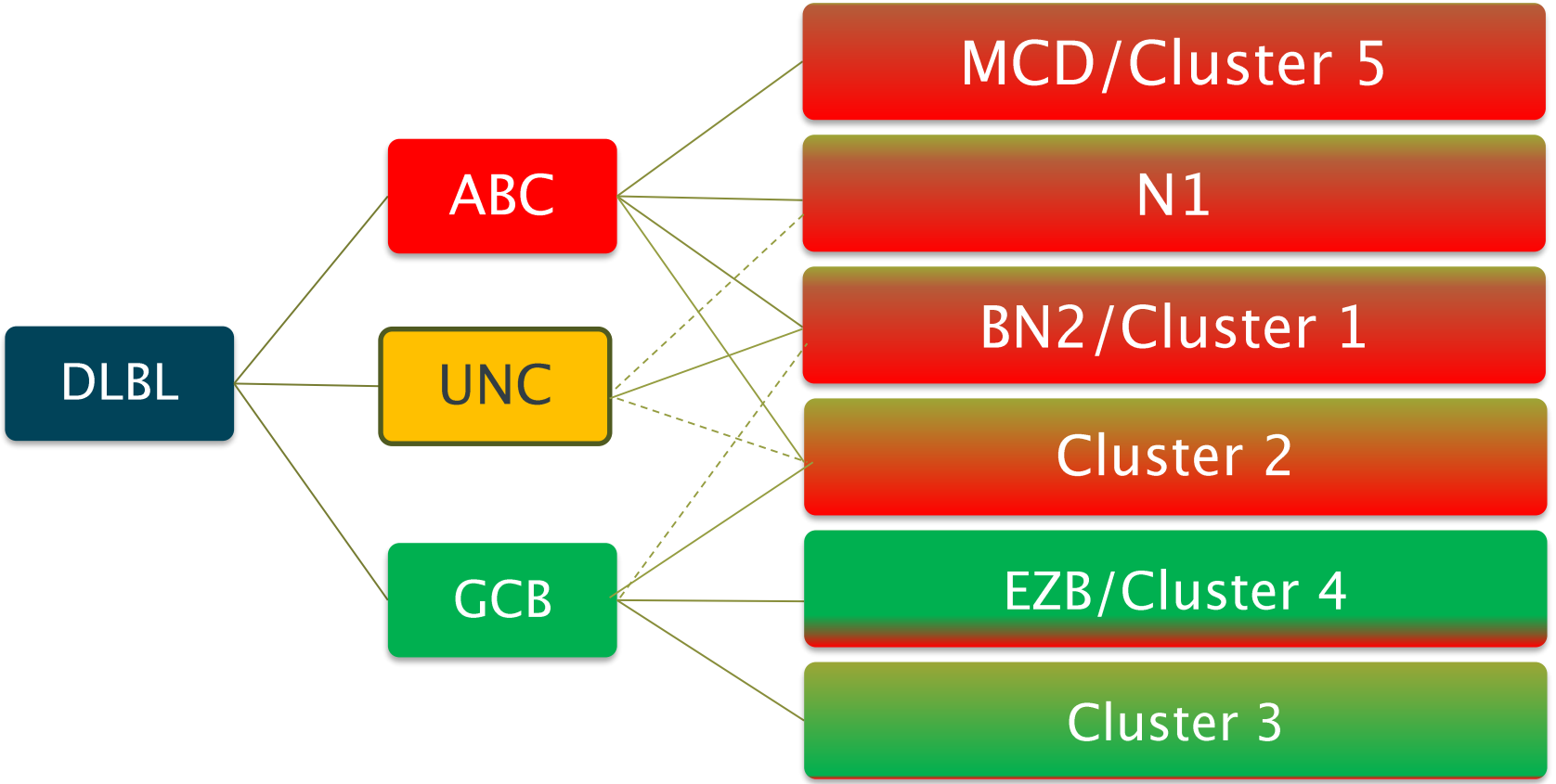


A Reddy et al., 2017;
Cell, 171:481-494

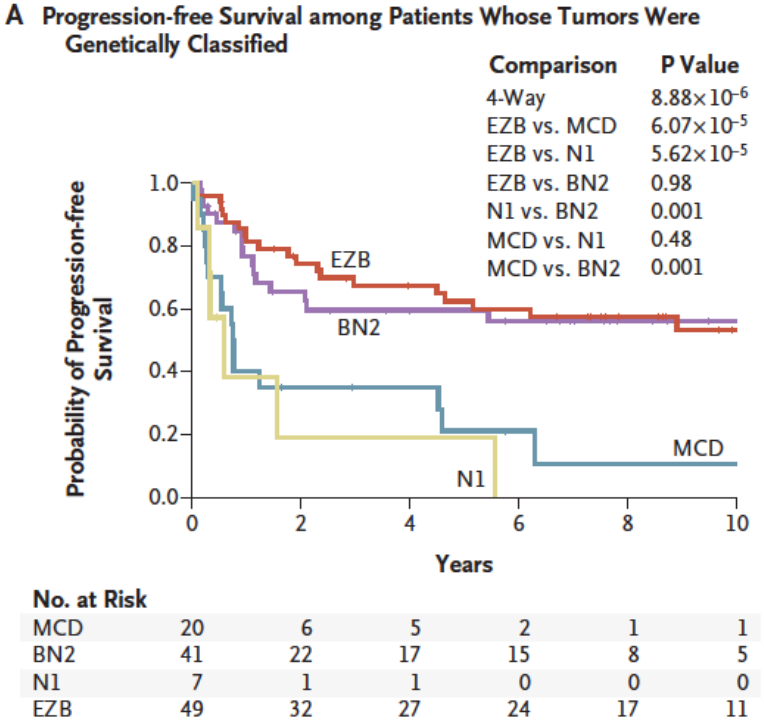
R Schmitz et al., 2018
N Engl J Med;378:1396-1407.

B Chapuy et al., 2018
Nat Med; 24:679–690

A new taxonomy ?



Differences in outcomes..



R Schmitz et al., 2018 N Engl J Med;378:1396-1407.

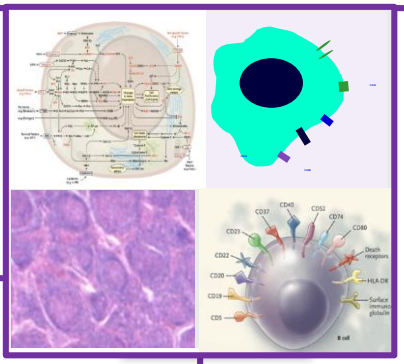
Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

- EZH2 — E7438
- CD79a/b — AEB071

- Proteosome inhibitors — Bortezomib
- Bcl-2 family inhibitors — ABT-263
- Survivin inhibitors — YM155
- Syk inhibitors — Fostamatinib, entosplentib



Pathways

- mTOR inhibitors — Everolimus, Temsirolimus
- PI3K inhibitors — Idelalisib, Copanlisib, Duvelisib, TGR-1202
- Btk inhibitors — Ibrutinib, ONO/GS-4059, ACP-196
- 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 inhibitors — MLN4924

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- Lenalidomide
- T-cell exhaustion

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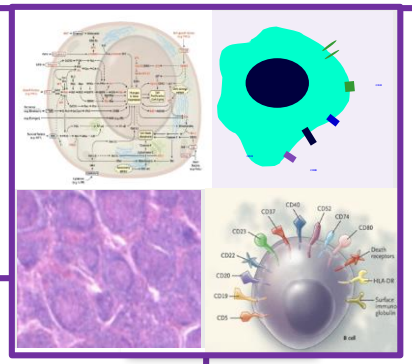

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- **Proteosome inhibitors** — Bortezomib
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- **Survivin inhibitors** — YM155
- **Syk inhibitors** — Fostamatinib, entosplentib
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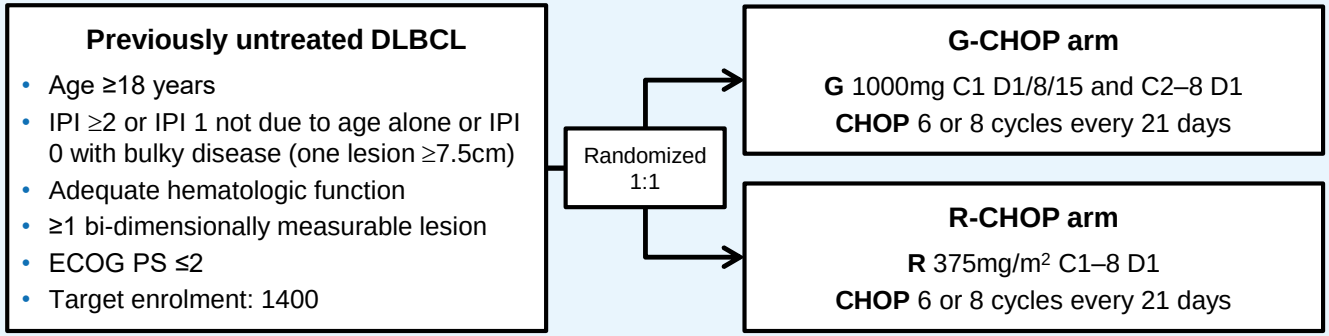
- **HDAC inhibitors** — Vorinostat, Panobinostat
- **PKC inhibitors** — Enzastaurin
- **Aurora kinase inhibitors**
- **Nedd8-activating enzyme inhibitors** — MLN4924

Using a novel anti CD20….no

Study design

International, open-label, randomized Phase III study in 1L DLBCL pts

- *Scientific support from the Fondazione Italiana Linfomi*

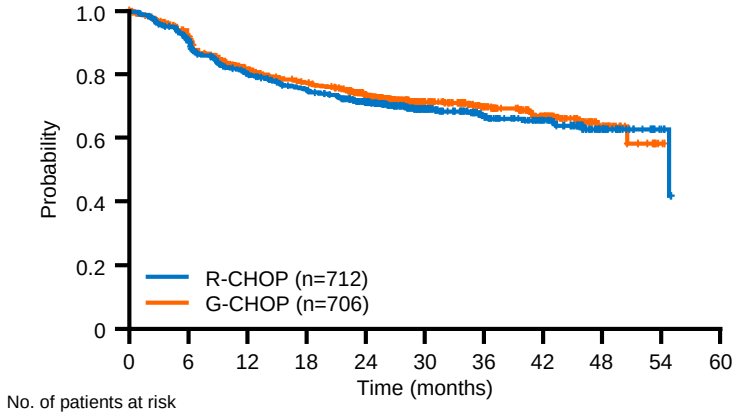


- Number of CHOP cycles pre-planned in advance for all pts at each site
- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region

Vitolo et al ASH 2016 and J Clin Oncol. 2017 Nov 1;35(31):3529-3537

Investigator-assessed PFS (primary endpoint)

Kaplan-Meier plot of investigator-assessed PFS by treatment arm



No. of patients at risk

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76, 1.11), p=0.3868	

Median follow-up: 29 months

*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles

Vitolo et al ASH 2016 and J Clin Oncol. 2017 Nov 1;35(31):3529-3537

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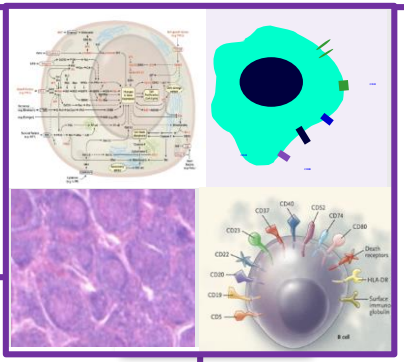

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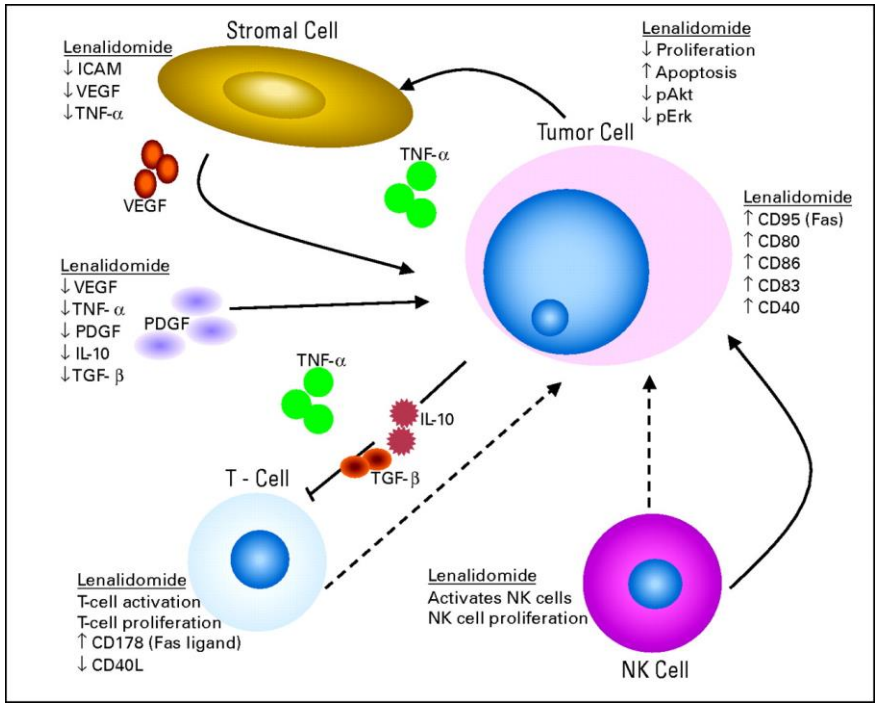
Lenalidomide

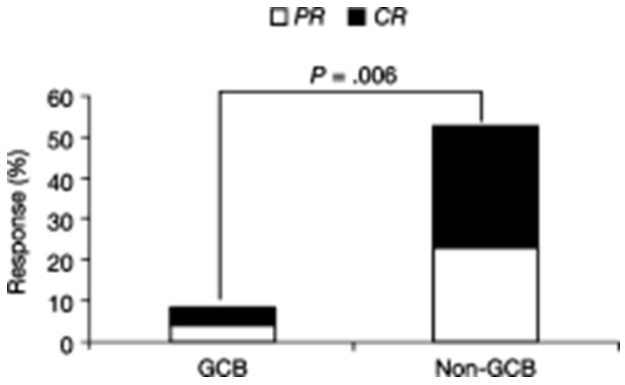
- Immunomodulatory properties
- Modulation of both cellular and cytokine tumour cell microenvironment
- Activates T cell and NK response to tumour cell
- Down regulates pro-survival cytokines
- Enhanced ADCC activity with rituximab



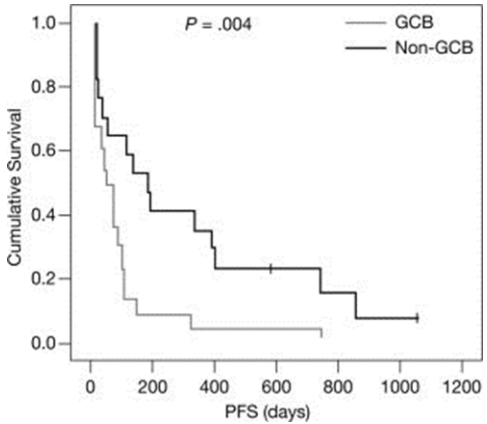
Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

Differential response according to cell of origin in DLBCL (n=40). Retrospective review.

Response rates



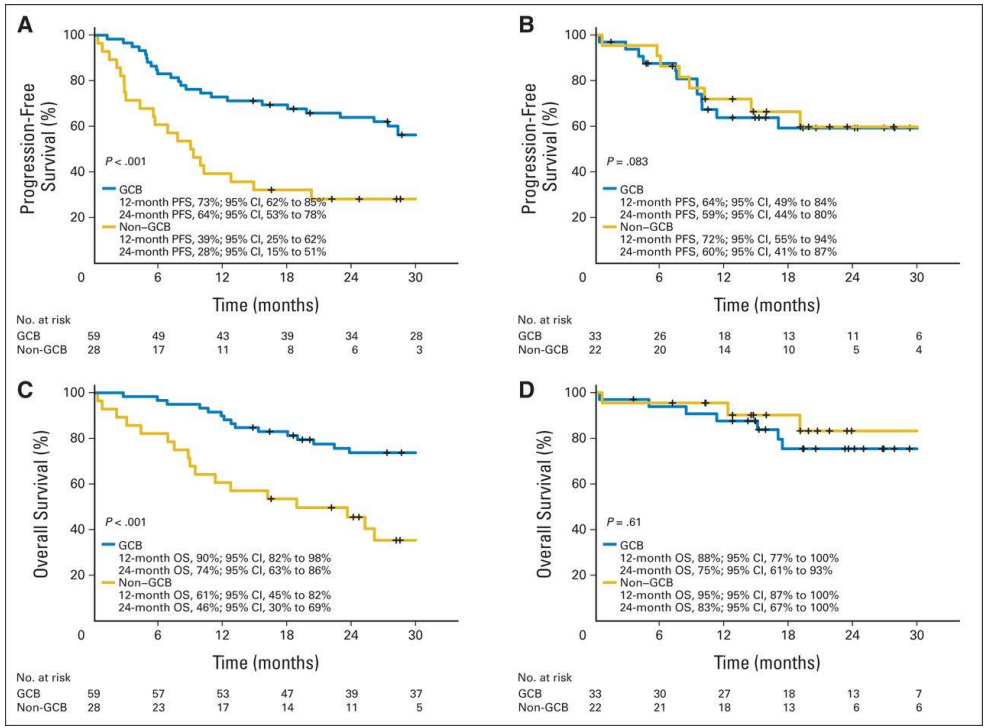
Progression-free survival



Hernandez-Ilizaliturri et al. Cancer 2011

Can over come the adverse outcome of ABC phenotype….

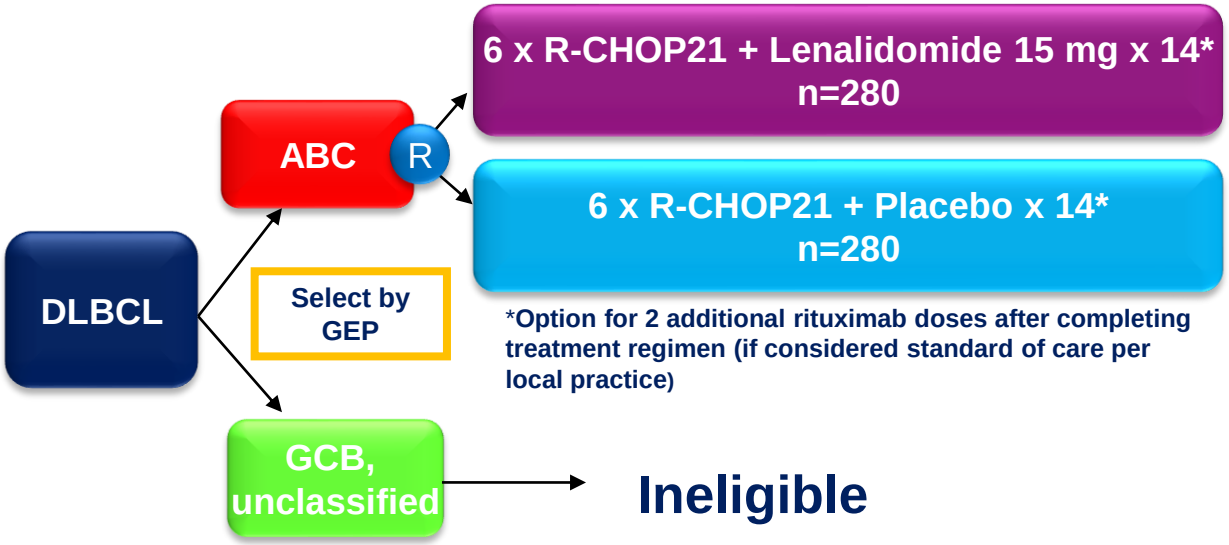
R-CHOP



R2-CHOP

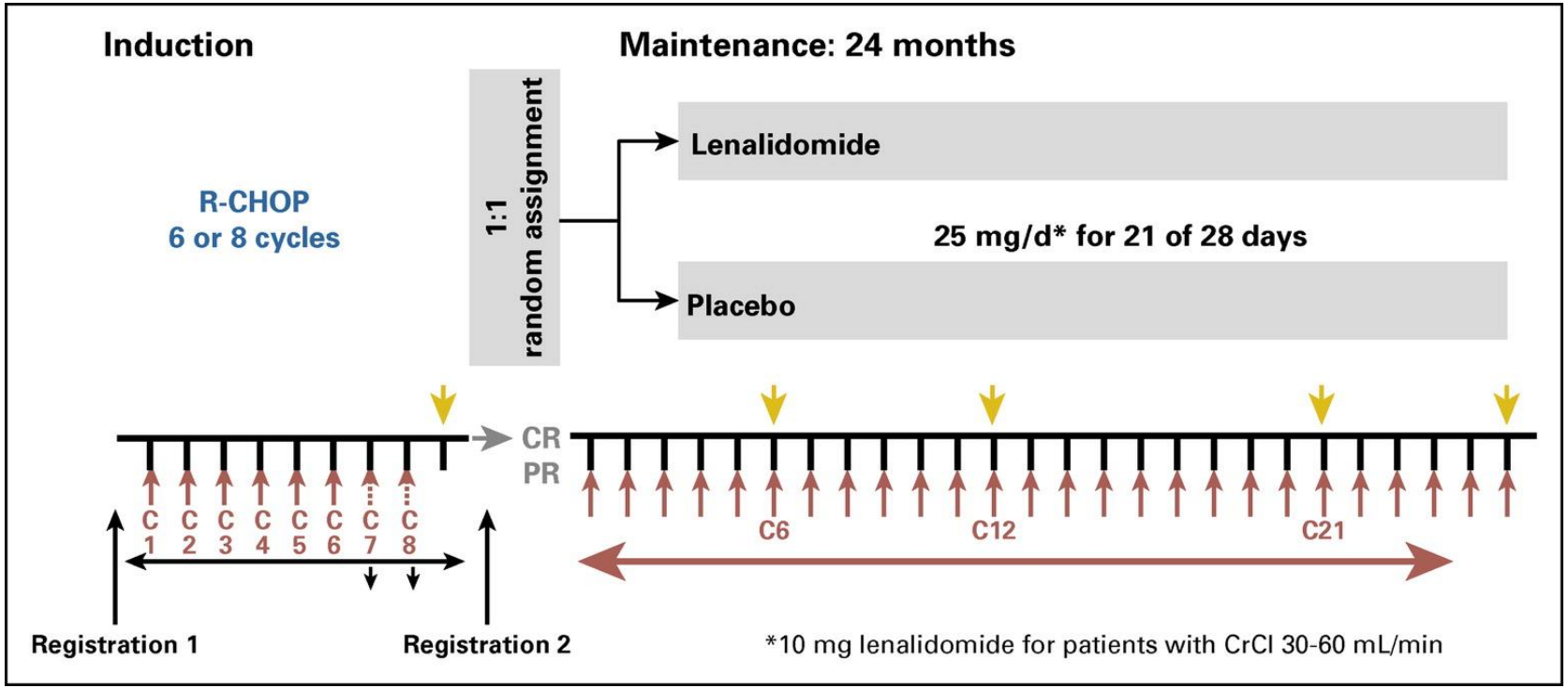
Grzegorz S. Nowakowski et al. JCO 2015;33:251-257

ROBUST
Clinical Study Design: Phase III double blind



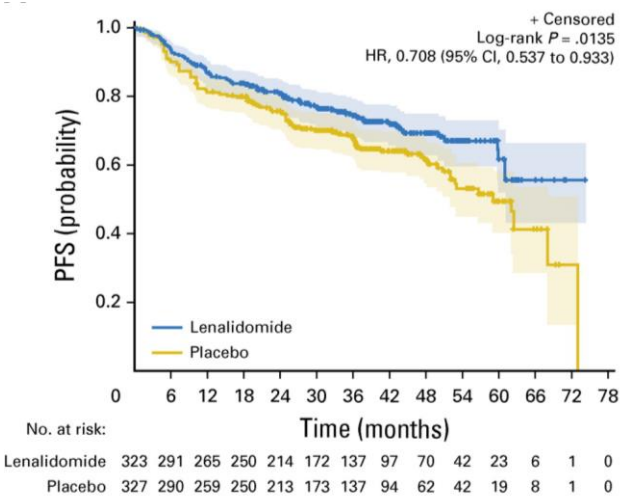
- Newly diagnosed DLBCL of ABC type
- IPI ≥ 2; ECOG PS ≤ 2; Age 18–80
- Primary Endpoint = PFS
- N = 560

REMARC: Lenalidomide maintenance (aaIPI≥1; 60-80 yrs)

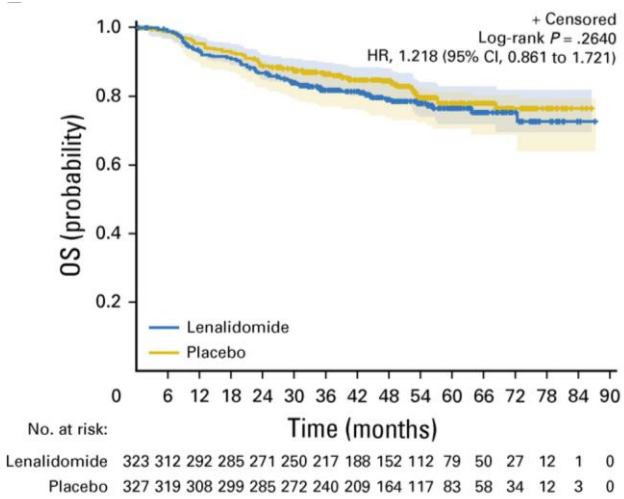


Thieblemont et al. JCO 2017

PFS



OS



Thieblemont et al. JCO 2017

36% patients discontinued therapy as a result of toxicity (vs 16% placebo)

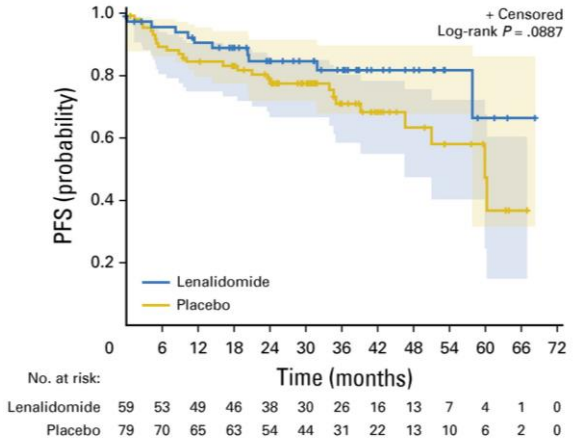
72% required a dose reduction

55% aged <70..? Fit for an alternative approach

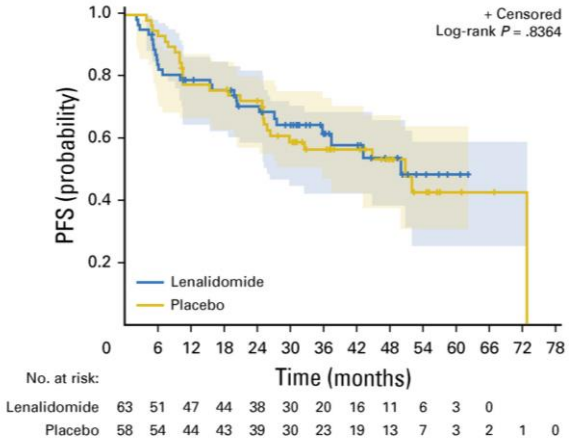
PET positive at end of induction had greatest benefit (HR=0.59 vs 0.78)

REMARC: Outcome by cell of origin

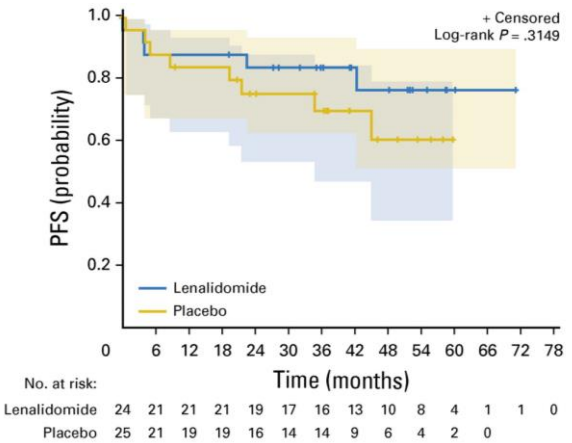
GCB



ABC



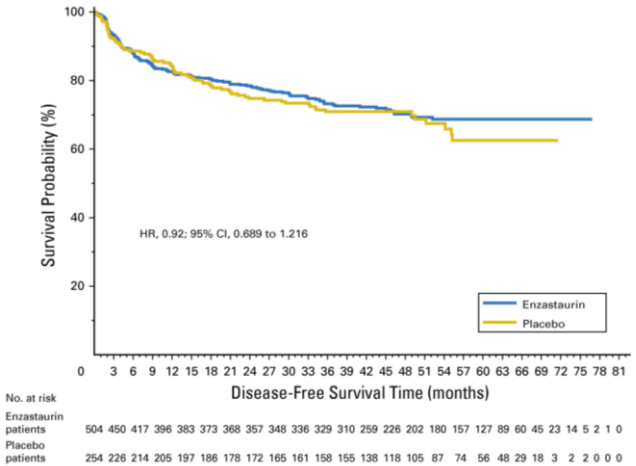
unclassified



Thieblemont et al. JCO 2017

Maintenance therapy in DLBCL

Enzastaurin



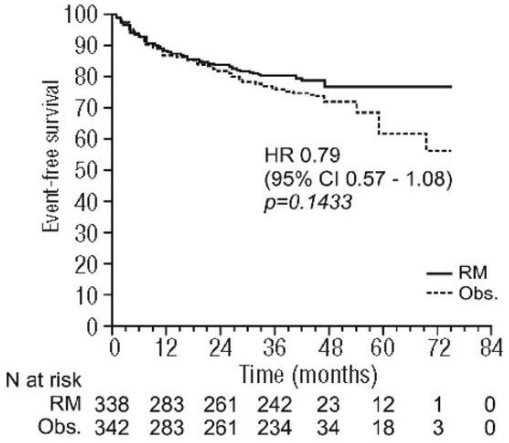
Crump et al. JCO 2016

Everolimus

DFS	0.92 (0.69–1.22)
OS	0.75 (0.51–1.10)

Witzig et al. ASCO 2016

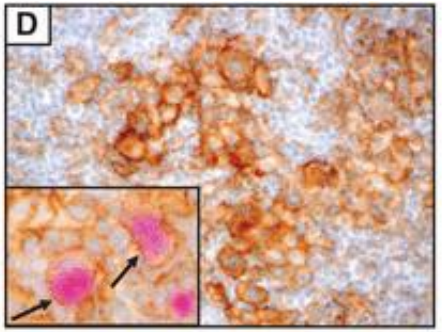
Rituximab



Jaeger et al. Haematologica 2015

PD1/PD-L1 in DLBCL

- Investigation of nivolumab (anti PD-1), pembrolizumab (anti PD-1), avelumab (PD-1), durvalumab (anti PD-L1) and atezoluimumab (PD-L1) in DLBCL
- PD-L1 expressed on about 10-30% of patients with DLBCL (more frequent in PMBL)
- High is EBV +ve DLBCL and TCRLCL (Chen et al. Clin Canc Res 2013)
- Nivoulumab ORR DLBCL 36% (n=11) median duration of response 22 weeks (Lesokhin et al. ASH 2014)
- Waiting for combination data…



(Chen et al. Clin Canc Res 2013)

Microenvironment

Lenalidomide

T-cell exhaustion

Actionable mutations

EZH2
E7438

CD79a/b
AEB071

Proteosome inhibitors
Bortezomib

Bcl-2 family inhibitors
ABT-263

Survivin inhibitors
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Syk inhibitors
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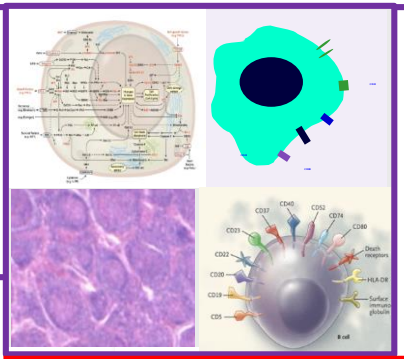


Pathways

mTOR inhibitors
Everolimus
Temsirolimus

PI3K inhibitors
Idelalisib
Copanlisib
Duvelisib
TGR-1202

Btk inhibitors
Ibrutinib
ONO/GS-4059
ACP-196

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

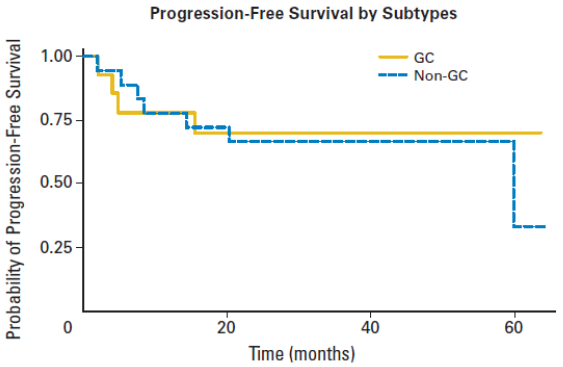
PKC inhibitors
Enzastaurin

Aurora kinase inhibitors

Nedd8-activating enzyme inhibitors
MLN4924

Is it possible to reverse the adverse outcomes of ABC DLBCL with bortezomib?...no

- The nuclear factor-kB (NF-kB) pathway is constitutively activated in ABC DLBCL[1]
- The proteasome inhibitor bortezomib is a potent inhibitor of NF-κB[2]; may therefore have specific utility in non-GCB DLBCL and overcoming the negative prognosis associated with non-GCB phenotype[3,4]

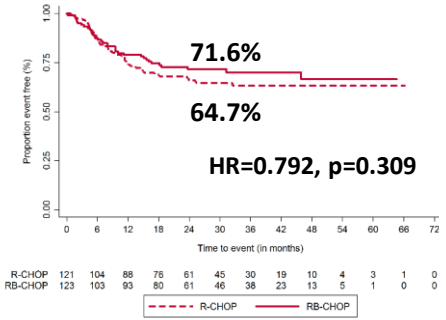


Ruan J et al. J Clin Oncol. 2011;29(6):690-697

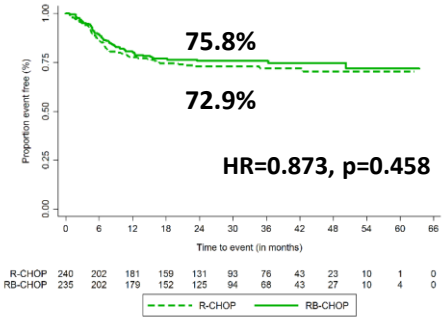
[1]Davis RE et al. J Exp Med. 2001;194(12):1861-1874.
[2]Bu R et al. Leuk Lymphoma. 2014; 55(2):415-424.
[3]Ruan J et al. J Clin Oncol. 2011;29(6):690-697.
[4]Dunleavy et al. Blood. 2009; 113(24):6069-6076.

Progression-free survival: Treatment arm and phenotype

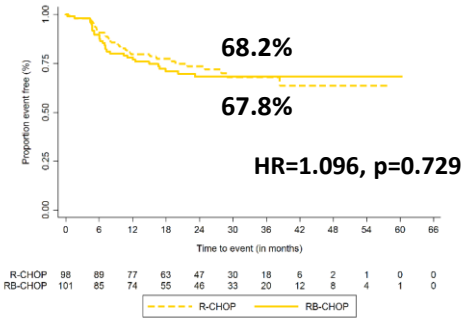
ABC: N=244



GCB: N=475



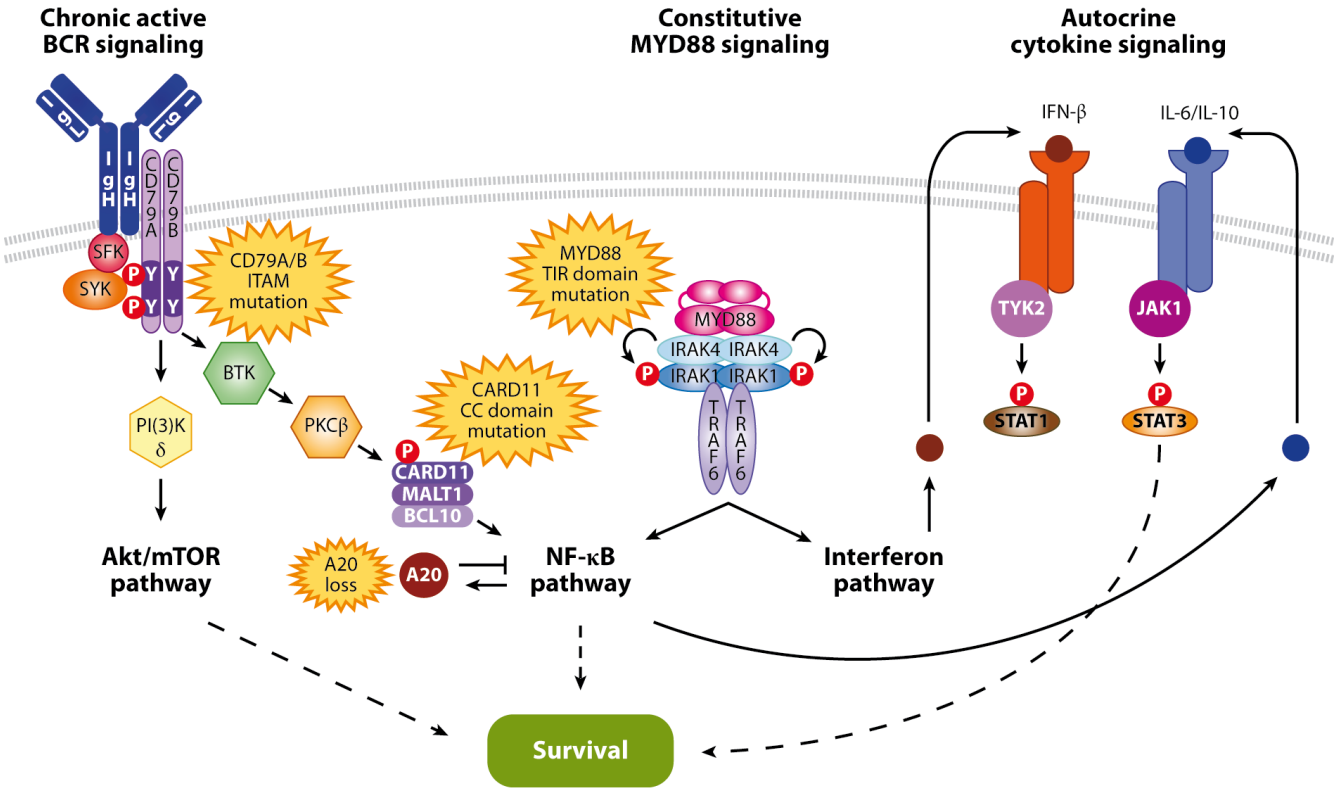
Unc. N=199



REMoDL-B

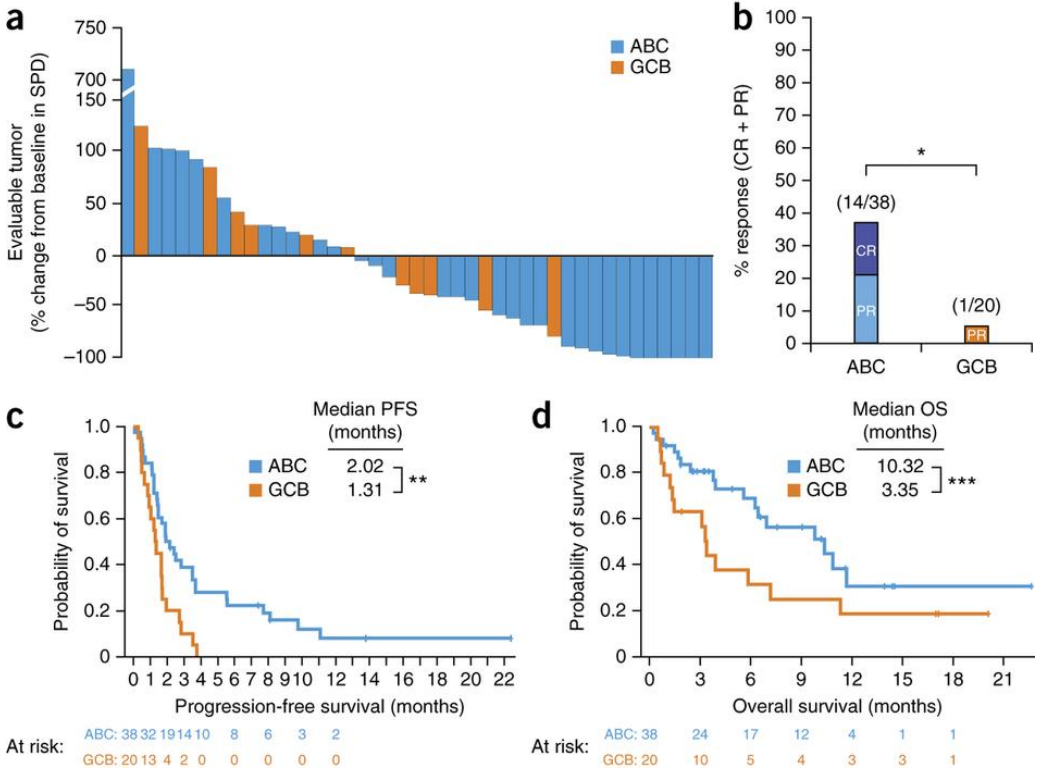
Davies et al ICML 2017

How about targeting BTK?...no



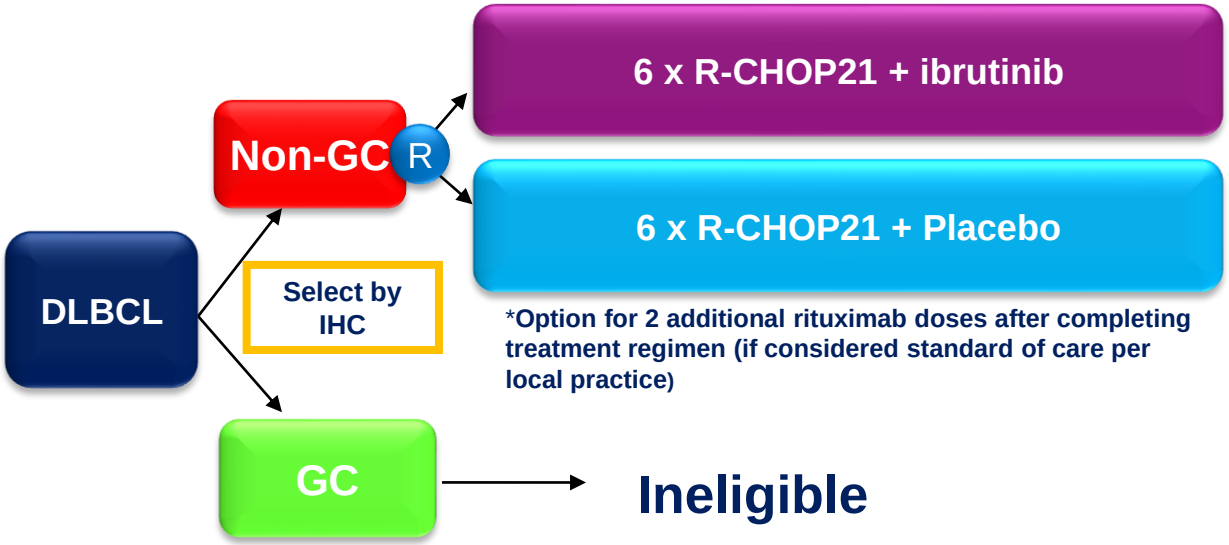
- Schaffer A L, et al. 2012. Ann. Rev. Immunol 30:565-610

Ibrutinib: Activity in ABC



Wilson et al 2015

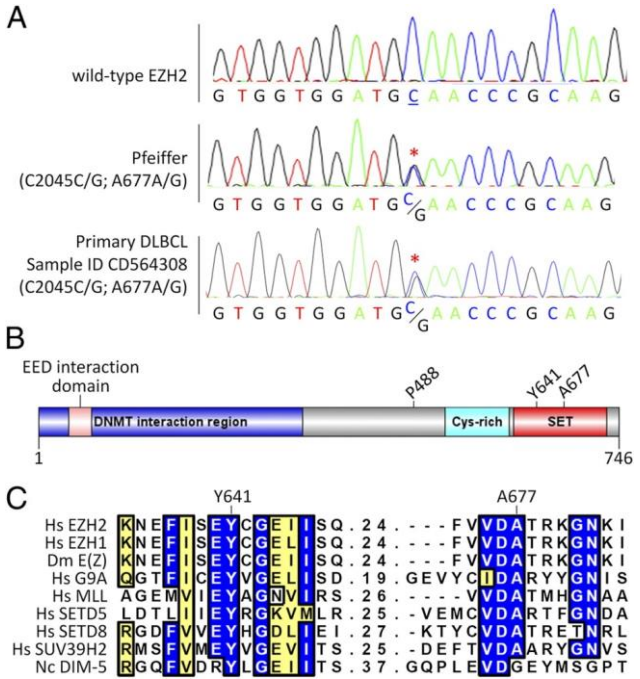
PHEONIX
Clinical Study Design: Double blind randomised phase III



- Newly diagnosed DLBCL of non-GC
- ECOG PS ≤ 2; Age 18–80
- Primary Endpoint = EFS
- N = 800

What about the GCB Phenotype?...anything yet in the front line?

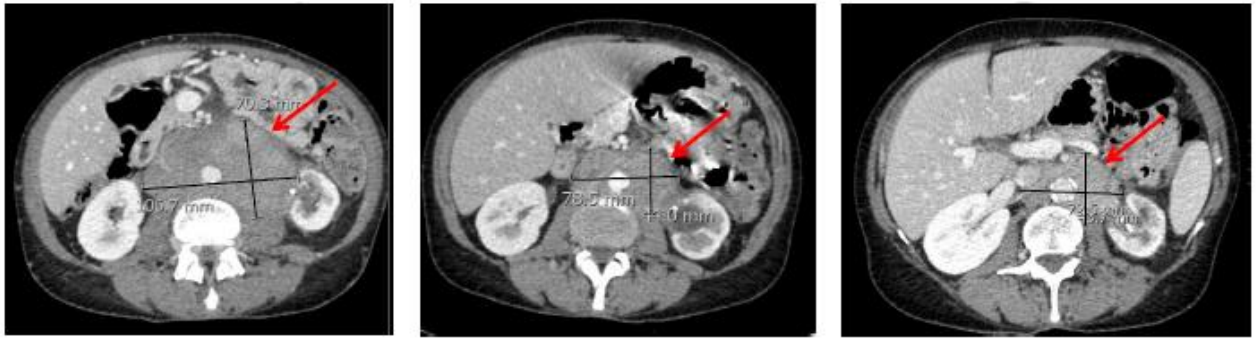
- Enhancer of Zeste 2 (EZH2) is the enzyme component of the Polycomb Repressive Complex 2 (PRC2) that methylates histone H3 on lysine 27 (H3K27)
- Somatic activating mutations in EZH2 have been identified in follicular and GCB-DLBCL *[Morin, 2010; Morin, 2011; Pasqualucci, 2011];*
- The frequency of the most prevalent mutation, Y641, 22% in DLBCL.
- Inhibitors in early phase investigation



McCabe M T et al. *Proc Nat Acad Sci USA* 2012;109:2989-2994

Activity in EZH2 mutated DLBCL (Ribrag et al ASH 2015)

53 year old female ($EZH2^{Y646H}$) treated at RP2D (800 mg BID)

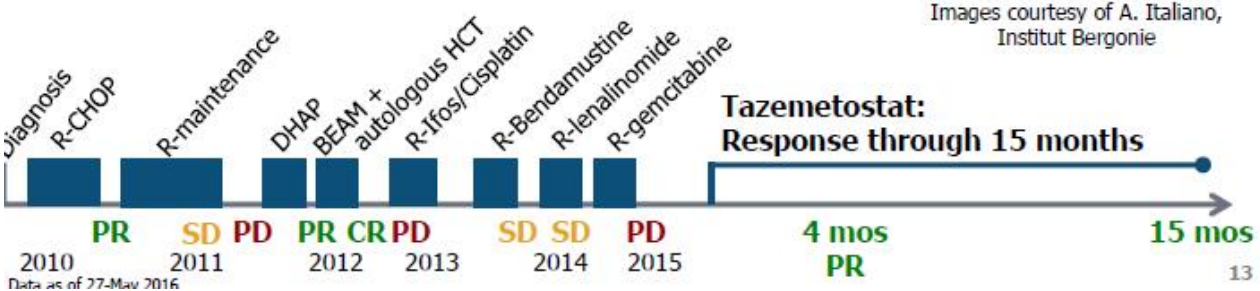


Baseline SPD: 8282mm²

Wk 16 SPD: 3864 mm² (PR)

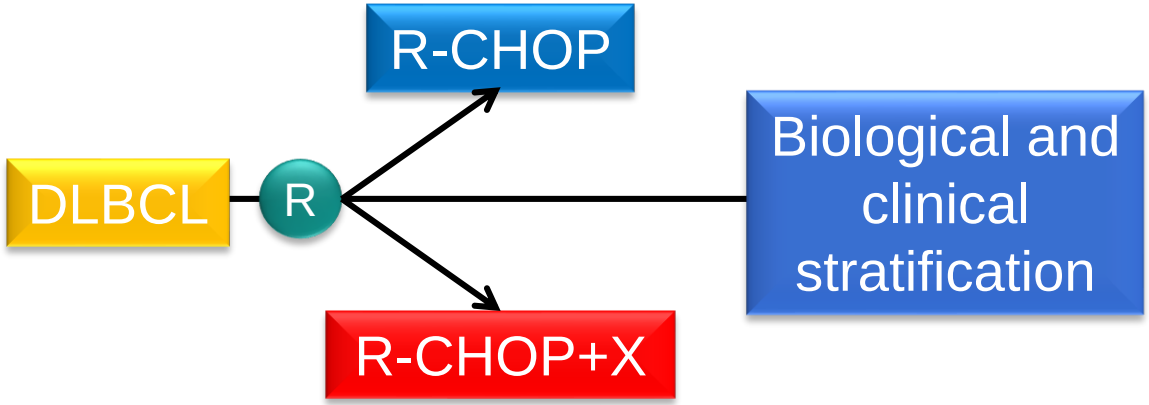
Wk 40 SPD: 3506 mm² (PR)

Images courtesy of A. Italiano, Institut Bergonie



Data as of 27-May 2016

The paradigm for study design….don’t change practice yet



Ongoing X=
Lenalidomide
Ibrutinib
Bortezomib
Brentuximab
Everolimus
Tazemetostat
More to come…

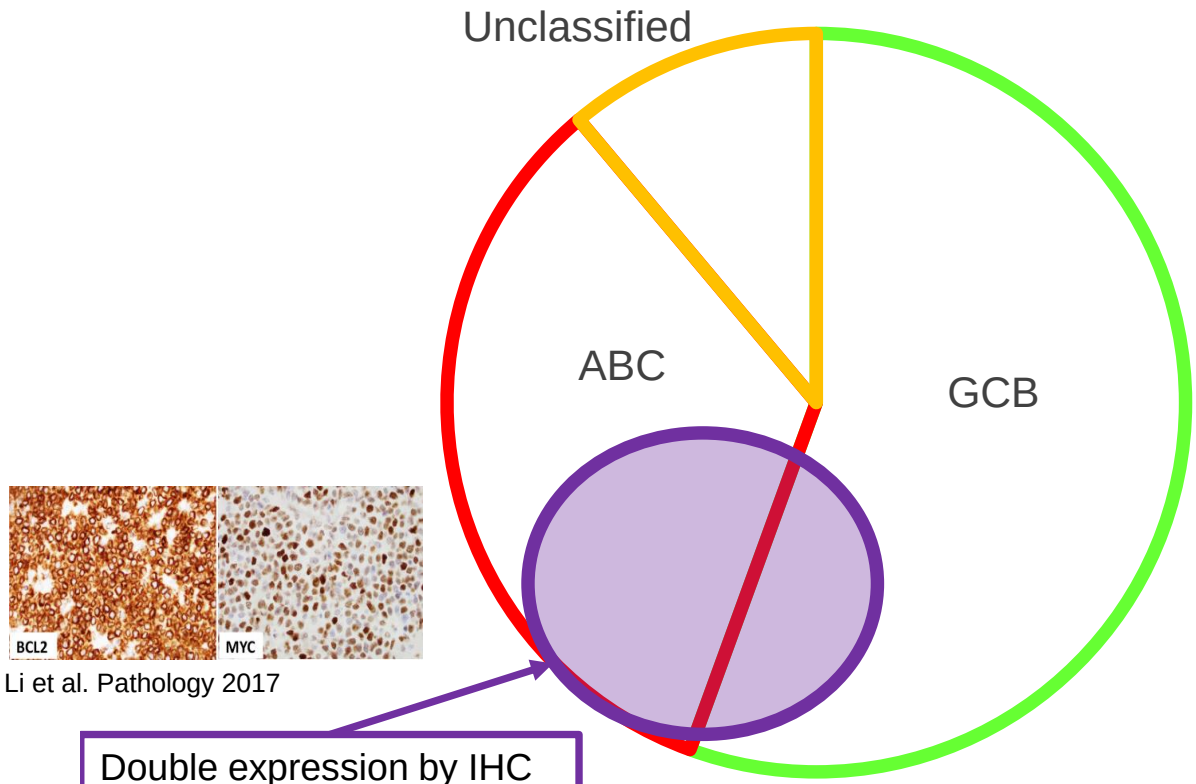
Can we practically deliver this design in phase III with so many agents?

Revision to WHO classification 2016

Diffuse large B-cell (NOS)	
	Germinal Centre B-cell type
	Activated B-cell type
T-cell/histiocyte rich large B-cell	
Primary DLBCL of central nervous system	
Primary cutaneous DLBCL leg type	
EBV+ DLBCL, NOS	
	EBV+ mucocutaneous ulcer
Primary mediastinal lymphoma	
Intravascular large B-cell lymphoma	
Primary effusion lymphoma	
Plasmablastic lymphoma	
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement	

Swerdlow et al. Blood 2016

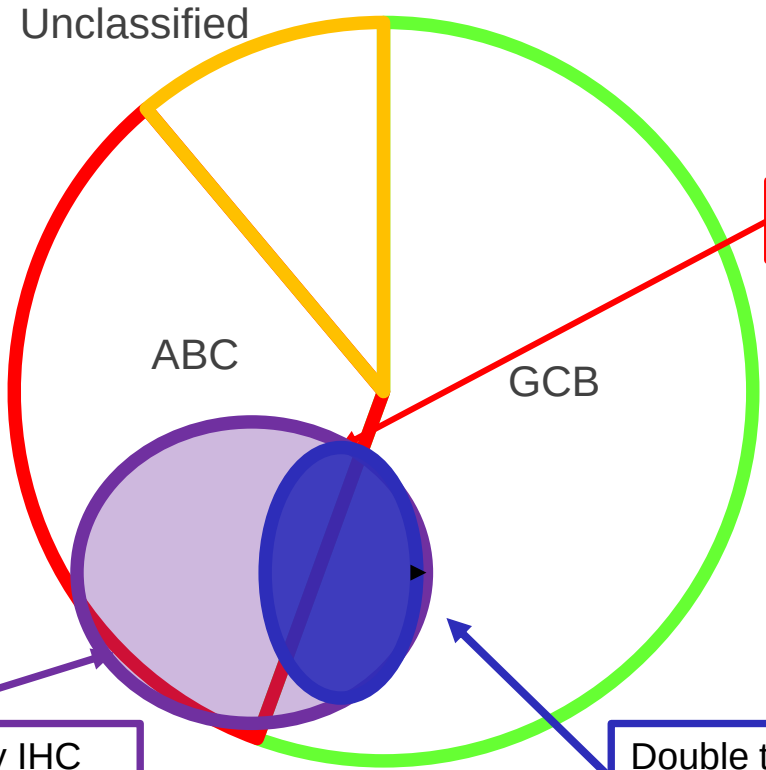
Double Expresser/Double Hit



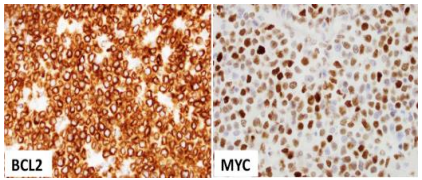
Li et al. Pathology 2017

Based on Friedberg Blood 2017

Double Expresser/Double Hit



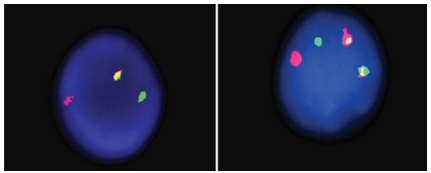
Probably MYC/BCL6



Li et al. Pathology 2017

Double expression by IHC
MYC and BCL2

MYC *BCL2*



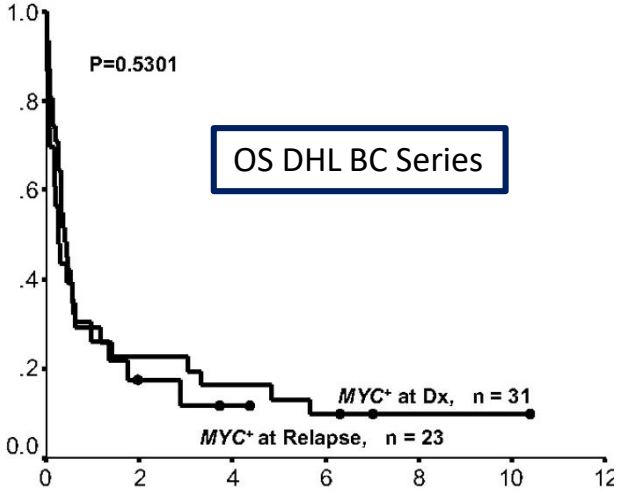
Mukhi and Chavez

Double translocation by FISH
MYC and *BCL2.*

Based on Friedberg Blood 2017

Double and Triple Hit…

- 5% of DLBCL patients
- Approx. 60% *BCL2*, 20% *BCL6* and 20% triple hit
- Limited data on *MYC/BCL6* DHL therapy
- R-CHOP is inadequate therapy
- Do we need to FISH all DLBCL cases? Low prevalence



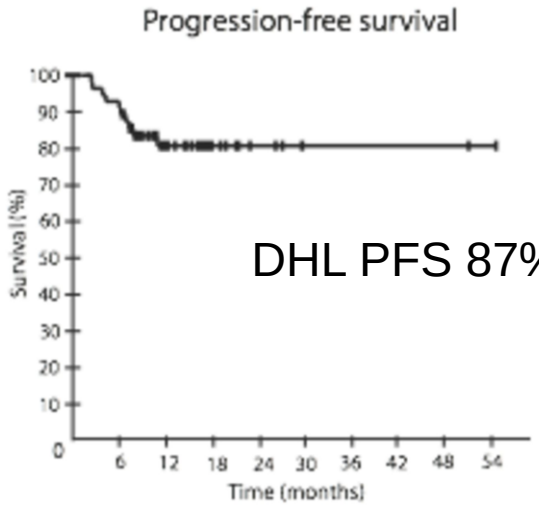
Johnson et al. Blood 2009

Clinical Features of *MYC/BCL2* and *MYC/BCL6* DHLs

Study	# DH	% Prev Ind NHL	Med Age	% Stage III/IV	% High LDH	% Pos BM	% Pos CNS
Bertrand	10	10	58	70	NA	NA	NA
Johnson	54	46	62	76	50	71	NA
Kanugo	14	None	55	NA	93	79	21
LeGouill	16	25	61	100	100	94	50
Macpherson	15	46	65	92	80	69	NA
Niitsu	19	None	61	100	100	84	21
Snuderl	20	15	64	95	100	59	45
Tomita	27	17	51	96	93	65	9
Oki	129	11	62	84	69	42	4
Petrich	181	22	60	81	76	41	7

DA-EPOCH-R

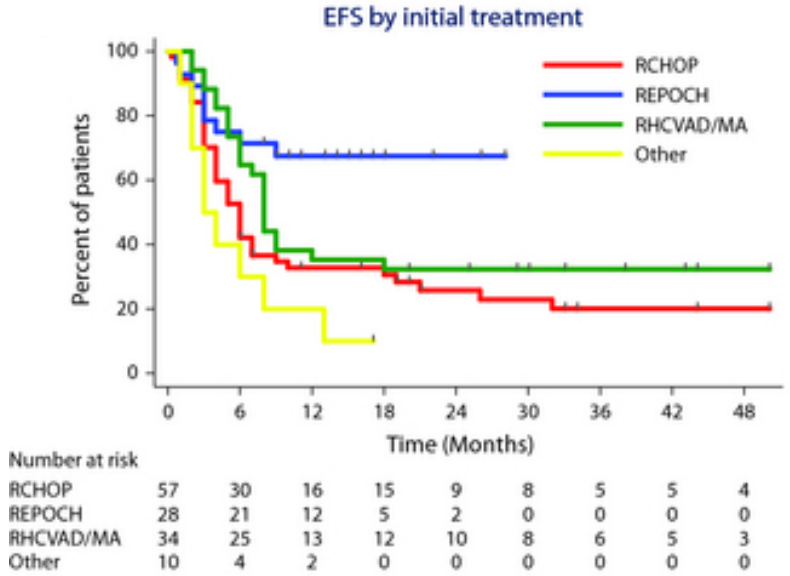
Prospective: *MYC* rearranged
(45 (14/31)% *BCL2* rearranged)



DHL PFS 87%

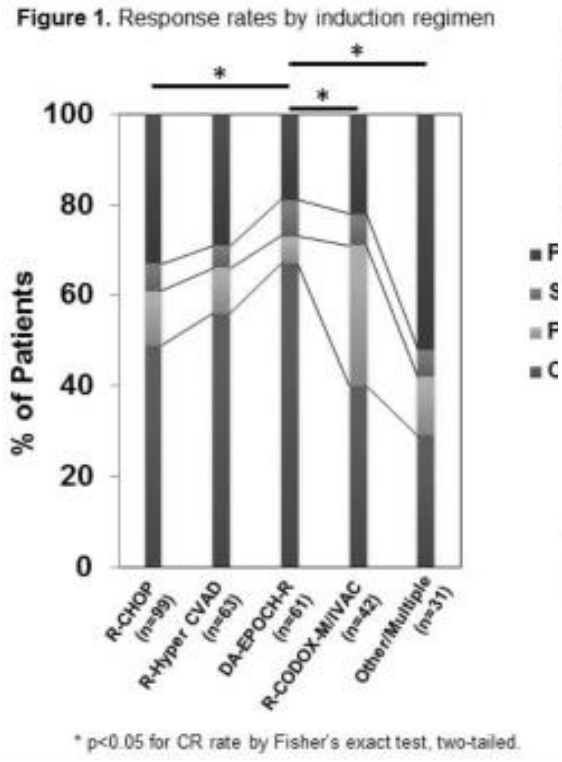
Dunleavy et al. ASH 2014

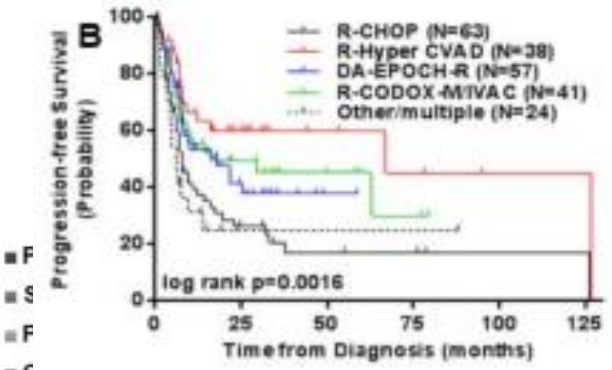
Retrospective: MDACC DHL



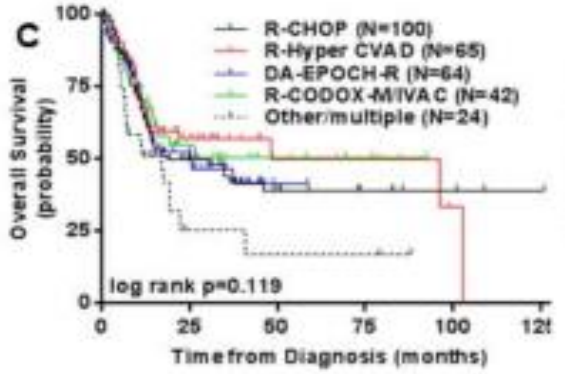
Oki et al. BJH 2014

A role for intensified therapies?.
Retrospective 23 US centres (n=311)





PFS

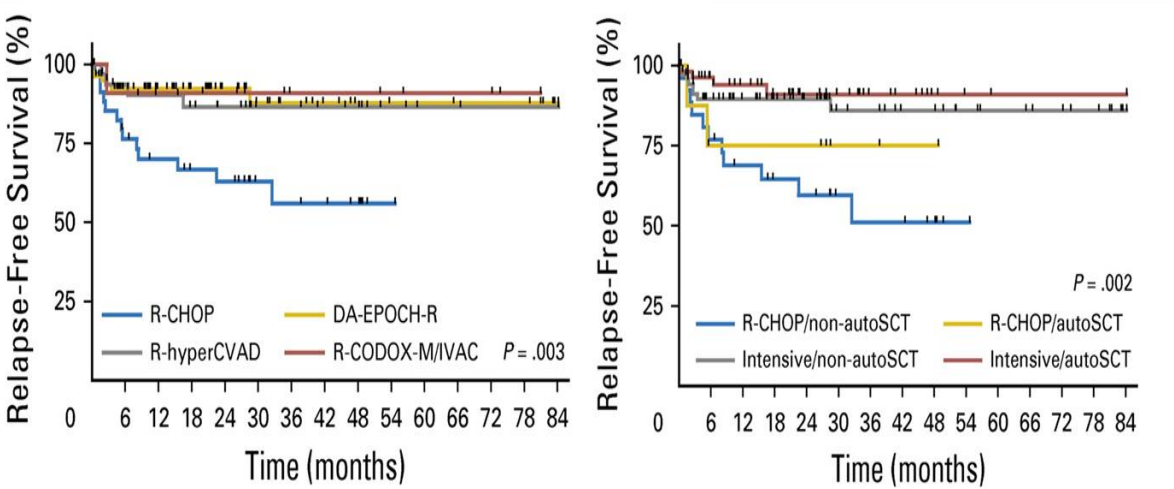


OS

Petrich at al Blood 2014

Sub-optimal induction needs consolidation

Landmark analysis: Time 0=three months after completion of therapy (n=159)

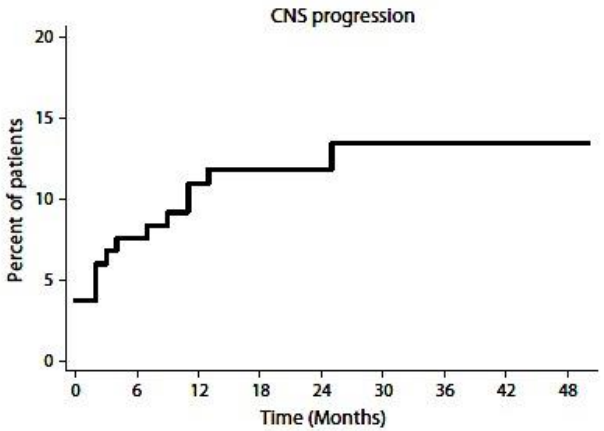


Landsburg et.al JCO 2017

CNS prophylaxis…yes

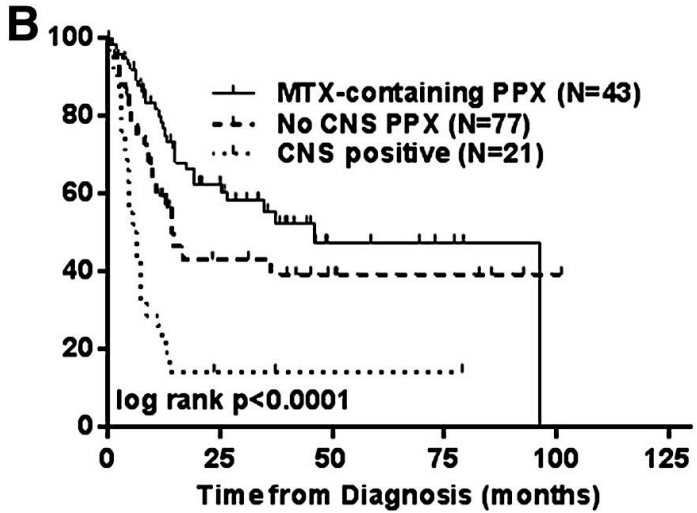
Incidence of CNS events high

13% cumulative risk of CNS progression in MDACC series



Oki et al B J Haem, 2014, 166, 891-901

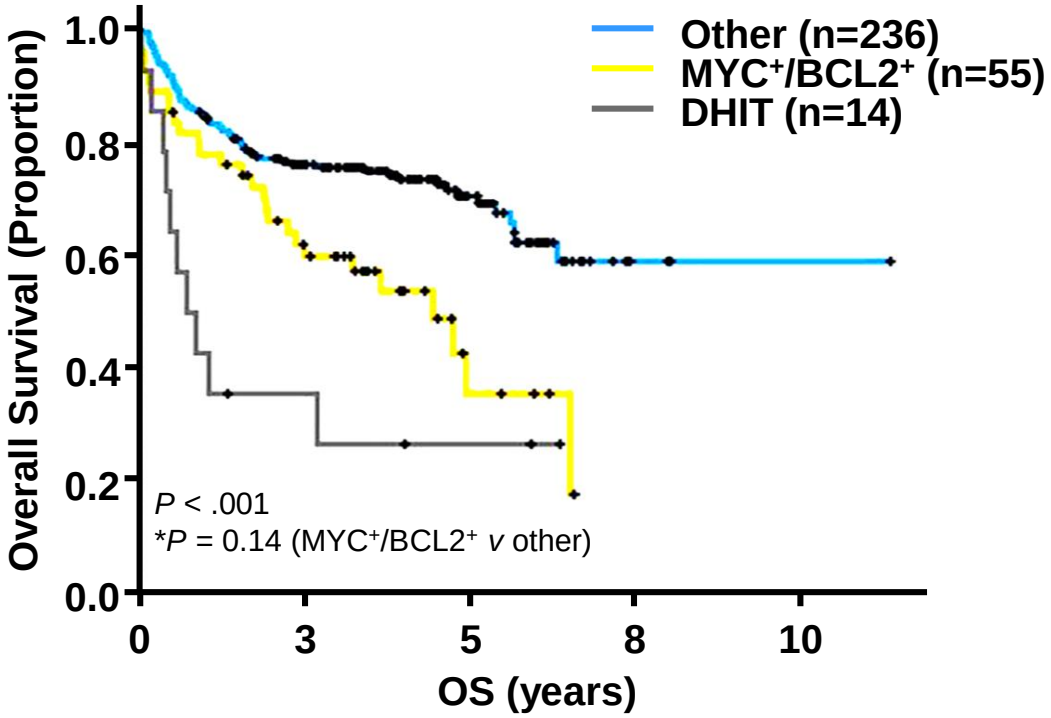
Attention to prophylaxis may improve outcomes



Petrich et al. Blood 2014;124:2354-2361

Double Expressers

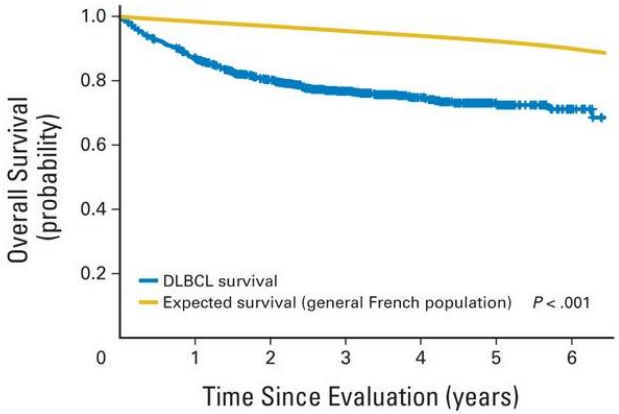
- Not recognised as a distinct entity. Biomarker for poor response
- Different IHC thresholds
- No prospective trials
- Priority for clinical investigations with novel agents
- At present R-CHOP



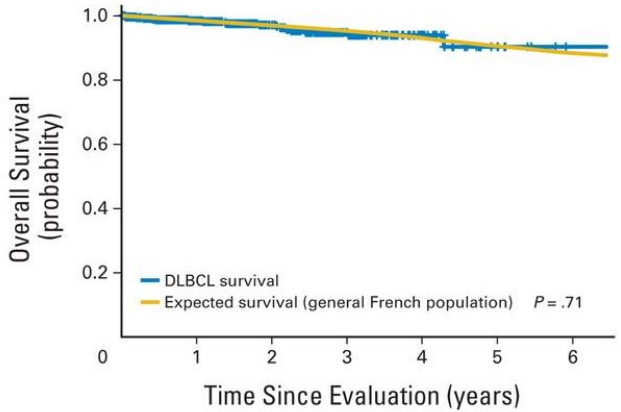
Johnson N A et al. JCO 2012;30:3452-3459

Events occur early…

Overall survival from diagnosis

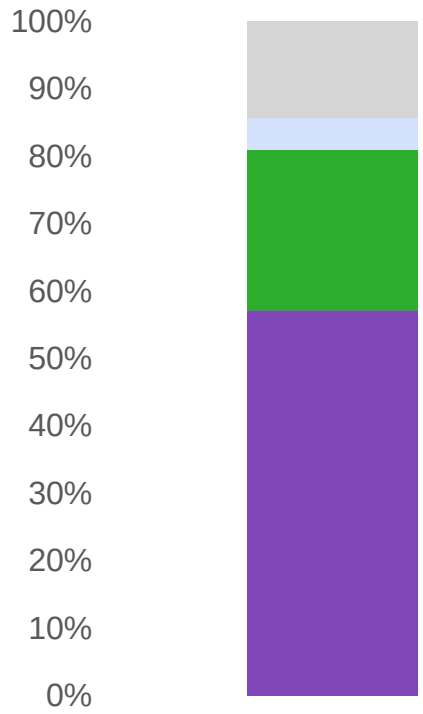


Overall survival from 2 years event free



Maurer M J et al. JCO 2014;32:1066-1073

Outcomes of R-CHOP population



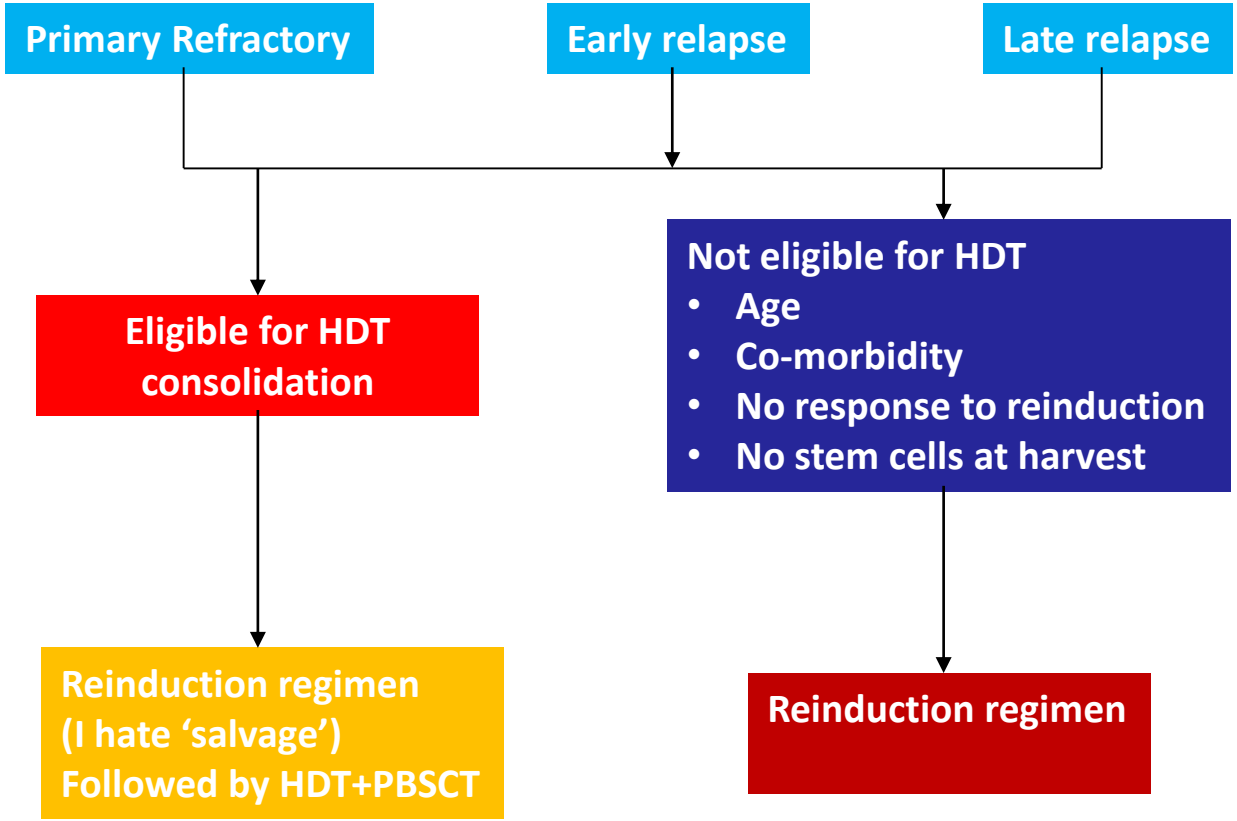
15-25% refractory

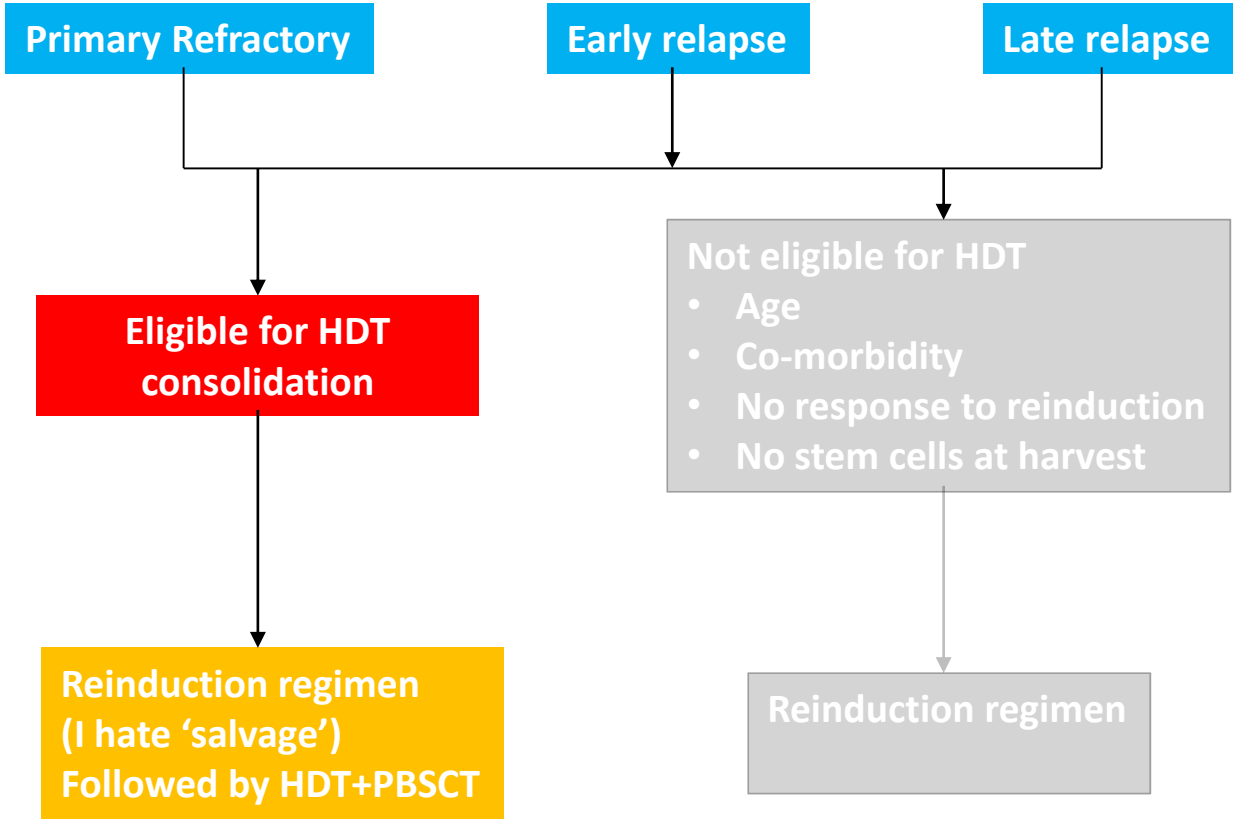
5% PR patients

20-30% relapses

50-60% cured

Coiffier and Sarkozy et al 2016


Primary Refractory
Early relapse
Late relapse
Eligible for HDT consolidation
Not eligible for HDT
• Age
• Co-morbidity
• No response to reinduction
• No stem cells at harvest
Reinduction regimen (I hate 'salvage') Followed by HDT+PBSCT
Reinduction regimen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• Age
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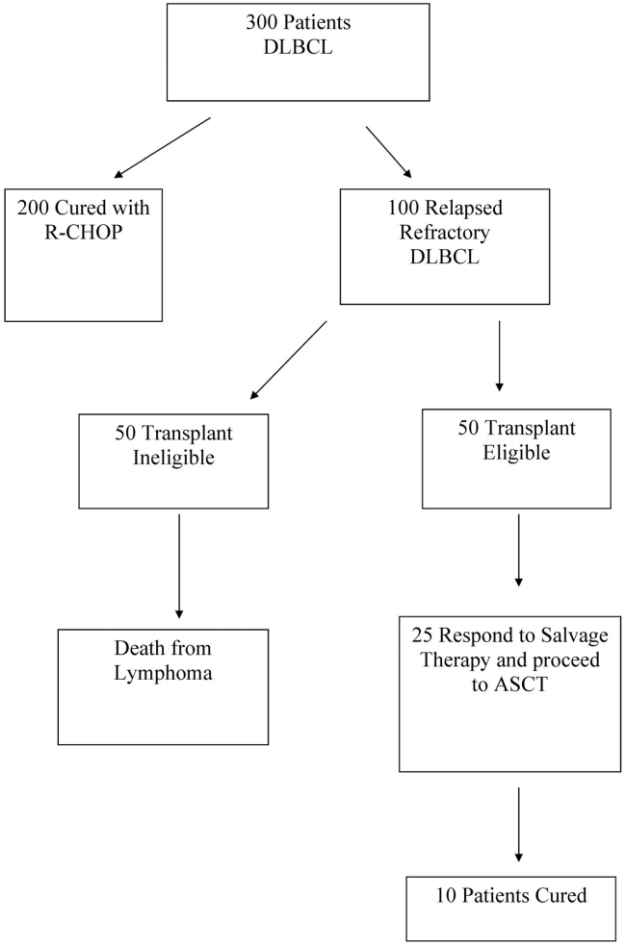
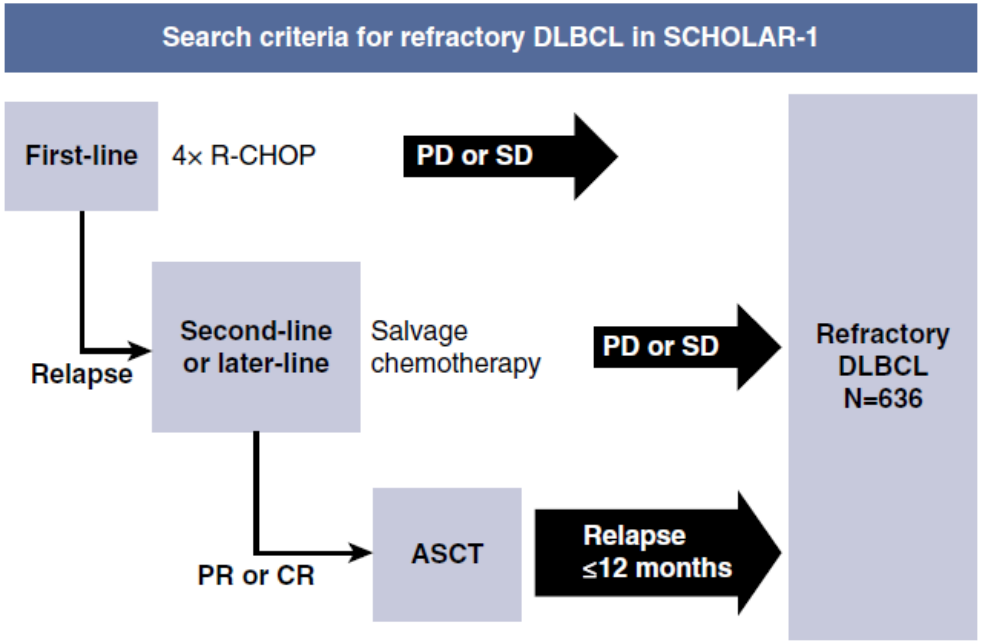
Reinduction regimen (I hate 'salvage') Followed by HDT+PBSCT
Reinduction regimen

The limited value of HDT+PBCT in relapsed DLBCL

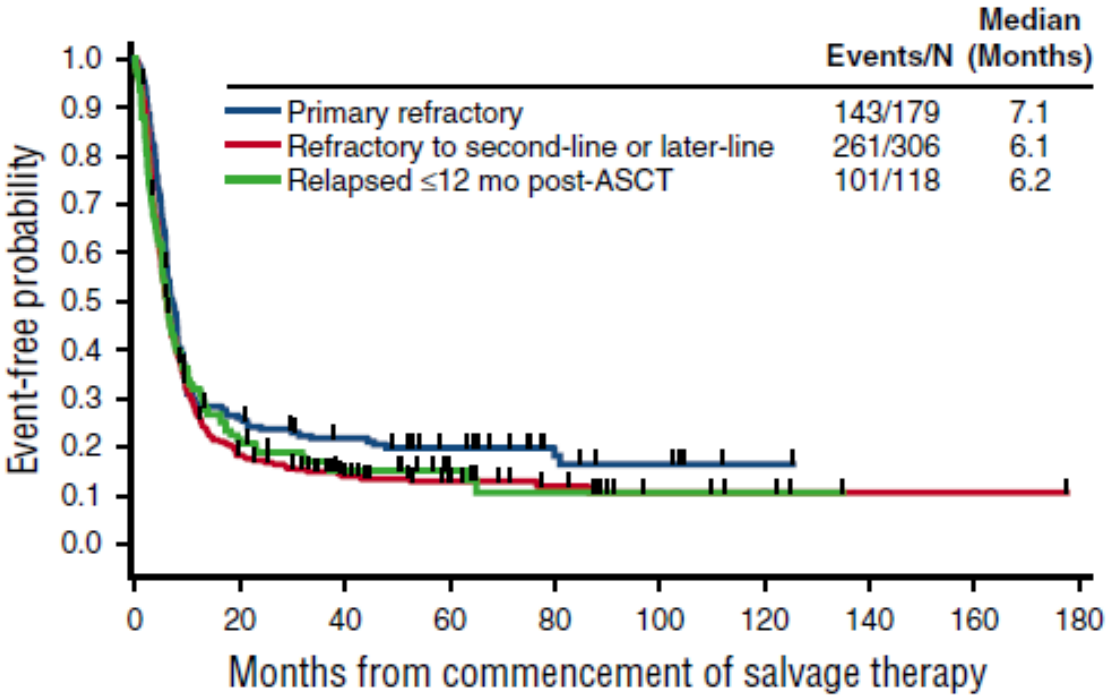


Friedberg 2011

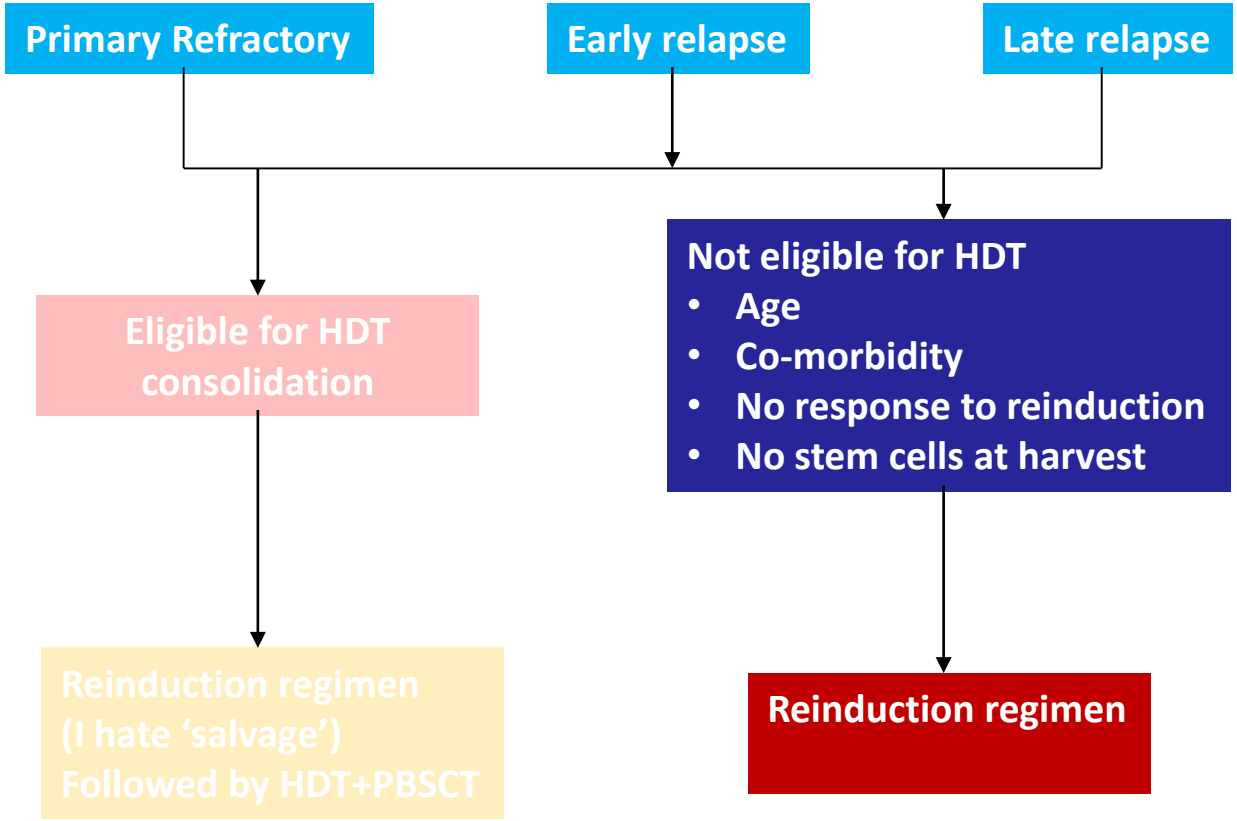
SCHOLAR-1



Crump et al. 2017



Crump et al. 2017


Primary Refractory
Early relapse
Late relapse
Eligible for HDT consolidation
Not eligible for HDT
• Age
• Co-morbidity
• No response to reinduction
• No stem cells at harvest
Reinduction regimen (I hate 'salvage') Followed by HDT+PBSCT
Reinduction regimen

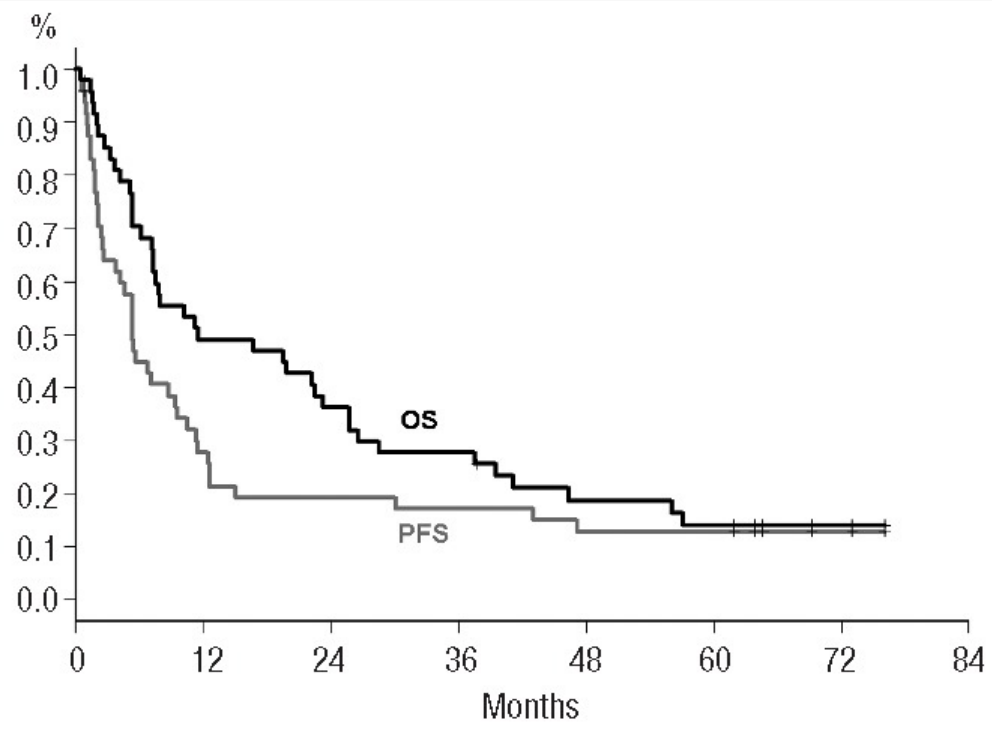
GemOX:

Characteristics	N. of patients (%) CR/Cru	PR	SD	ORR (%)	PD	P	Total n.
All	11/10 (44)	8 (17)	5 (10)	61	14 (29)		48
Prior high-dose therapy							
Yes	3/0 (17)	4	1	41	2	0.05	17
No	8/10 (58)	4	1	71	3		31
Prior treatment with rituximab							
Yes	7/6 (42)	4 (13)	3 (10)	55	11(35)	0.29	31
No	4/4 (48)	4 (24)	2 (12)	71	3 (18)		17
Duration of response to last treatment							
< 1 year	2/2 (18)	4 (18)	4 (18)	36	10 (45)	0.002	22
> 1 year	9/8 (66)	4 (15)	1 (4)	81	4 (15)		26
Saa IPI							
0-1	3/1 (33)	3 (25)	2 (17)	58	3 (25)	0.90	12
2-3	8/9 (47)	5 (14)	3 (8)	61	11(31)		36
Saa IPI							
0-2	3/1 (27)	3 (20)	3 (20)	47	5 (33)	0.19	15
3-5	8/9 (51)	5 (15)	2 (6)	66	9 (27)		33
Subtype							
GC	3/5 (61)	3	0	84	1	0.11	13
Non-GC	6/4 (45)	3	1	59	3		22

CR: complete response; CRu: unconfirmed CR; PR: partial response; SD: stable disease; ORR: overall response rate; PD: progressive disease, GC germinal center. Saa-IPI score: secondary age-adjusted International Prognostic Index score.

Mournier et al.

R-GemOX in R/R DLBCL



Mournier er al.

Pixantone

- Phase III open label

Aggressive Lymphoma*
Relapsed ≥2 therapies (inc 1 anthracycline with response >24 weeks)
LVEF≥50%

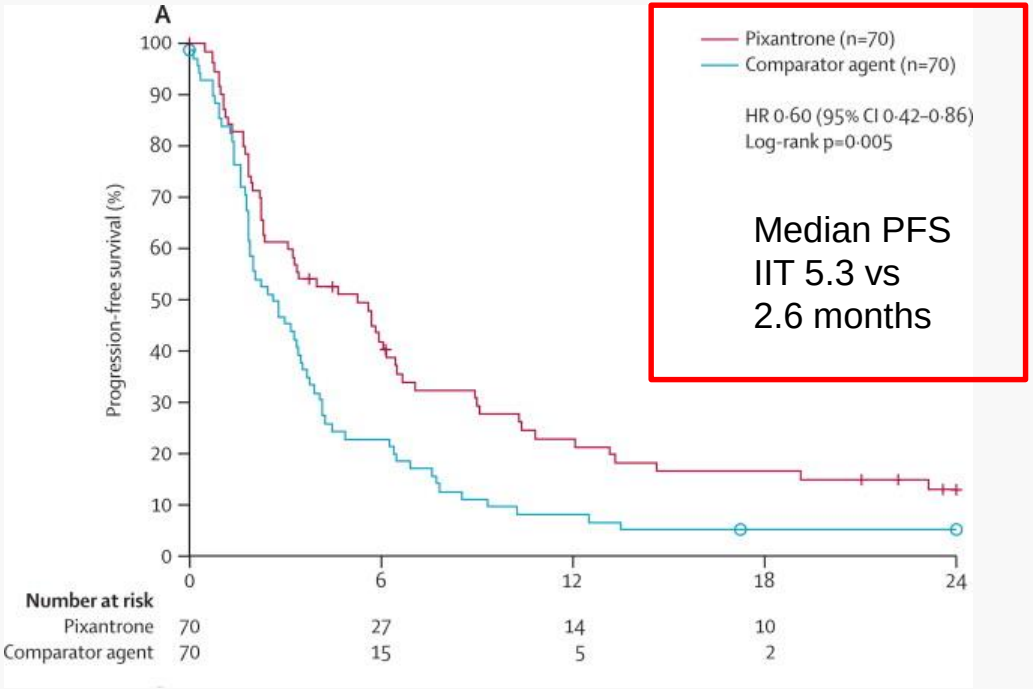
1º Endpoint: CR/CRu
2º Endpoints: ORR, PFS, OS

R

Pixantrone	85mg/m^2	1, 8 and 15	28 days
Vinorelbine	30 mg/m^2	1, 8, 15, and 22	4 weeks
Oxaliplatin	100 mg/m^2	1	3 weeks
Ifosfamide	3000 mg/m^2	1 and 2	4 weeks
Etoposide	100 mg/m^2	1, 2, 3, 4, and 5	4 weeks
Etoposide	50 mg/m^2	Daily for 21 days	4 weeks
Mitoxantrone	14 mg/m^2	1	3 weeks
Gemcitabine	1250 mg/m^2	1, 8, and 15	4 weeks
Rituximab	375 mg/m^2	1, 8, and 15 of cycle 1 and day 1 of cycle 2	3 weeks

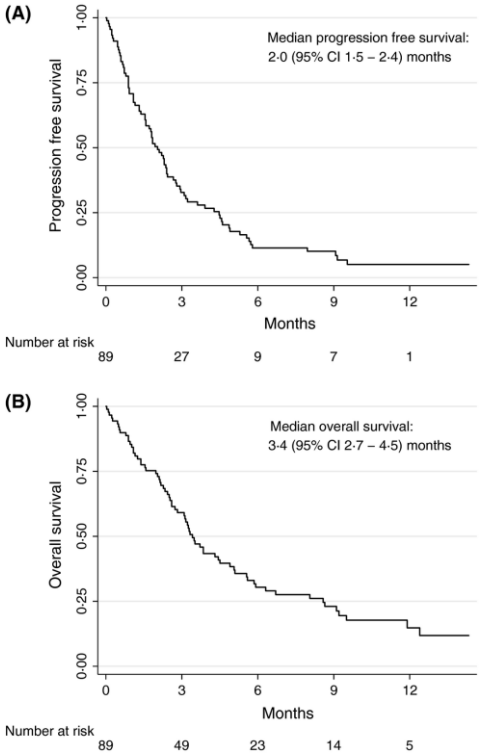
* Exclusion of Burkitt's, lmyphoblastic, Mantle, CNS, HIV related

Pixantrone….



Pettengell et al. Lancet Oncol 2012

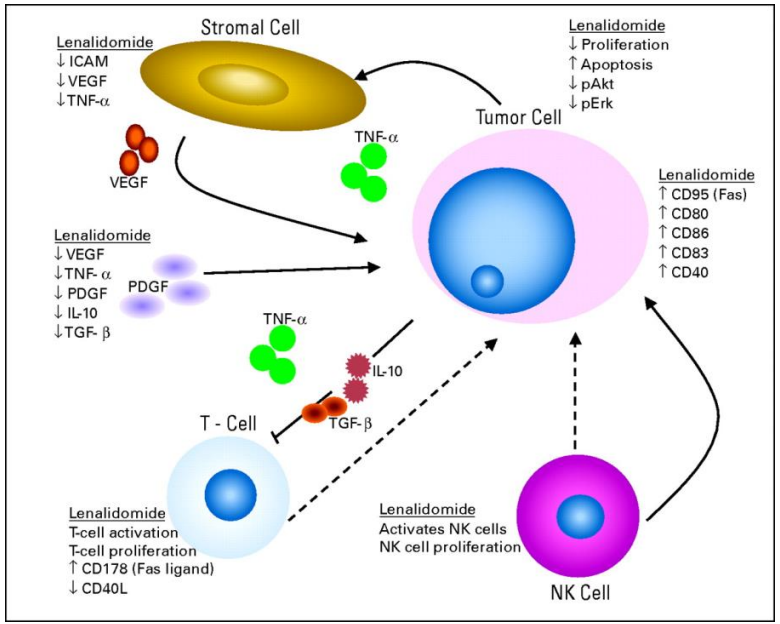
Pixantrone..real world experience (Eyre et al 2016)



92 R/R DLBCL
85% refractory disease
72% had an international prognostic index (IPI) 3–5
Median PFS 2·0 months (95% confidence interval (CI) 1·5–2·4
Median OS was 3·4 months (95% CI 2·7–4·5).
ORR 24% (complete response 10%; partial response 14%).

Lenalidomide

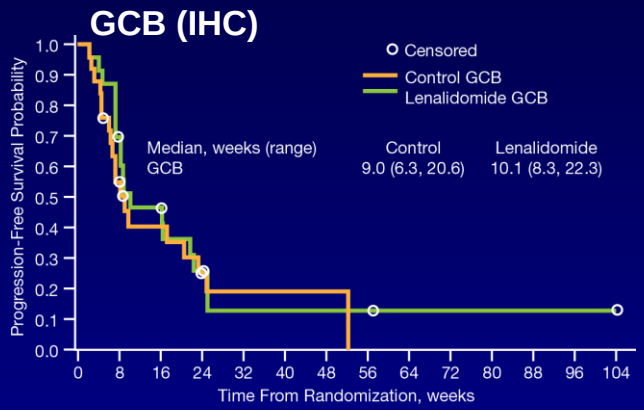
- Immunomodulatory properties
- Modulation of both cellular and cytokine tumour cell microenvironment
- Activates T cell and NK response to tumour cell
- Down regulates pro-survival cytokines
- Approval in myeloma

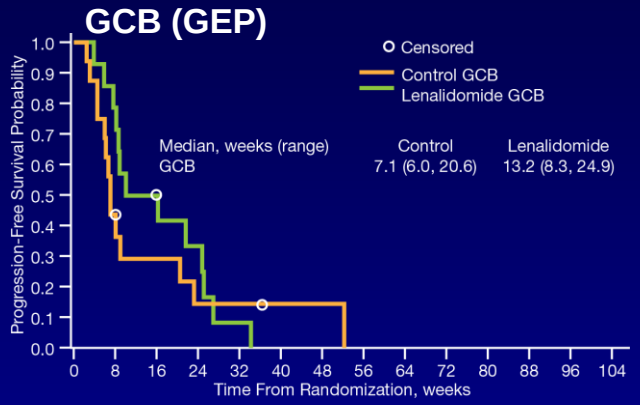


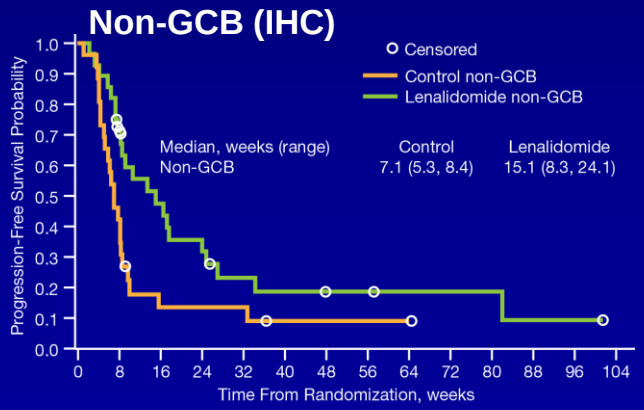
Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

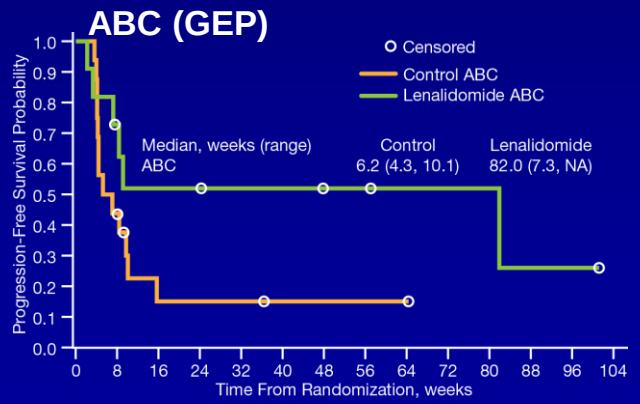
DLC-001: Lenalidomide in R/R DLBCL Subtypes

Progression-free Survival (IHC versus GEP) Czuczman et al ASH 2014









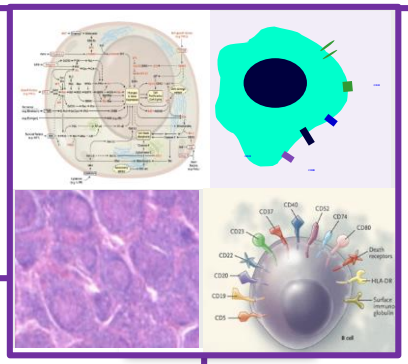
Abbreviations: ABC, activated B-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; GEP, gene expression profiling; IC, investigator's choice; IHC, immunohistochemistry; L, lenalidomide; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; wk, weeks.

Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

- **EZH2** — E7438
- **CD79a/b** — AEB071



Surface markers

- **Anti CD20 moAb**: Ofatumumab, GA-101
- **Anti CD40 moAb**: Dacetuzumab
- **Anti CD22**: Epratuzumab, Inotuzumab Ozogamicin, polatuzumab

Pathways

- **Proteosome inhibitors**: Bortezomib
- **Bcl-2 family inhibitors**: ABT-263
- **Survivin inhibitors**: YM155
- **Syk inhibitors**: Fostamatinib, entosplentib
- **mTOR inhibitors**: Everolimus, Temsirolimus
- **PI3K inhibitors**: Idelalisib, Copanlisib, Duvelisib, TGR-1202
- **Btk inhibitors**: Ibrutinib, ONO/GS-4059, ACP-196
- **Hsp 90 inhibitors**: KW 2478
- **HDAC inhibitors**: Vorinostat, Panobinostat
- **PKC inhibitors**: Enzastaurin
- **Aurora kinase inhibitors**
- **Nedd8-activating enzyme inhibitors**: MLN4924

Targeted chemotherapy in clinical development

Polatuzumab
Vedotin

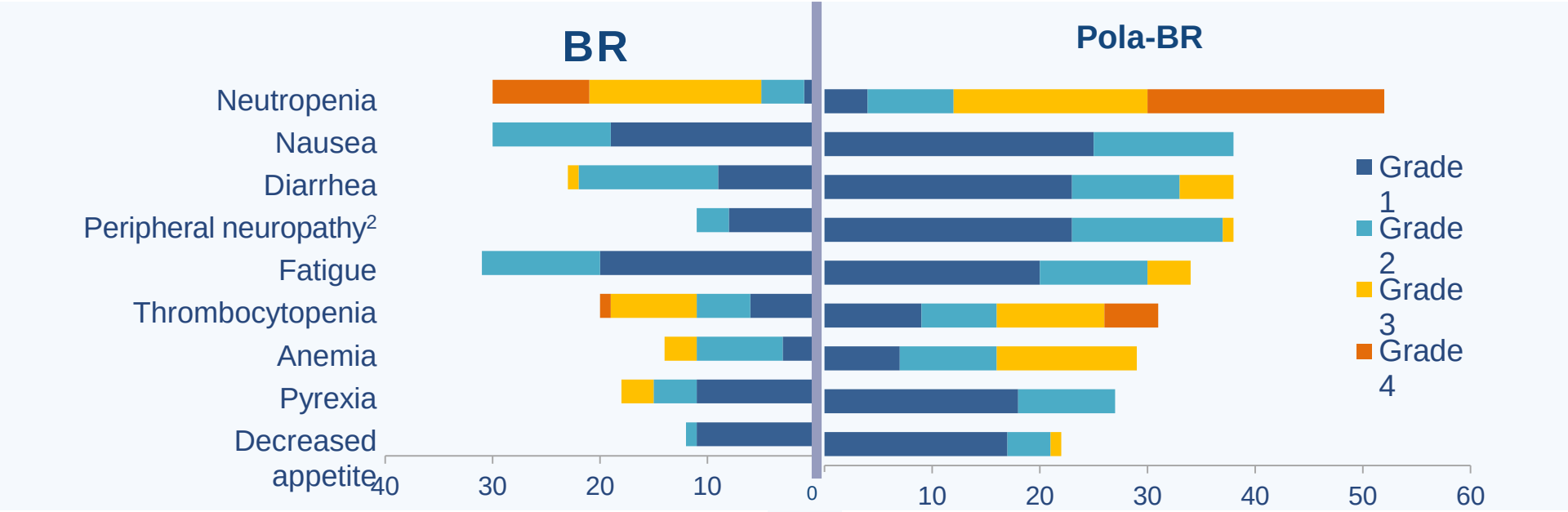
Target CD79b

Phase 2 Study Design

Stratification	**DOR ≤12 mo vs >12 mo** **High vs low disease burden**	**DOR ≤12 mo vs >12 mo**
Schedule	FL: 28-day cycles × 6	DLBCL: 21-day cycles × 6
	Polatuzumab vedotin (1.8 mg/kg IV × 1 day); bendamustine (90 mg/m^2 IV × 2 days); rituximab (375 mg/m^2 IV × 1 day)	
Primary endpoint	**PET-CR* by IRC, 6–8 weeks post end of treatment (EOT)**	

*Modified Lugano 2014 criteria: PET-CR requires negative bone marrow; PET-PR required CT criteria be met.
DOR, duration of response; IRC, independent review committee

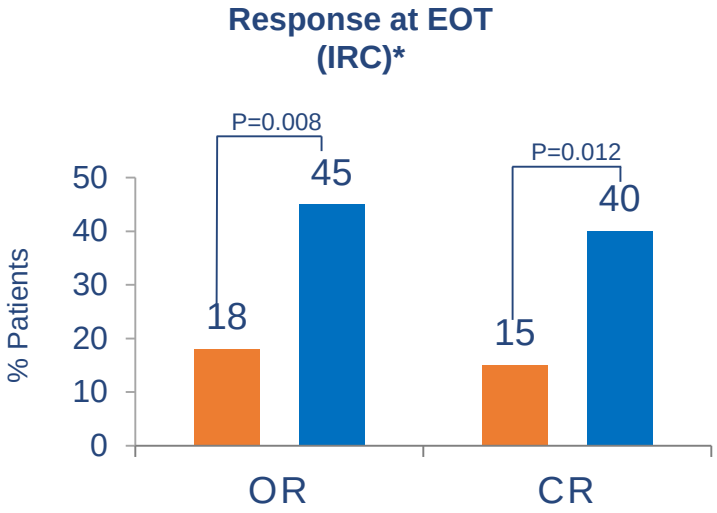
Adverse Events at Rate ≥20% by Treatment Group[1]

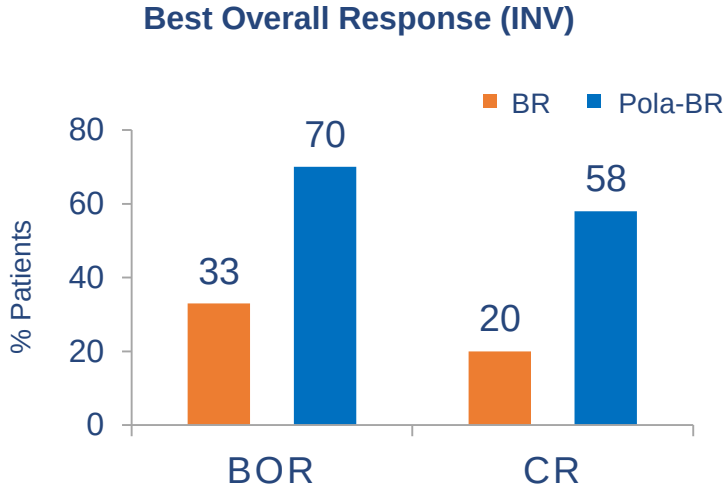


- SAEs occurred more frequently in pola-BR (33% BR vs 55% pola-BR)
  - Most common were infections (18% vs 23%) and febrile neutropenia (3% vs 12%)

[1]Combined DLBCL and FL cohorts [2]Peripheral neuropathy reported by MedRA SMQ (Standardized MedRa Query)

DLBCL: Significantly Higher PET-CR with Pola-BR



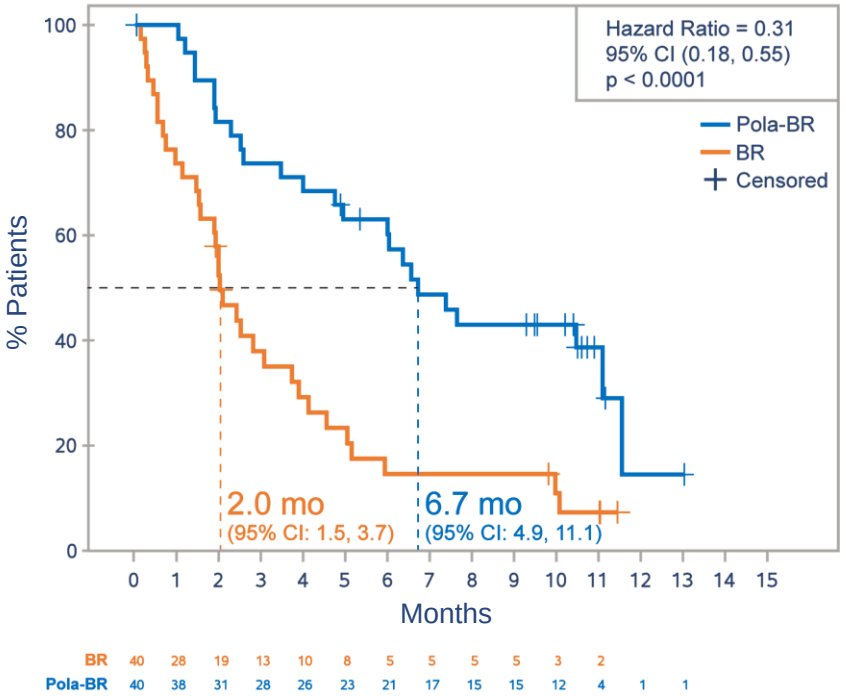


*Primary endpoint

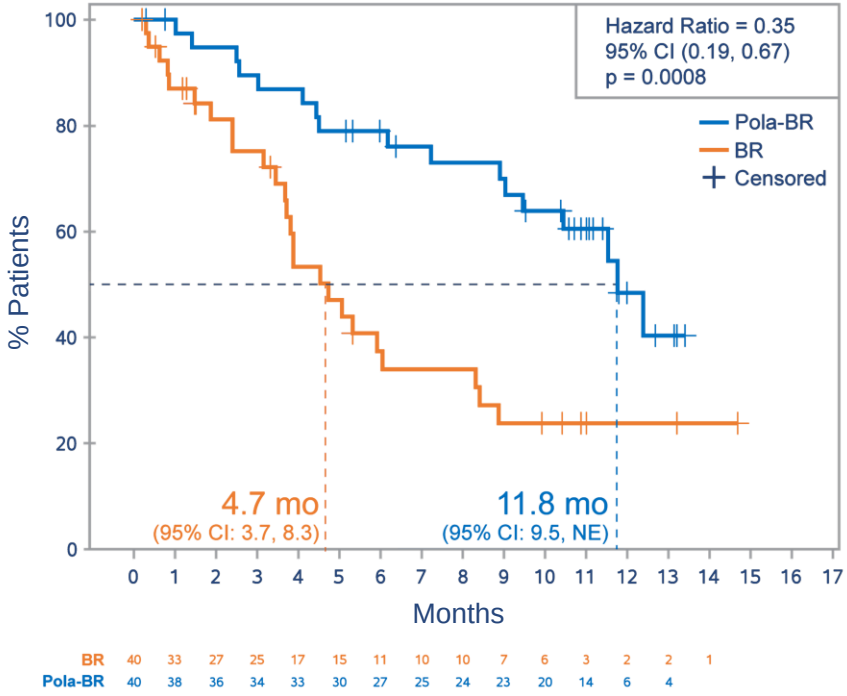
Note: EOT IRC and INV assessments were highly concordant (>90%)
BOR, best overall response; CR, complete response; INV, investigator; IRC, independent review committee; EOT, end of treatment

DLBCL: PFS and OS significantly longer with Pola-BR

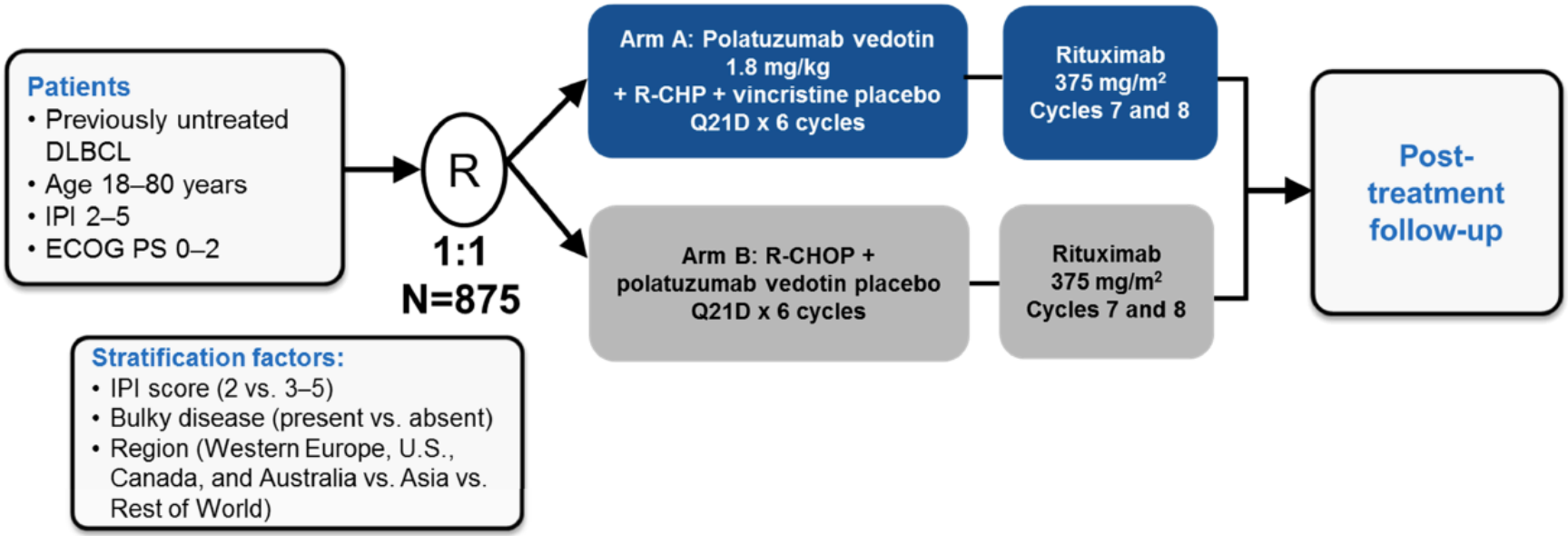
Progression Free Survival



Overall Survival



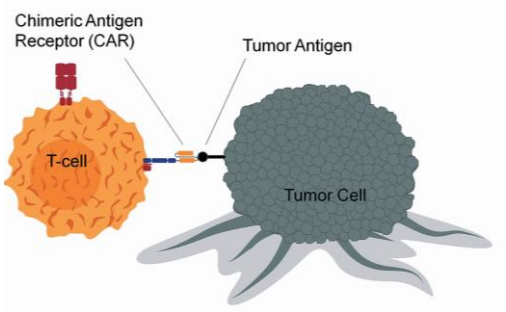
Front line study: POLARIX



CAR-T

Where will they fit in?

- Current approval for third line therapy in DLBCL
- On-going trials in second line compared to high-dose therapy



A molecular precision approach to DLBCL?...almost

- Don’t think of DLBCL as one disease
- There are challenges in defining molecular sub-groups in a timely fashion and the appropriate diagnostic platform.
- Targeted therapies may potentially change the landscape of therapy for DLBCL...not yet. Next year it may be different.
- DHL is a special case..
- Much still needs to be proved and phase III studies are needed (no matter how difficult)…
- We need to better refine the molecular heterogeneity and to continue to better exploit our new knowledge of the biology. Outcomes in patients with R/R disease are unsatisfactory

ESTRO School

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KING'S HEALTH PARTNERS
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KING'S College LONDON
University of London

Guy's and St Thomas' NHS
NHS Foundation Trust

RT for Aggressive NHL

Role, Volumes, doses & Technologies (including Protons)

Prof George Mikhaeel

Professor of Radiation Oncology, King's College London

Consultant Clinical Oncologist, Guy's Cancer Centre
London, UK

Guy's Cancer

ESTRO School

Outline

- Who benefits from RT
- Volumes
- Doses
- Techniques – Mediastinal RT
- Protons

Who benefits from RT in Agg NHL

- Early stage disease

- Advanced stage disease: Consolidation RT improves outcome after RCHOP:
  - Sites of initial bulky disease
  - Extranodal sites
  - Skeletal sites
  - *(Contralateral testis)*

- Patients who have CMR *may* still benefit from consolidation RT:
  - Retrospective evidence
  - Prospective evidence awaited

- Selected patients with persistent PET +vity can be cured with RT without transplant

- Salvage: Radiotherapy has a role in:
  - Peri-transplant: consolidation or part of debulking
  - Salvage in transplant ineligible pts

Benefit – Toxicity considerations
Differences from HL

- Prognosis:
  - HL is highly curable
  - DLBCL is curable in 60-65% in population-based studies
  - Salvage is more successful in HL > DLBCL (especially >RCHOP)

- Age: median age 60-65

- Late effects:
  - No evidence of increased risk of 2nd malignancy in NHL
  - Explanation:
    - 2nd malignancy risk is small > age 45
    - Competing causes of death: disease-related, co-morbidities

Studies of second malignancy in NHL

- Mudie NY et al

Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study.

Journal of clinical oncology 2006;24(10):1568-74.

- Moser EC et al

Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study.

Haematologica. 2006;91(11):1481-8.

- Sacchi S et al

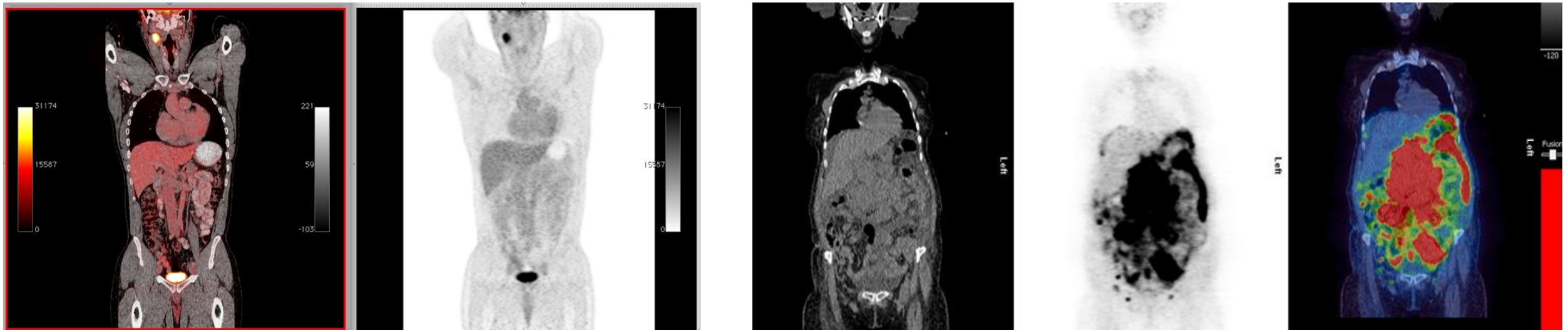
Second malignancies after treatment of diffuse large B-cell non-Hodgkin's lymphoma: a GISL cohort study.

Haematologica. 2008;93(9):1335-42.

DLBCL is a much more **lethal** disease than Hodgkin lymphoma

The main concern in DLBCL is **curing** the disease

When to give consolidation RT?

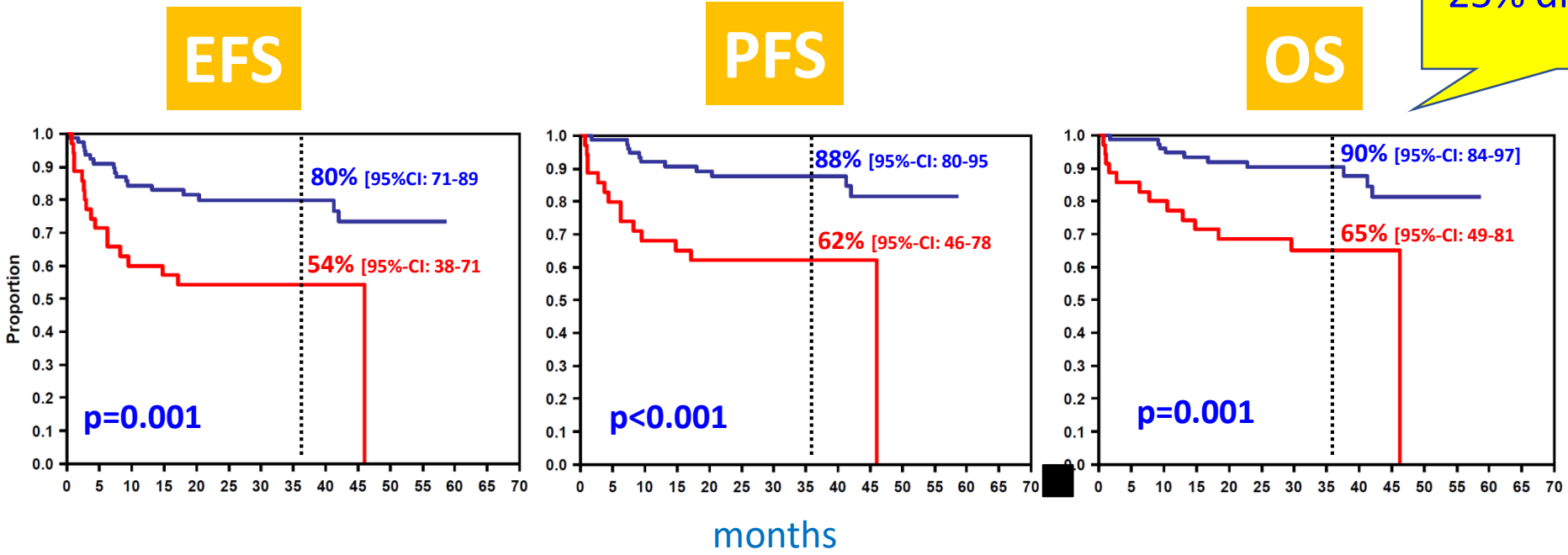


Bulk

RICOVER-60-no-RT

per protocol Analysis

25% difference



RICOVER-60 (n=78)

RICOVER-60-no-RX (n=35)

Held, JCO 2014

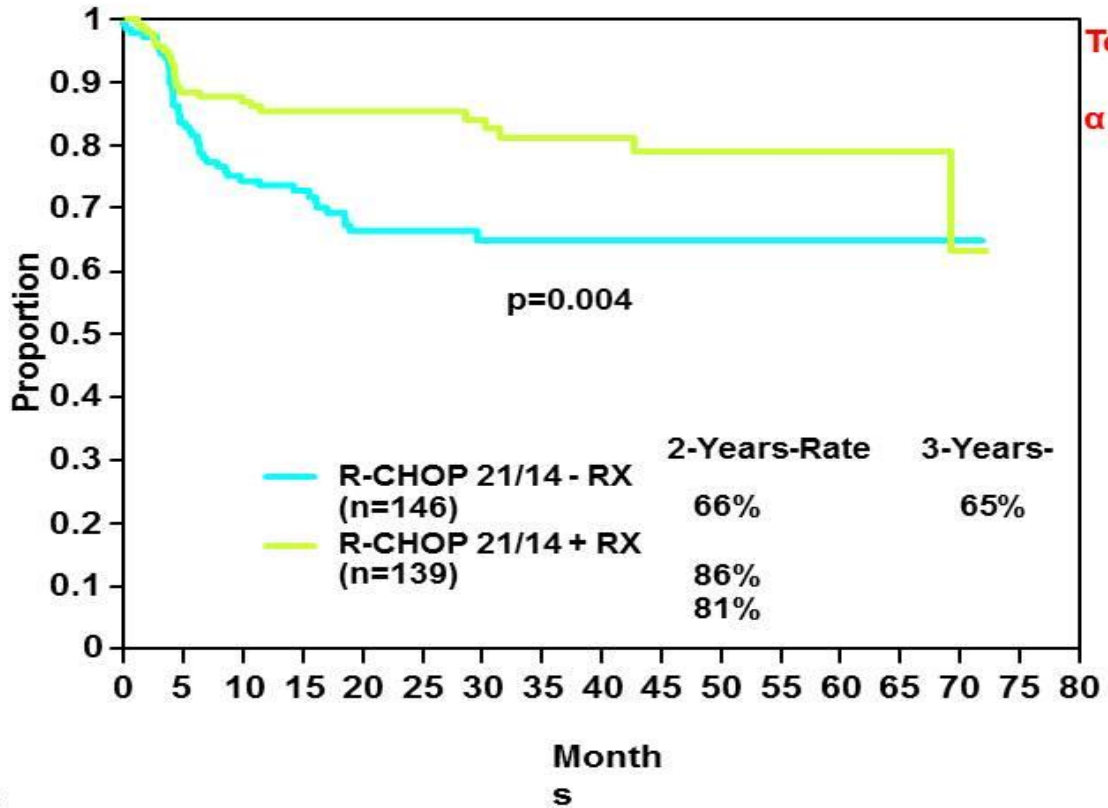
DSHNHL

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)



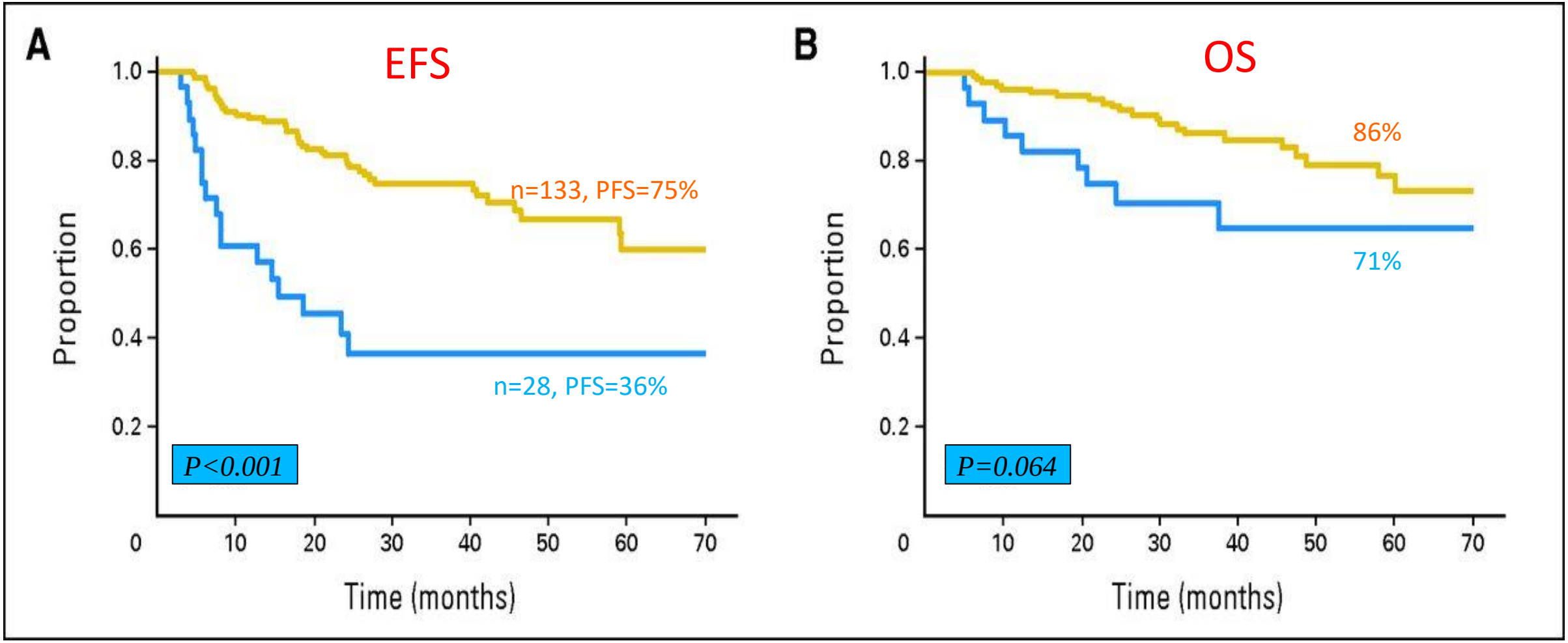
Termination!!!

α Spending 0.008

DSHNHL 01.07.12

Skeletal involvement

RT improves EFS and OS



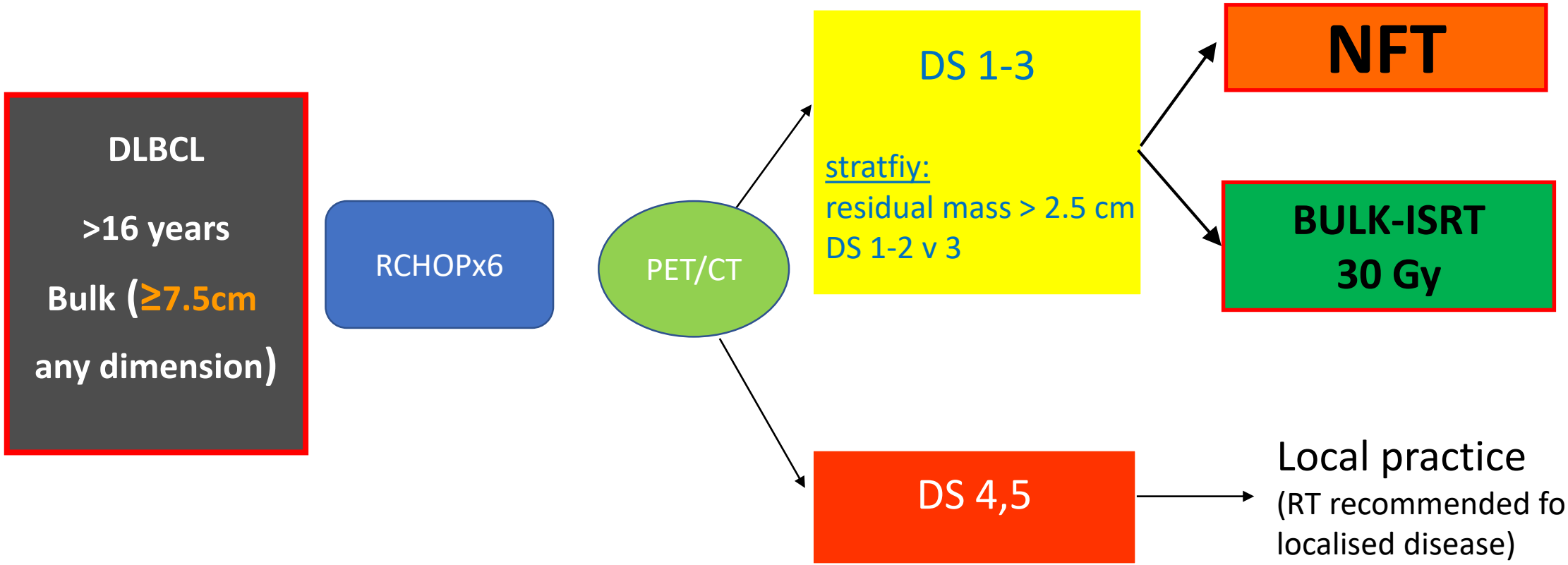
Gerhard Held et al. JCO 2013;31:4115-4122

Does RT improve outcome after CR?

Does RT improve outcome after CR? Retrospective evidence:

Study	No of patients	% CR by PET	% receiving RT	Local Control		PFS / EFS		OS	
				RT	No RT	RT	No RT	RT	No RT
Emory Univ. (Shi 2013)	110	86%	13%	92%	49%	85%	44%	92%	69%
Duke Univ. (Dorth 2012)	79	83%	48%	92%	69%	85%	65%	85%	78%
MDACC (Phan 2010)	469	100%	30%	100%	NA	82%	59%	91%	68%

UK Phase 3 study in preparation



Co-CI: T Illidge, G Mikhaeel

Salvage RT

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

J. A. Dorth[1], J. P. Chino[1], L. R. Prosnitz[1], L. F. Diehl[2], A. W. Beaven[2], R. E. Coleman[3] & C. R. Kelsey[1]*

Departments of [1]Radiation Oncology; [2]Medicine, Division of Medical Oncology; [3]Radiology, Division of Nuclear Medicine, Duke University Medical Center, Durham, USA

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.‖

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*

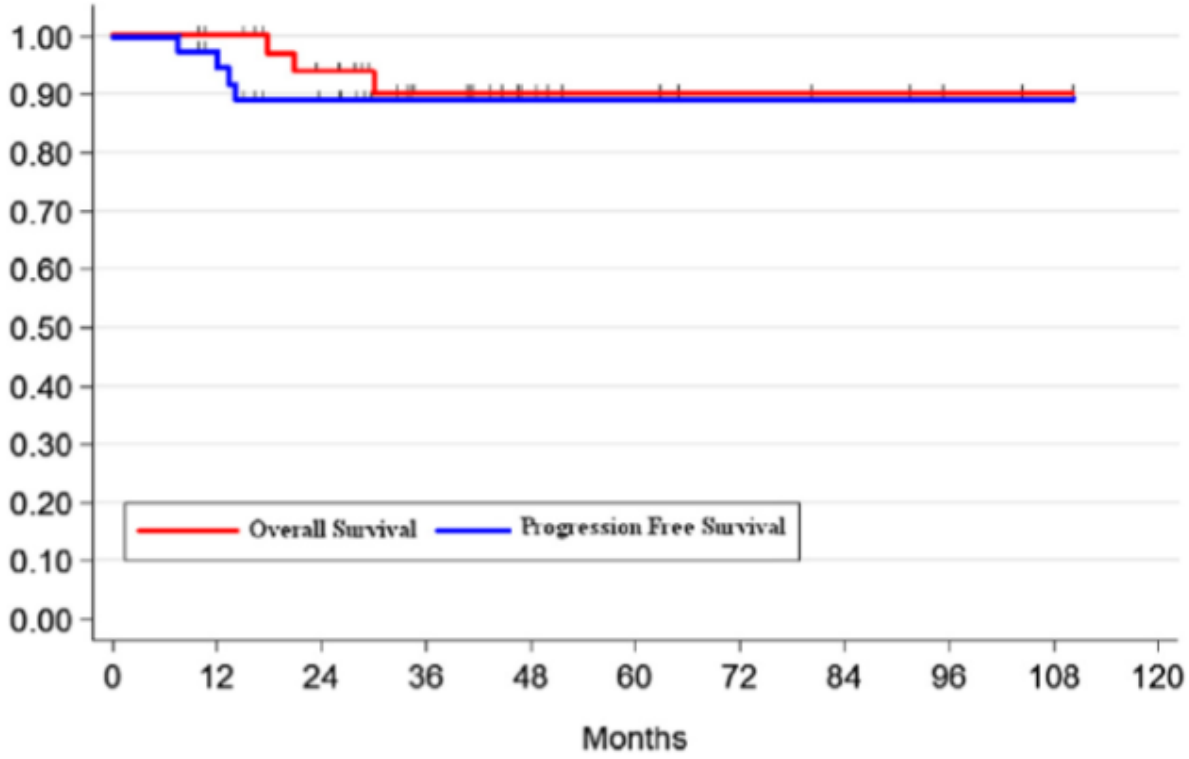
Halasz

	3y-LC	3y-PFS	Death
PET -ve	100%	97%	1 (2nd lymphoma)
PET +ve	90%	90%	1 (relapse)

Clinical Investigation: Lymphoma

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*



- 37 pts
- DS 1-3 = 51%
- DS 4 = 38%

1/33 relapsed

- DS 5 = 11%

3/4 relapsed

Int J Radiation Oncol Biol Phys, Vol. 87, No. 2, pp. 311–316, 2013

ELSEVIER

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*§

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%

Who benefits from RT in Agg NHL

- Early stage disease

- Advanced stage disease: Consolidation RT improves outcome after RCHOP:
  - Sites of initial bulky disease
  - Extranodal sites
  - Skeletal sites
  - *(Contralateral testis)*

- Patients who have CMR *may* still benefit from consolidation RT:
  - Retrospective evidence
  - Prospective evidence awaited

- Selected patients with persistent PET +vity can be cured with RT without transplant

- Salvage: Radiotherapy has a role in:
  - Peri-transplant: consolidation or part of debulking
  - Salvage in transplant ineligible pts

Dose

Dose Selection

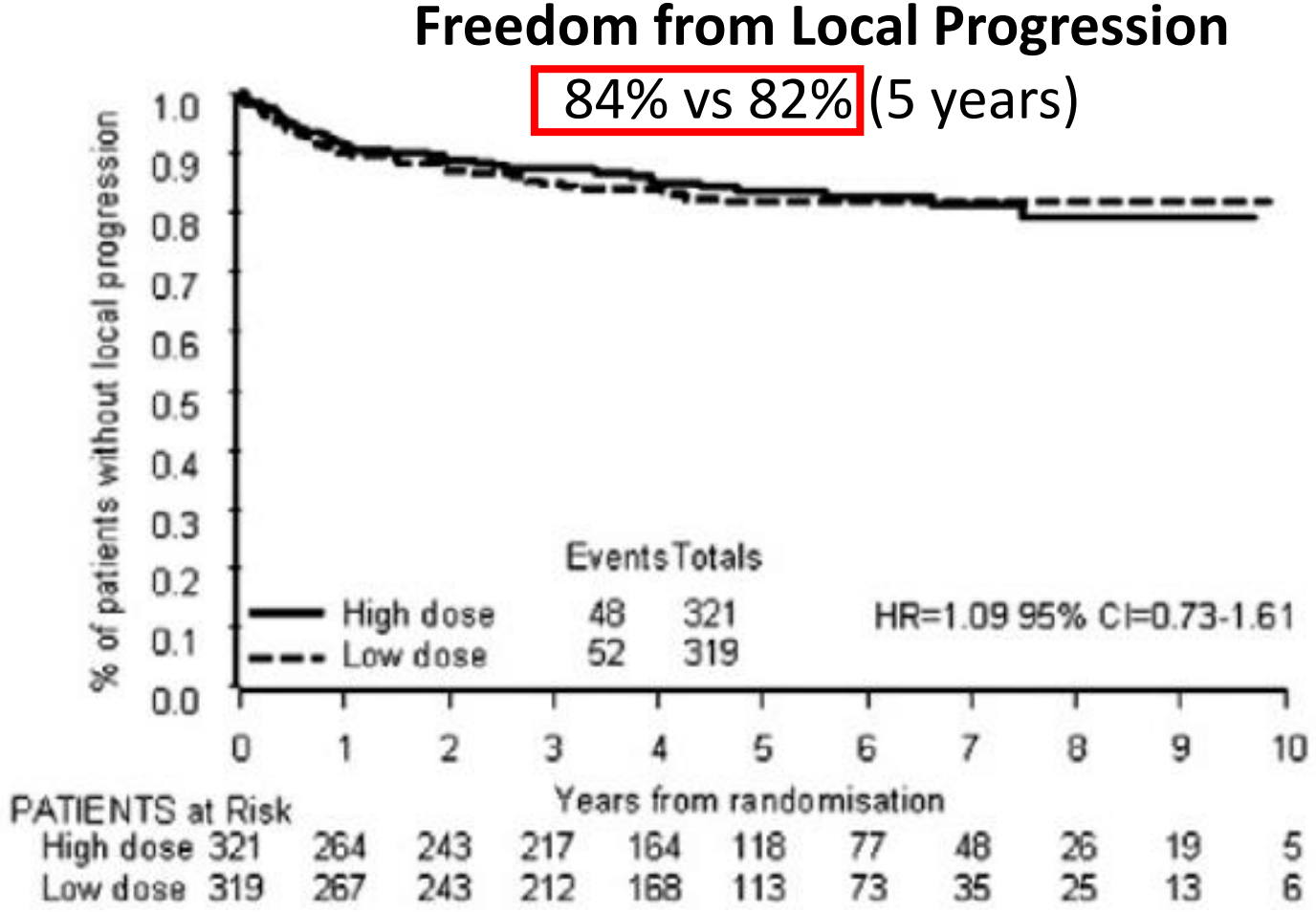
- Consolidation > CMR to chemo: 30 Gy
- Residual Lymphoma: 36 -40 Gy *± 2 dose levels*
- Refractory / Relapse: 36 – 44 Gy
- Palliation: Wide dose range – some evidence for low dose

UK-BNLI study

- 640 pts, Aggressive, high-grade NHL
  - Consolidation (80%)
  - Definitive (12%)
  - Palliative (8%)

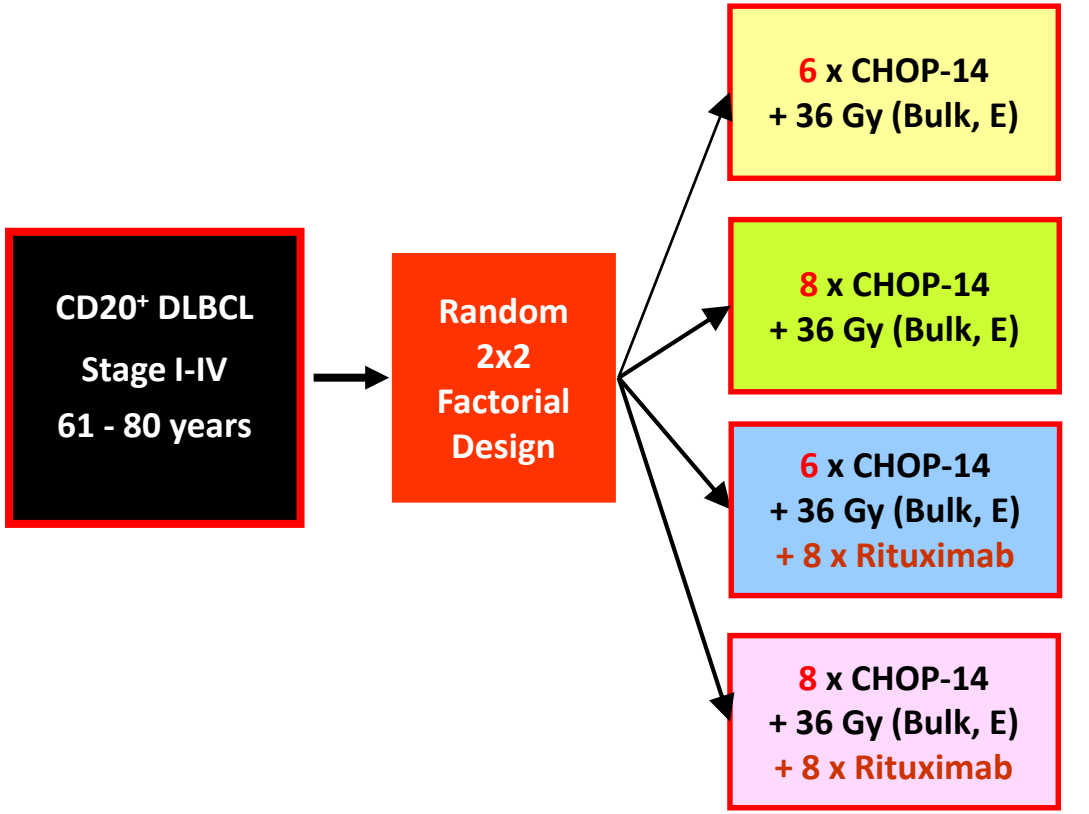
- Randomized to:
  - 40-45 Gy
  - 30 Gy

- Rituximab (~10%)



Radiotherapy & Oncology 2011;100:86

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

Phase II Study of Dose-Reduced Consolidation Radiation Therapy in Patients with Diffuse Large B-Cell Lymphoma

CR Kelsey, G Broadwater, O James, J Chino, L Diehl, AW Beaven, LR Prosnitz

Duke University Medical Center

ASTRO 2017

Patient Characteristics

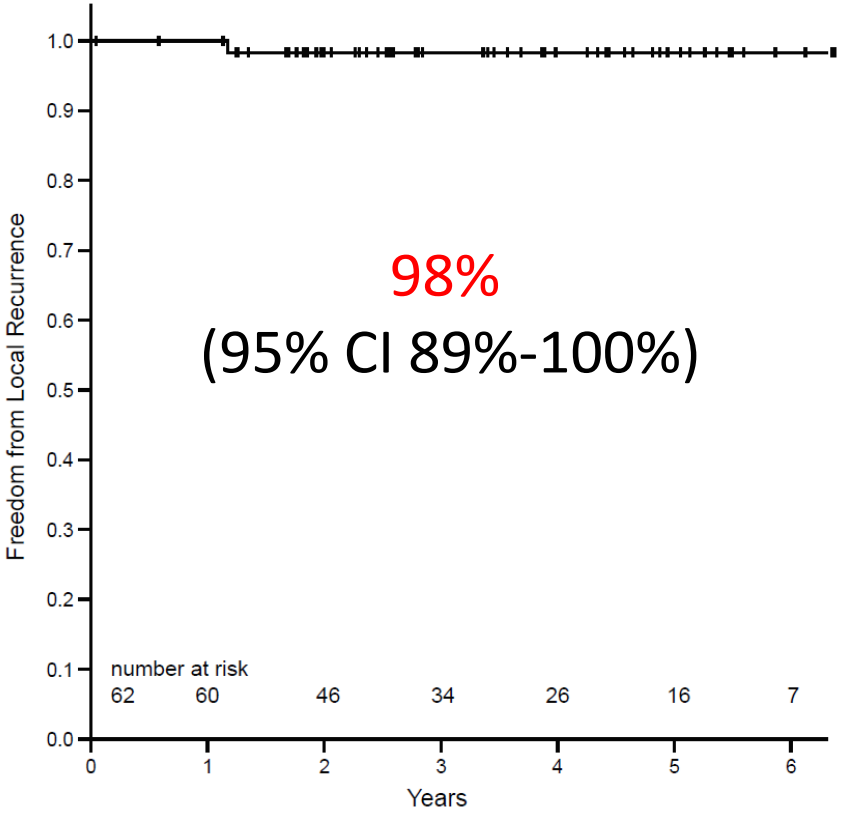
- N= 62 (2010-2016)
- DLBCL NOS: n=50 (81%); Primary mediastinal B-cell lymphoma: n=12 (19%)
- Median age: 58 (range, 24-86)
- RCHOP 94% R-DA-EPOCH 6%

- Stage: I= 39%; II= 40%; III= 6%; IV= 15%
- Extra-nodal disease- 35 (56%); Skeletal involvement- 14 (23%)

- Median tumor size: 5.7 cm
  - Bulky (≥ 7.5 cm): n=23 (40%)
  - Bulky (≥ 10 cm): n=16 (28%)

5y results

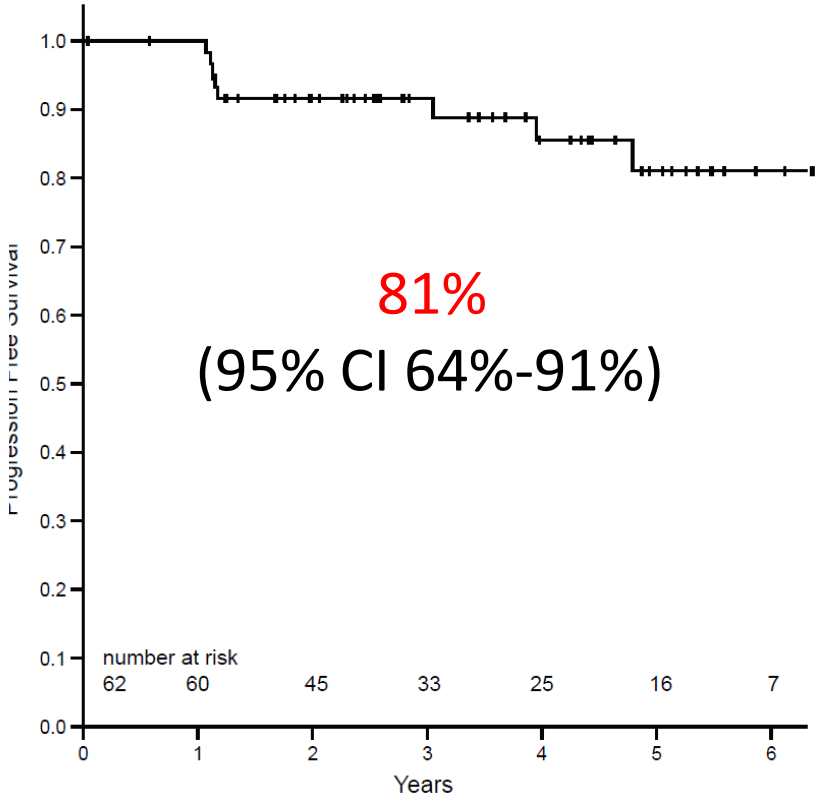
62 patients, Median follow-up: 43 months (range, 1-81)



98%

(95% CI 89%-100%)

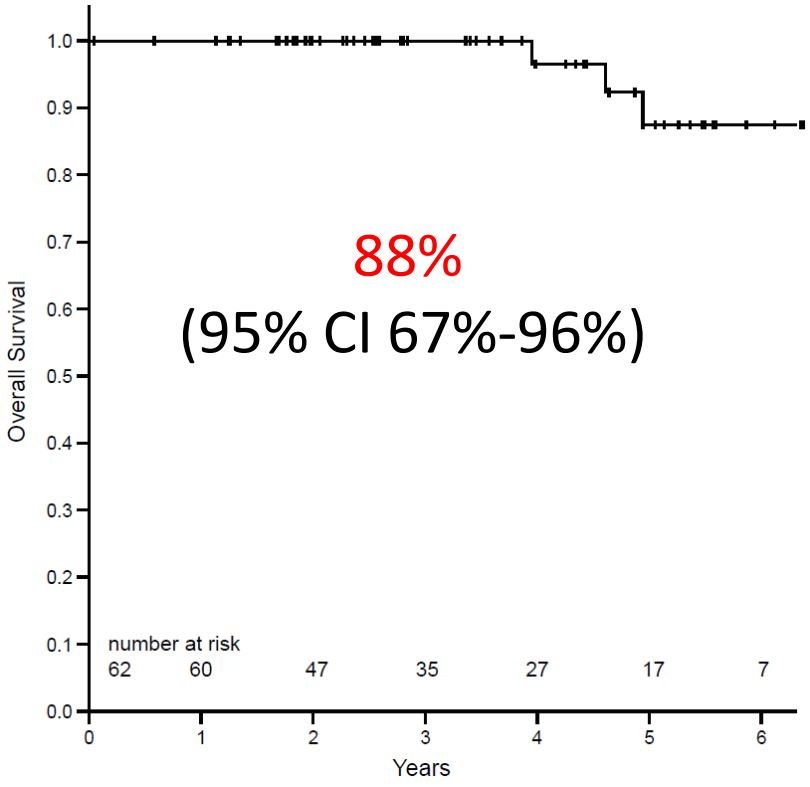
Local Control



81%

(95% CI 64%-91%)

PFS



88%

(95% CI 67%-96%)

OS

Application: ?? 2 dose levels in some PET+ve cases (20-30 Gy pre-chemo, 36 - 40Gy to residual PET+ve sites)

Palliative low dose RT

Number of patients	**17**
Number of sites	**43**
Histological subtype	
DLBCL	14 (37 sites)
MCL	3 (6 sites)
Median time from diagnosis to LDRT (months)	22 (0.23-195.1)
Median number of systemic therapies	3 (0-7)

- LC = 90%
- Patients surviving > 6m: 7 sites remaining controlled at 12 m
- Max response duration was 127 months (0.5-126.6)

- median OS 2.4 m (0.03-126.7)
- 4-8 Gy

Treatment outcome	ORR	CR	LR
All	91% (39/43)	49% (21/43)	10%
Site			
- **Skin (23)**	100% (23)	74%	4% (1/23)
- **Nodal/EN (15)**	87% (13)	27%	8% (1/13)
- **Bone (5)**	60% (3)	0	77% (2/3)
Dose			
- **4Gy (16)**	88%	63%	14%
- **6-8Gy (27)**	93%	41%	8%
Histology			
- **DLBCL**	92%	51%	12%
- **MCL**	83%	33%	0
No of previous lines of treatment			
- **≤2**	86%	38%	17%
- **>2**	96%	59%	5%

Brady ESTRO 2016

Dose Selection

- Consolidation > CMR to chemo: 30 Gy
- Residual Lymphoma: 36 -40 Gy *± 2 dose levels*
- Refractory / Relapse: 36 – 44 Gy
- Palliation: Wide dose range – some evidence for low dose

Volumes

Guidelines for radiotherapy of lymphomas

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

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

IJROBP 2014; 89: 49-58

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

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

Practical Radiation Oncology 2015; 5: 85-92

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

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

IJROBP 2015; 92: 32-39

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

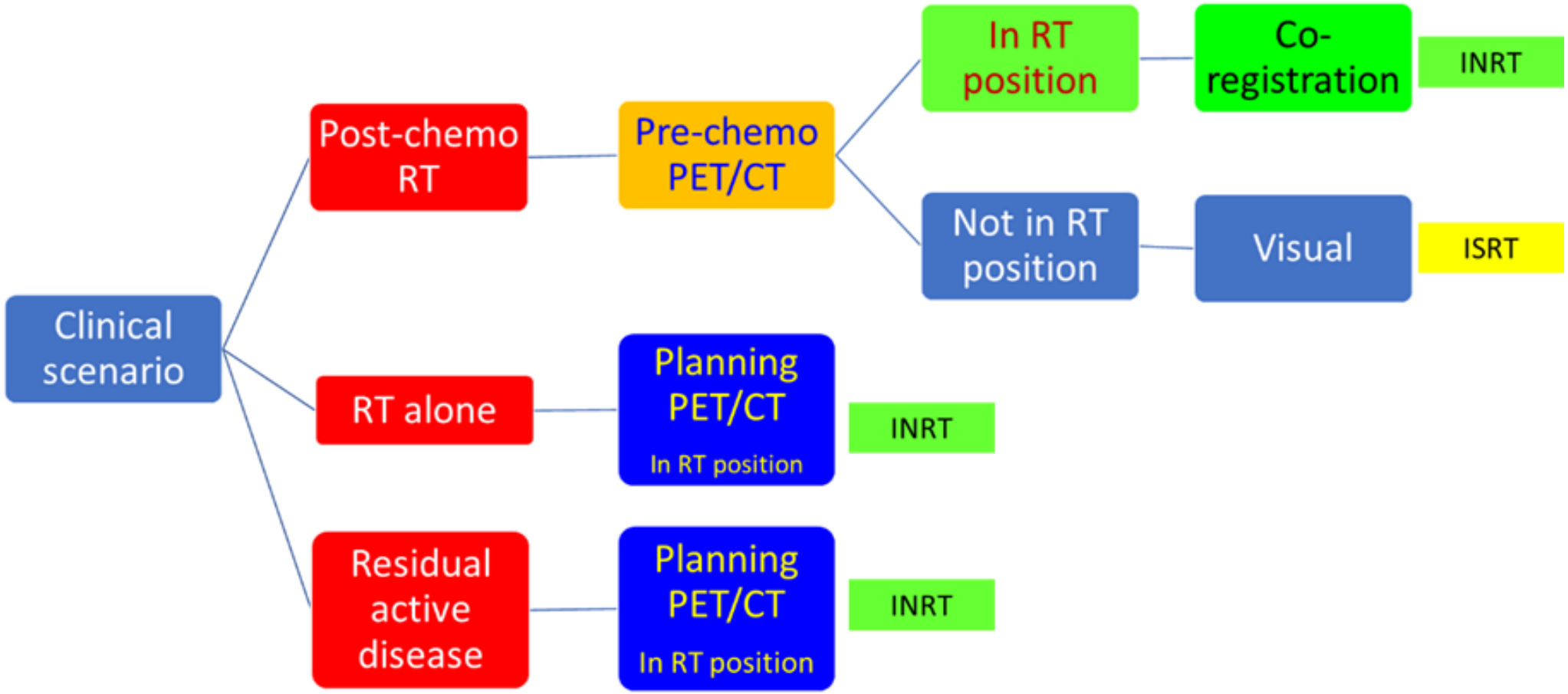
Lena Specht, MD, PhD,* Joachim Yahalom, MD,† Tim Illidge, MD, PhD,‡ Anne Kiil Berthelsen, MD,§ Louis S. Constine, MD,‖ Hans Theodor Eich, MD, PhD,¶ Theodore Girinsky, MD,# Richard T. Hoppe, MD,** Peter Mauch, MD,†† N. George Mikhaeel, MD,‡‡ and Andrea Ng, MD, MPH††, on behalf of ILROG

IJROBP 2014; 89: 854-62

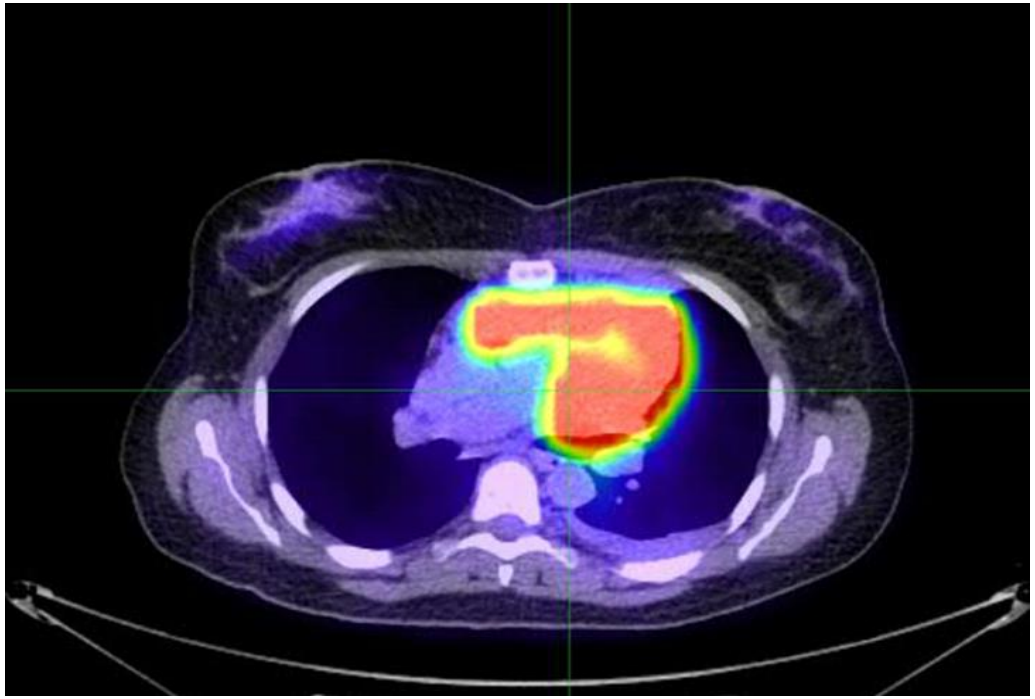
Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

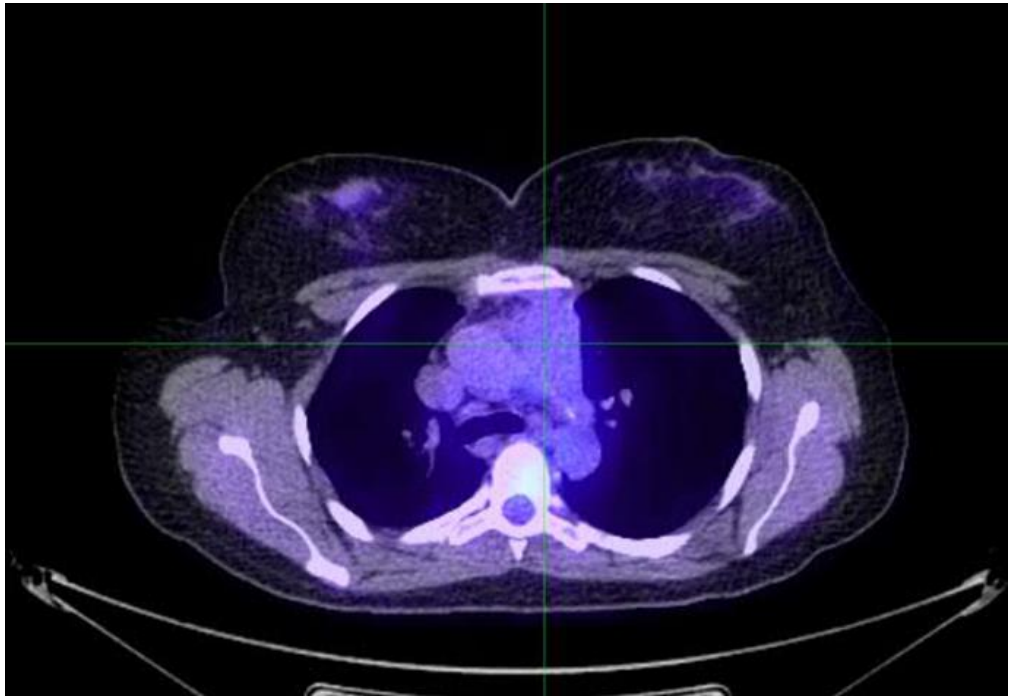
Joachim Yahalom, MD,* Tim Illidge, MD, PhD,† Lena Specht, MD, PhD,‡ Richard T. Hoppe, MD,§ Ye-Xiong Li, MD,‖ Richard Tsang, MD,¶ and Andrew Wirth, MD#, on behalf of the International Lymphoma Radiation Oncology Group

IJROPB 2015; 92: 11-31

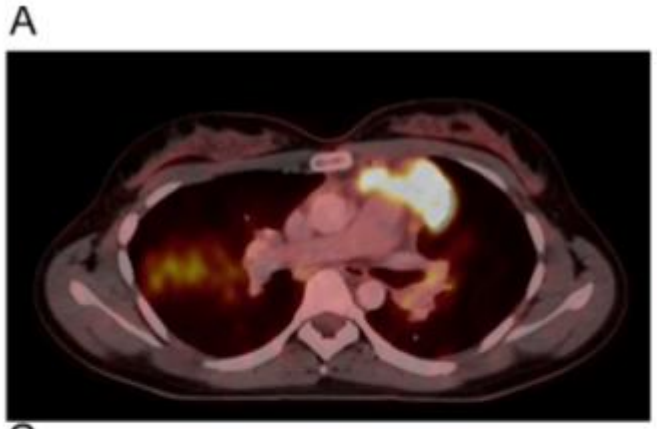

Clinical scenario
Post-chemo RT
Pre-chemo PET/CT
In RT position
Co-registration
INRT
Not in RT position
Visual
ISRT
RT alone
Planning PET/CT
In RT position
INRT
Residual active disease
Planning PET/CT
In RT position
INRT

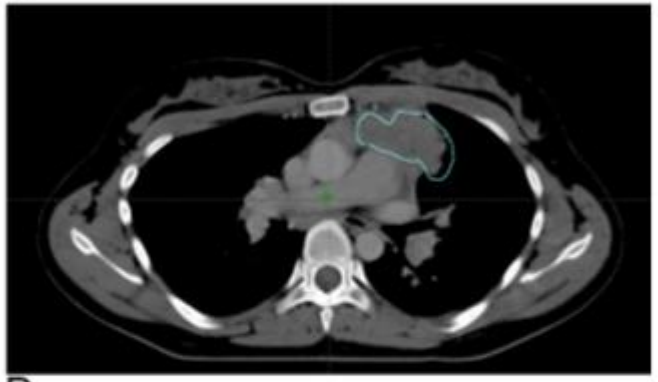
Post chemo RT





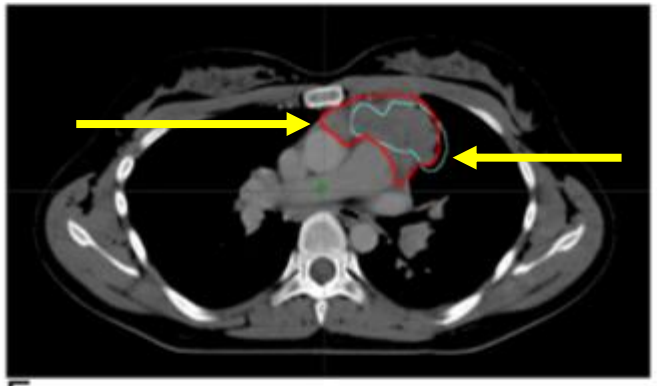
Pre-chemo PET

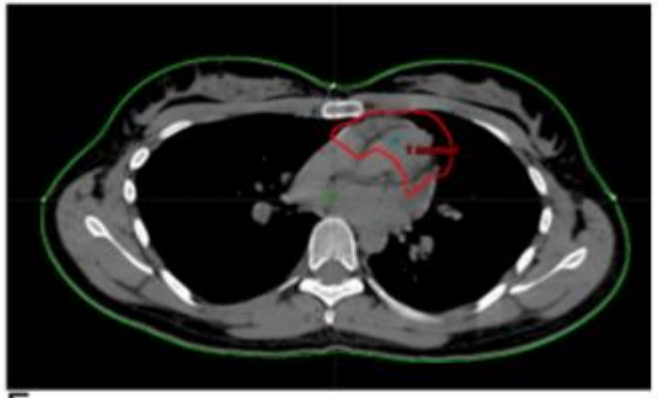




Pre-chemo PET-GTV

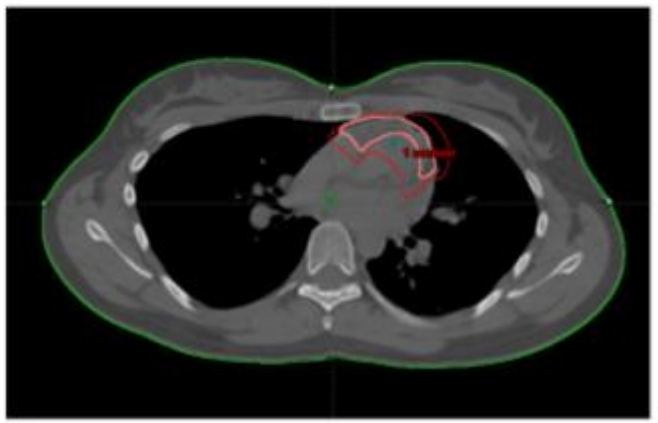
Pre-chemo CT-GTV

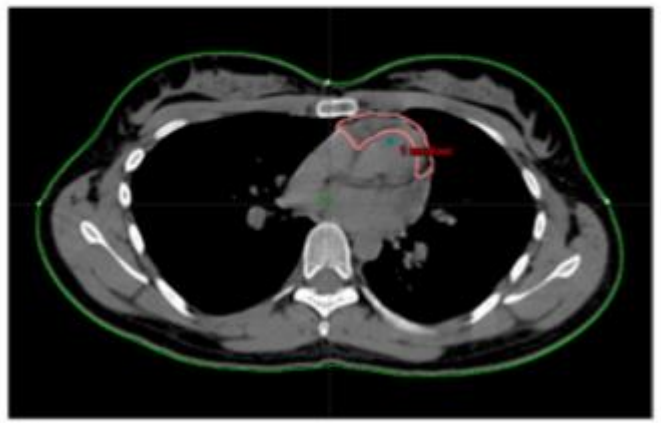




Pre-chemo GTV superimposed on post-chemo CT

Pre-chemo CTV excluding normal structures

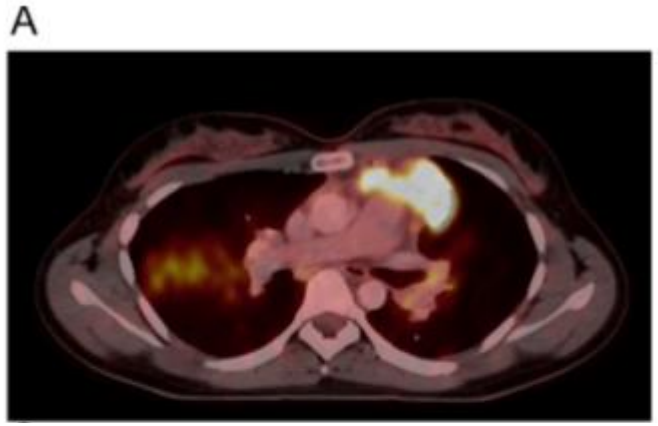


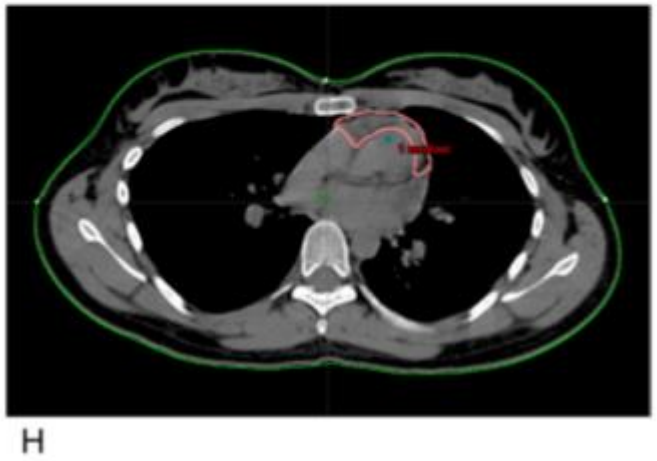


Final CTV

ILROG NHL guidelines
IJROBP 2014 89: 49

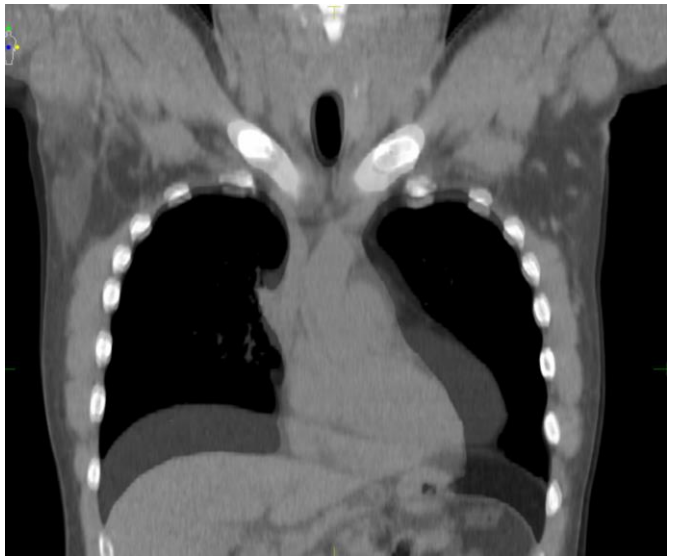
Pre-chemo PET

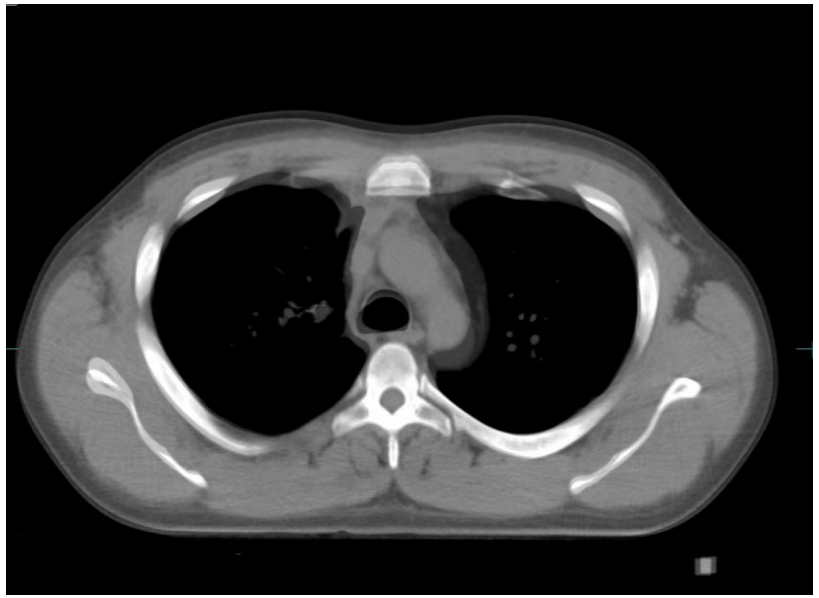


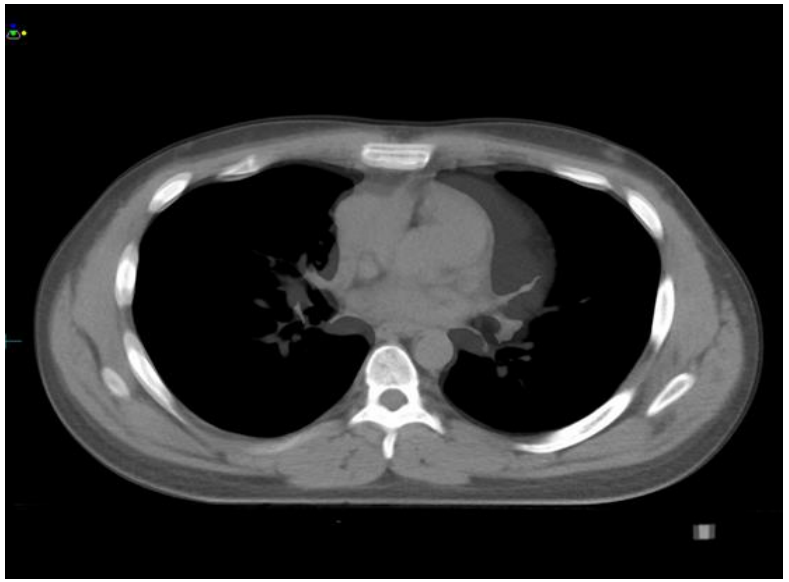


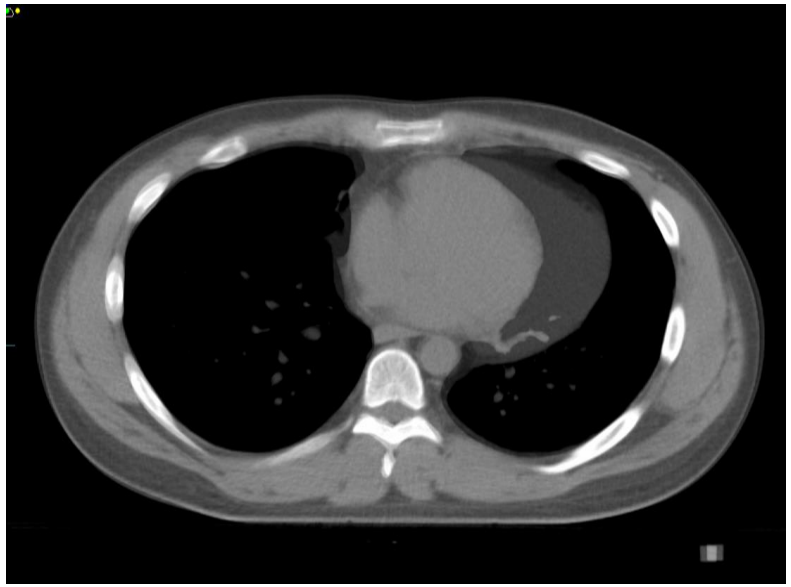
Final CTV

Change in anatomy with Deep Inspiration Breath Hold



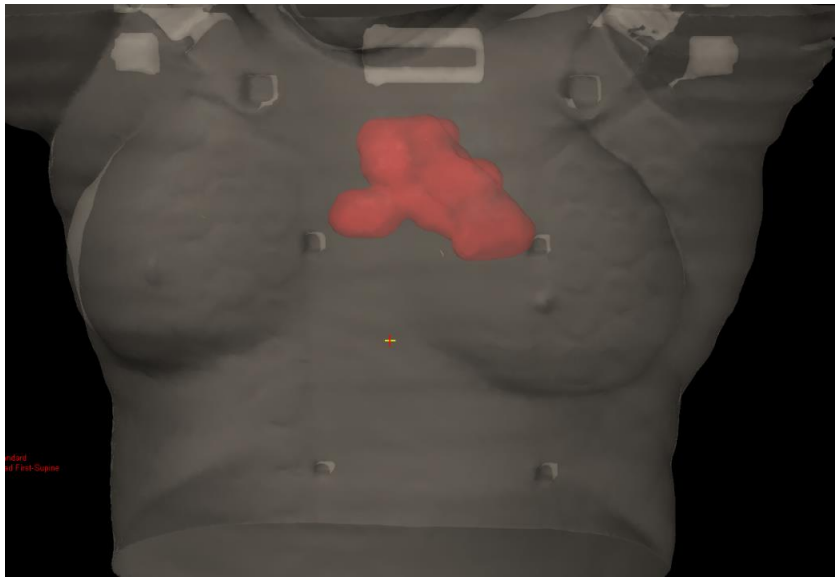


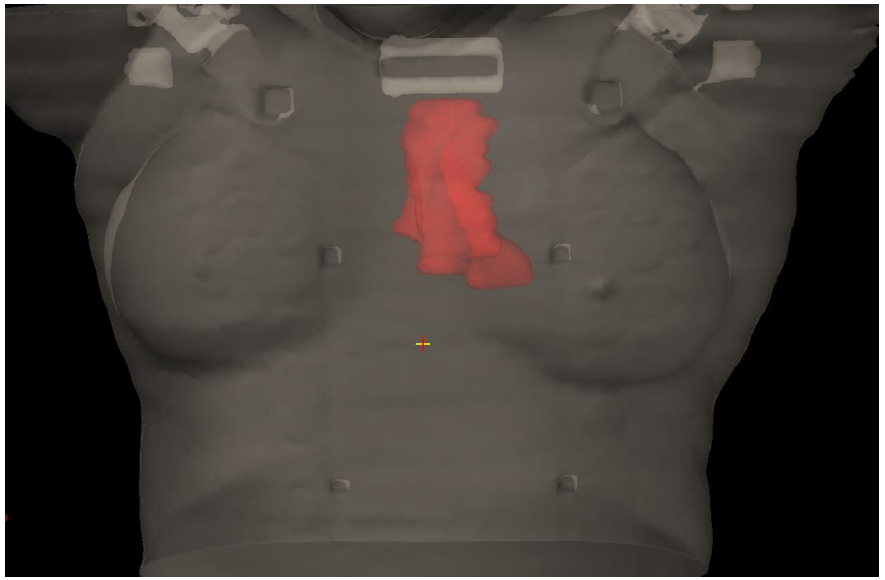


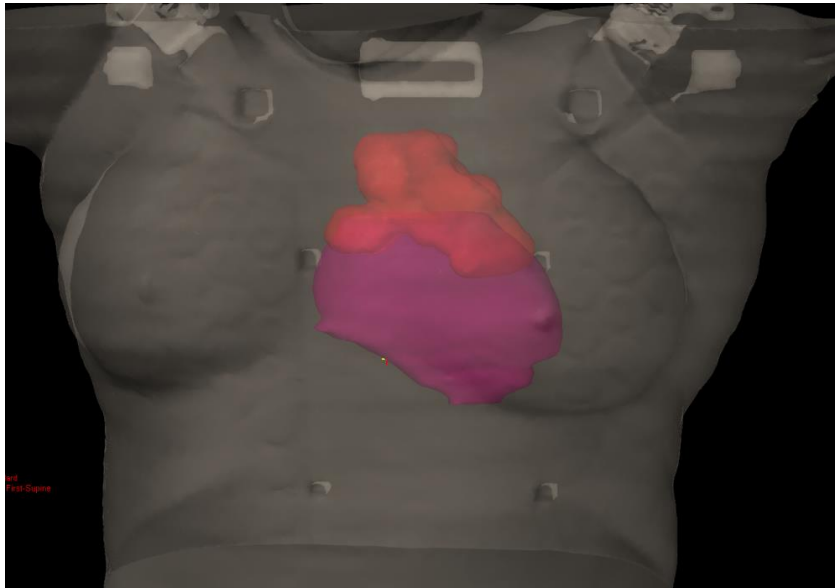


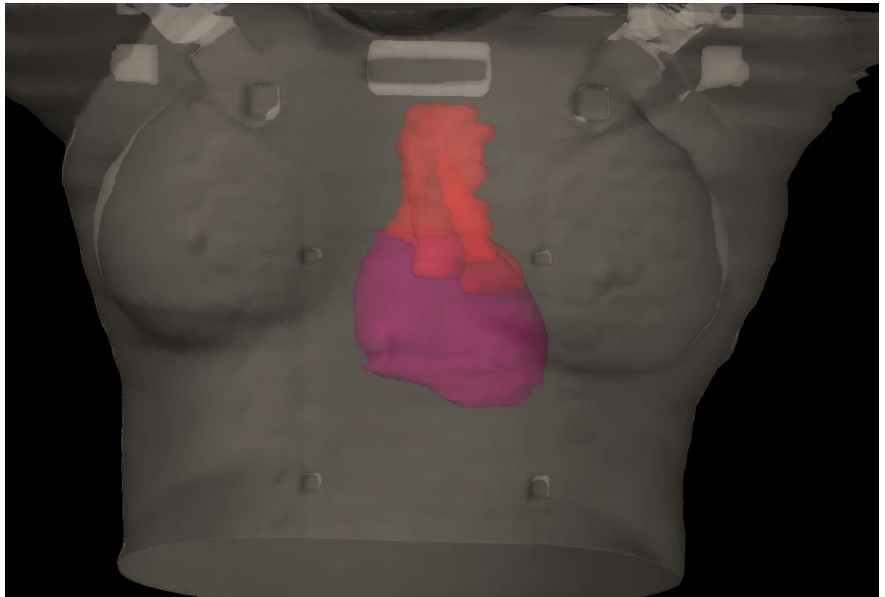
Free Breathing

DIBH







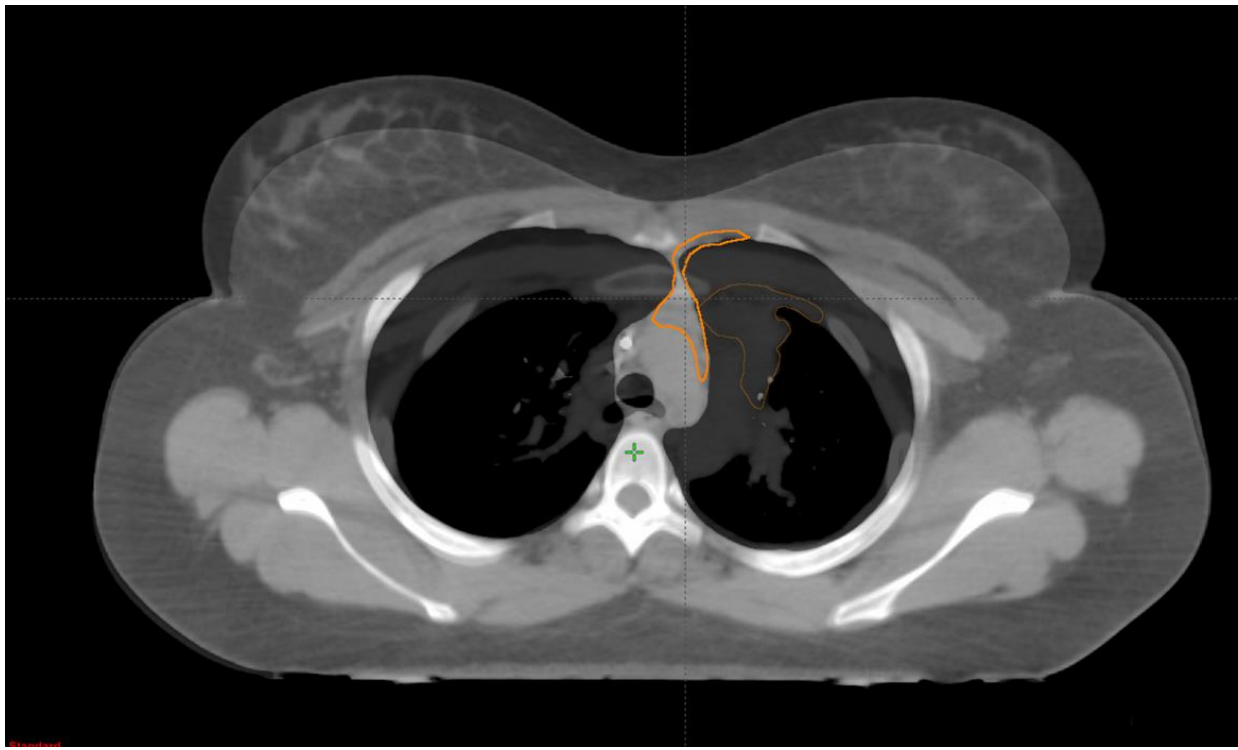


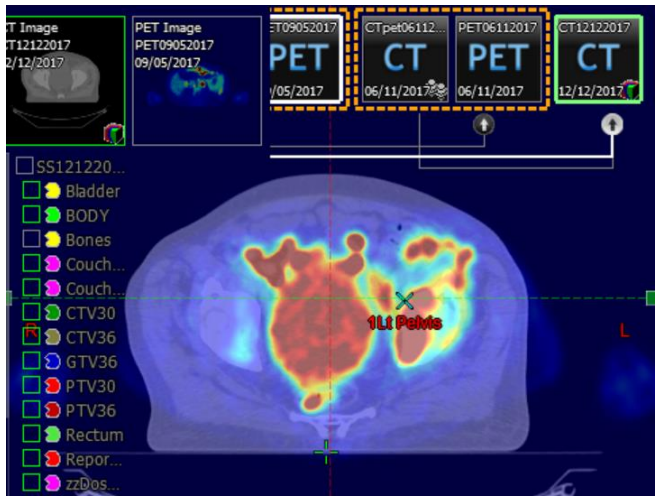
How to handle change of anatomy with DIBH

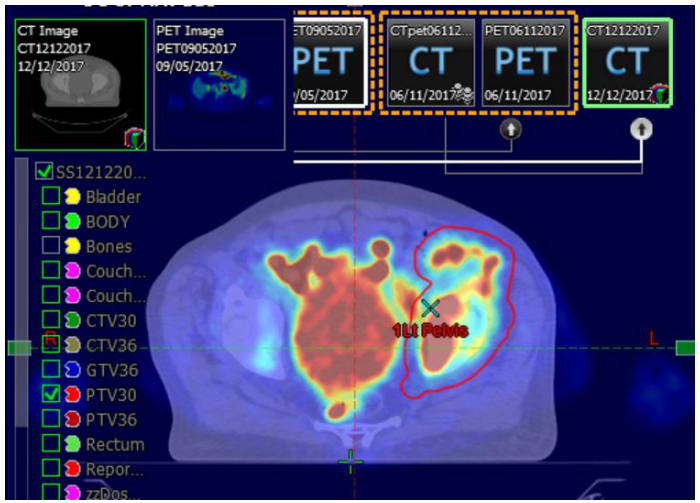
- Limited PET chest view in DIBH

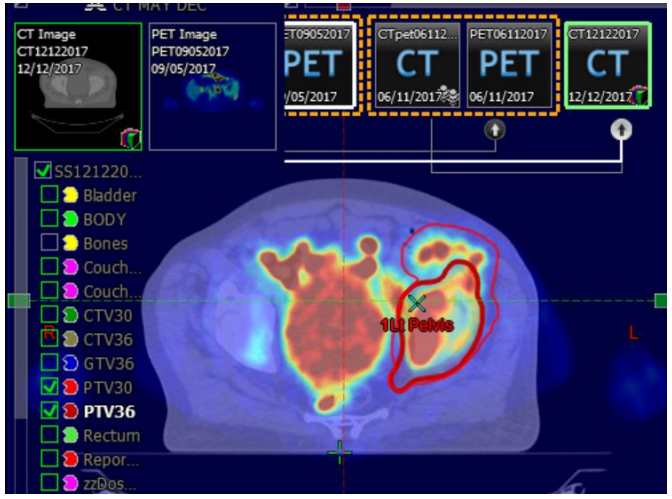
OR

- 2 step contouring:
  - CTV on FB planning scan
  - CTV on DIBH scan

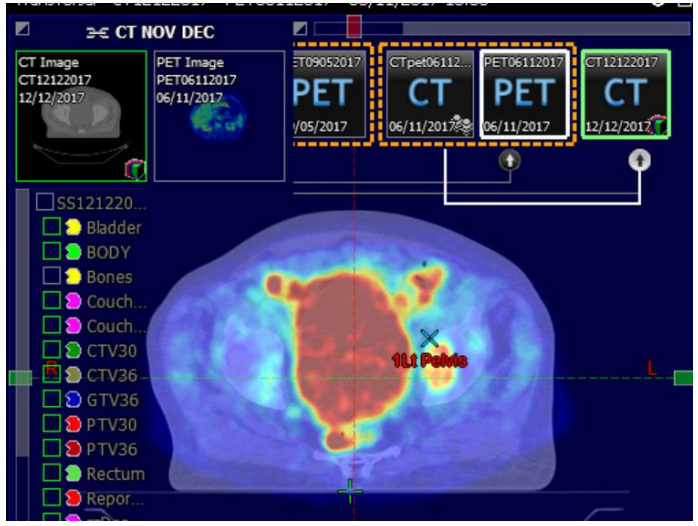


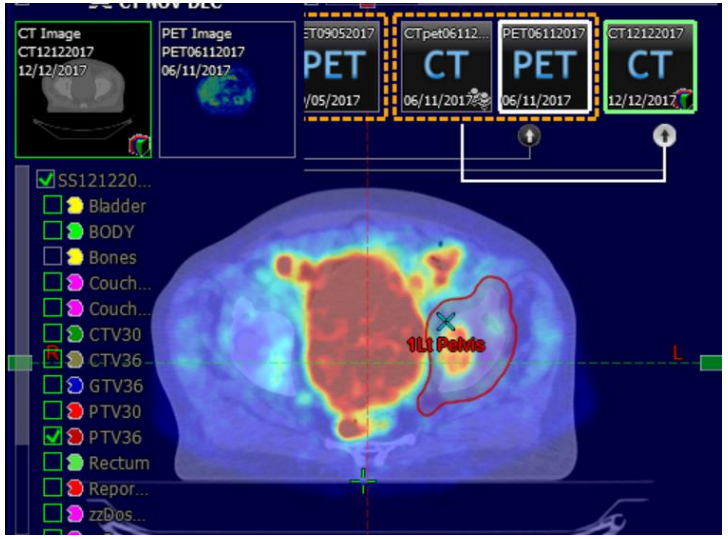


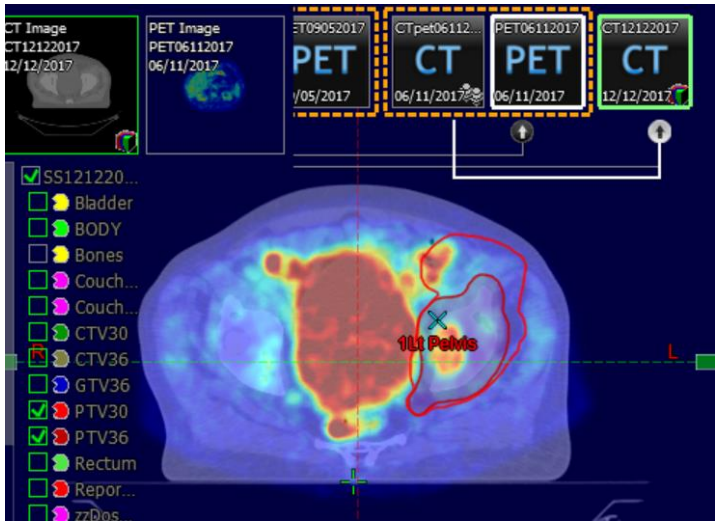




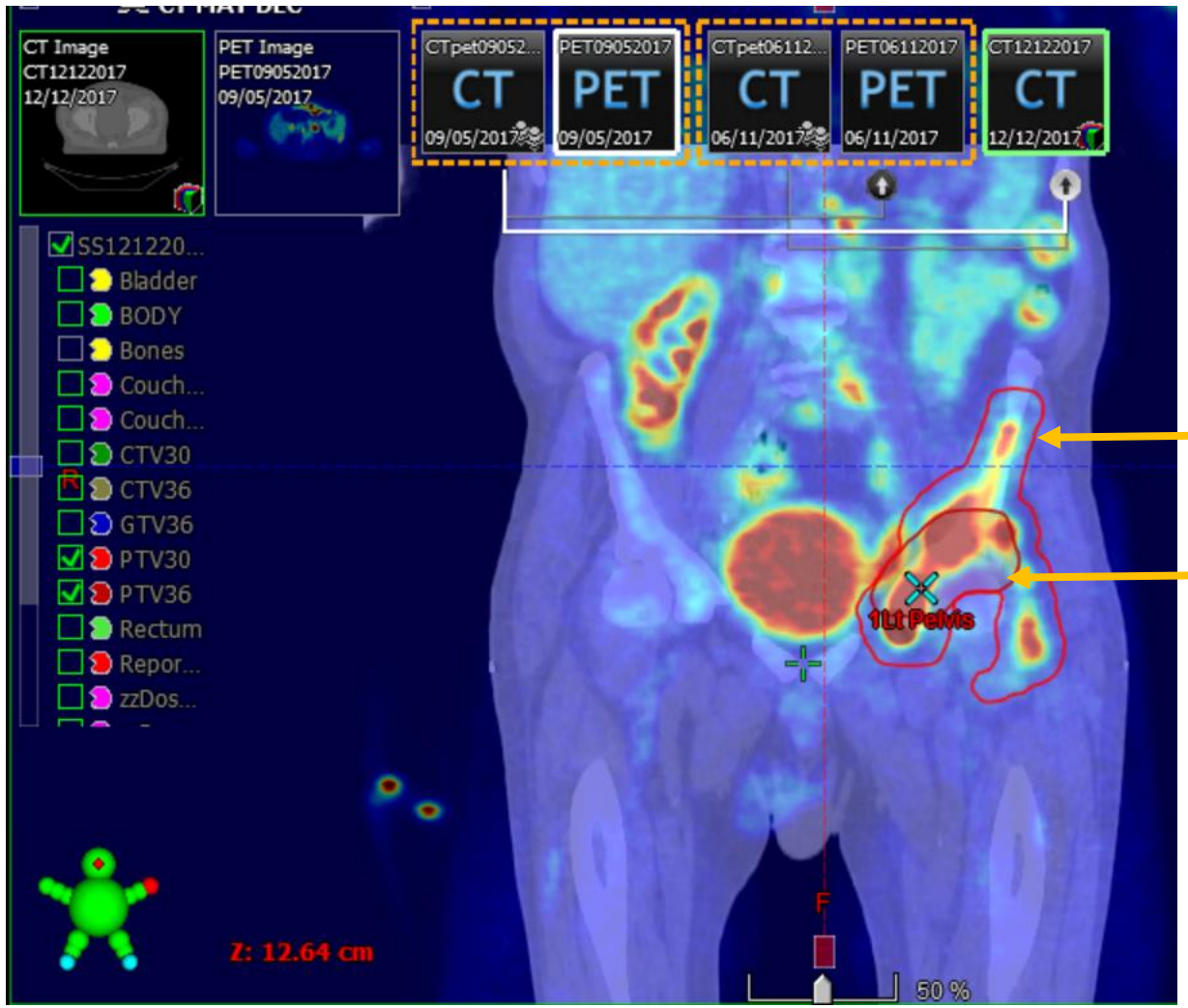
PTV 30Gy







PTV 36Gy

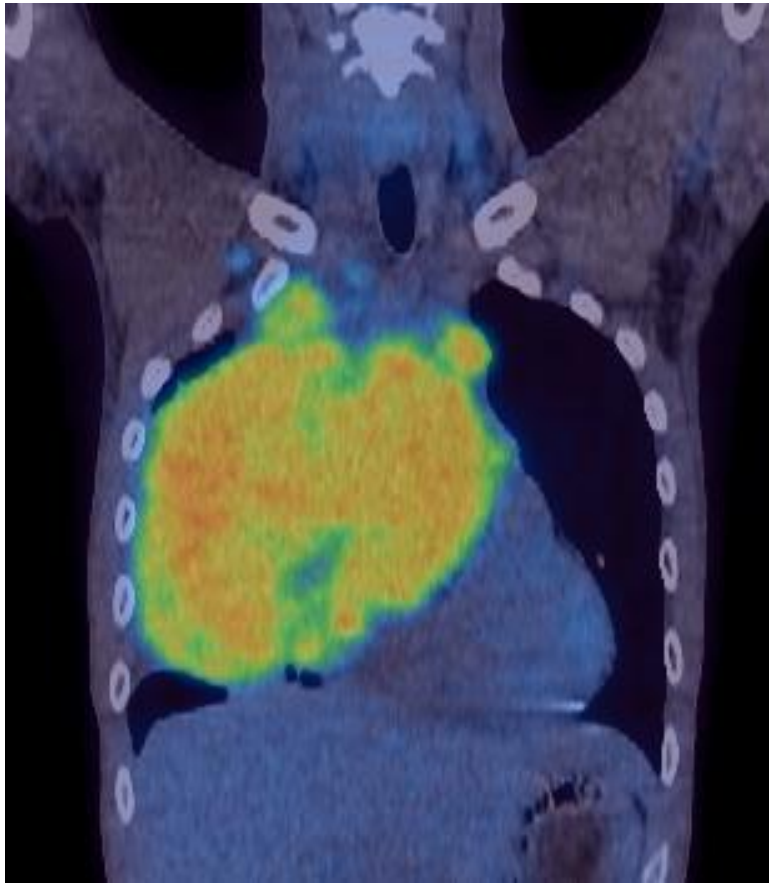


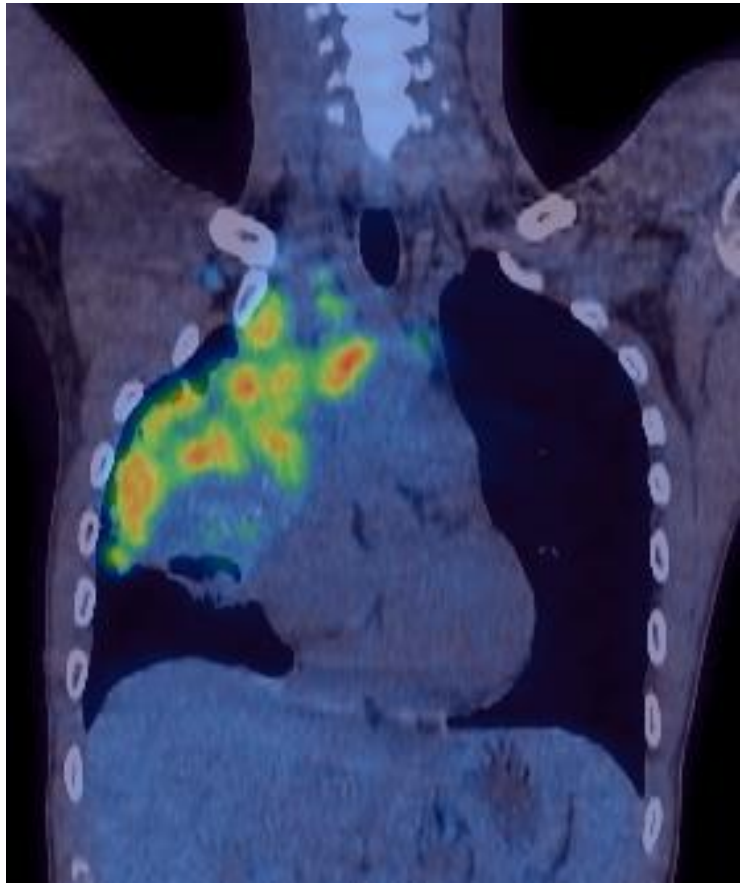
PTV 30Gy

PTV 36Gy

Refractory DLBCL

- Aim: 40 – 44 Gy
- Accept higher OARs



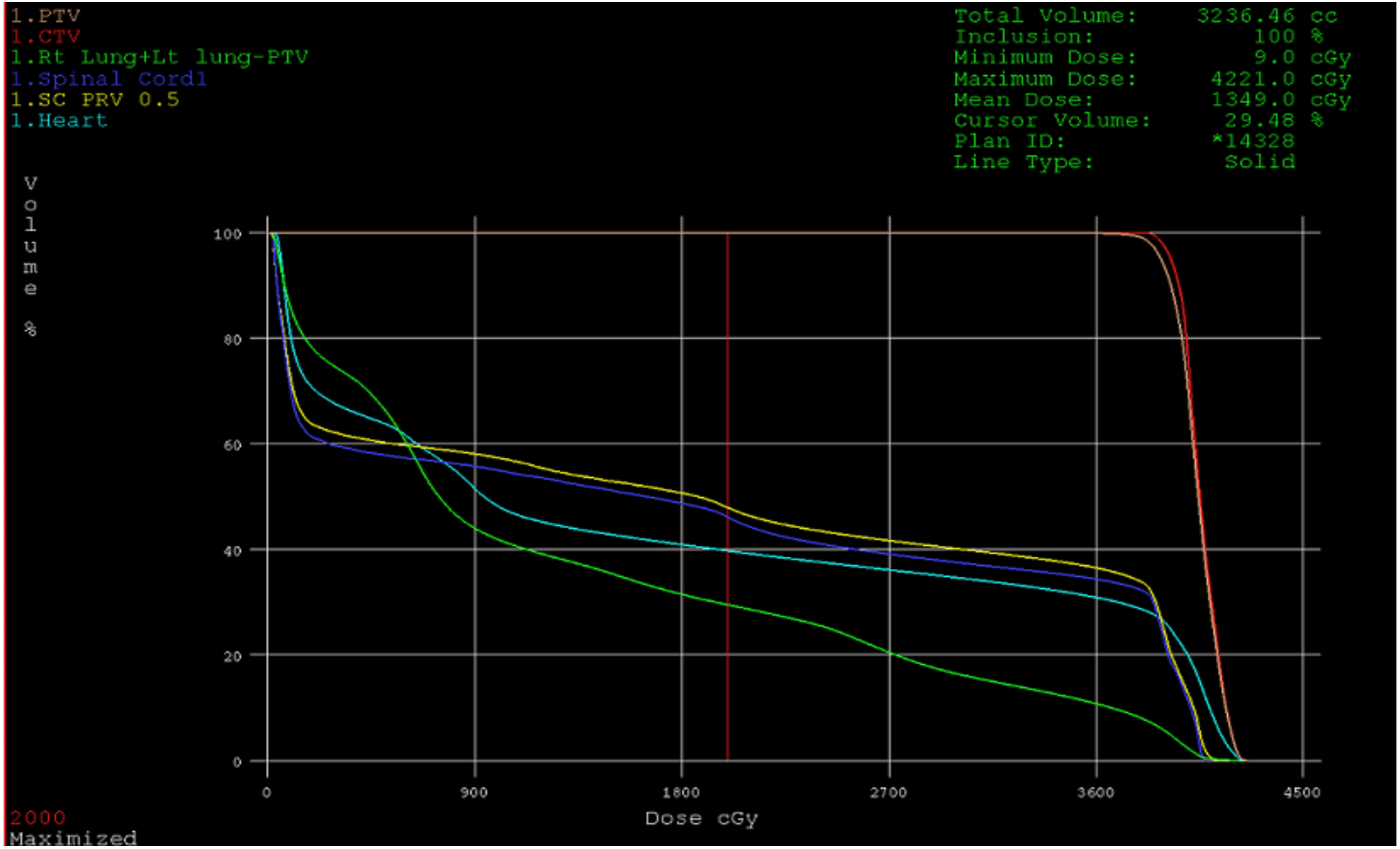


Radiotherapy plan showing:

- GTV (dark blue)
- CTV (yellow)
- PTV (red)

And
beam arrangement

40Gy / 20# / 4 weeks



PTV:
V95: 98.9%

Lung:
V20 29.5%
mean: 13.5Gy

Heart :
V30 34.6%
mean 17.8 Gy
median 9.5 Gy

Sp cord max:
40.8 Gy

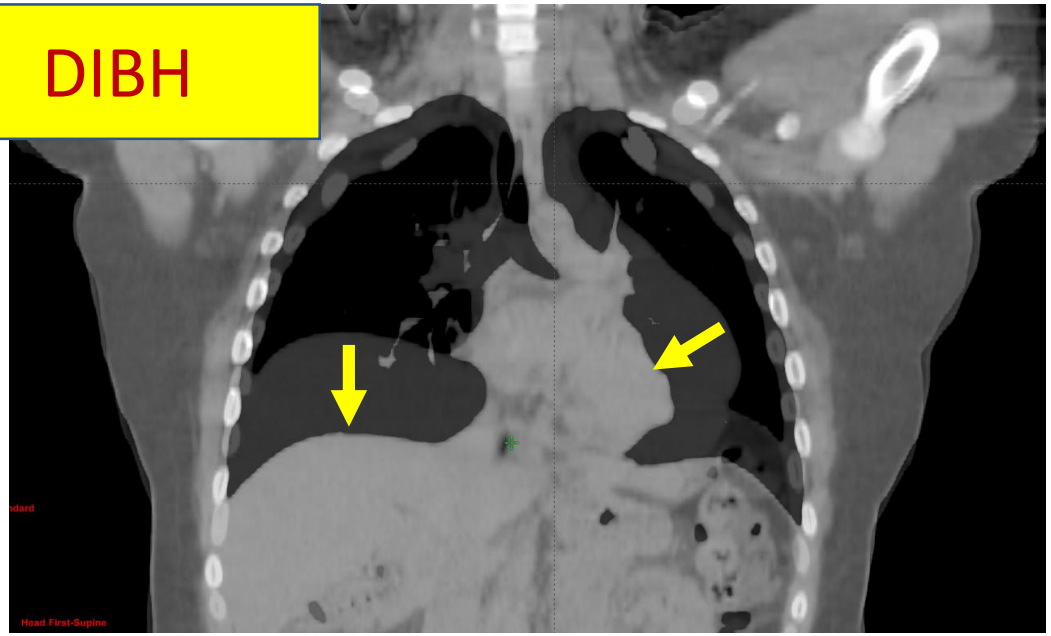
Techniques

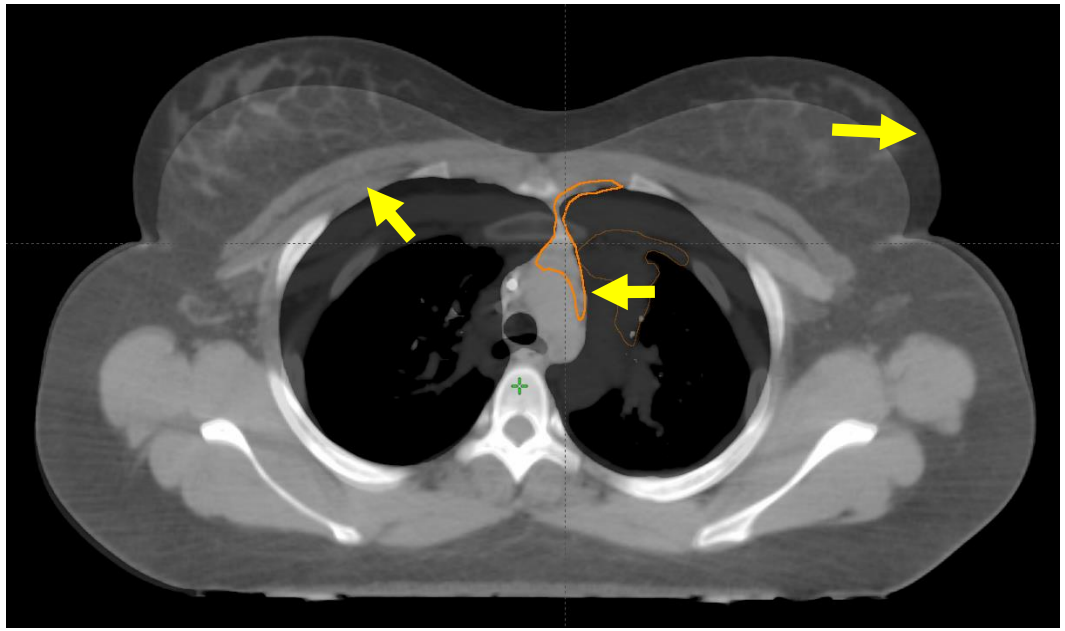
Techniques

Mediastinal lymphoma

- Breathing Control: DIBH
- Intelligent IMRT: Butterfly IMRT or Butterfly VMAT
- Protons

DIBH

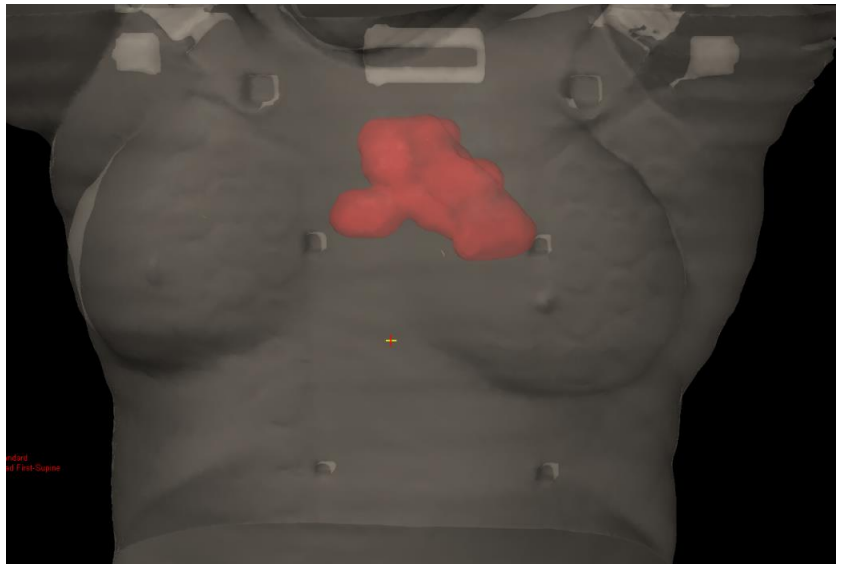


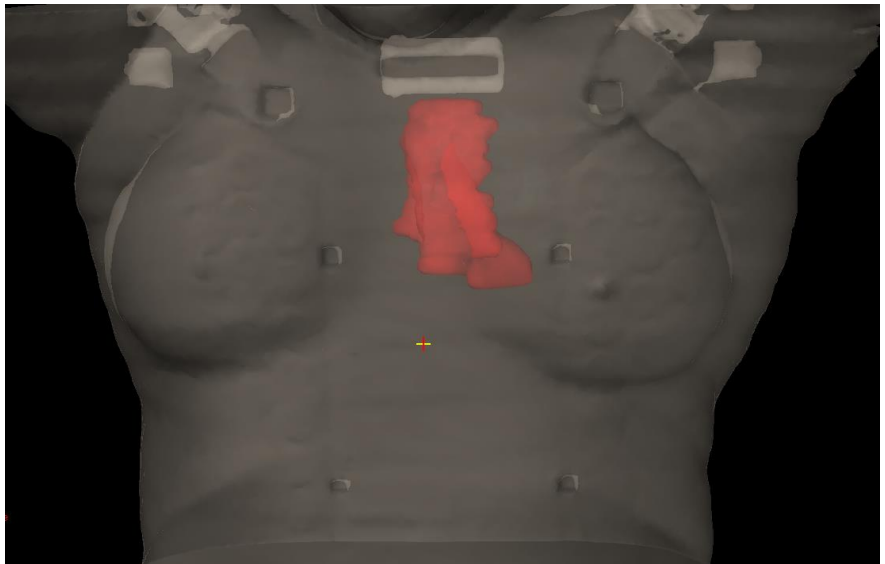


DIBH: Displacement of heart and lung
No respiratory movement

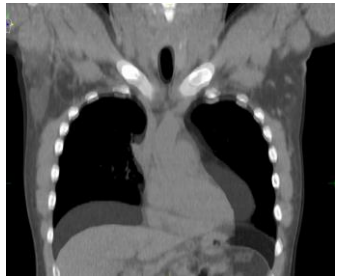
Reduction of heart and lung doses

Free Breathing



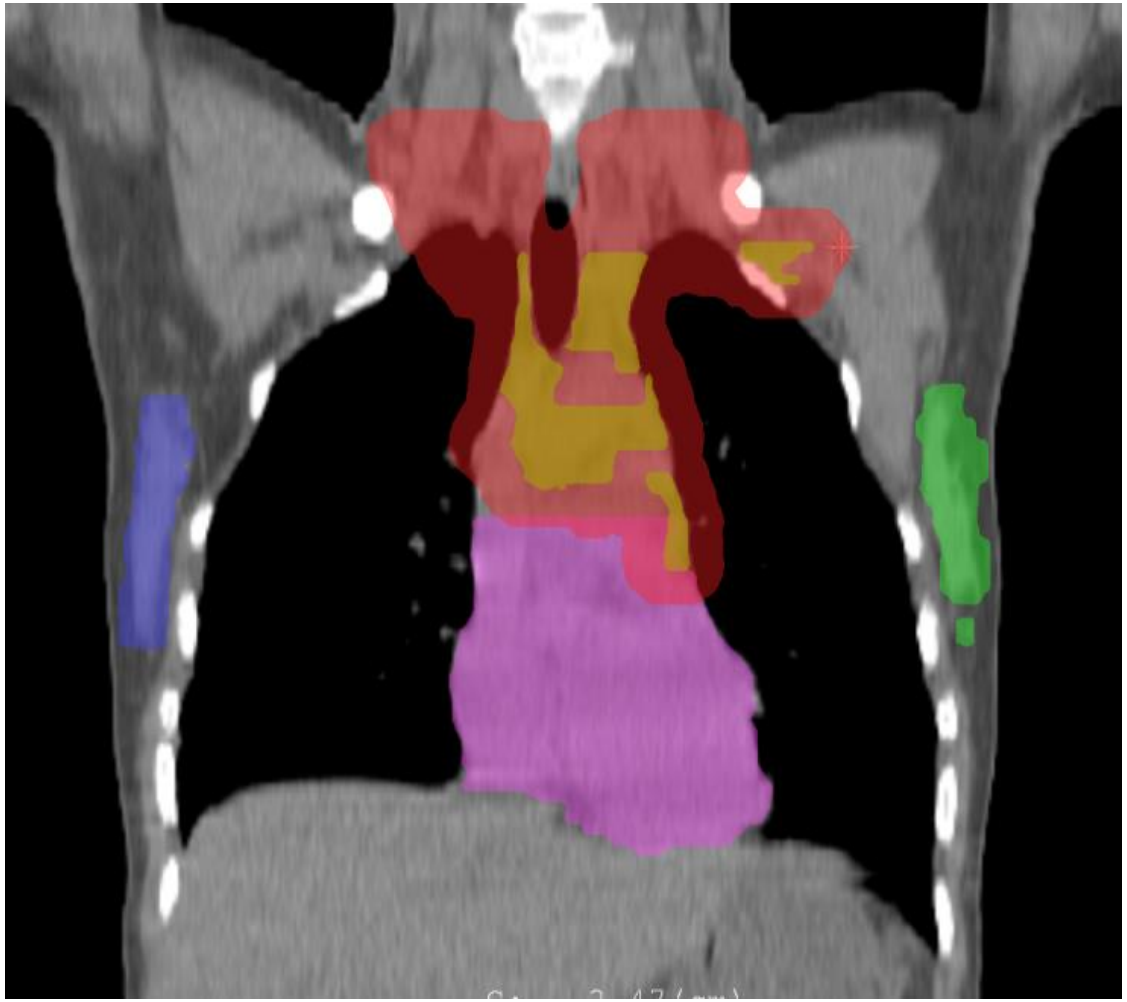


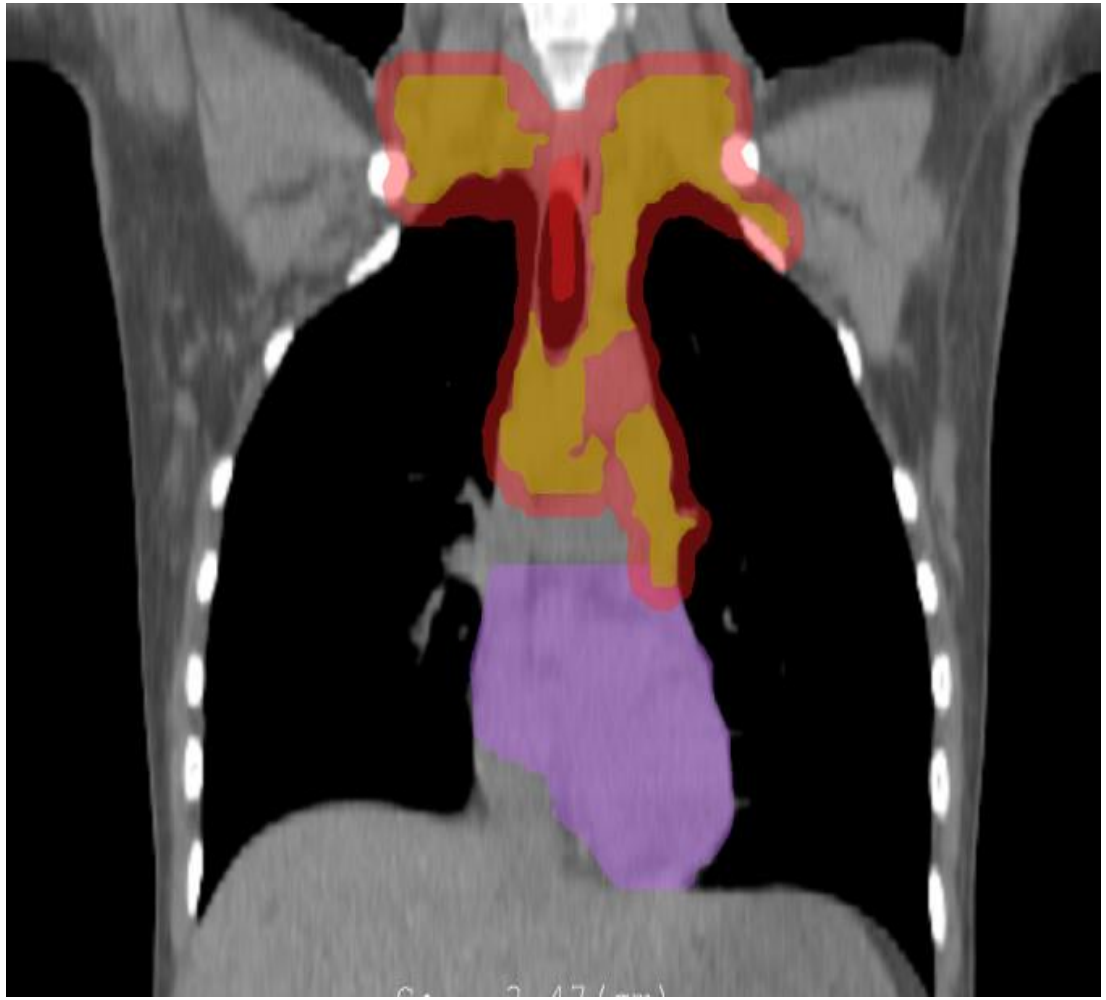
DIBH



Free Breath

DIBH

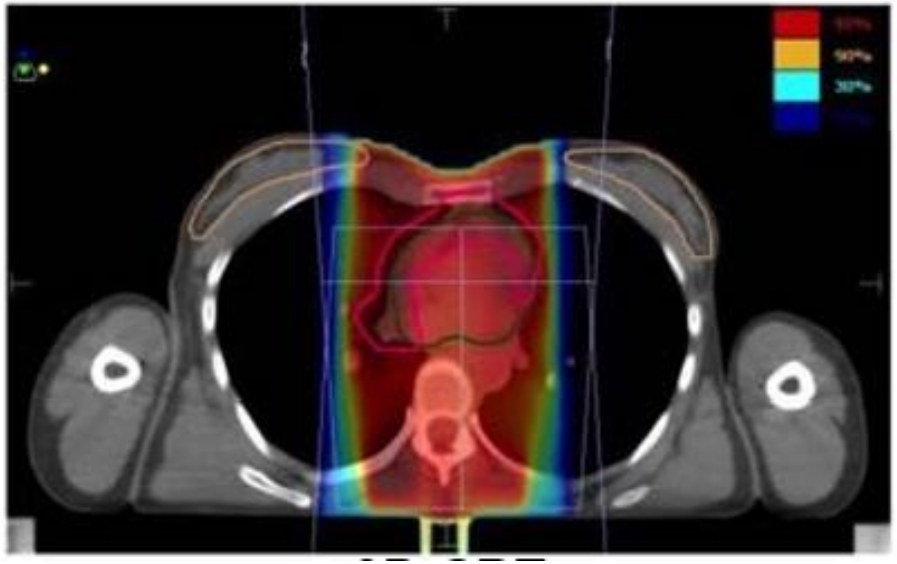




IMRT for MEDIASTINUM

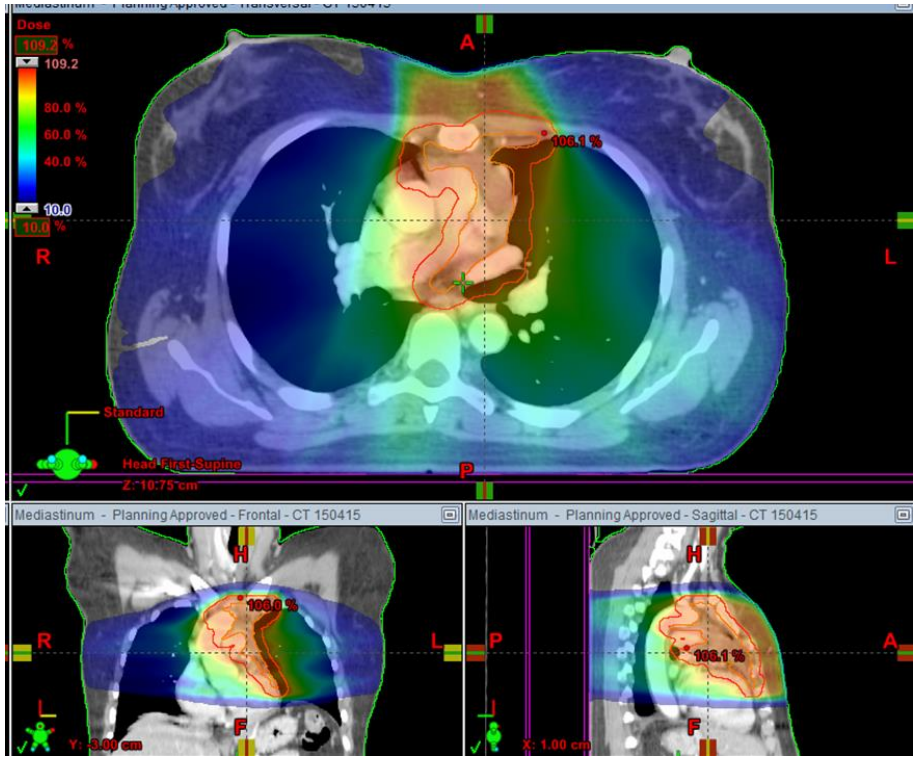
AP/PA

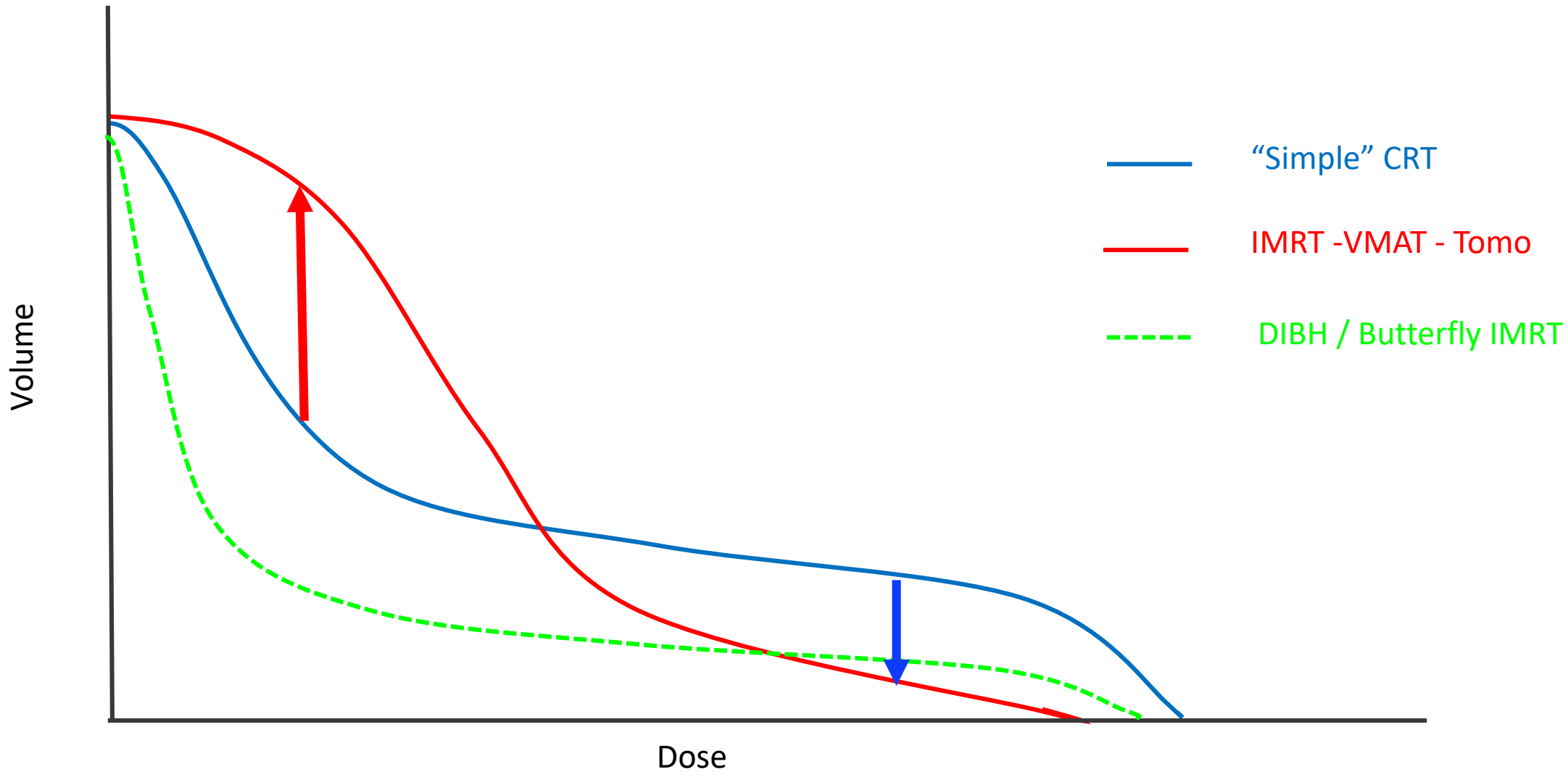
- Less lung
- Less breast
- High dose middle may include heart



VMAT

- Less heart dose
- Low dose bath to breast and lungs
- High lung V5

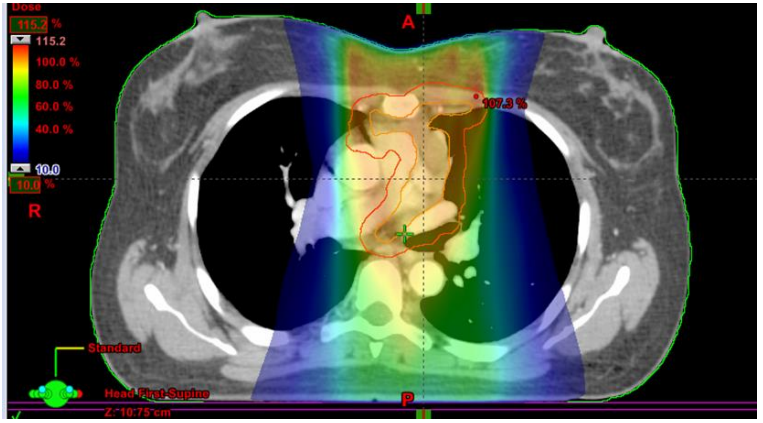



Volume
Dose
“Simple” CRT
IMRT -VMAT - Tomo
DIBH / Butterfly IMRT

What are “butterfly” techniques

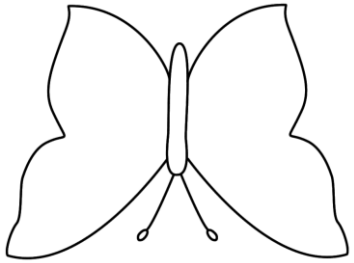
- IMRT delivered through centre of chest & not lat lungs or breasts

- Resultant dose distribution resembles *butterfly*.



- 2 techniques described in literature:

1. Butterfly VMAT
2. Butterfly IMRT (fixed beams)

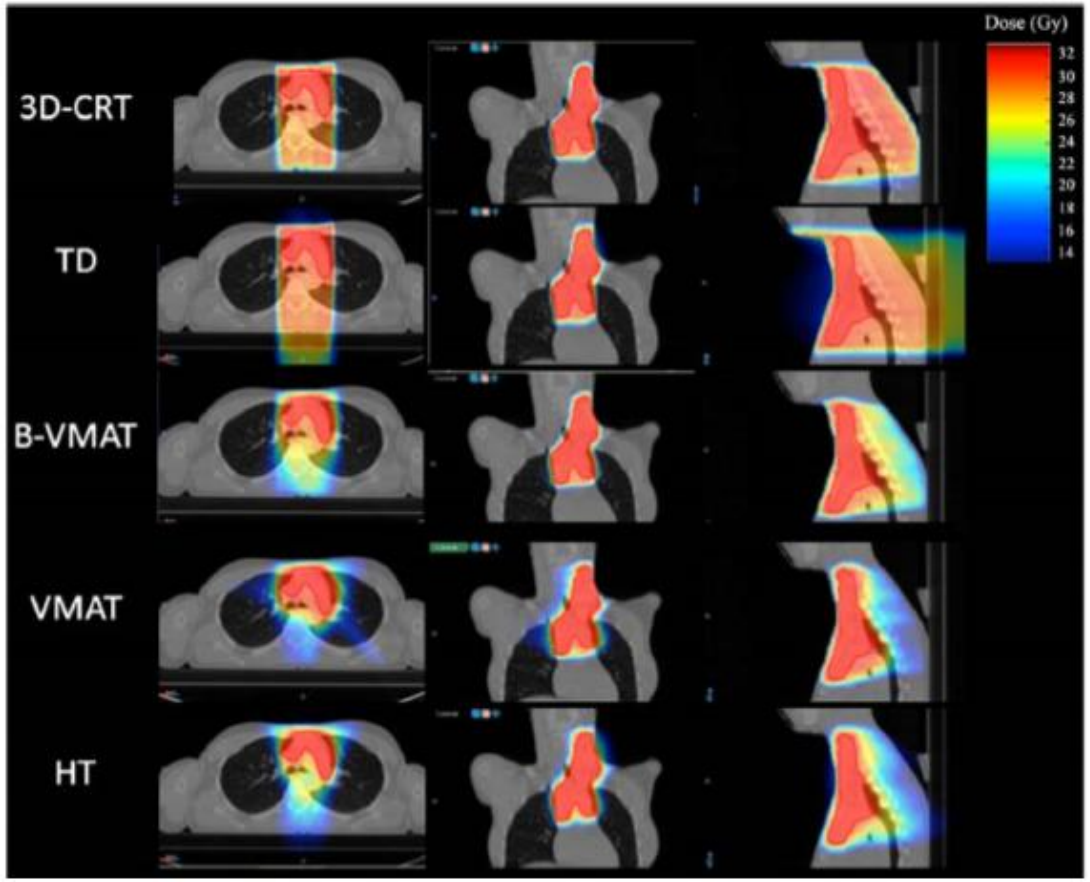


Different IMRT solutions vs. 3D-Conformal Radiotherapy in early stage Hodgkin's lymphoma: dosimetric comparison and clinical considerations

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]

RADIATION ONCOLOGY

Radiation Oncology 2012, **7**:186



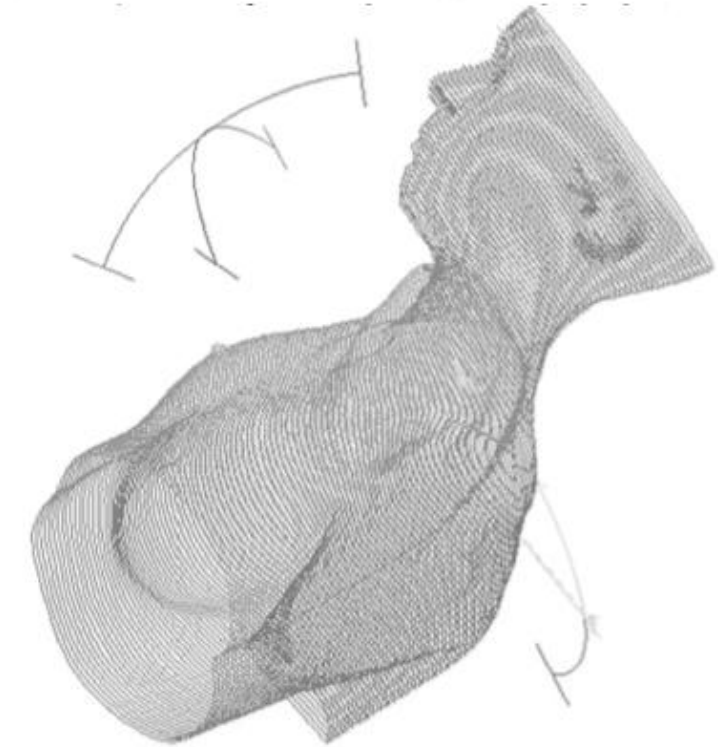
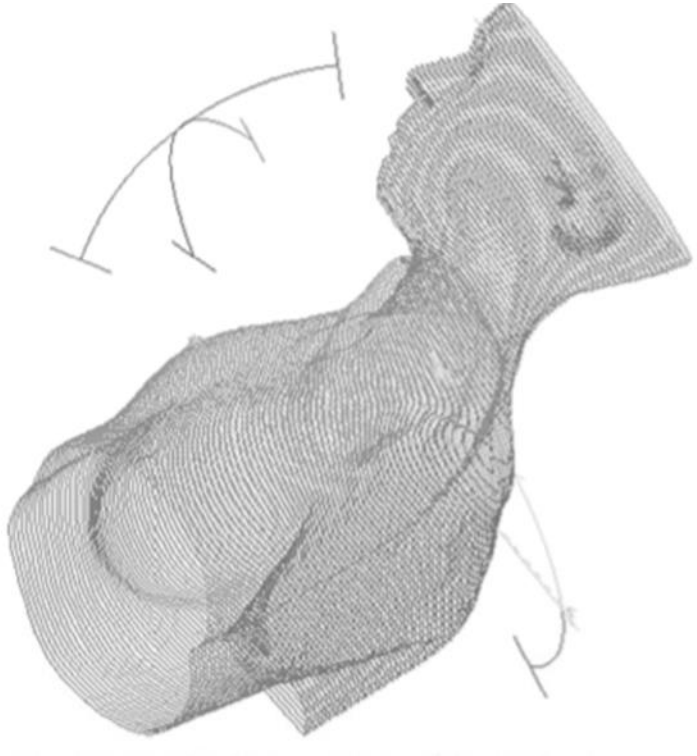
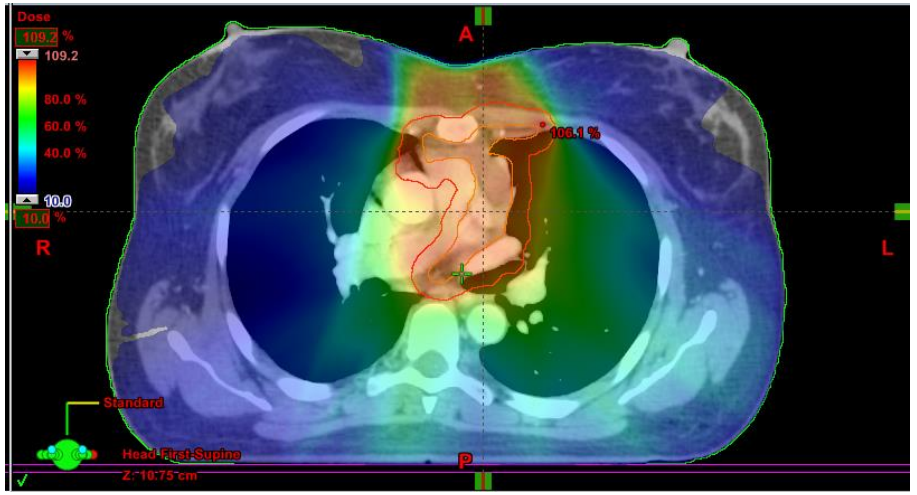
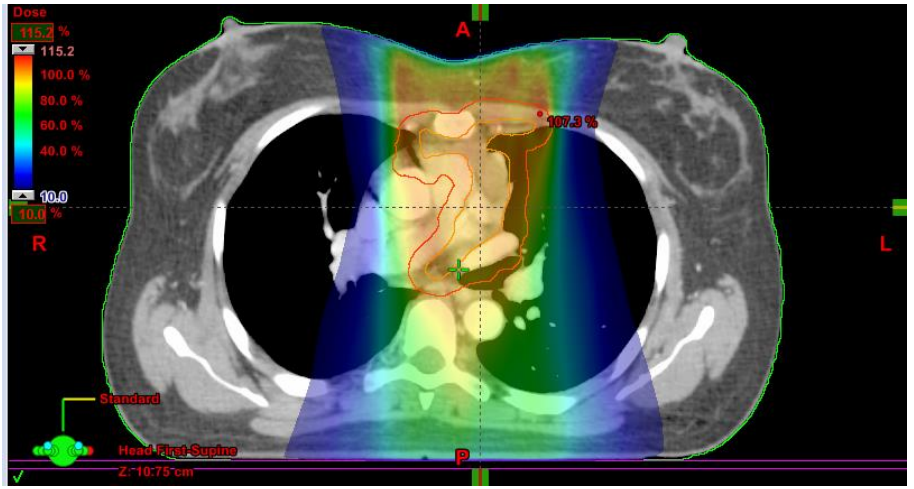


Figure 1 3D-graphical representation of the arc /beams configuration employed in Butterfly VMAT (B-VMAT) approach.

Butterfly VMAT







Butterfly VMAT uses non-coplanar partial arcs to deliver radiation through the middle part of the chest avoid lungs and female breast

3 Arcs: 2 Ant + post 60^{o}
1 Carnio-caudal 60^{o}

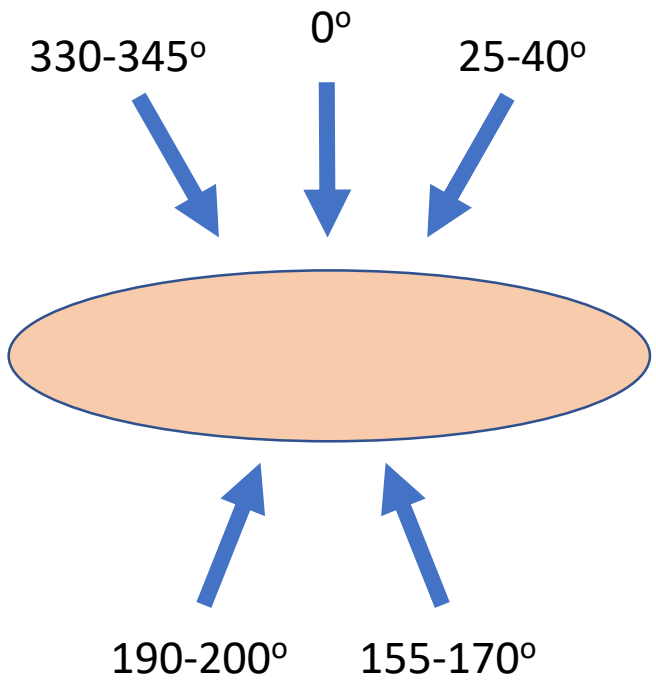
Voong et al. Radiation Oncology 2014, 9:94
http://www.ro-journal.com/content/9/1/94

RADIATION ONCOLOGY

RESEARCH Open Access

Dosimetric advantages of a "butterfly" technique for intensity-modulated radiation therapy for young female patients with mediastinal Hodgkin's lymphoma

Khinh Ranh Voong[1], Kelli McSpadden[1], Chelsea C Pinnix[1], Ferial Shihadeh[1], Valerie Reed[1], Mohammad R Salehpour[2], Isidora Arzu[1], He Wang[2], David Hodgson[3], John Garcia[1], Michalis Aristophanous[2] and Bouthaina S Dabaja[1*]



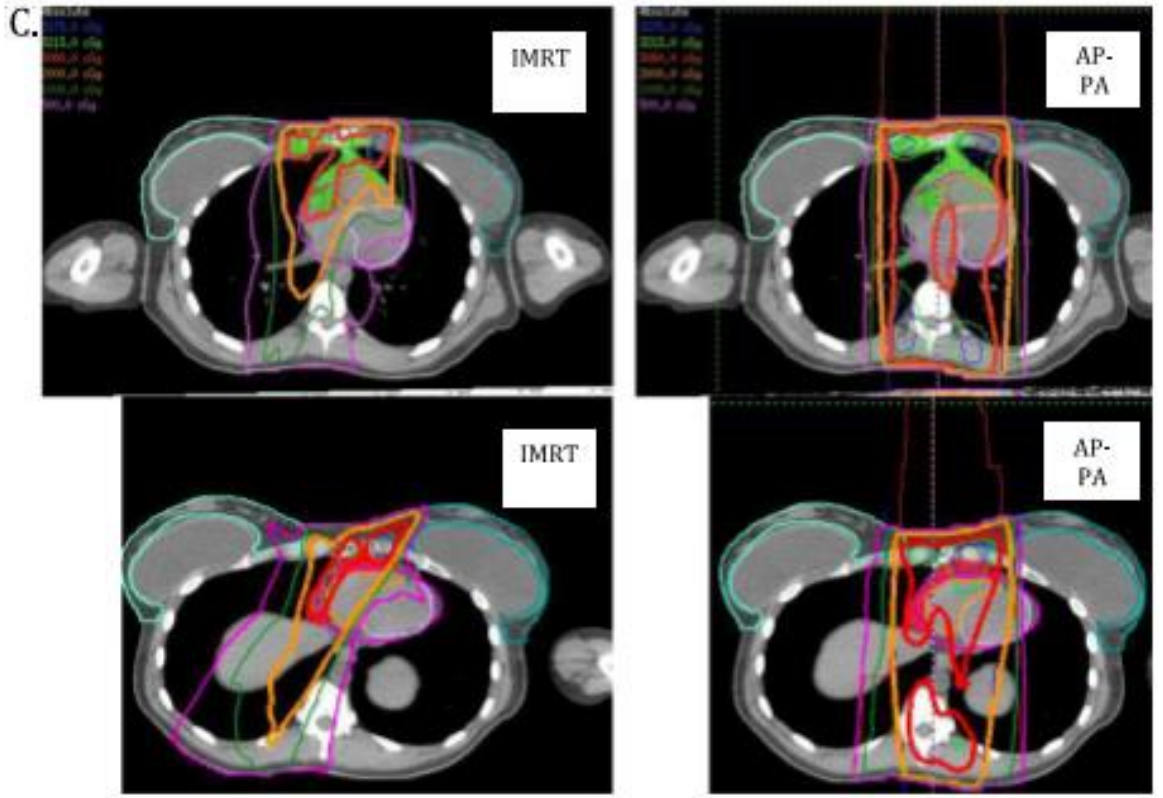
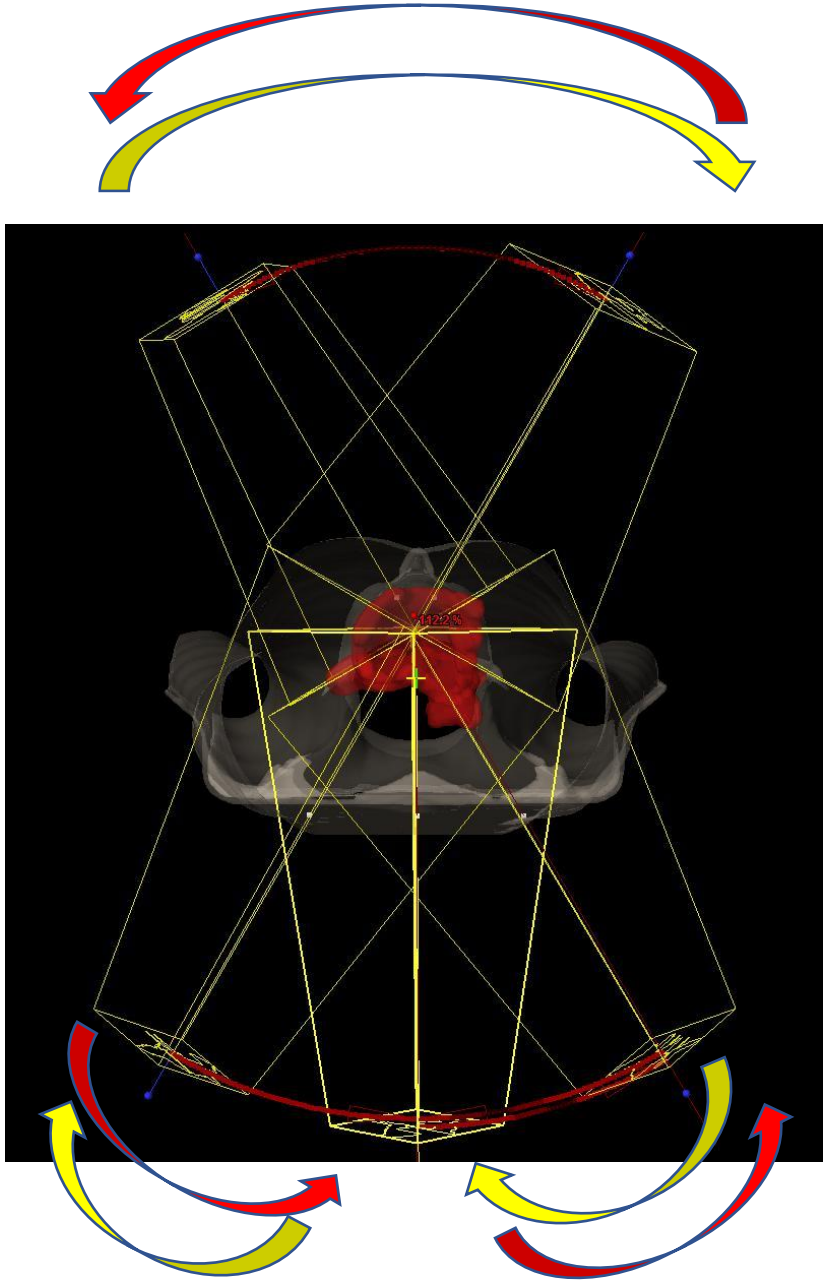
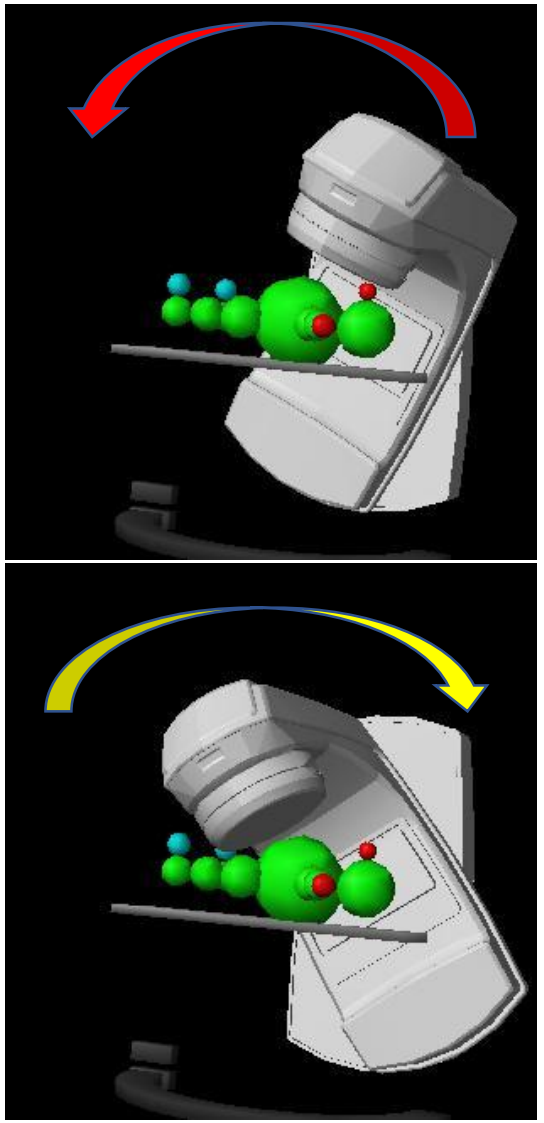


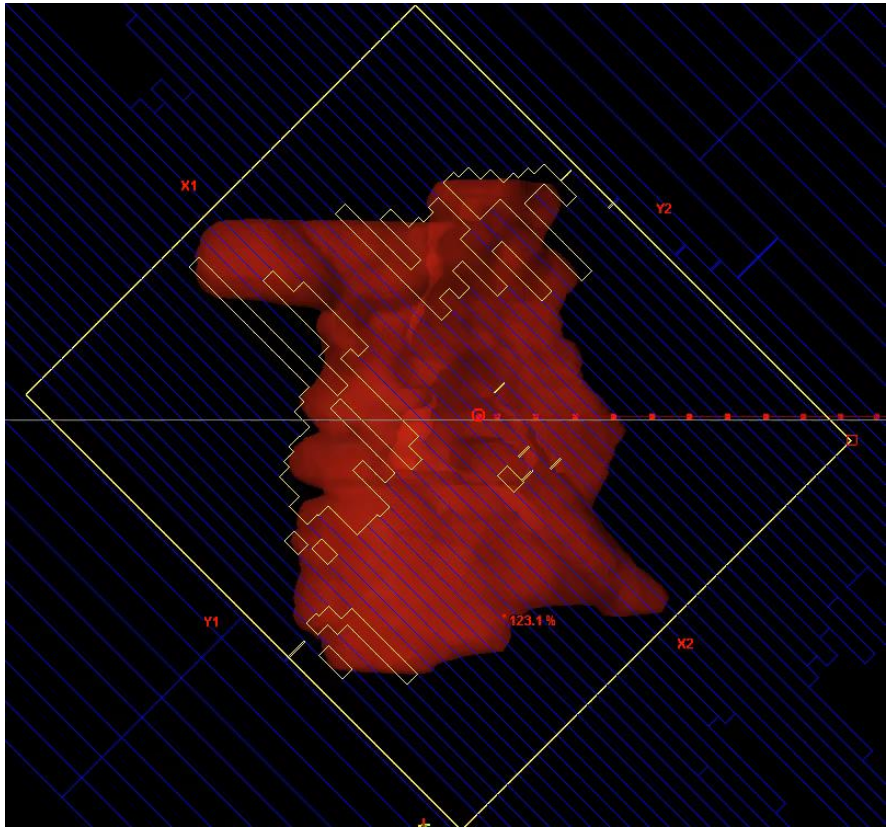
Figure 4 Coronal (A), sagittal (B), and axial (C) views of a butterfly intensity-modulated radiation therapy (IMRT) plan (left) and plan using anteroposterior-posteroanterior (AP-PA) photon beams (right). Red isodose lines represent 30.6 Gy; orange, 20 Gy; green, 10 Gy; and purple 5 Gy. The clinical target volume (shaded green) includes initial sites of nodal involvement. The Butterfly IMRT plan limits the 30.6-Gy dose to the breasts (panel **C**).

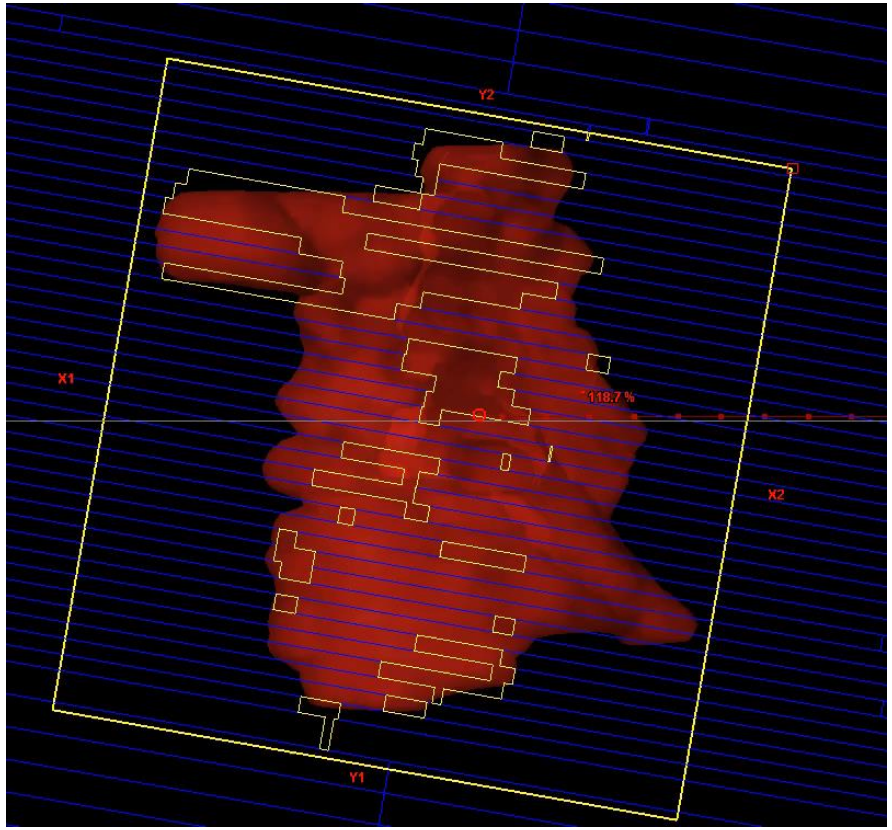
The Butterfly VMAT Arc arrangement





Why double partial arcs?





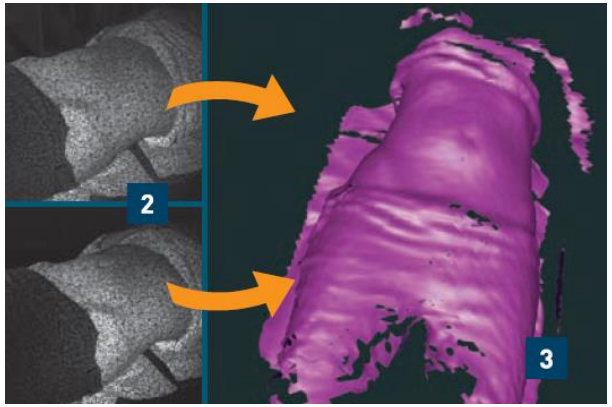
How does it work?

Projects speckled near infra-red light pattern onto patient's surface

Stereo HD camera pods image pattern in 3D

Software reconstructs full surface

Surface matched in real time to reference image from CT or AlignRT. Patient monitored in all 6 degrees of freedom.

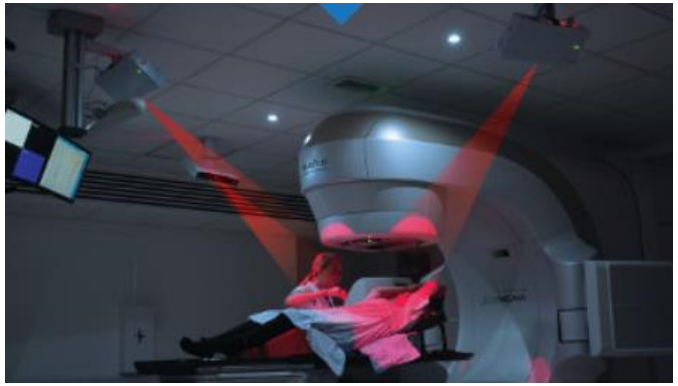


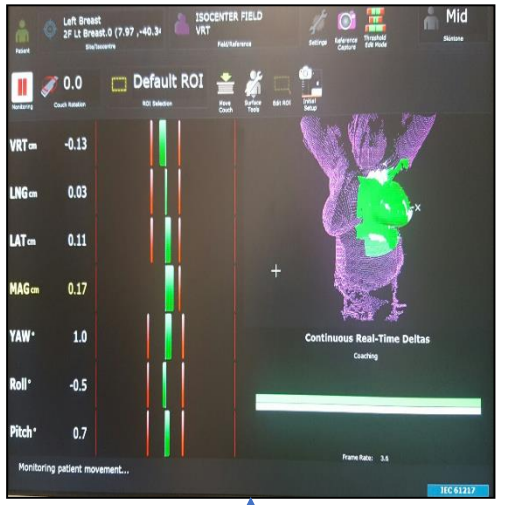
DIBH Workflow

Utilisation –

Patient Set up

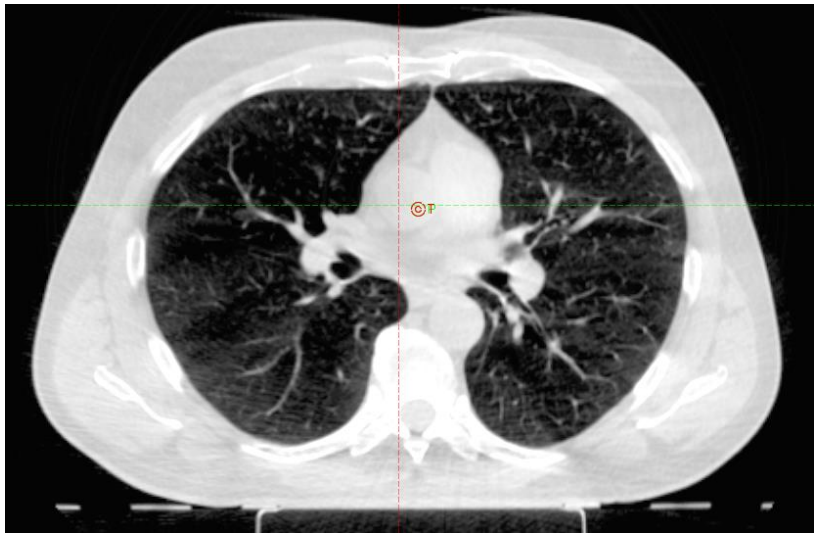
- Tracks the position of the treatment site in **six degrees of freedom** throughout breath hold
- Provides a coaching tool for assisting breath hold
- Automated beam hold.



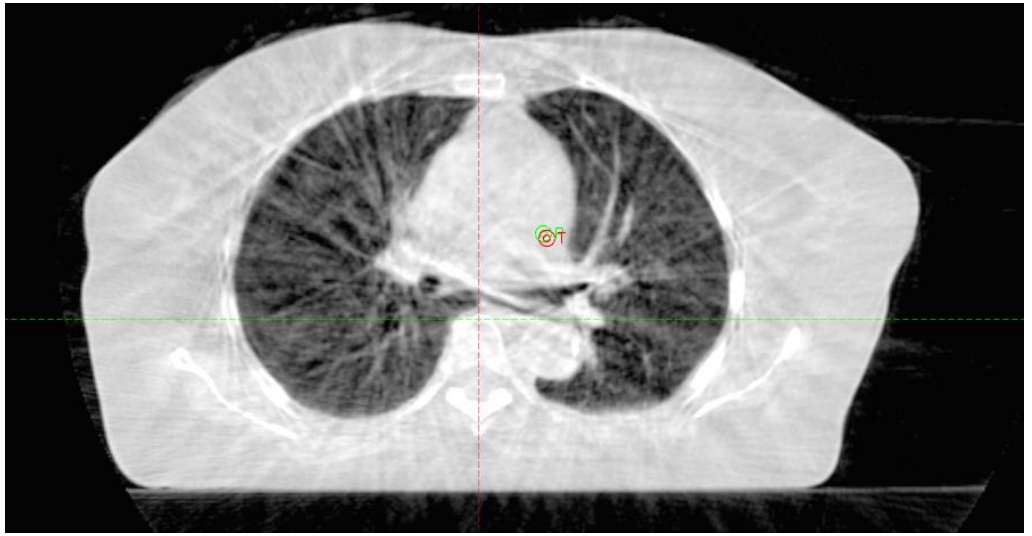


CBCT

What is the image quality like?



BH



FB

Radiotherapy and Oncology xxx (2018) xxx–xxx

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journal homepage: www.thegreenjournal.com

Original article

Comparison of butterfly volumetric modulated arc therapy to full arc with or without deep inspiration breath hold for the treatment of mediastinal lymphoma

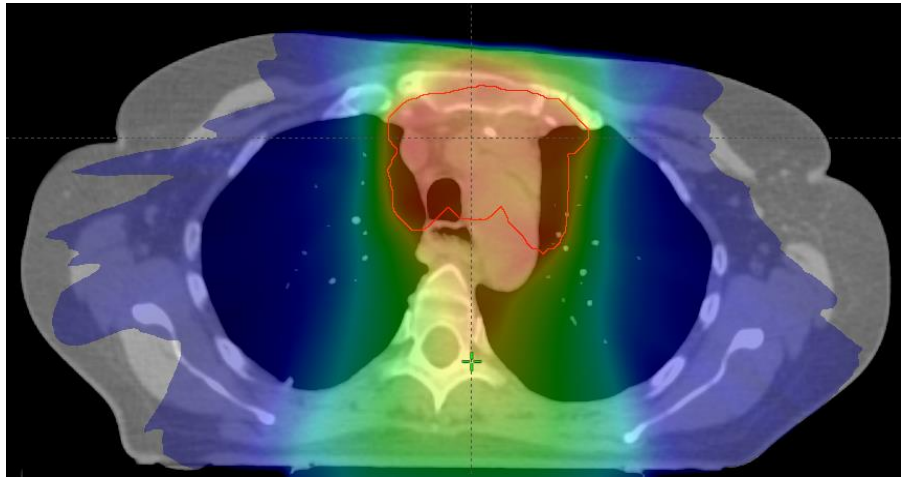
Alison Starke [a], Jonathan Bowden [a,*], Rebecca Lynn [b], Keith Hall [a], Kate Hudson [a], Ana Rato [a], Emma Aldridge [a], Dean Robb [a], Paula Steele [a], Jessica Brady [b], N. George Mikhaeel [a,b,c]

[a] *The London Radiotherapy Centre, Part of HCA Healthcare UK, Guy's Hospital, UK;* [b] *Guy's Cancer Centre, Guy's & St Thomas' NHS Trust, London; and* [c] *Cancer Division, Faculty of Life Sciences and Medicine, King's College London University, UK*

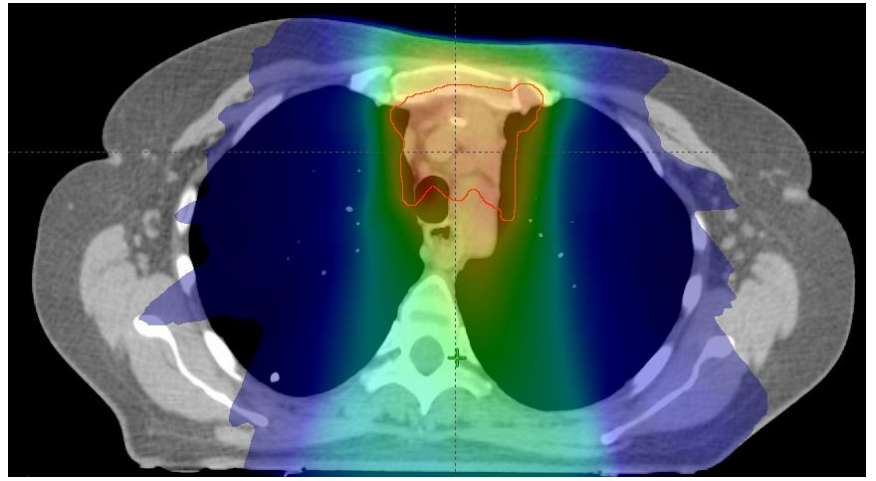
4 plan comparison

Doses >10% (3.6Gy) shown

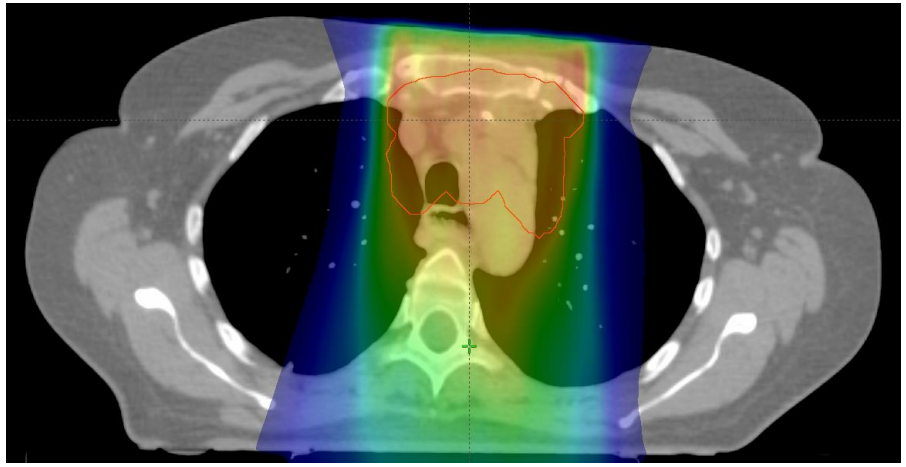
Full arc
+
FB



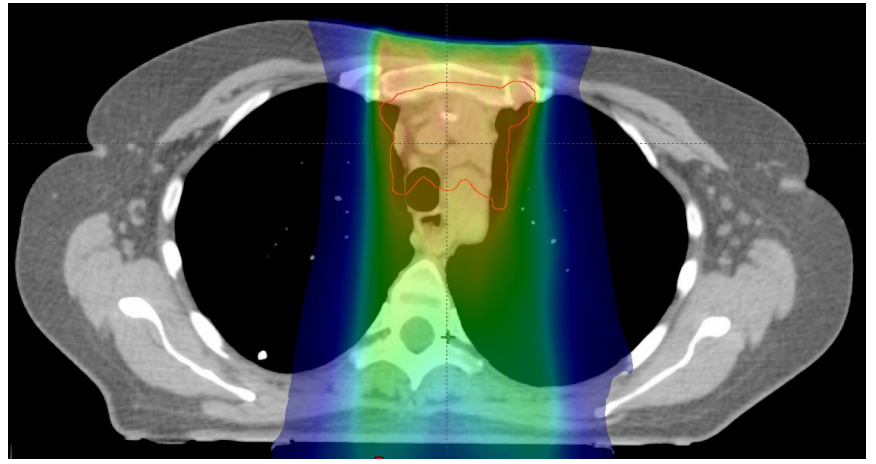
Full arc
+
DIBH



B-VMAT
+
FB



B-VMAT
+
DIBH



	N=20			
	FB F-VMAT	FB B-VMAT	DIBH F-VMAT	DIBH B-VMAT
PTV volume (cc)	611 (252-1055)[3,4]		405 (189-884)[1,2]	
PTV V90% (%)	99.7 (98.4-100.0)[2]	99.4 (97.6-100.0)[1,3]	99.8 (97.9-100.0)[2,4]	99.6 (98.0-99.9)[3]
PTV V95% (%)	96.2 (91.5-99.6)	95.8 (91.1-99.2)	96.1 (90.9-99.2)	96.3 (91.0-99.4)
PTV V107% (%)	0.0 (0-6.0)[2,4]	1.7 (0-13.4)[1,3,4]	0.0 (0-9.3)[2,4]	0.4 (0-10.0)[1,2,3]
CN 95%	0.85 (0.62-0.90)[2,3,4]	0.63 (0.55-0.77)[1,3,4]	0.78 (0.68-0.85)[1,2,4]	0.56 (0.47-0.73)[1,2,3]
HI	0.10 (0.06-0.15)[2,4]	0.14 (0.08-0.21)[1,3,4]	0.11 (0.08-0.14)[2,4]	0.12 (0.07-0.16)[1,2,3]
PTV mean (Gy)	30.5 (30.4-31.1)[2]	30.6 (30.5-31.1)[1,3]	30.6 (30.4-31.3)[2]	30.6 (30.5-31.3)
Total lung volume (cc)	2758 (1276-4331)[3,4]		4694 (2587-6997)[1,2]	
MLD (Gy)	8.2 (4.8-11.4)[2,3,4]	7.2 (3.8-10.9)[1,3,4]	6.1 (2.6-9.5)[1,2,4]	4.9 (2.6-8.4)[1,2,3]
Lung V30Gy (%)	3.2 (1.5-6.6)[2,3,4]	3.7 (2.1-7.5)[1,3,4]	1.0 (0.4-1.7)[1,2,4]	1.4 (0.7-2.9)[1,2,3]
Lung V25Gy (%)	8.0 (3.0-13.1)[2,3,4]	10.5 (4.3-17.2)[1,3,4]	3.7 (1.5-5.7)[1,2,4]	6.0 (2.1-9.7)[1,2,3]
Lung V20Gy (%)	13.9 (4.8-53.3)[2,3,4]	14.7 (6.1-43.0)[1,3,4]	6.7 (2.8-47.2)[1,2,4]	9.0 (3.3-34.3)[1,2,3]
Lung V15Gy (%)	18.9 (8.5-31.9)[3,4]	18.4 (8.3-30.5)[3,4]	12.4 (5.6-22.2)[1,2]	12.5 (5.0-21.7)[1,2]
Lung V10Gy (%)	30.4 (15.4-50.4)[2,3,4]	24.5 (11.4-39.4)[1,4]	21.7 (10.9-64.1)[1,4]	16.7 (7.4-46.8)[1,2,3]
Lung V5Gy (%)	50.3 (22.5-84.0)[2,3,4]	37.8 (18.0-72.5)[1,4]	38.3 (23.1-71.1)[1,4]	24.7 (12.6-60.8)[1,2,3]
Heart volume (cc)	672 (374-1249)[3,4]		617 (408-1109)[1,2]	
Heart mean dose (Gy)	6.1 (1.4-13.5)[2,3,4]	6.2 (1.5-15.3)[1,3,4]	3.8 (0.6-10.4)[1,2,4]	4.3 (0.5-12.3)[1,2,3]
Heart V30Gy (%)	5.4 (0.1-16.1)[3,4]	4.1 (0.1-12.2)[3,4]	1.4 (0-6.2)[1,2]	1.7 (0-7.8)[1,2]
Heart V20Gy (%)	11.9 (1.5-37.1)[2,3,4]	12.7 (1.1-42.8)[1,3,4]	5.7 (0-21.5)[1,2,4]	8.1 (0-29.4)[1,2,3]
Heart V15Gy (%)	15.2 (2.4-42.2)[2,3,4]	15.9 (2.2-48.5)[1,3,4]	9.6 (0-28.3)[1,2,4]	11.3 (0-36.5)[1,2,3]
Heart V10Gy (%)	19.7 (3.4-47.7)[2,3,4]	19.6 (3.5-55.7)[1,3,4]	12.0 (0-39.5)[1,2]	14.0 (0-47.2)[1,2]
Heart V5Gy (%)	29.9 (4.8-63.6)[3,4]	27.9 (6.4-65.6)[3,4]	19.8 (0-60.0)[1,2]	19.9 (0-60.0)[1,2]
Breast mean dose (Gy)	3.1 (1.1-6.0)[2,3,4]	1.3 (0.3-3.0)[1,3]	2.7 (1.2-5.0)[1,2,4]	1.3 (0.4-2.4)[1,3]
Breast V10Gy (%)	4.4 (0.6-25.4)[3,4]	3.5 (0.2-10.2)[3,4]	2.1 (0.1-5.5)[1,2]	2.0 (0-7.2)[1,2]
Breast V4Gy (%)	18.4 (4.9-51.3)[2,3,4]	7.7 (0.9-23.4)[1,3]	14.0 (3.2-49.2)[1,2,4]	8.1 (0.9-27.5)[1,3]
Spinal canal max dose (Gy)	27.7 (23.1-32.0)[3]	29.5 (15.3-32.3)[3]	24.3 (13.6-29.5)[1,2,4]	28.9 (22.3-32.3)[3]

LUNGS:

lowest MLD: DIBH + BVMAT.

Lowest **V30, V25, V20**, V15: FVMAT + DIBH

while **V5, V10** is lowest with B VMAT + DIBH

HEART:

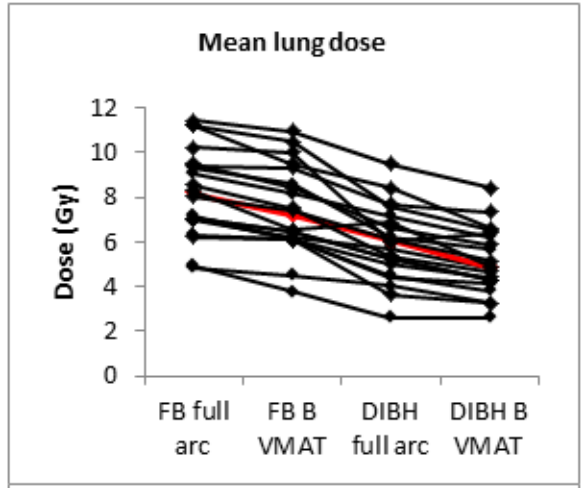
lowest doses: F-VMAT + DIBH with a significant difference from FB plans.

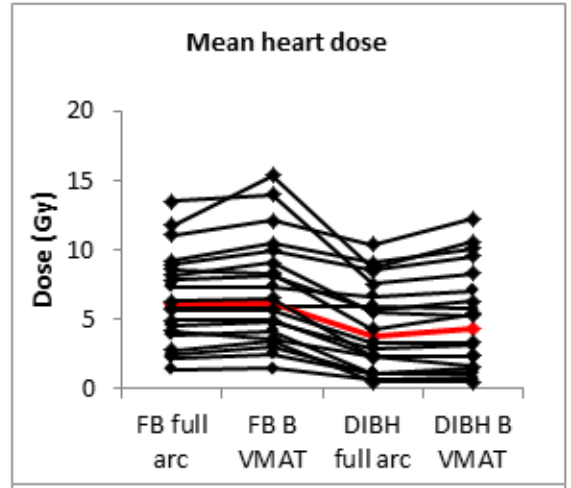
B-VMAT+DIBH doses were marginally higher but the difference was **not** statistically significant apart from **V15, V20**.

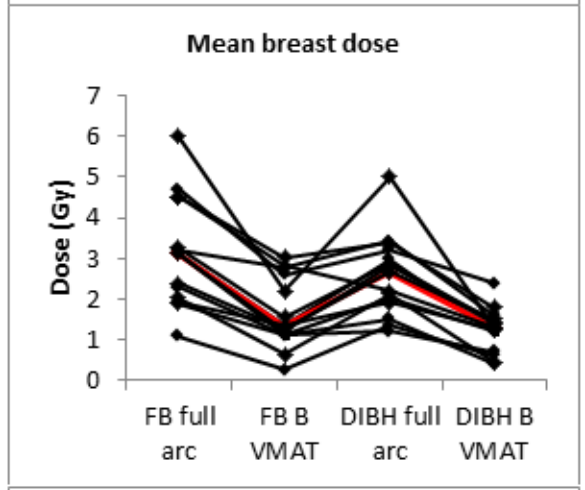
BREASTS:

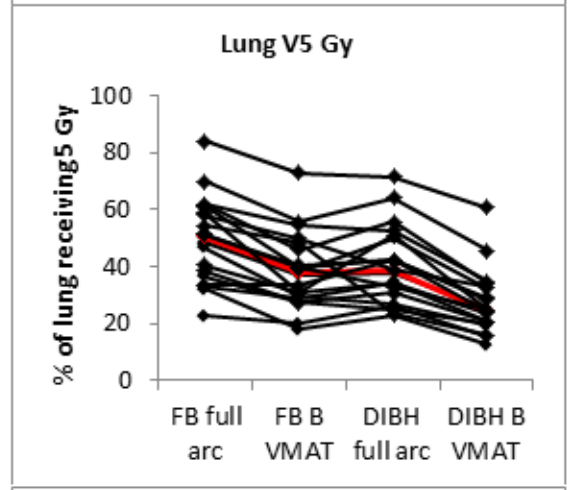
Best breast doses: B-VMAT + DIBH

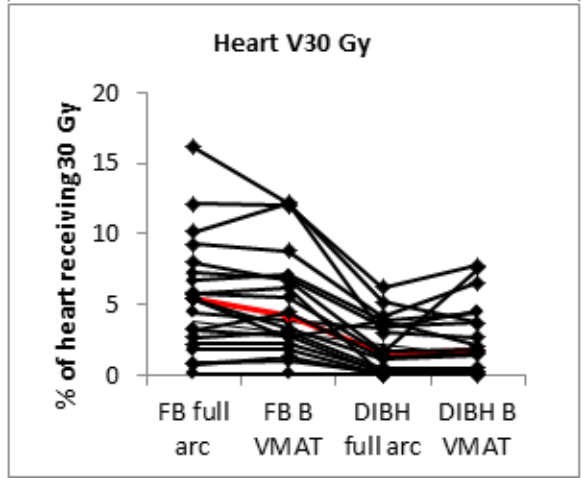
Particularly **V4**

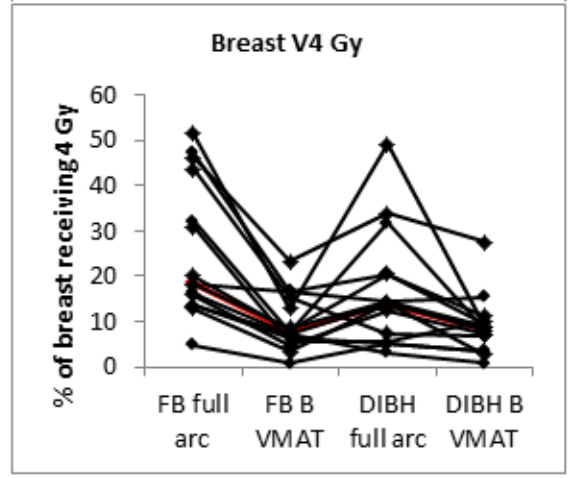

Mean lung dose
Dose (Gy)
0
2
4
6
8
10
12
FB full arc
FB B VMAT
DIBH full arc
DIBH B VMAT

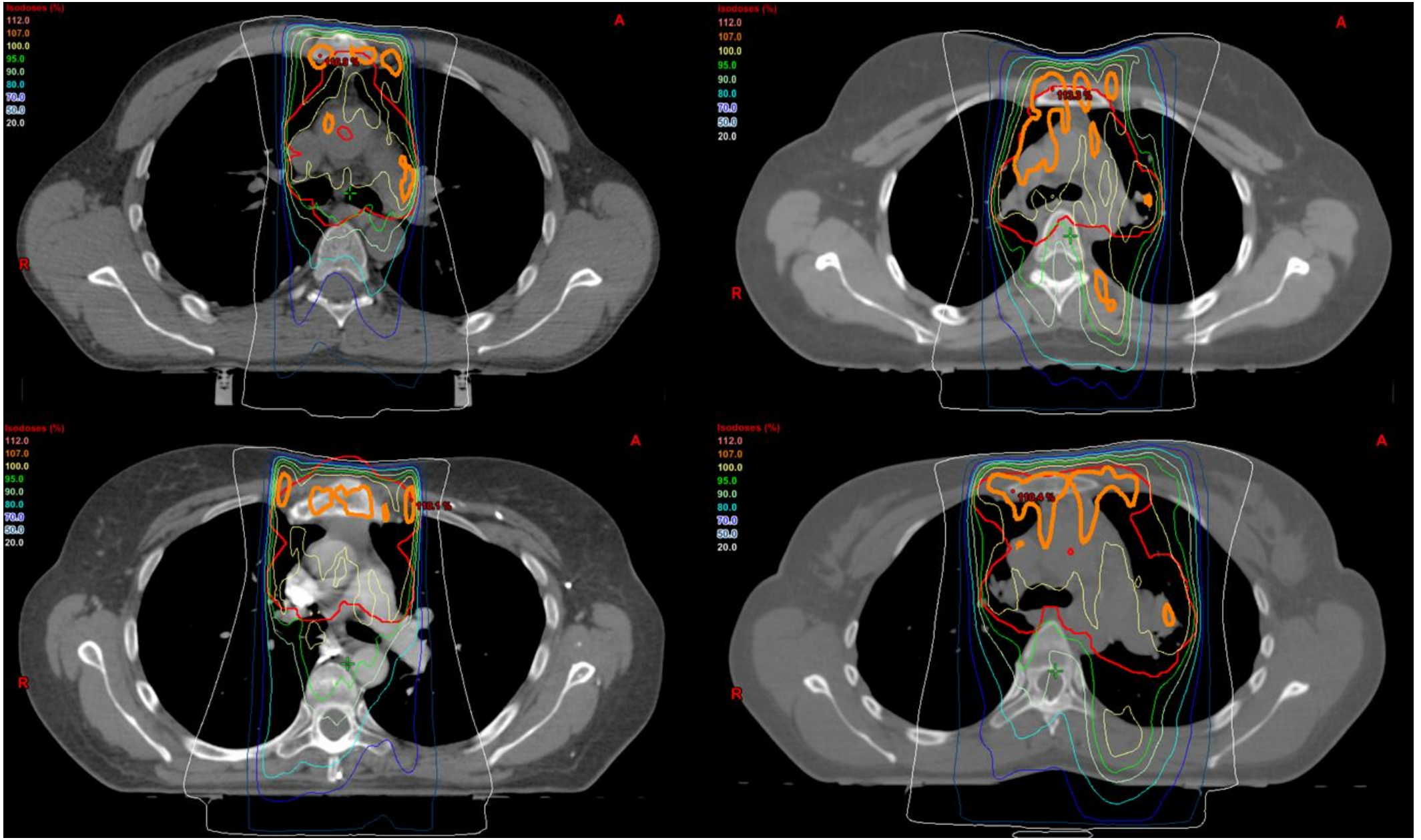

Mean heart dose
Dose (Gy)
0
5
10
15
20
FB full arc
FB B VMAT
DIBH full arc
DIBH B VMAT


Mean breast dose
Dose (Gy)
0
1
2
3
4
5
6
7
FB full arc
FB B VMAT
DIBH full arc
DIBH B VMAT


Lung V5 Gy
% of lung receiving5 Gy
0
20
40
60
80
100
FB full arc
FB B VMAT
DIBH full arc
DIBH B VMAT


Heart V30 Gy
% of heart receiving30 Gy
0
5
10
15
20
FB full arc
FB B VMAT
DIBH full arc
DIBH B VMAT


Breast V4 Gy
% of breast receiving4 Gy
0
10
20
30
40
50
60
FB full arc
FB B VMAT
DIBH full arc
DIBH B VMAT



107% isodose

So, which technique should we use for MRT

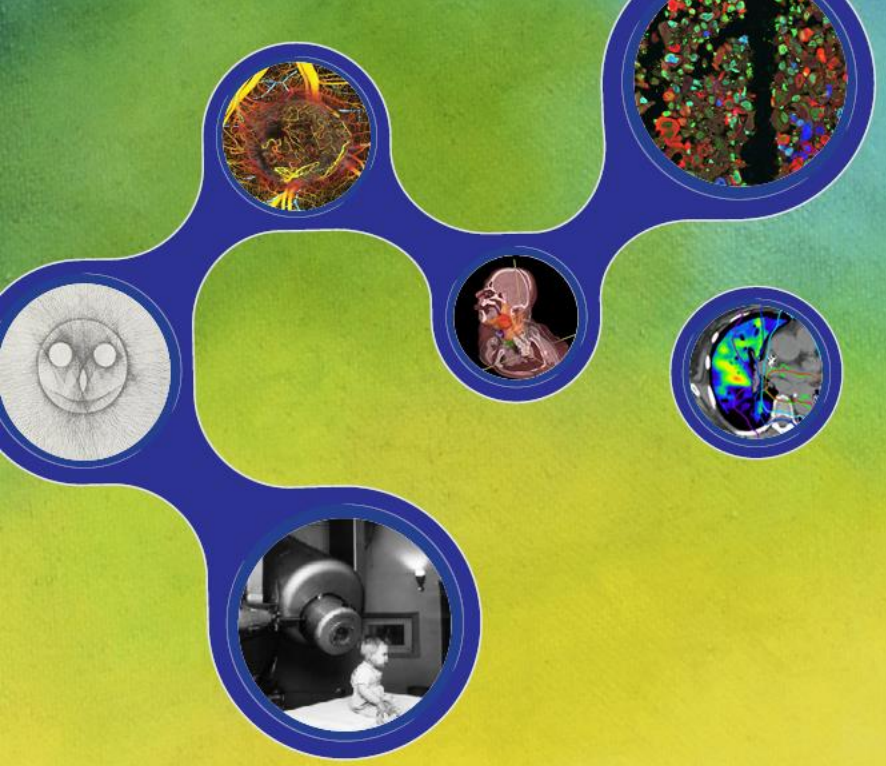
- DIBH in all cases?
  - Yes
- B-VMAT for all cases?
  - Benefit for V5-V10 lung and V4 breast
  - Full arc VMAT may be preferred:
    - *(High neck disease)?*
    - Axillary disease
    - Heart constraints can not be met with B-VMAT: eg PTV extends inf around heart (ant/lat/post)
- Butterfly-IMRT or B-VMAT?
  - Local set up and expertise
  - B-VMAT: class-solution, rapid delivery, narrower corridor
  - B-IMRT: more individualised?

……But what about protons

- Physical properties of protons:
  - Reduce low dose irradiation with IMRT
  - Advantageous where there is an OAR behind PTV

- However photons techniques have significantly improved:
  - Intelligent IMRT
  - DIBH
  - Positioning and IGRT

- Questions:
  - With the gap narrowing, how much better is protons cf best photons?
  - What is effect of DIBH on protons (not widely available)?
  - Which cases benefit most?



ASTRO'S 59TH ANNUAL MEETING

the healing art and science of radiation oncology

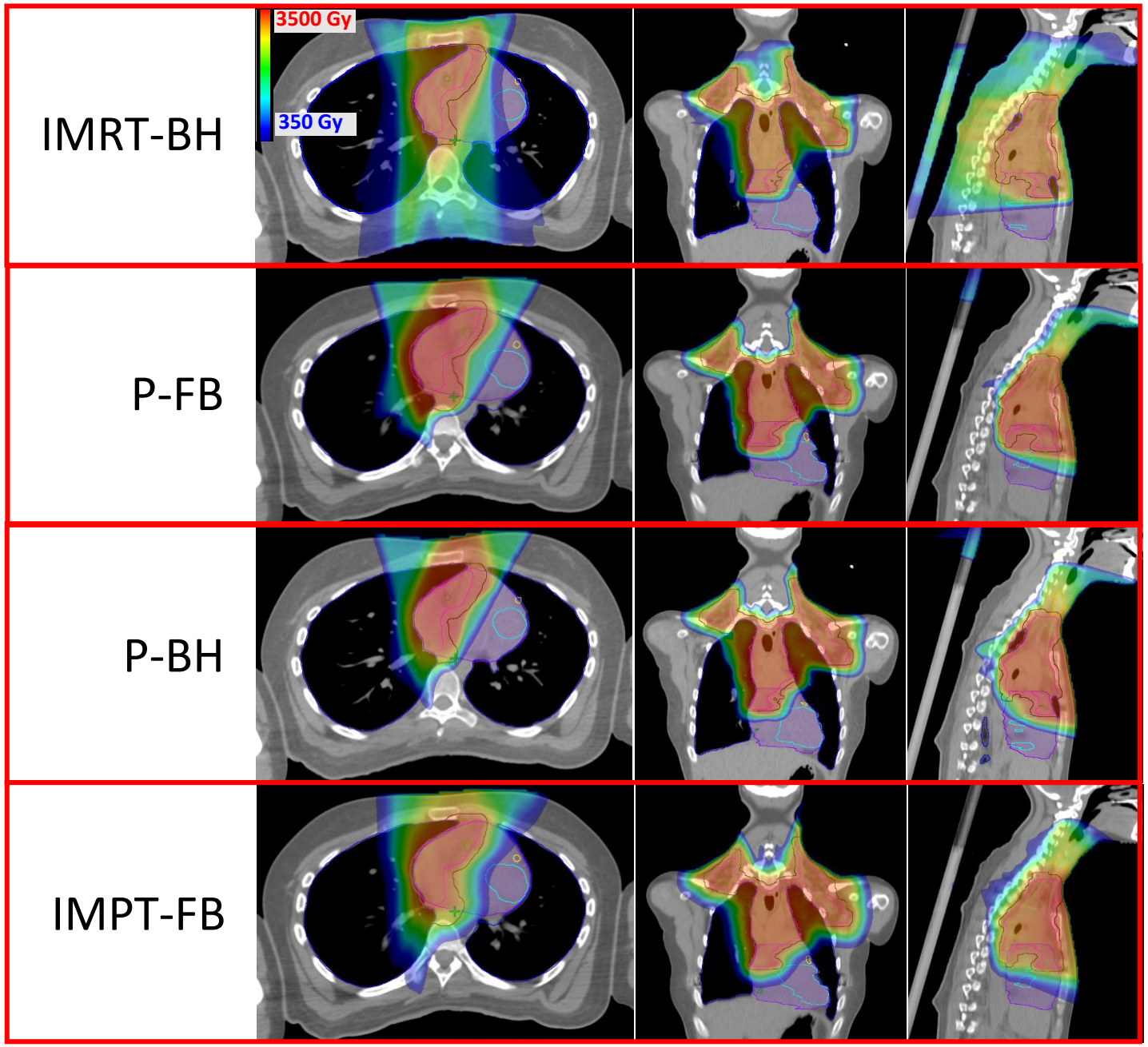
Dosimetric Comparison of Intensity-Modulated Radiotherapy via Breath Hold Technique and Proton Therapy With or Without Breath Hold for Mediastinal Lymphoma

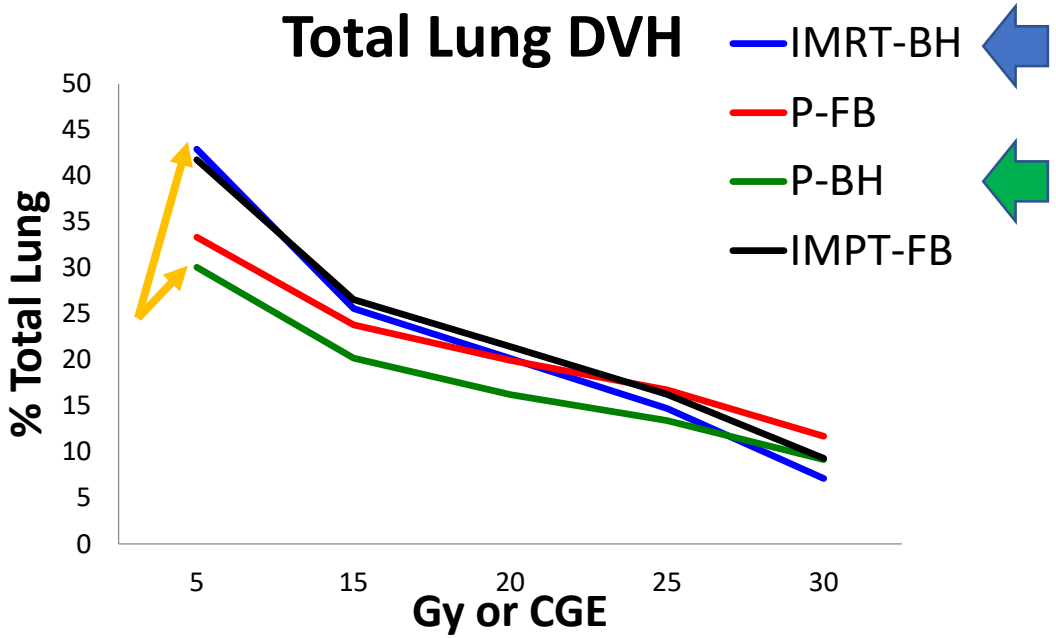
IMRT photons v Potons ± DIBH

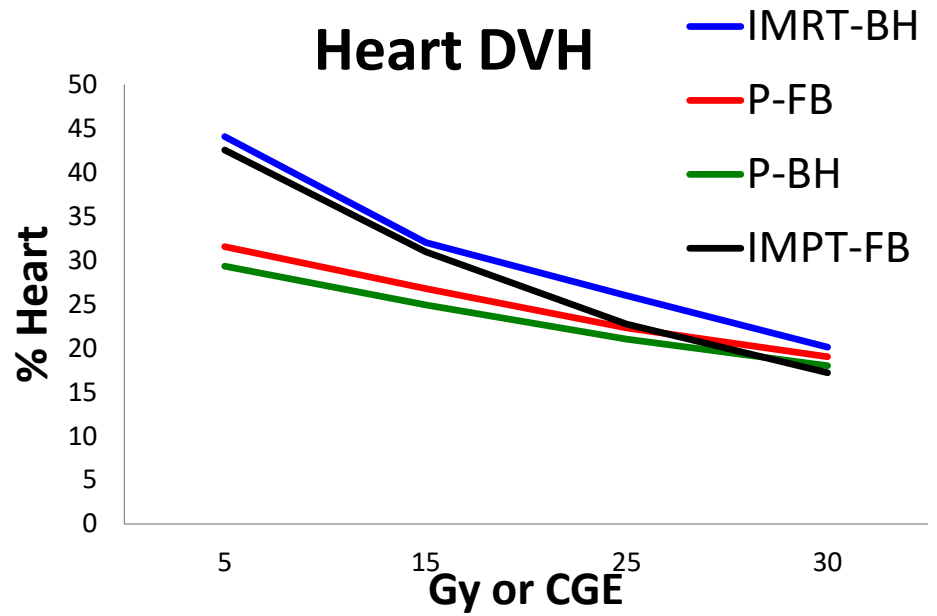
Amy Moreno, M.D., Bouthaina Dabaja, M.D., Sarah Milgrom, M.D., Therese Andraos, M.D., Clifton Fuller, M.D., Ph.D, Manny Oyervides, C.M.D., B.S., Tyler Williamson, C.M.D., Amy Liu, Richard Wu, MS, Ronald Zhu, PhD, Chelsea Pinnix, M.D. PhD.

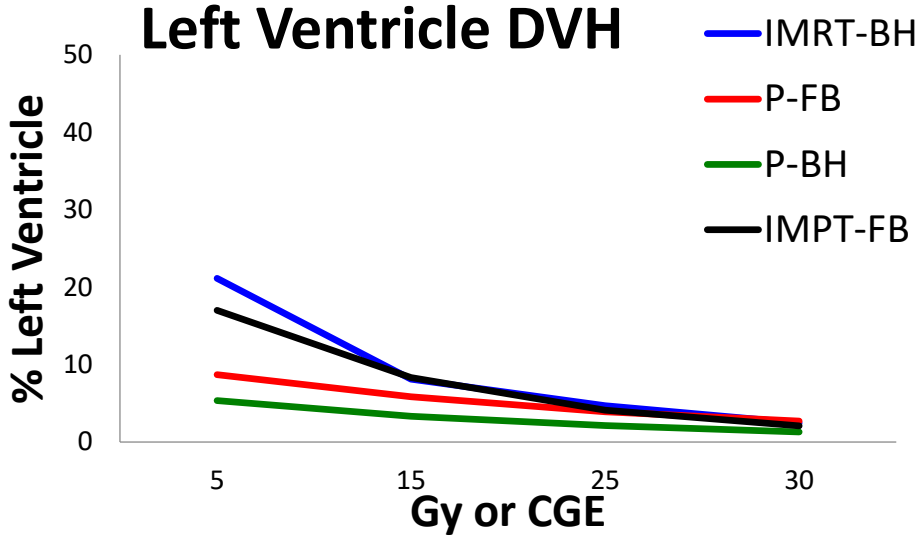
Results:
Plan Comparison

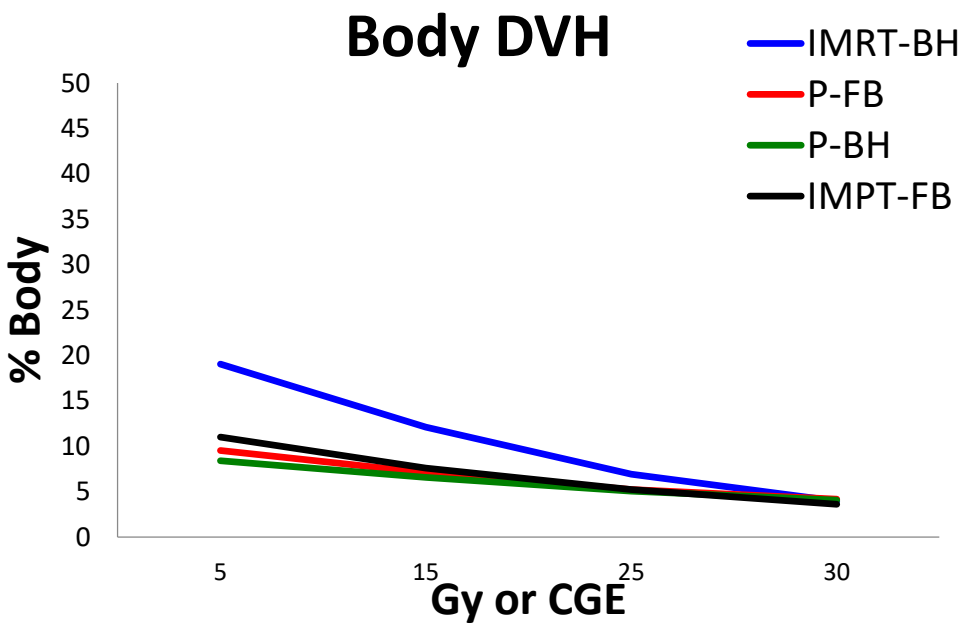
- Comparison plans for patient #3 (female)




Total Lung DVH
IMRT-BH
P-FB
P-BH
IMPT-FB
% Total Lung
0
5
10
15
20
25
30
35
40
45
50
5
15
20
25
30
Gy or CGE


Heart DVH
IMRT-BH
P-FB
P-BH
IMPT-FB
% Heart
0
5
10
15
20
25
30
35
40
45
50
5
15
25
30
Gy or CGE


Left Ventricle DVH
IMRT-BH
P-FB
P-BH
IMPT-FB
% Left Ventricle
0
10
20
30
40
50
5
15
25
30
Gy or CGE


Body DVH
IMRT-BH
P-FB
P-BH
IMPT-FB
% Body
0
5
10
15
20
25
30
35
40
45
50
5
15
25
30
Gy or CGE

Conclusions

- P-BH provides the maximum dosimetric benefit to the heart, LV, and lungs compared to all other plans
  - Consider extent of disease when choosing RT modality
- IMRT-BH was comparable to P-FB and IMPT-FB plans (with exception of body and esophageal dose)
- IMPT-FB did not improve doses compared to P-BH
- P-BH currently theoretical at our institution

Literature

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Life years lost attributable to late effects after radiotherapy for early stage Hodgkin lymphoma: The impact of proton therapy and/or deep inspiration breath hold

Laura Ann Rechner [a,b,*], Maja Vestmø Maraldo [a], Ivan Richter Vogelius [a], Xiaorong Ronald Zhu [c], Bouthaina Shbib Dabaja [d], Nils Patrik Brodin [e], Peter Meidahl Petersen [a], Lena Specht [a], Marianne Camille Aznar [b,f]

[a] *Department of Oncology, Rigshospitalet, University of Copenhagen;* [b] *Niels Bohr Insitute, University of Copenhagen;* [c] *Department of Radiation Physics, The University of Texas MD Anderson Cancer Center;* [d] *Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center;* [e] *Institute for Onco-Physics, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, USA;* [f] *Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom*

- Plans for IMRT-FB, IMRT-BH, P-FB, P-BH were created for 22 patients
- Life years lost (LYL) estimated based on OAR dose
- The combination of DIBH and proton therapy significantly reduced the LYL vs. IMRT-FB
- No significant difference in LYL between IMRT-BH and P-FB

Rechner et al. Radiotherapy and Oncology 2017

Predicted Cardiac and Second Cancer Risks in Hodgkin Lymphoma Patients Treated with Proton Beam Therapy (abstract No. 1026)

G. Ntentas[1], K. Dedeckova[2], M. Andrilik[2], M. C. Aznar[1], B. George[1], S. C. Darby[1], and D. Cutter[1]

1. University of Oxford, Oxford, United Kingdom
2. Proton Therapy Center Praha, Prague, Czech Republic

Summary slides for the Hematologic ePoster Discussion session:
Date: 9/24/2017 Time: 4:45 p.m. - 6:15 p.m.

Discussants: Bouthaina Dabaja, MD and George Mikhaeel, MD

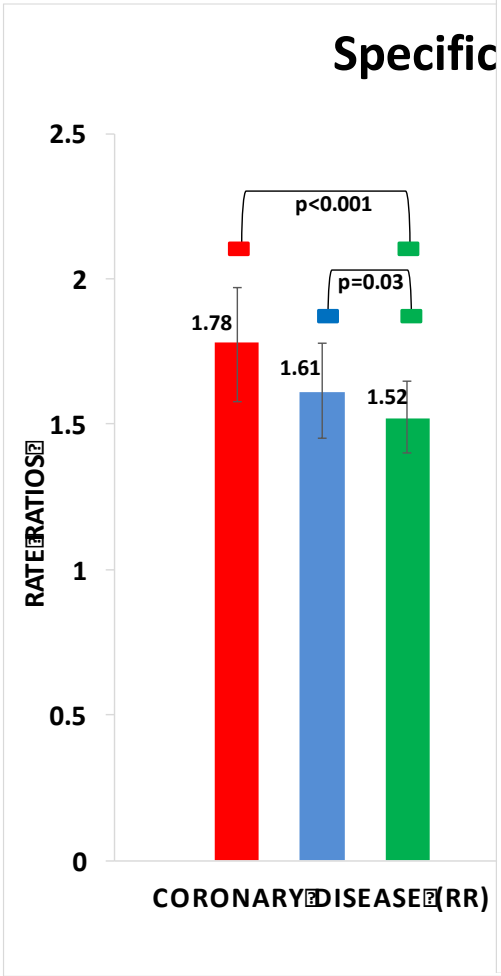
UNIVERSITY OF OXFORD

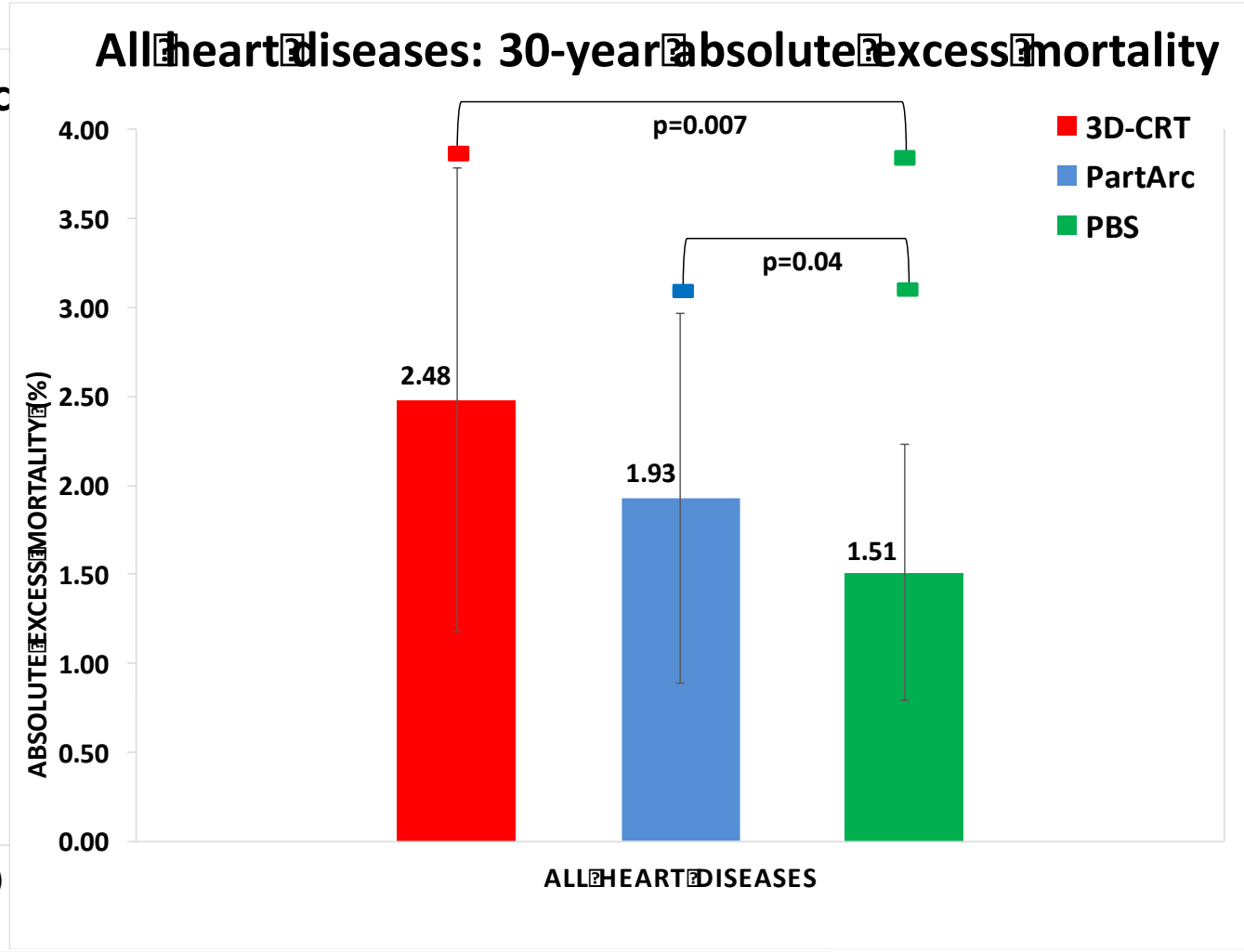
CANCER RESEARCH UK

British Heart Foundation

Key points of this study (Cardiac Risks)

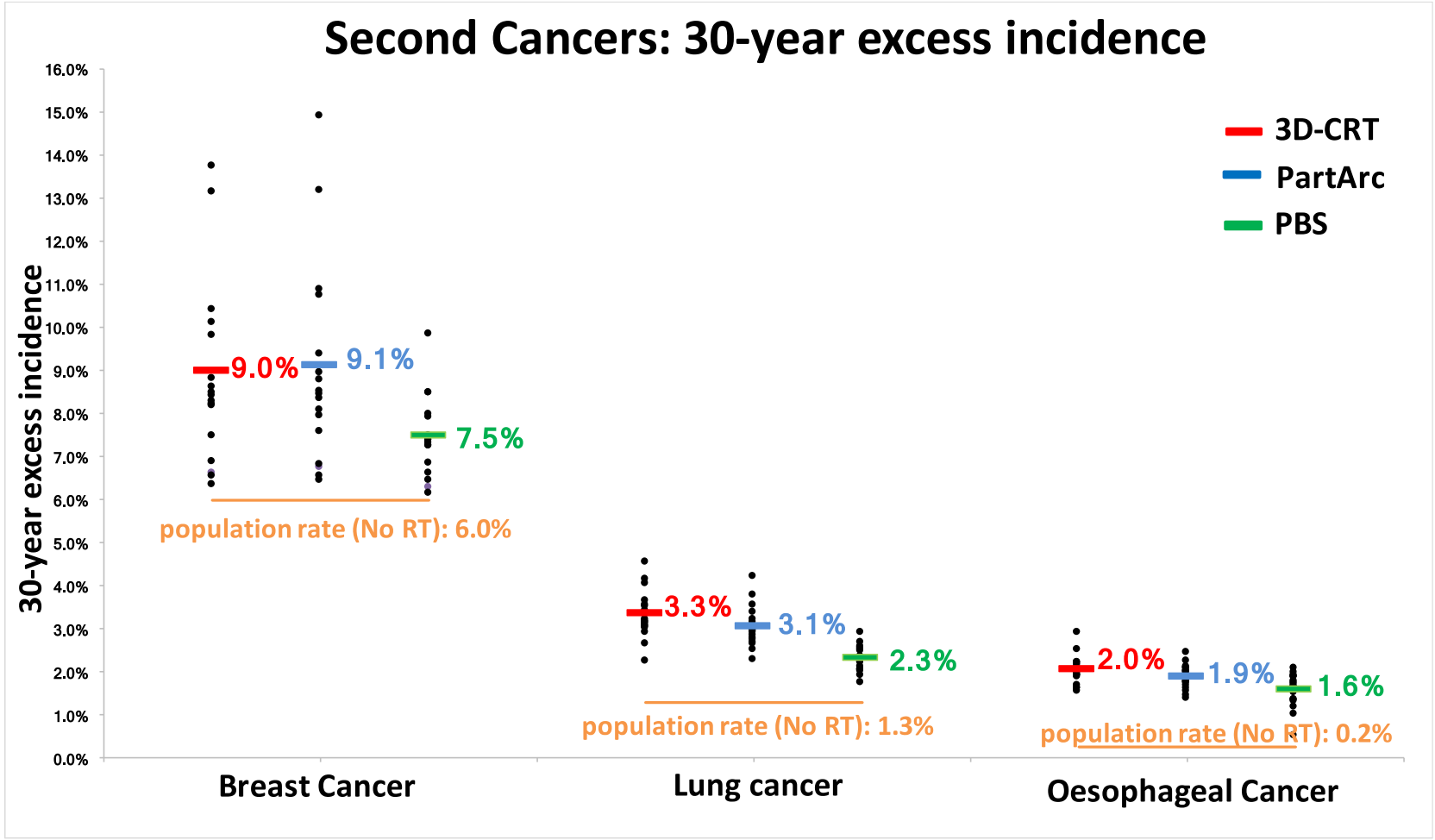
- Rate ratios for coronary and valvular disease (but not heart failure) were significantly lower for PBS.
- 30-year absolute excess cardiac mortality was significantly reduced with PBS





Key points of this study (Second Cancer Risks)

30-year excess incidence was significantly lower with PBS compared to both photon techniques (p values for all comparisons were <0.001).



PROTON THERAPY FOR ADULTS WITH MEDIASTINAL LYMPHOMAS: THE INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP (ILROG) GUIDELINES

Bouthaina Shbib Dabaja, Bradford S. Hoppe, John P. Plastaras, Wayne Newhauser, Katerina Rosolova, Stella Flampour, Radhe Mohan, N. George Mikhaeel, Youlia Kirova, Lena Specht, and Joachim Yahalom

Blood 2018 :blood-2018-03-837633; doi: https://doi.org/10.1182/blood-2018-03-837633

Patient Selection:

- HEART: mediastinal disease extending below the origin of coronaries.

- BREAST: young females where proton therapy can reduce breast dose and subsequent risk of secondary breast cancer.

- Heavily pretreated patients who are at higher risk of radiation related toxicities to the heart or lung

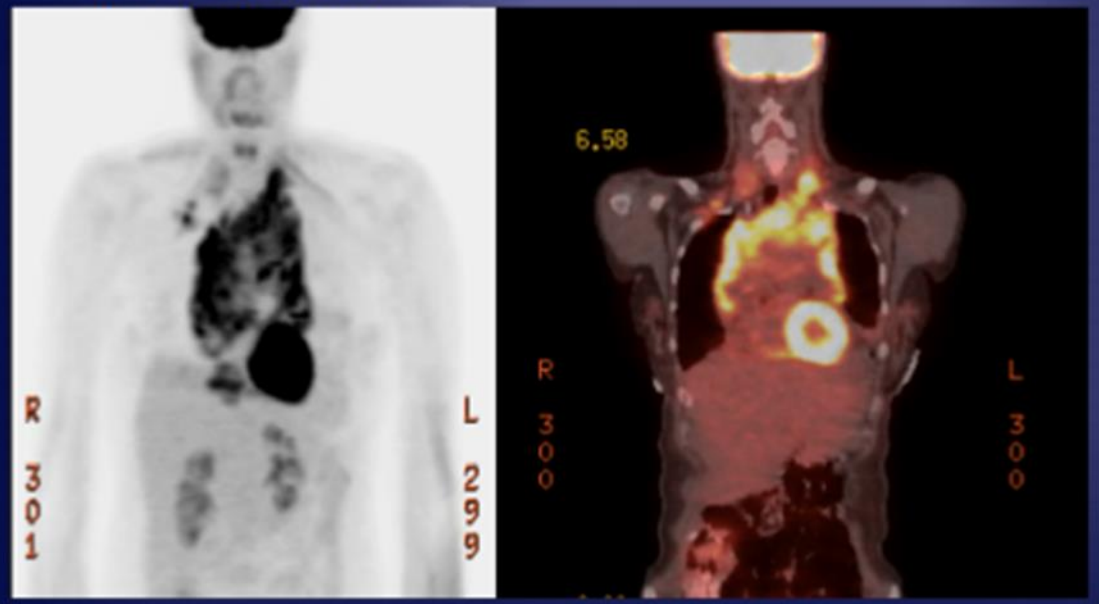
When using proton therapy, the treating physician should:

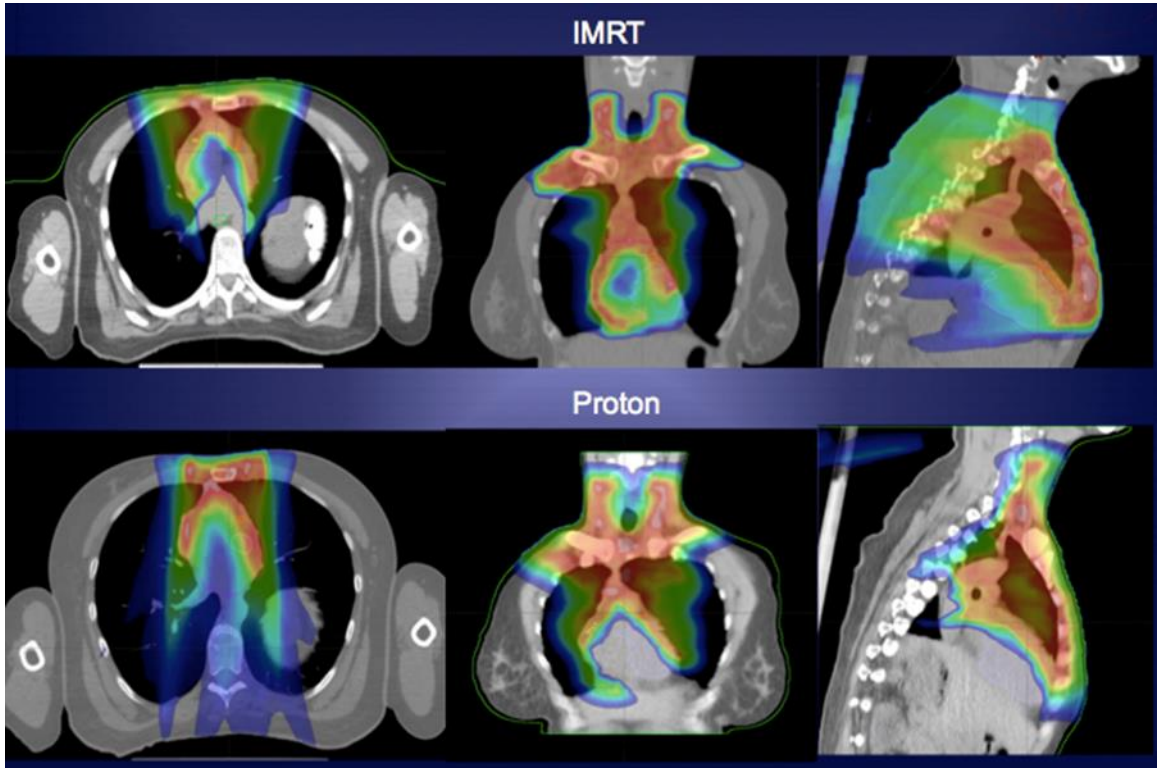
-Demonstrate a benefit for the patient, due to the increased costs and difficulty in delivering the treatment compared with photons.

-Understand that lymphoma proton planning is complex, due to the management of uncertainties, and evolving with utilization of PBS, in-room volumetric imaging, and robustness optimization

-Utilize deep inspiration breath hold when warranted to further minimize dose to the OARs, understanding the increased complexity of using DIBH with proton therapy compared with photon therapy

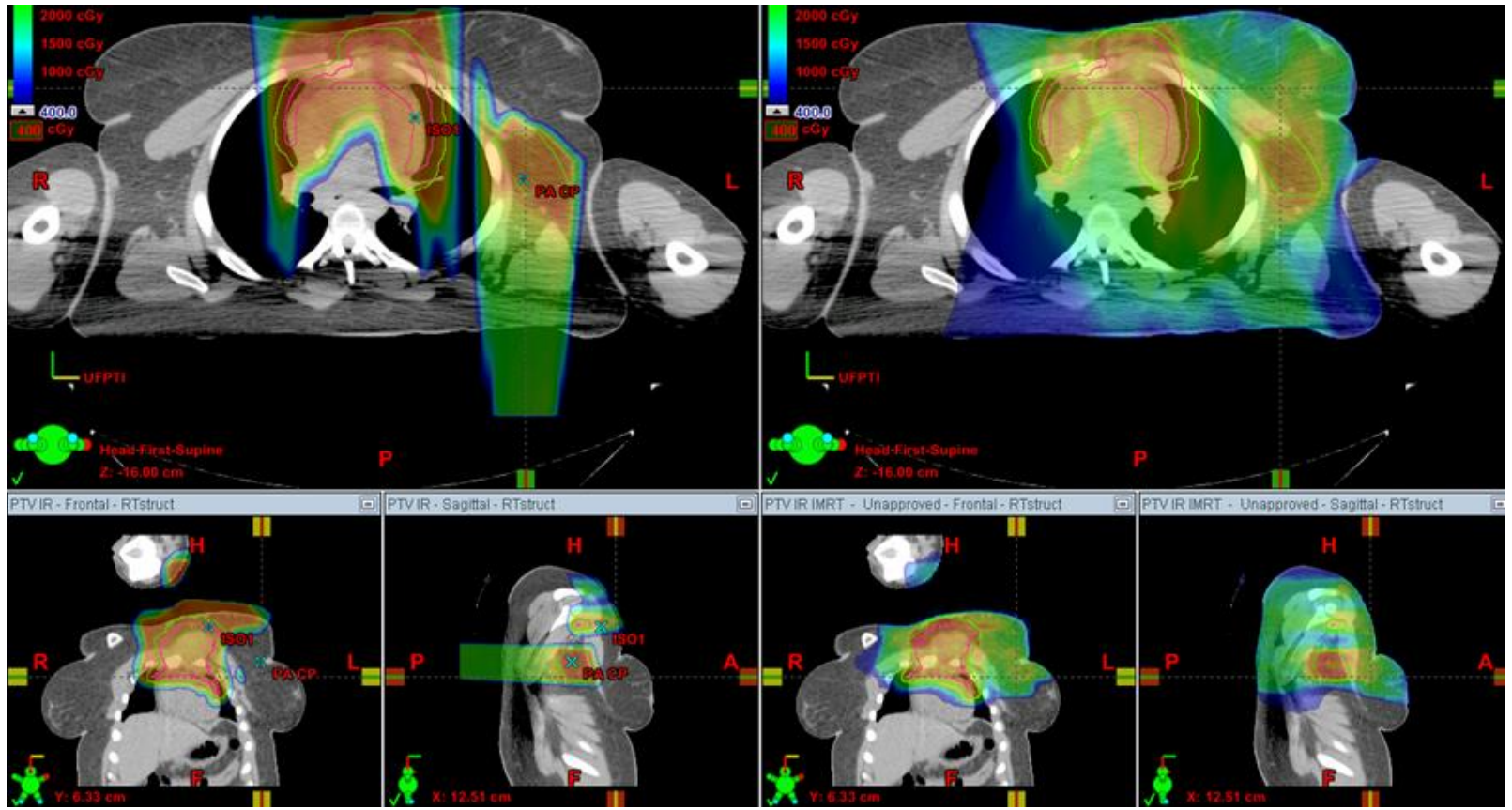
30 year old presenting with HL spanning on both side of the heart



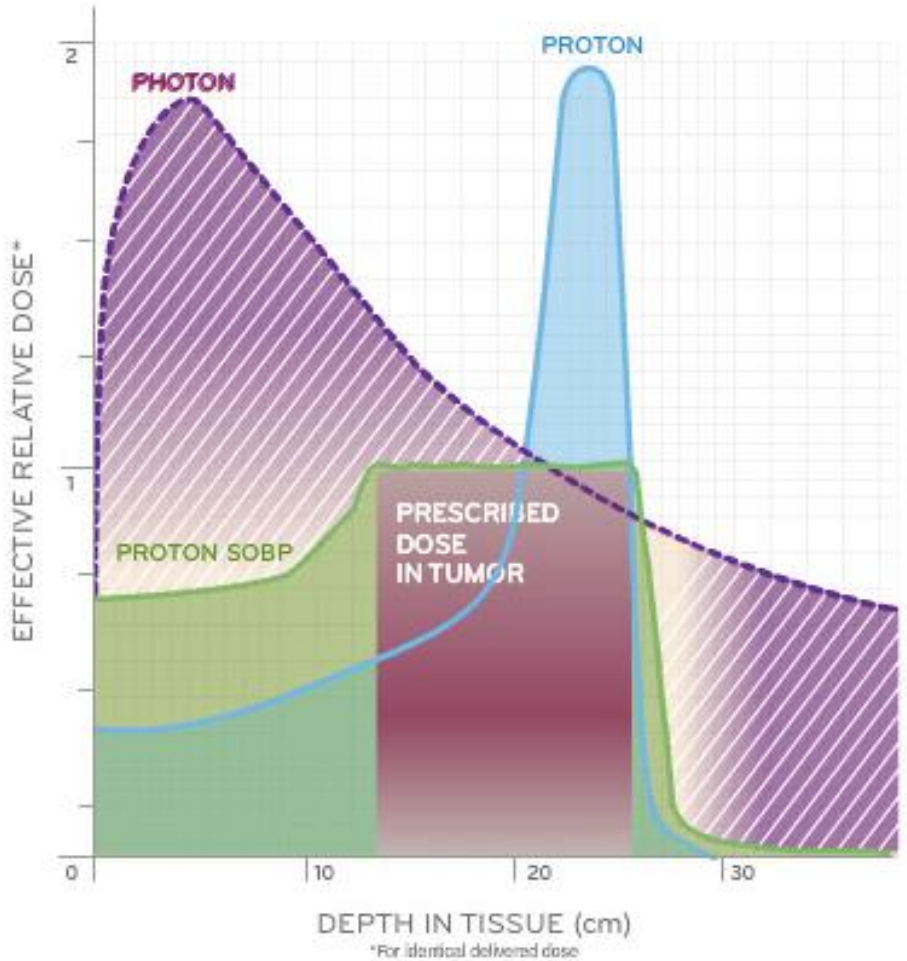


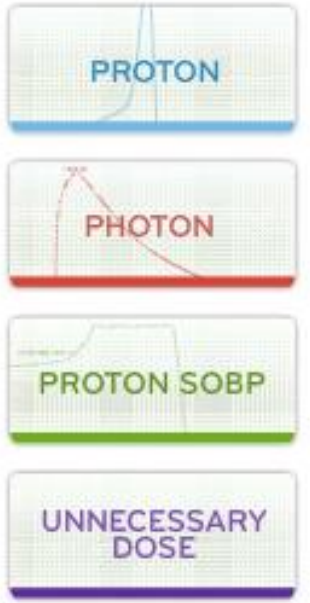
	IMRT / mean dose	Proton/ mean dose
Esophagus	20.8	13.2
Heart	25.2	13.5
LAD	39.7	27.7
LV	22.2	6.4
RCA	36.7	36.3
Lungs	12.0	10.8
Body	7.1	2.36

PBT for sparing heart and breast



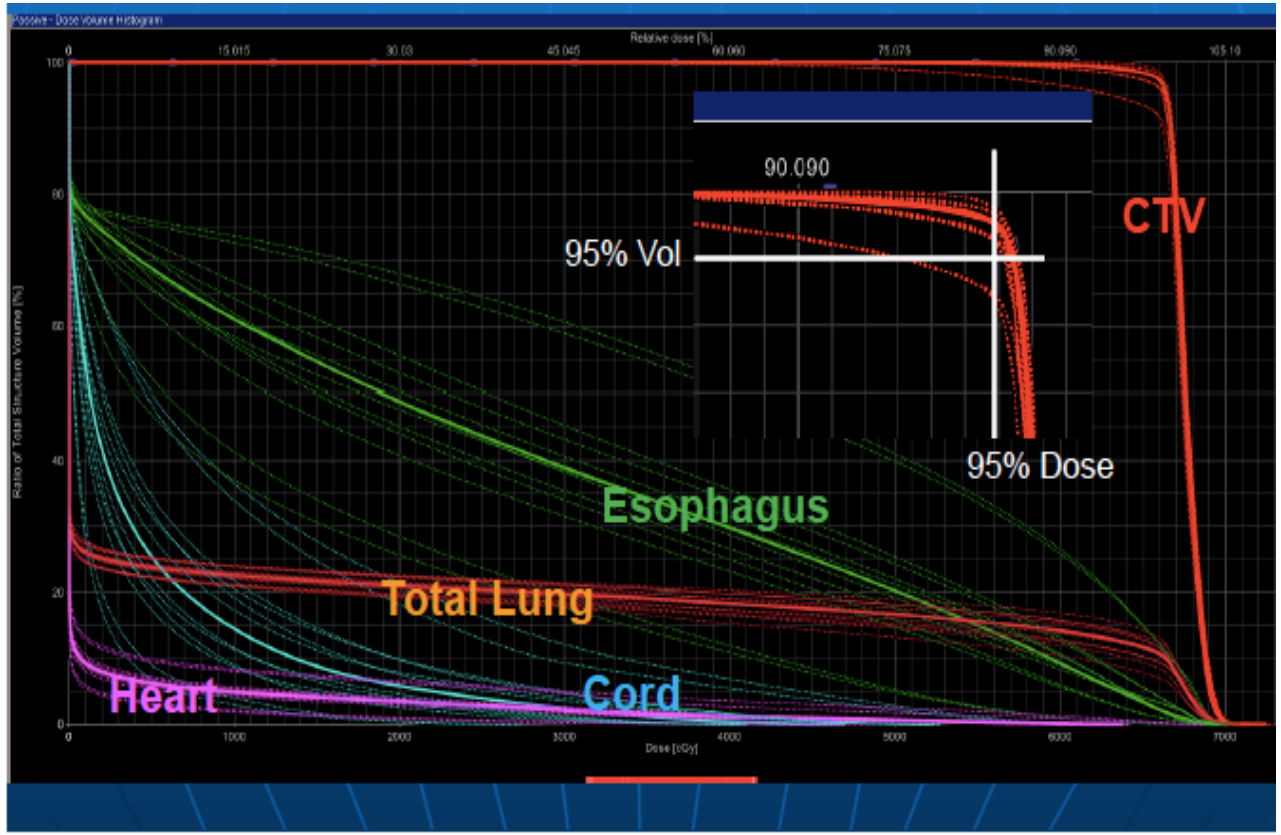
THE BRAGG PEAK





Technical considerations

- Range uncertainty:
  - Tissue homogeneity
  - Motion
- RBE value and change
- Robustness planning



Key points

- NO best technique for each patient
- Patient and technique selection: experience
- Make best use of technology – push OARs doses to minimum (ALARA)
- “Ask a friend” (colleague)

Thank you

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INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Primary extranodal lymphomas, definition

- The presenting lesion is extranodal
- The extranodal lesion constitutes the predominant disease bulk
- Although Waldeyer's ring, thymus, and Peyer patches are excluded from the original Ann Arbor classification of extra-nodal disease, lymphomas in these sites are usually included
- Only meaningful for stage I-II disease (CS IE and IIE)
- Extranodal involvement as part of disseminated lymphoma is not included

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Primary extranodal lymphomas are special

- May arise in any organ outside the lymph nodes
- The histopathological lymphoma subtypes occur in distinct patterns in different extranodal sites
  - E.g., Marginal zone lymphoma most common in stomach, T-cell lymphomas most common in skin, diffuse large B-cell lymphoma (DLBCL) most common in tonsils
- The particular site of extranodal involvement may be associated to the etiology
  - E.g., gastric lymphomas associated with H. pylori infection
- The particular site of extranodal involvement is important for prognosis and management, independent of the importance of the histologic subtype
  - E.g., DLBCL: in the brain (long-term survival in less than 25%), the tonsils (80-90%), and the testes (40-50%)

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Guidelines published by the International Lymphoma Radiation Oncology Group (ILROG)

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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

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

IJROPB 2015; 92: 11-31

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

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

IJROBP 2015; 92: 32-39

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Primary extranodal lymphomas, treatment decision

- Histopathological type
- Anatomic extent of disease
- Specific extranodal involvement
- Should ideally be based on randomized trials, but:
  - Even fewer exist than for nodal lymphomas
  - Nearly all studies with reasonable follow-up were carried out in the pre-Rituximab era (important for B-cell lymphomas)
- Generally based on retrospective series or Phase II studies
- For rarer extranodal presentations no large patient materials exist, extrapolation from most ’similar’ cases

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Primary extranodal lymphomas, treatment

- Radiation remains the most active single modality in the treatment of most types of lymphoma
- Radiation therapy is an important part of the treatment of localized extranodal lymphomas

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Primary extranodal lymphomas, occurrence

- Constitute about ½ of localized lymphomas (stage I-II)
- Constitute 20-25% of all non Hodgkin lymphomas (NHL)
- Most common sites:
  - Gastrointestinal tract
  - Skin
  - Waldeyer's ring
  - CNS
  - Salivary glands
  - Ocular adnexae

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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, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

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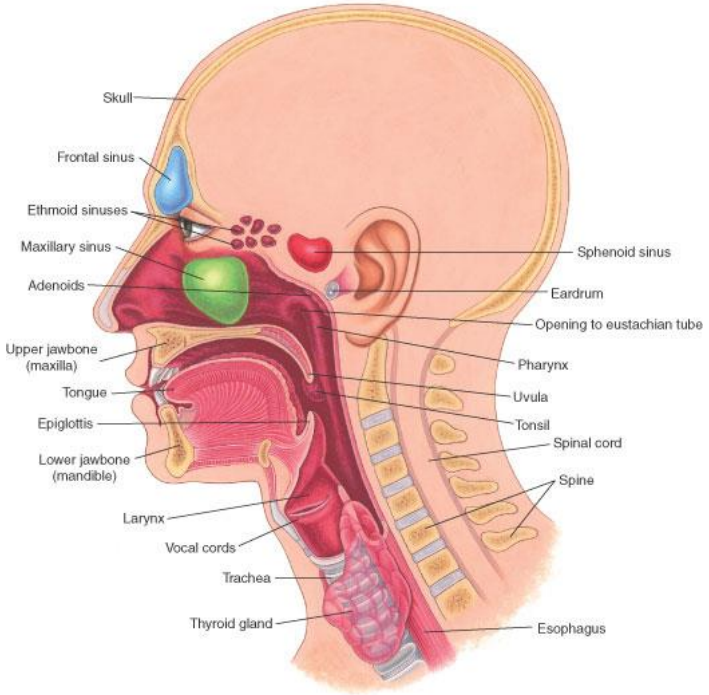
Extranodal (not necessarily extralymphatic) sites in the upper aerodigestive tract



- 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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Primary extranodal lymphomas, occurrence

- Constitute about ½ of localized lymphomas (stage I-II)
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- Most common sites:
  - Gastrointestinal tract
  - Skin
  - Waldeyer's ring
  - CNS
  - Salivary glands
  - Ocular adnexae

Head & neck lymphomas, general principles

- Pre-treatment work-up:
  - Detailed ENT examination incl. fiberoptic examination, if necessary under general anaesthesia
  - Imaging with PET and CT, MRI for skull base, cranial cavity, cranial nerve, sinuses, and infratemporal fossa

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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

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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

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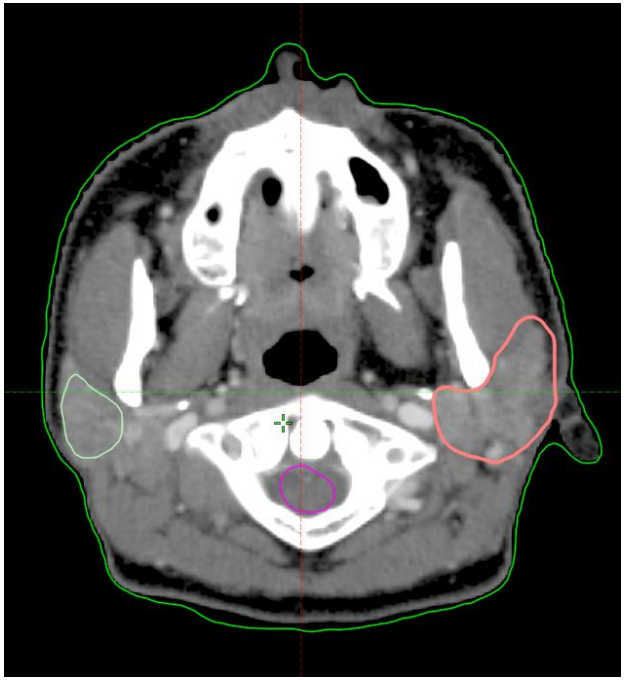
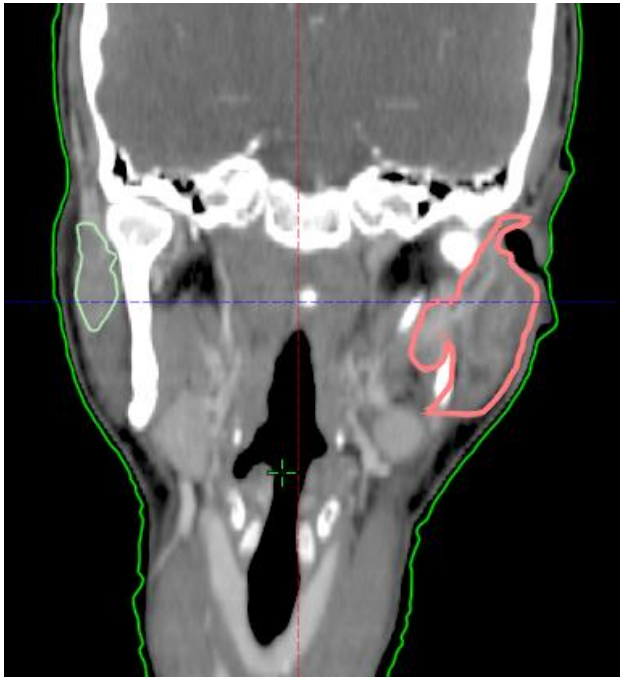
MALT lymphoma in left parotid gland

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.

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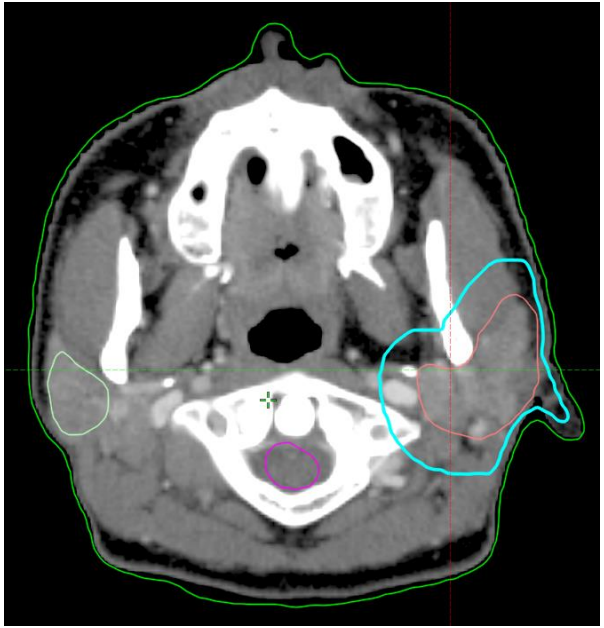
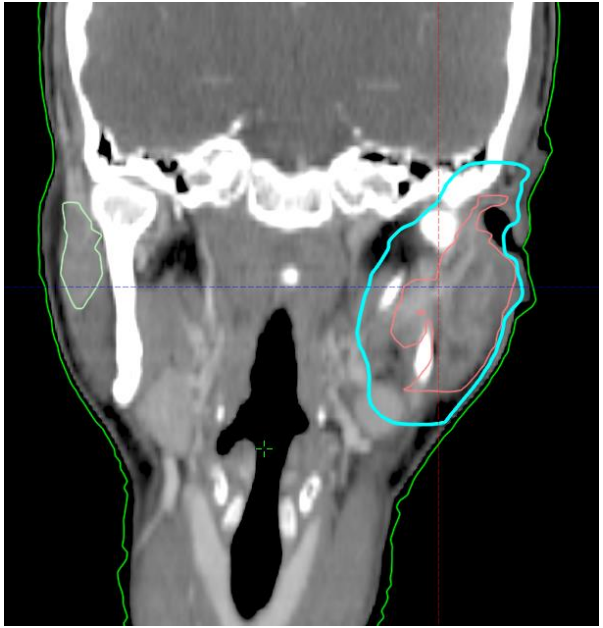
PTV





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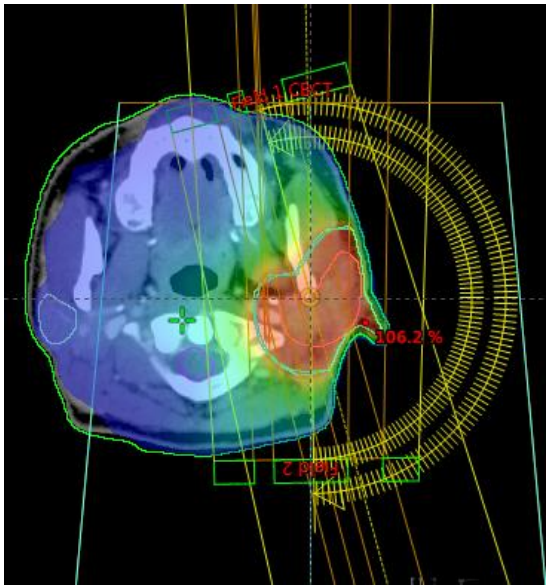
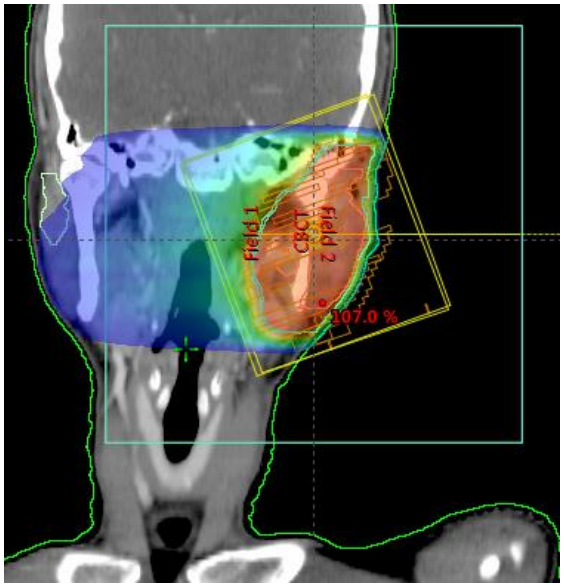
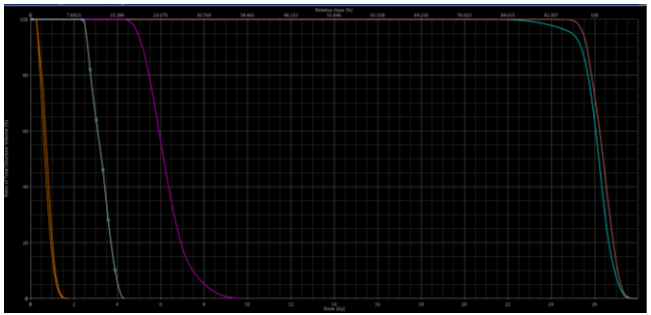
Treatment plan (RapidArc)







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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)

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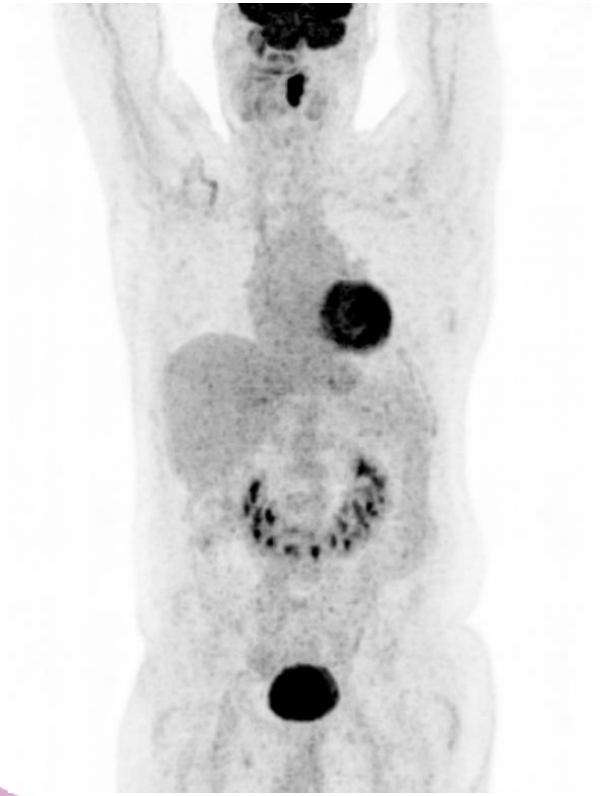
DLBCL in tonsil



- 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

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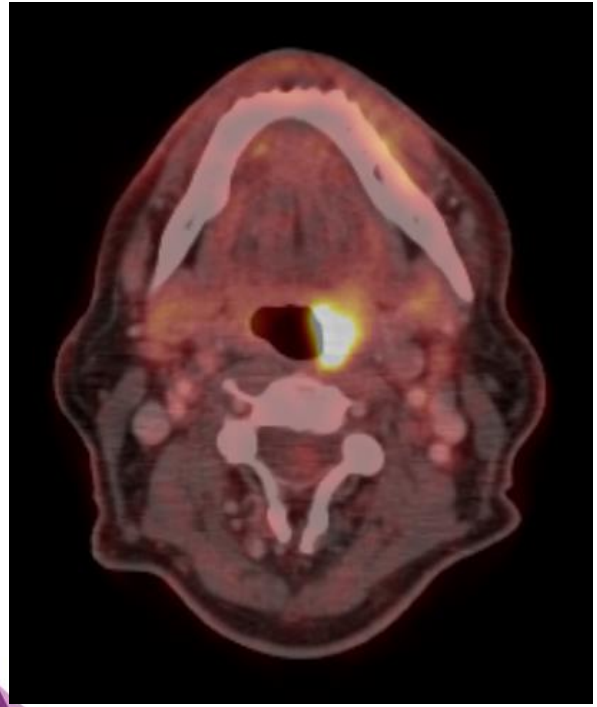
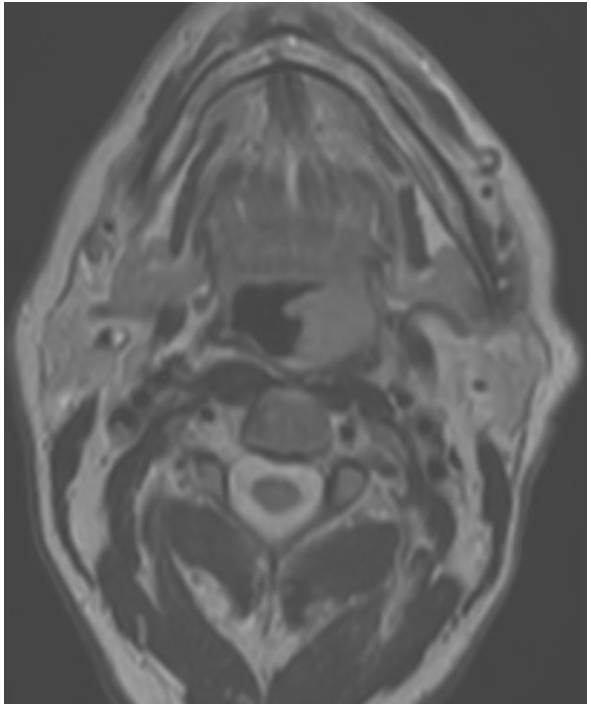
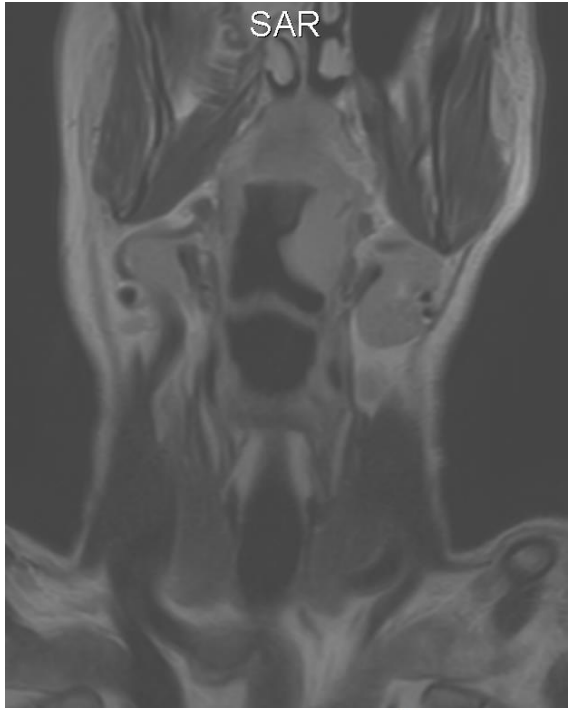
Pre-chemo images







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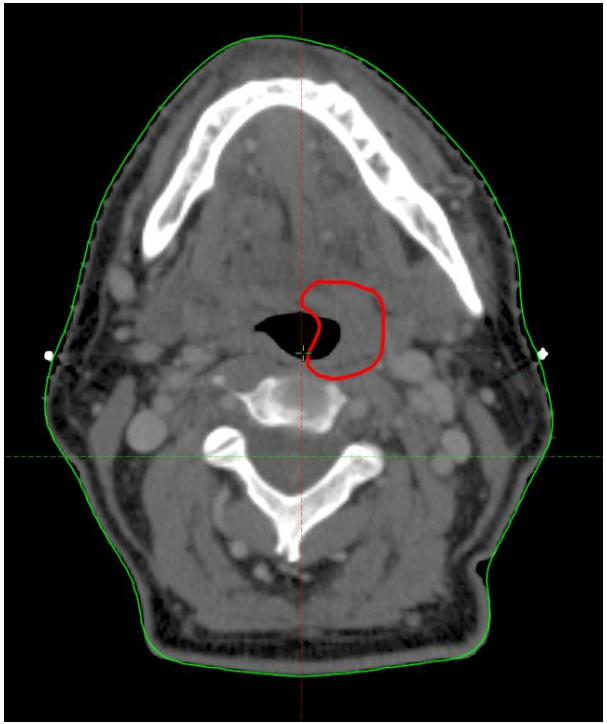
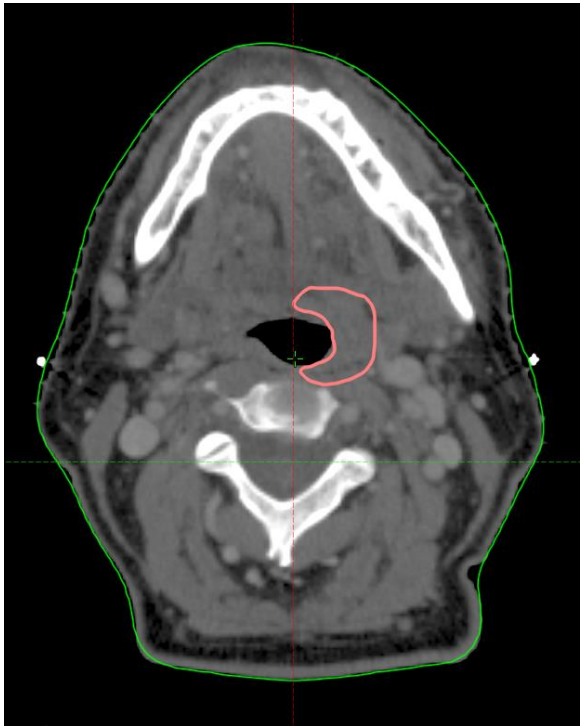
Post-chemo planning CT

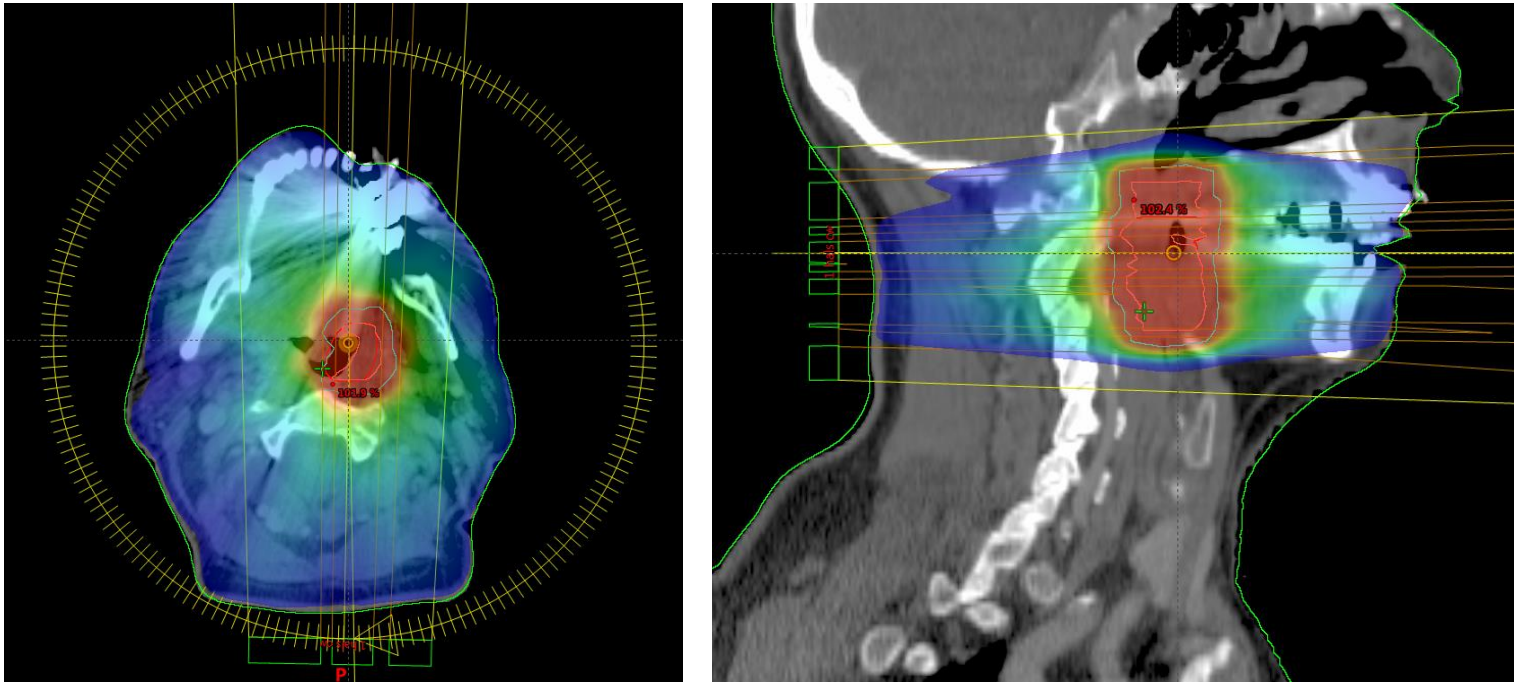
Pre-chemo
GTV





Post-chemo
CTV

Treatment plan (RapidArc)



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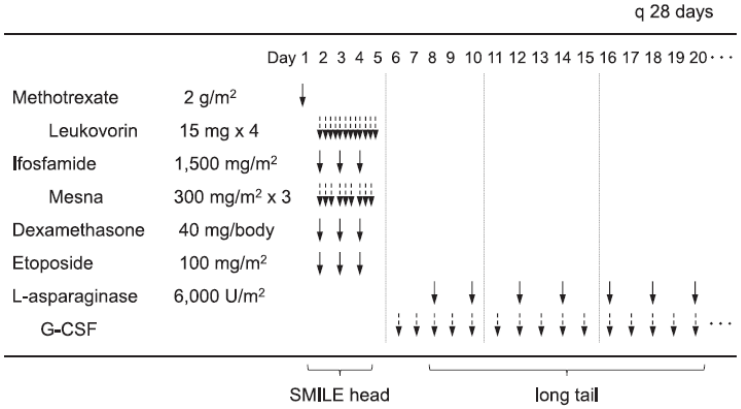
NK/T-cell lymphomas, nasal type

- 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



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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

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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!

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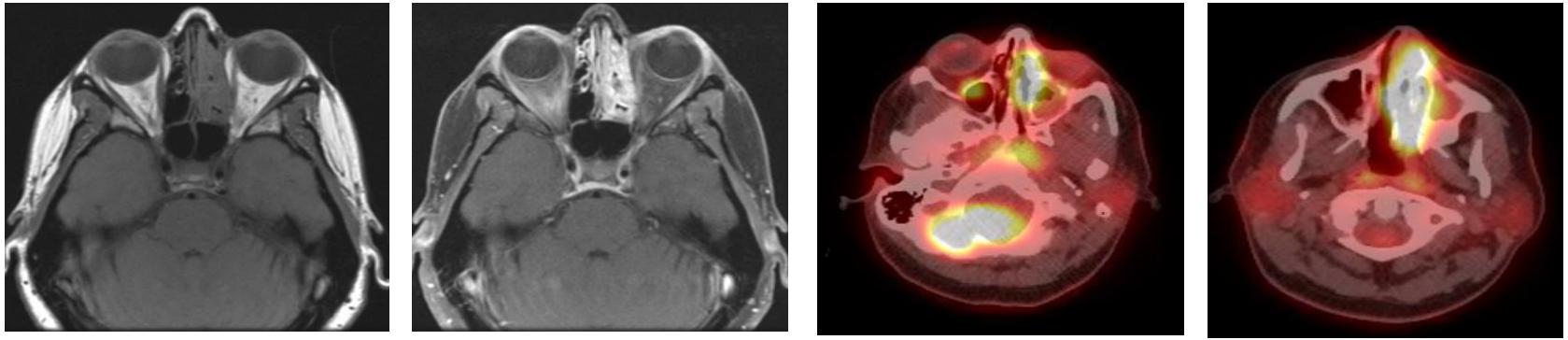
Extranodal NK/T cell lymphoma, nasal type, CS IEA, involving left nasal cavity, IPI: 0

- 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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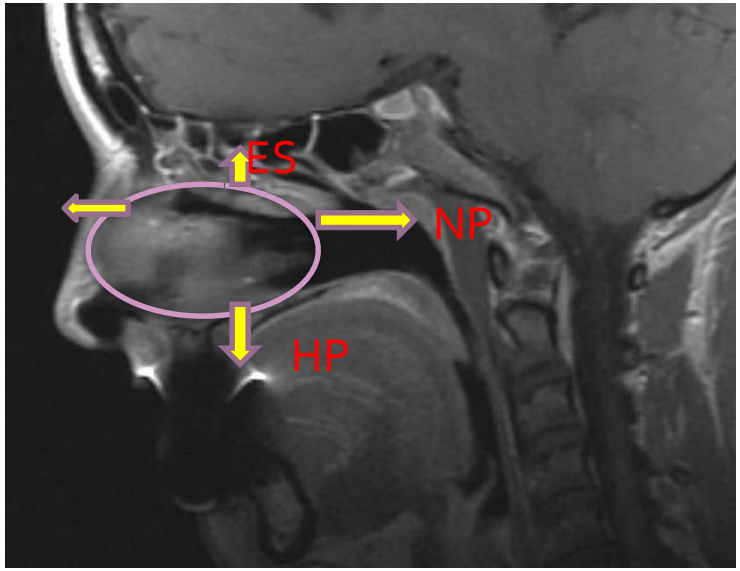
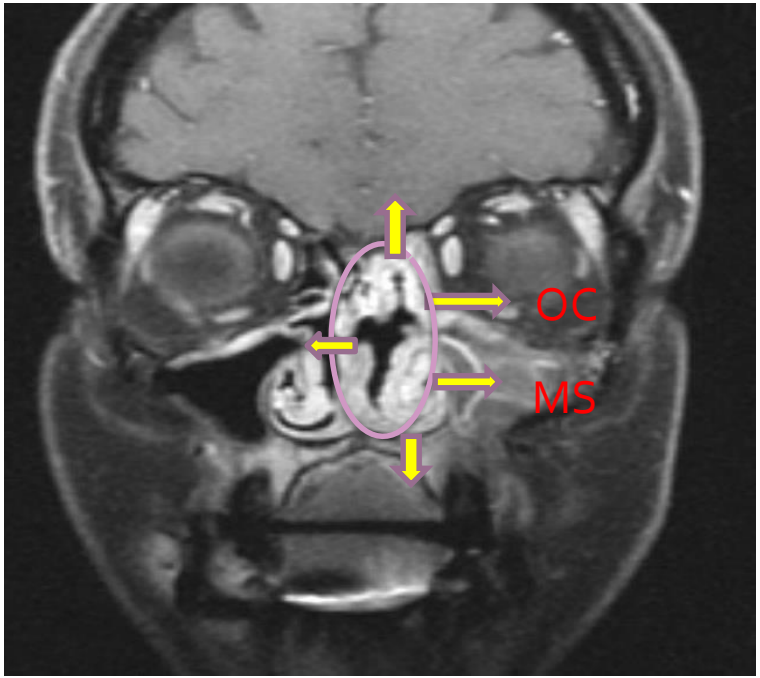
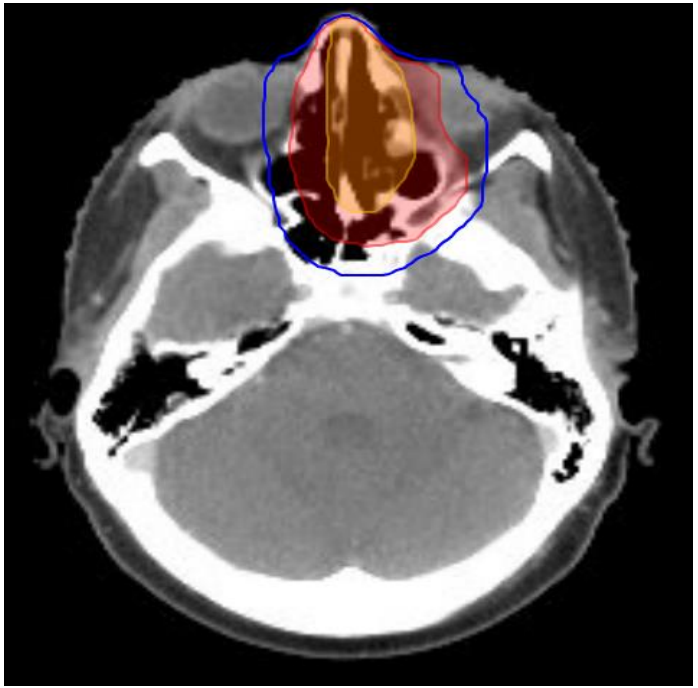
Nasal cavity and adjacent structures





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

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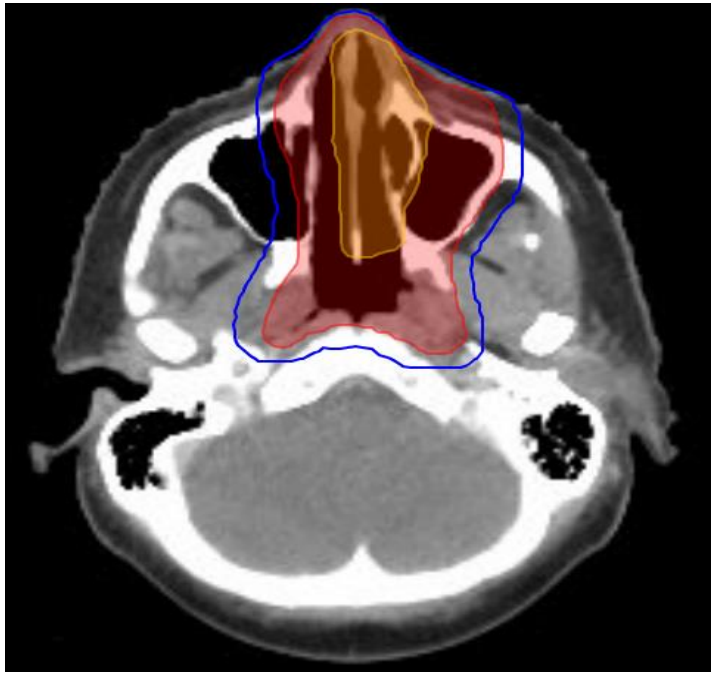
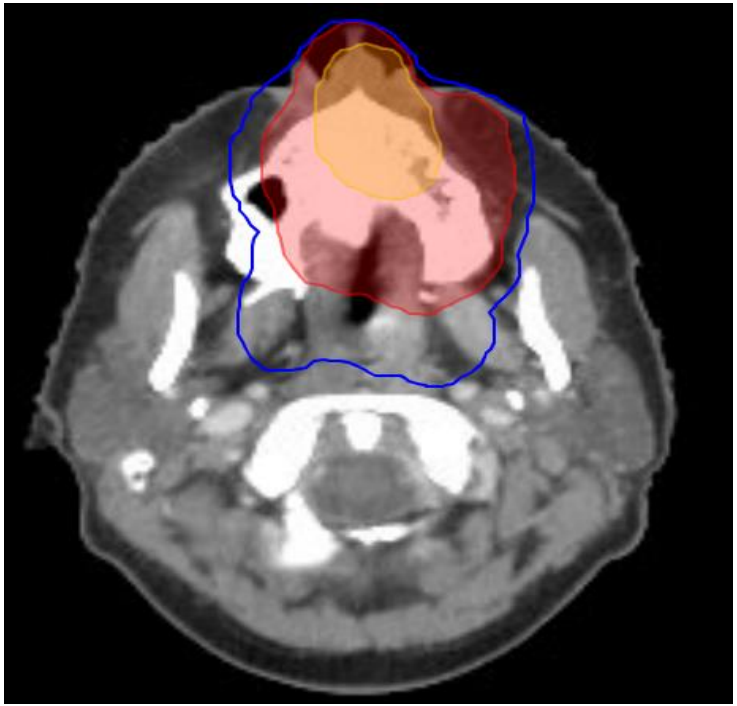
CTV



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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University of London

Guy's and St Thomas' NHS
NHS Foundation Trust

Thyroid Lymphoma

Prof George Mikhaeel

Professor of Radiation Oncology, King's College London

Consultant Clinical Oncologist, Guy's & St Thomas' Hospital
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

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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

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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.

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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
  - Non-bulky: RCHOP x3-4 + RT
  - Bulky: RCHOP x6 + RT

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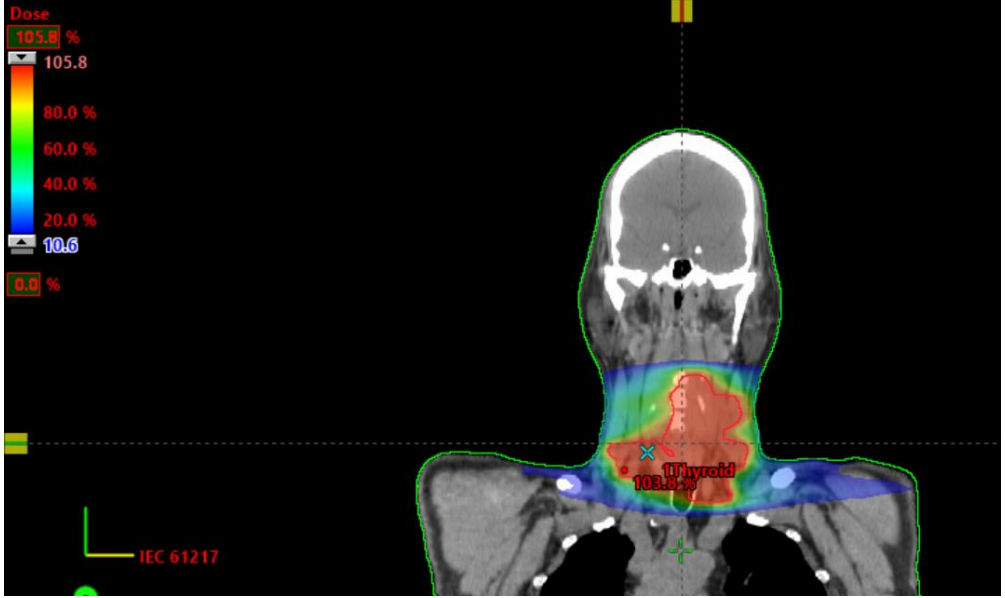
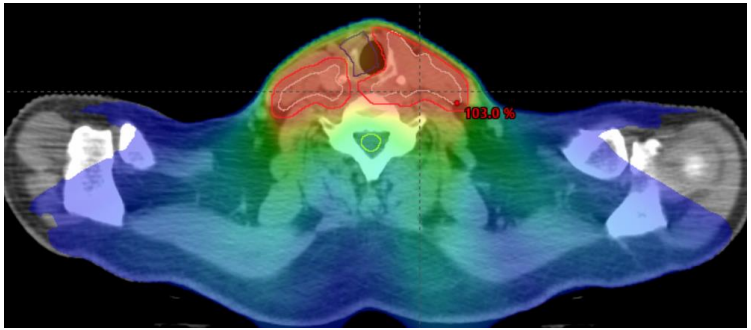
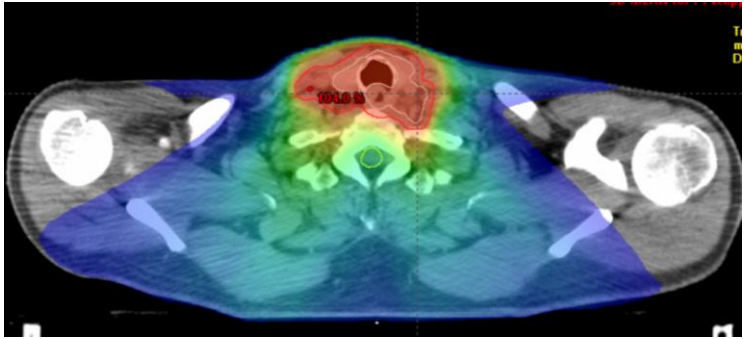
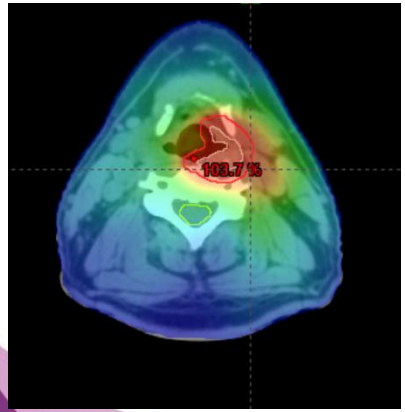
- CTV: whole thyroid + any involved nodes
- Dose:
  - Indolent 24Gy / 12#
  - Agg: 30 – 36 Gy according to response

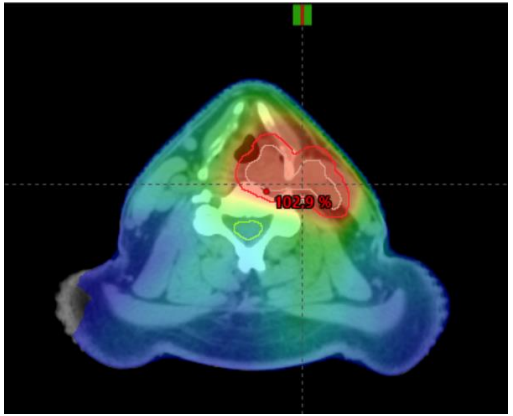
- Technique:
  - 3D Conformal
  - IMRT / VMAT











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QUESTIONS?

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Extranodal lymphomas:
Orbital (ocular adnexal) lymphoma

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

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ENL: Most common sites

- Primary CNS Lymphoma
- **Orbital (Ocular Adnexal) Lymphomas**
- Lymphomas of the Head and Neck
- Breast Lymphoma
- Lymphoma of the Lung
- Gastric Lymphoma
- Testicular Lymphoma
- Bone Lymphoma
- Skin Lymphomas

Orbital (ocular adnexal) Lymphoma

- 1-2% of all NHL
- 7-8% of extranodal lymphomas
- Ocular adnexa lymphomas (OAL) include:
  - orbit
  - extra ocular muscles
  - conjunctiva
  - eyelids
  - lacrimal gland
  - apparatus
- Most cases of extraocular orbital lymphoma are Marginal Zone Lymphoma (MZL)
- Approximately 15% of such cases are bilateral (synchronous or metachronous)

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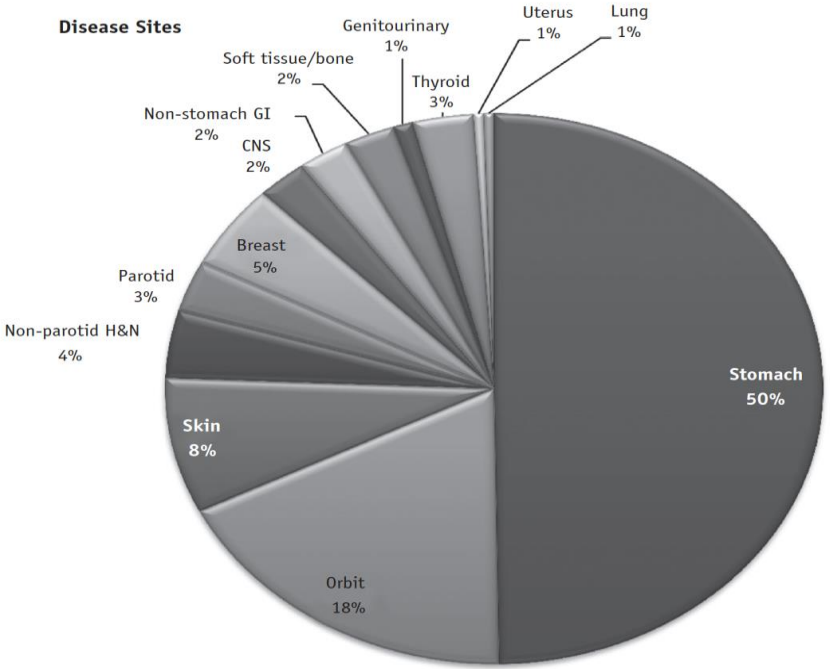
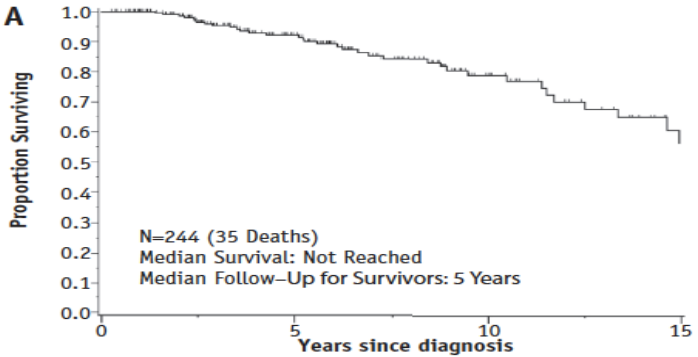
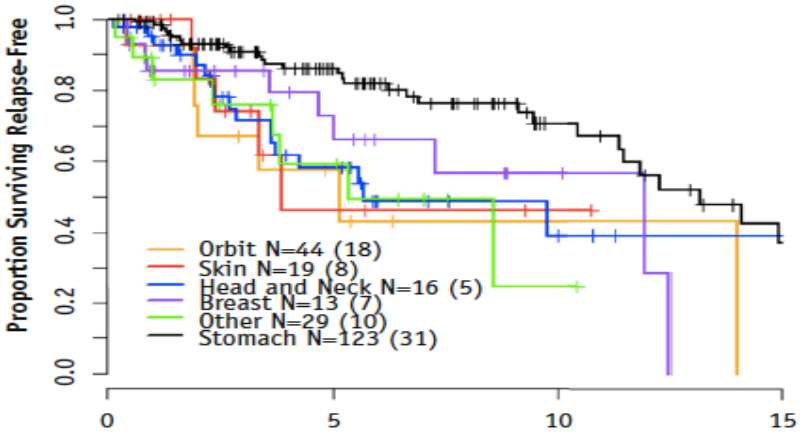
Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 130–137, 2015

Sewit Teckie, MD,* Shunan Qi, MD,* Shona Lovie, MPH,* Scott Navarrett, BS,‡ Meier Hsu, MS,§ Ariela Noy, MD,|| Carol Portlock, MD,|| and Joachim Yahalom, MD*







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

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Clinical presentation

- 5^{th} - 7^{th} 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)

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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

Chlamydophila 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

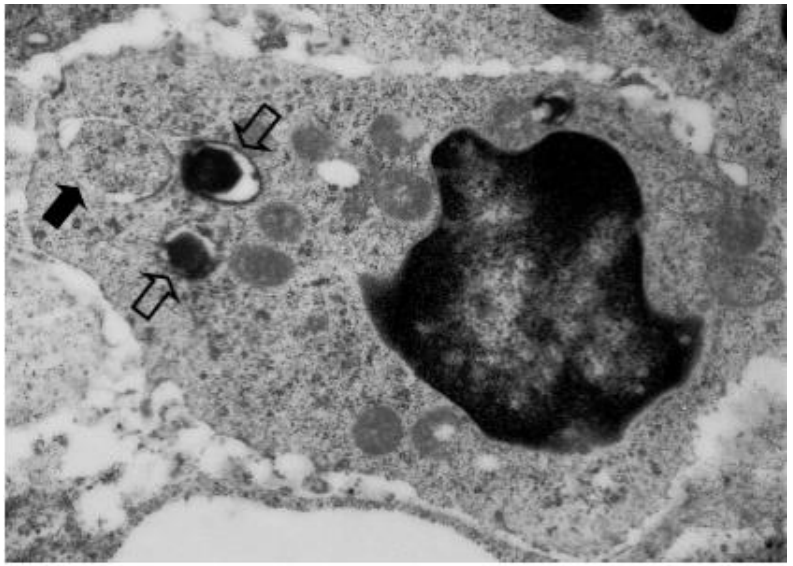

Fig. 2. Elementary bodies (CEB; open arrows) and reticulate body (CRB; full arrow) in an intratumor macrophage of a case of ocular adnexae MALT lymphoma assessed by electron microscopy. Chlamydial infection starts with attachment of a CEB to the host cell, followed by cell invasion. Within eukaryotic 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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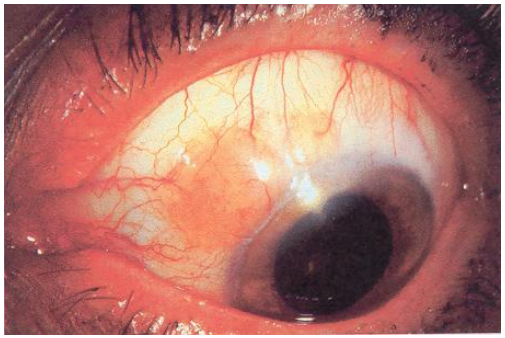
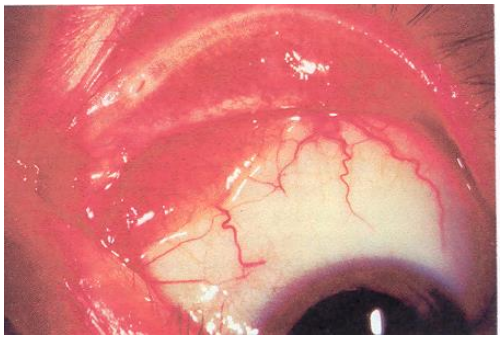
Clinical presentation

- 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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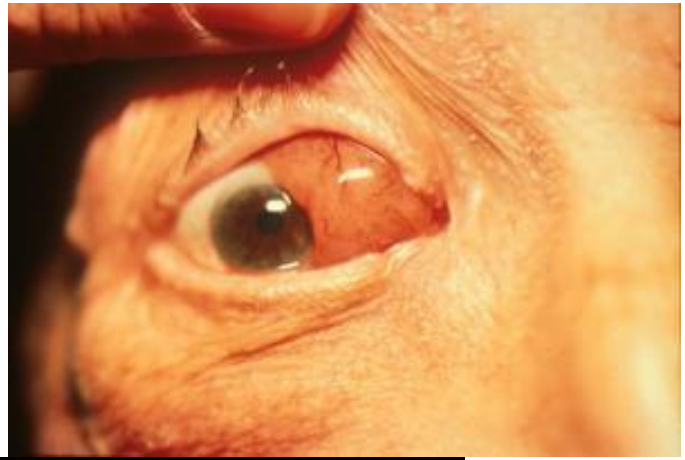
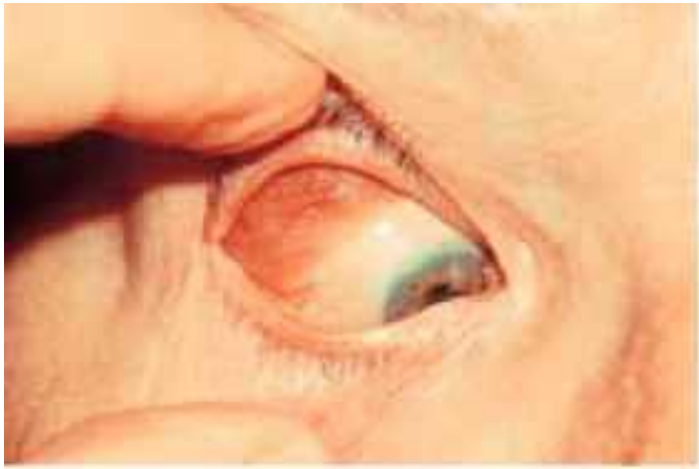
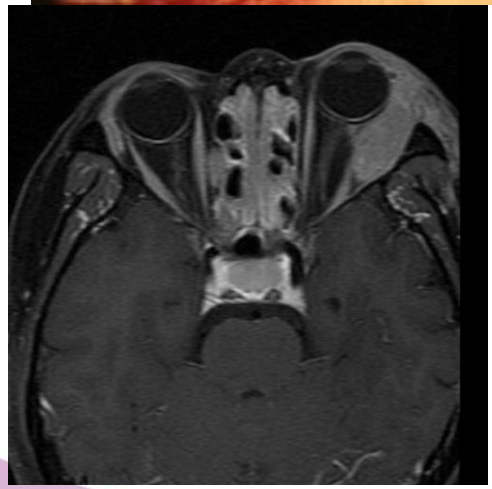
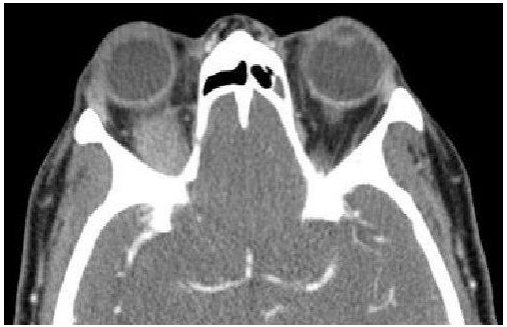
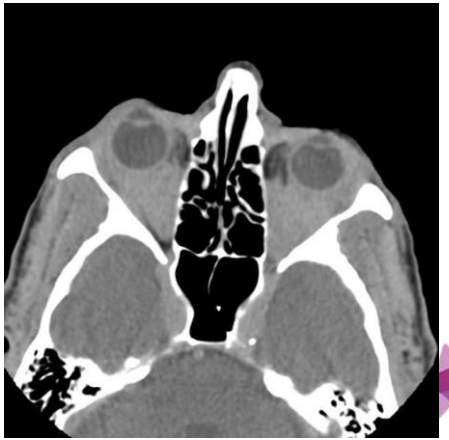
Clinical presentation











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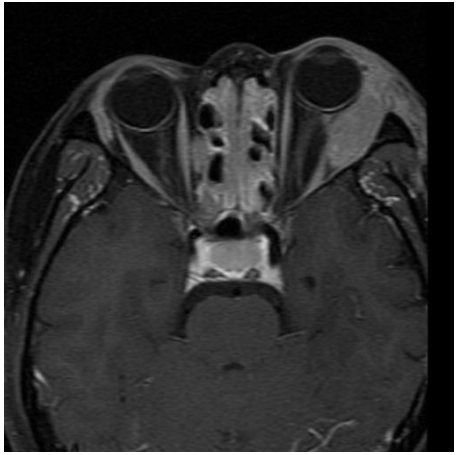
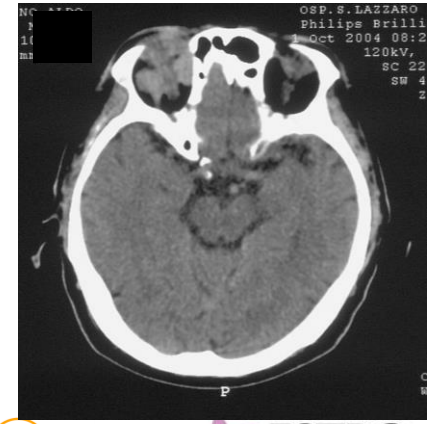
Diagnosis and staging

- 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

Diagnosis and staging

- Ann Arbor system

- Localized disease (stage I) = 85%-90%
- Nodal involvement = 5%
- Bone marrow involvement = 5-8%

Treatment
Surgery

- Biopsy: mandatory for diagnosis and 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

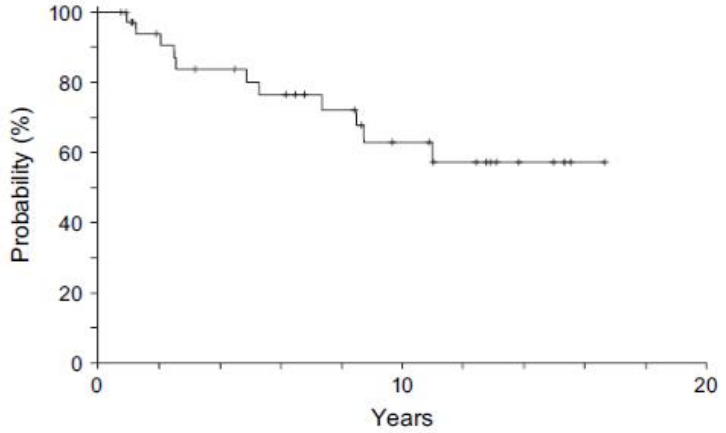

Figure 3. Freedom from requiring treatment. After 5, 10 and 15 years, freedom from requiring treatment was 80%, 63% and 57%, respectively.

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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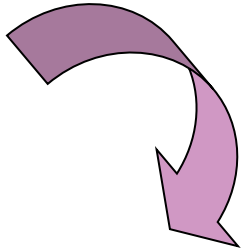
Treatment
Chemotherapy

- 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

IELSG 39

International prospective phase 2 trial addressing the efficacy of first-line *Chlamydophila psittaci*-eradicating therapy with protracted administration of doxycycline followed by eradication monitoring and antibiotic re-treatment at infection re-occurrence in patients with newly diagnosed Ocular Adnexal Marginal Zone Lymphoma (OAMZL)

44 patients (accrual completed)

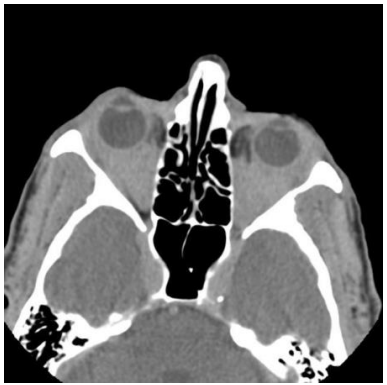
(A. Ferreri, E. Zucca, S. Govi)

Aim of the study is to establish in a prospective, multicentre phase 2 trial, the efficacy of an upfront targeted therapy consisting of *Cp*-eradicating therapy with prolonged administration of doxycycline followed by eradication monitoring and antibiotic re-treatment at infection re-occurrence in patients with newly diagnosed OAMZL.

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



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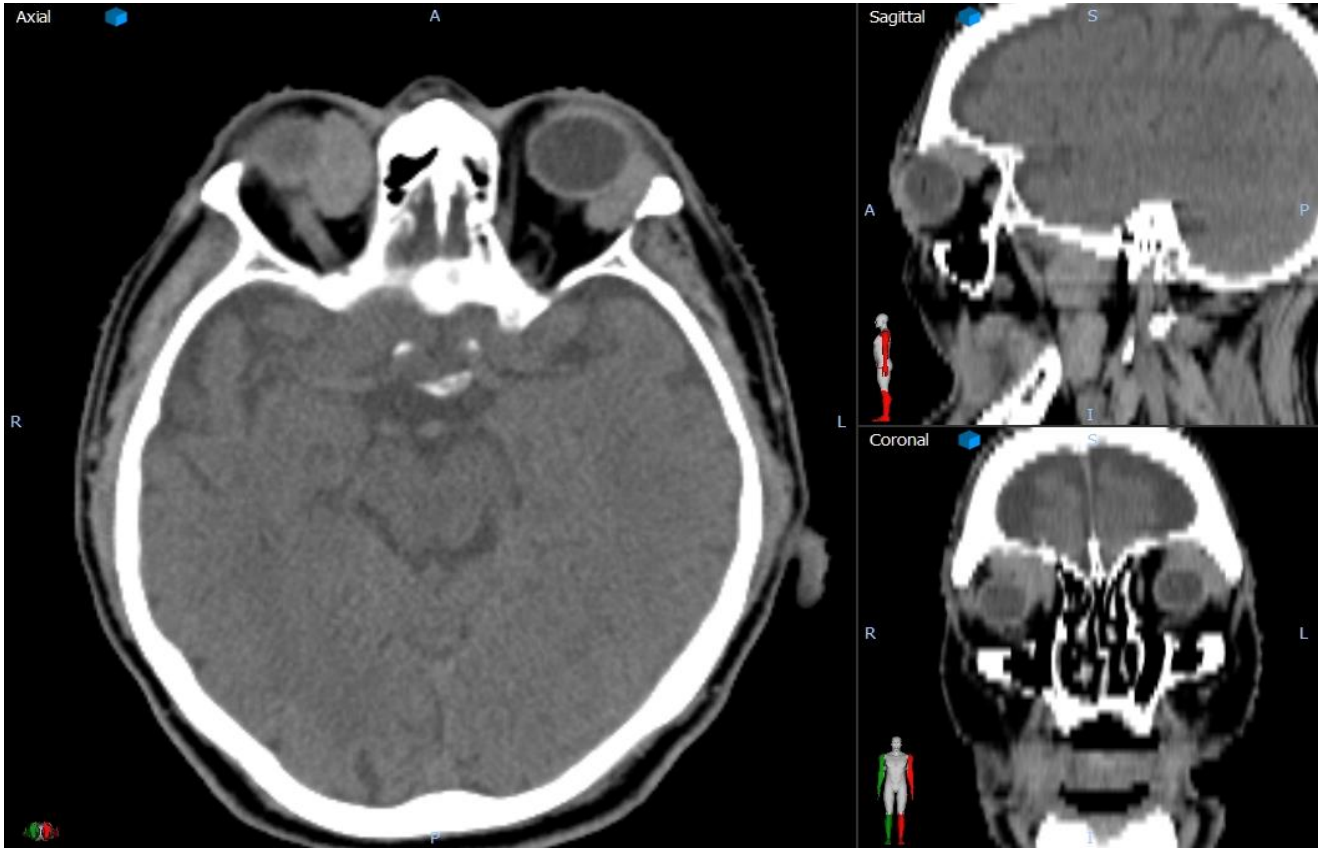

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Reference, year	No. of patients	Stage I, %	Gy	CR, %	LR, %	DR, %	Survival, %	LRM, %
Stafford et al. 2001	40	85	15-54	98	2	25	5-y RFS 88 5-y OS 74 5-y DSS 100	0
Le et al. 2002	31	100	30-40	100	0	16	10-y PFS 71 10-y OS 73	3
Fung et al. 2003	48	81	30.6	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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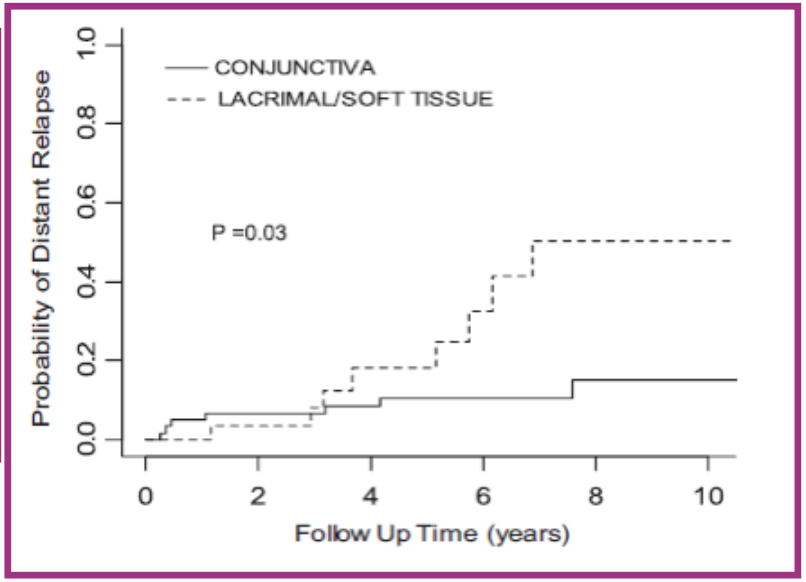
Disease subsite may be a significant prognostic factor

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

Considerations on RT dose

- A dose of 24 Gy is required to provide optimal local control and minimize the rate of local failures in OAML

Low dose RT for Orbital Lymphomas

BOOM BOOM

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Boom Boom RT in Orbital Lymphoma (MALT)

Clinical Investigation: Lymphoma

Low-Dose Radiation Therapy (2 Gy × 2) in the Treatment of Orbital Lymphoma

Carolina E. Fasola, MD, MPH,* Jennifer C. Jones, MD, PhD,† Derek D. Huang, MD,‡ Quynh-Thu Le, MD,* Richard T. Hoppe, MD,* and Sarah S. Donaldson, MD*

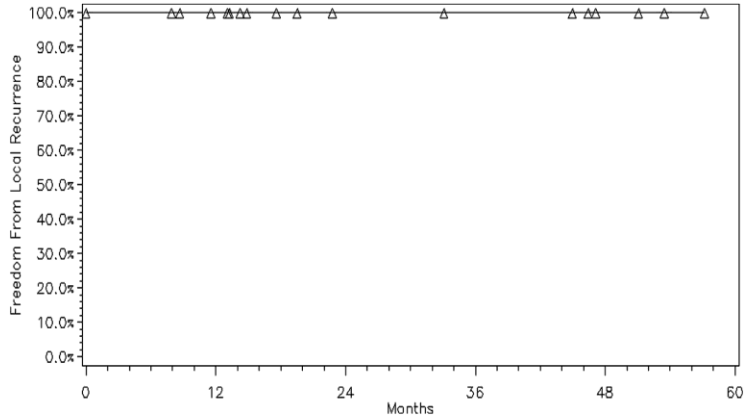
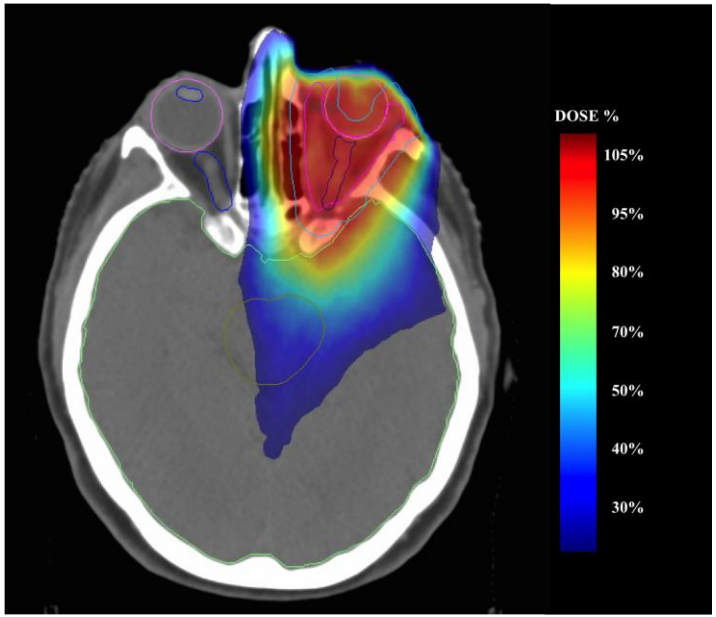


Fig. 1. Freedom from local relapse for all sites with complete response treated with low-dose radiation therapy (N = 23).



LOCAL CONTROL: 100%

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Principles of ISRT for Extranodal Sites

Site	Volume	Dose
Orbital	CTV = whole orbit	24-30 Gy (Indolent)
Tonsil	CTV=tonsil or tonsillar bed	Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)
Salivary gland	CTV = superficial and deep lobe of the parotid Regional nodes if involved	24-30 Gy (Indolent) Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)
Thyroid	CTV=Thyroid gland Consider including regional node (levels 3,4, and 6)	30 Gy (Indolent) Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)
Breast	CTV = whole breast	30 Gy (Indolent) Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)

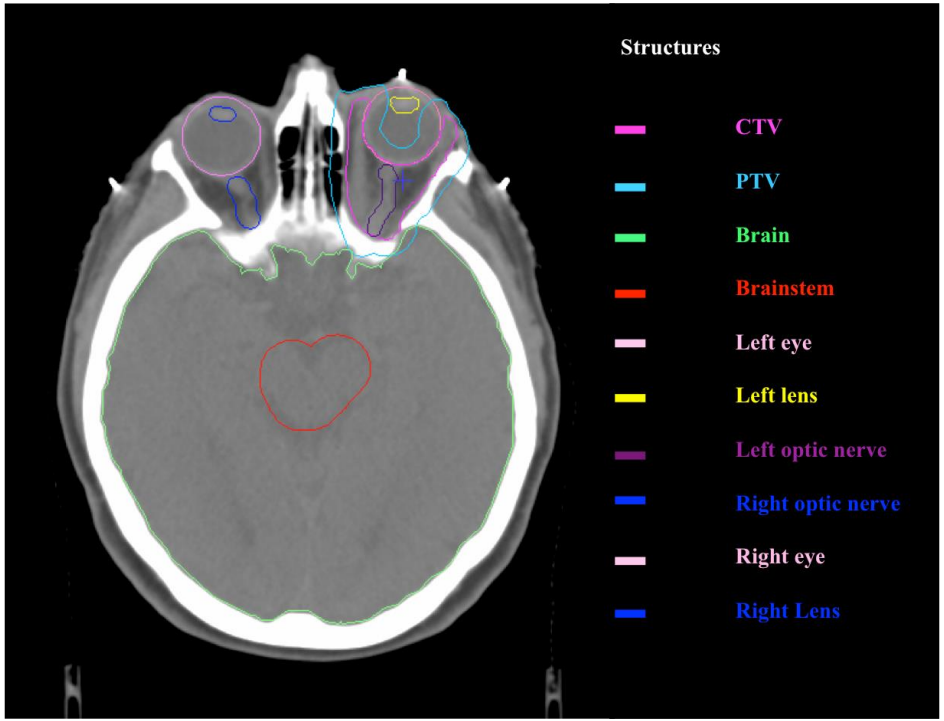
For most sites, the whole organ is the CTV

Considerations on RT volumes

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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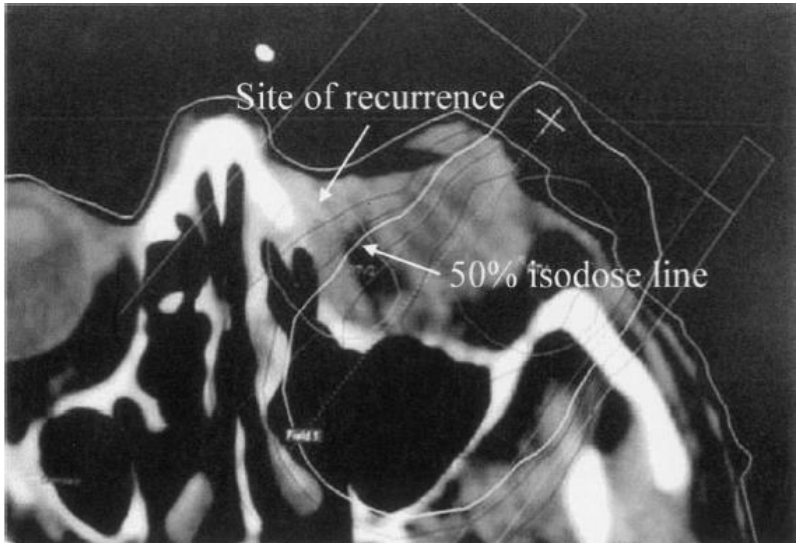
Is it necessary to treat the entire orbit?

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

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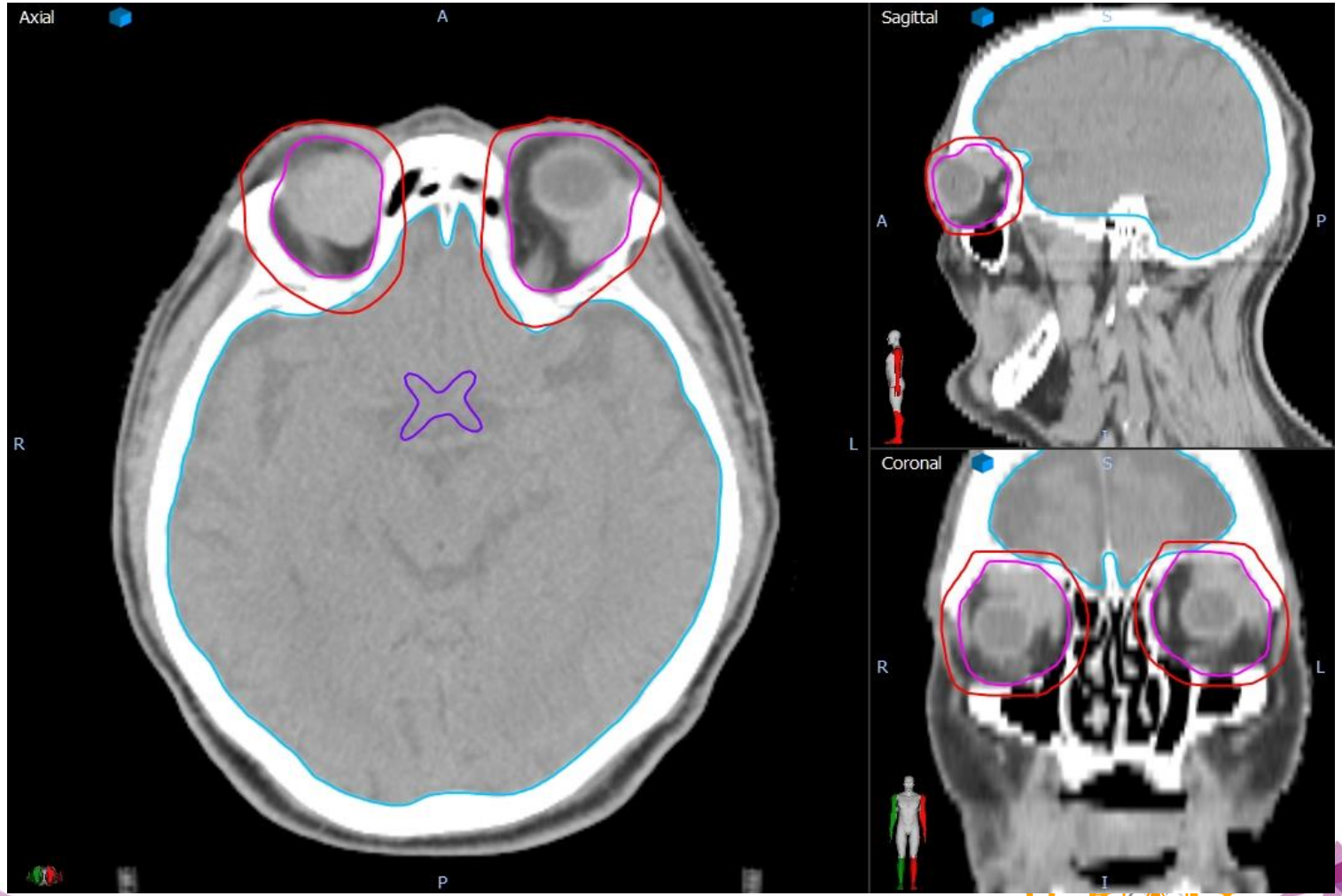

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RT technique

- 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

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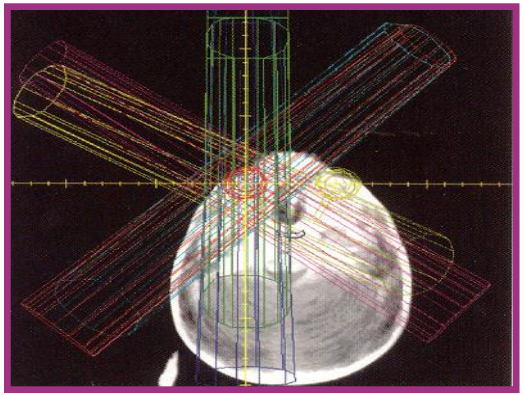
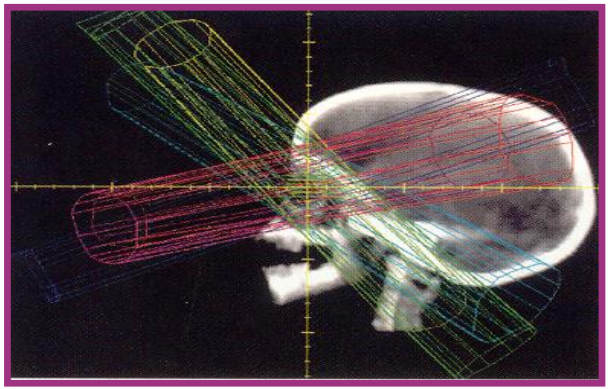
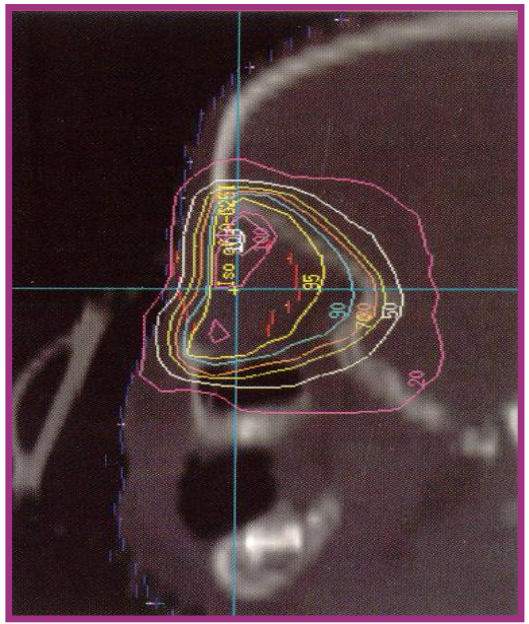
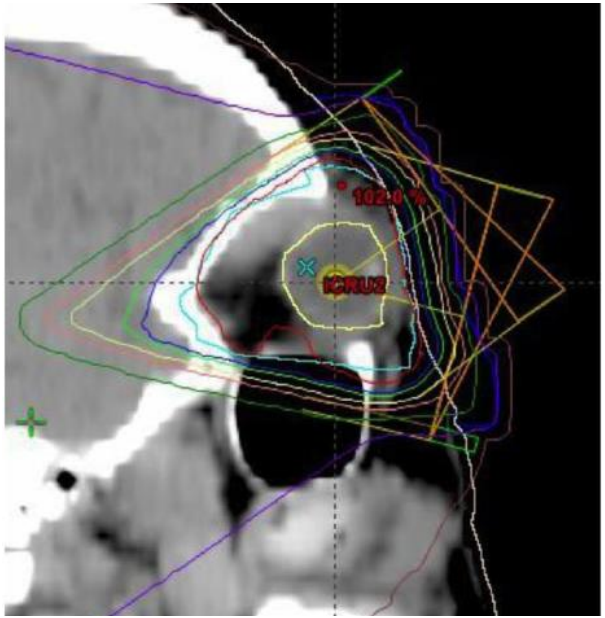
3D CRT

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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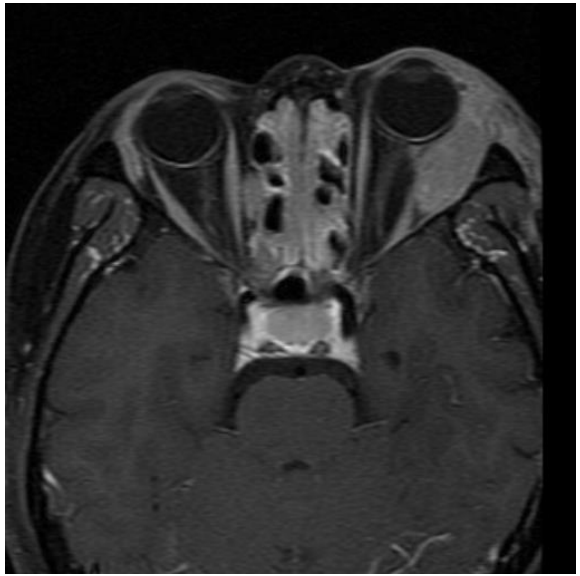
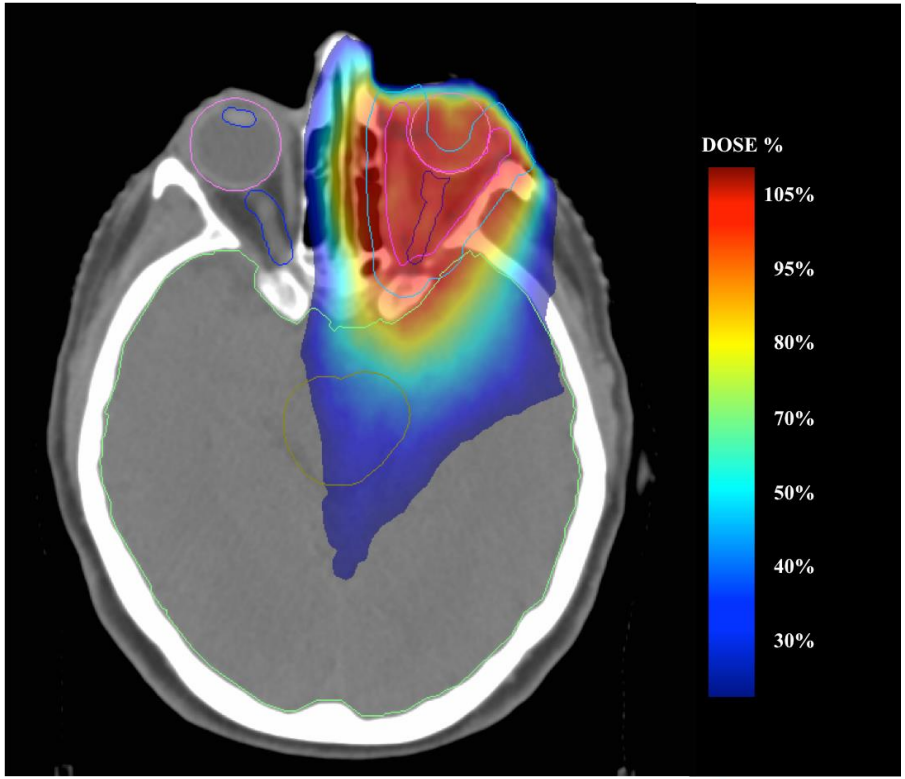
IMRT (VMAT)





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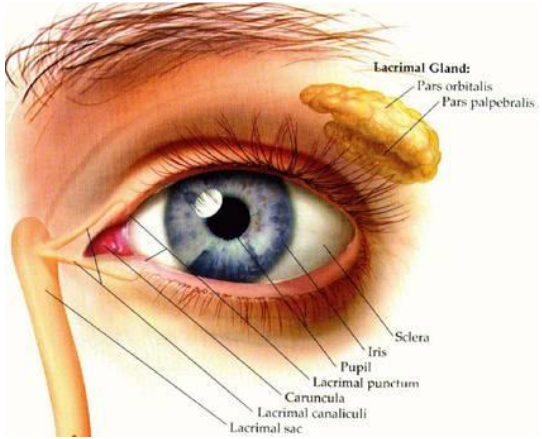
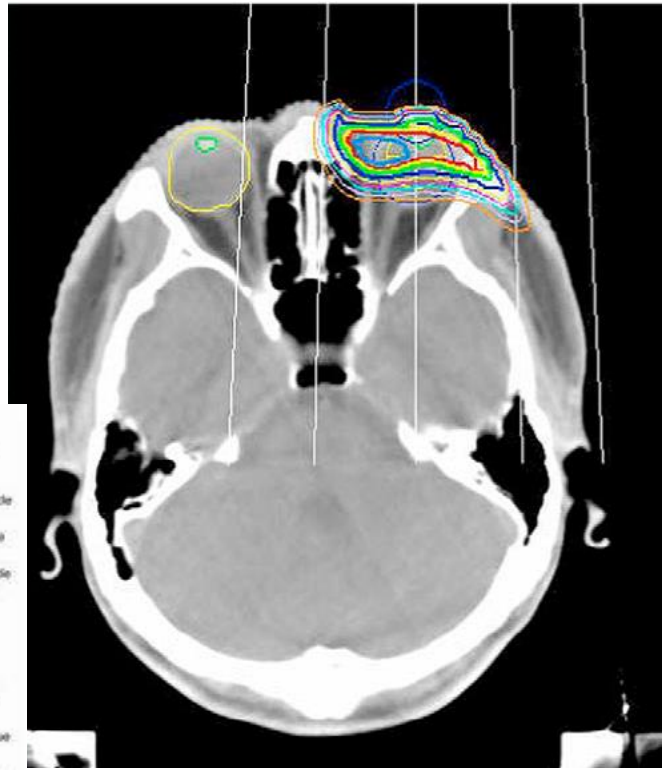
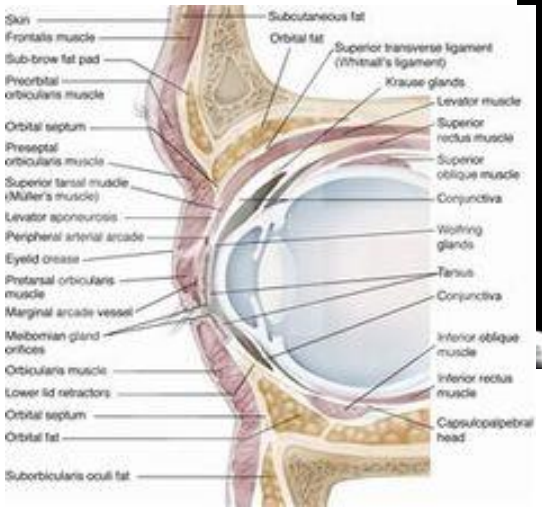
Tumors confined to the conjunctiva or eyelid

CTV = entire conjunctival reflection to the fornices (not to include the entire orbit)







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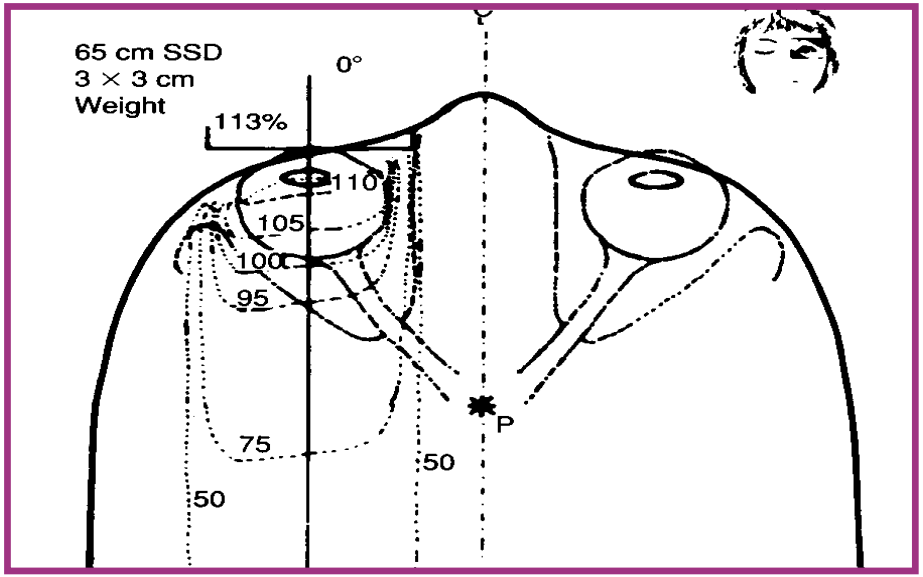
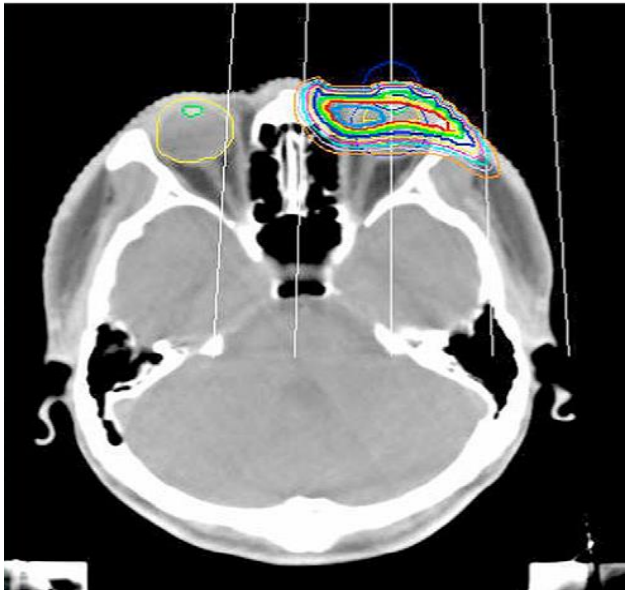
Tumors confined to the conjunctiva or eyelid (CTV = entire conjunctival reflection to the fornices)





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

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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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

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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

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Ocular adnexae DLBCL

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Role of RT

- Consolidation RT after R-chemotherapy

- Radical RT in patients “unfit” for chemotherapy

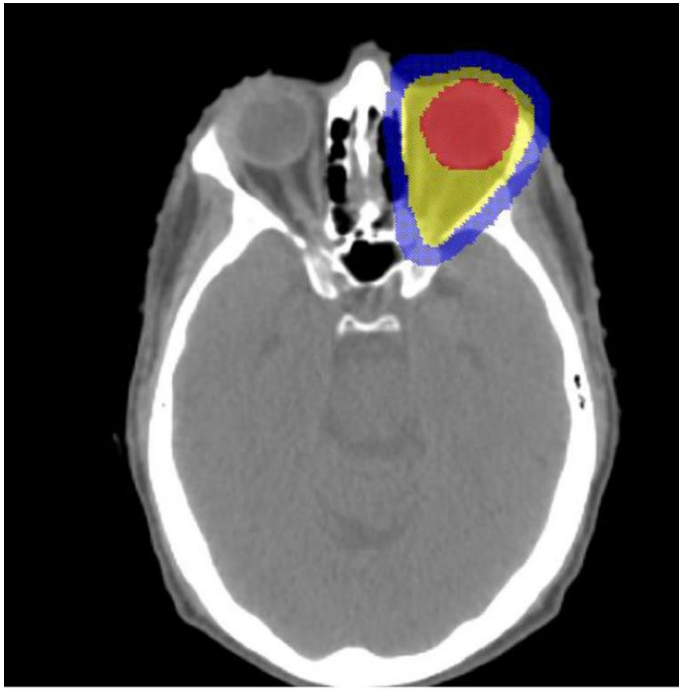
Considerations on RT volume

• **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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Primary CNS Lymphoma (PCNSL)

Berthe M.P. Aleman

Radiation Oncologist
The Netherlands Cancer Institute

Acknowledgment: Joachim Yahalom, M.D.

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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

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PCNSL: epidemiology

- 3.1% of all primary CNS tumors
- Incidence: 0.46/100,000 person years (US)
- ~1000-1500 cases per year (US)
- Median age at diagnosis = 60
- Gender: men: women - 1:1
- Rise in incidence
- Pathology: mostly DLBCL

Central Brain Tumor Registry of the United States (CBTRUS), 1998-2002

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PCNSL: 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)

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PCNSL in “immunocompetent” hosts

(non-HIV)

PCNSL: clinical features

Symptom	Frequency (%)
Focal deficits	70
Neuropsychiatric symptoms	43
High intracranial pressure	33
Seizure	14
Other: headache, ocular symptoms, confusion and lethargy	

Ferreri, Blood 2011

PCNSL: A unique lymphoma entity

- 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)

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PCNSL: Baseline Evaluation

- **Clinical Evaluation**
  - Complete medical, neurological, cognitive examination
  - Determination of prognostic factors (age, PS)
- **Pathologic Evaluation**
  - Centralized confirmation of pathology with immunopathology when possible
- **Laboratory Evaluation**
  - HIV, LDH, creatinine clearance

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PCNSL: Baseline Evaluation

- **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

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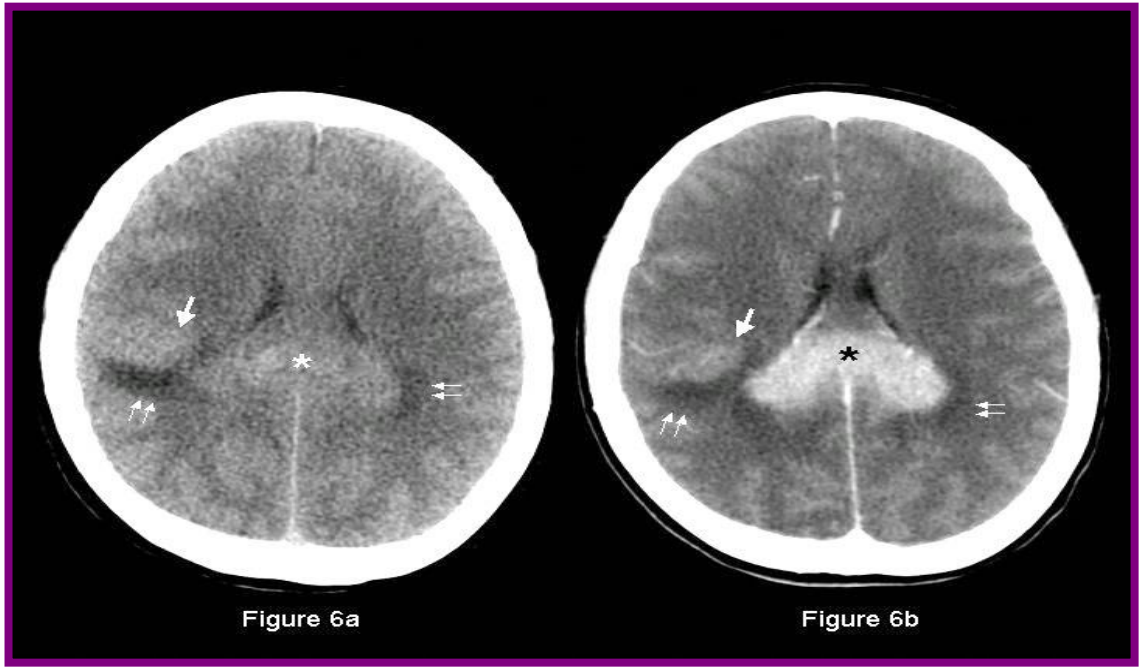
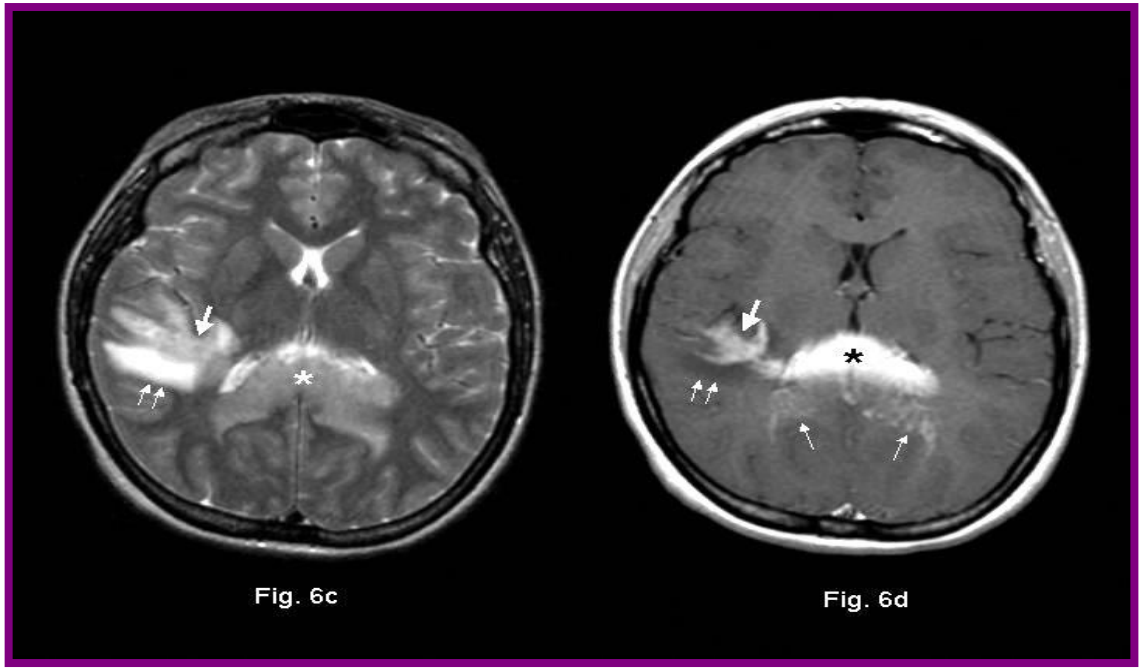
PCNSL: appearance on CT-scan



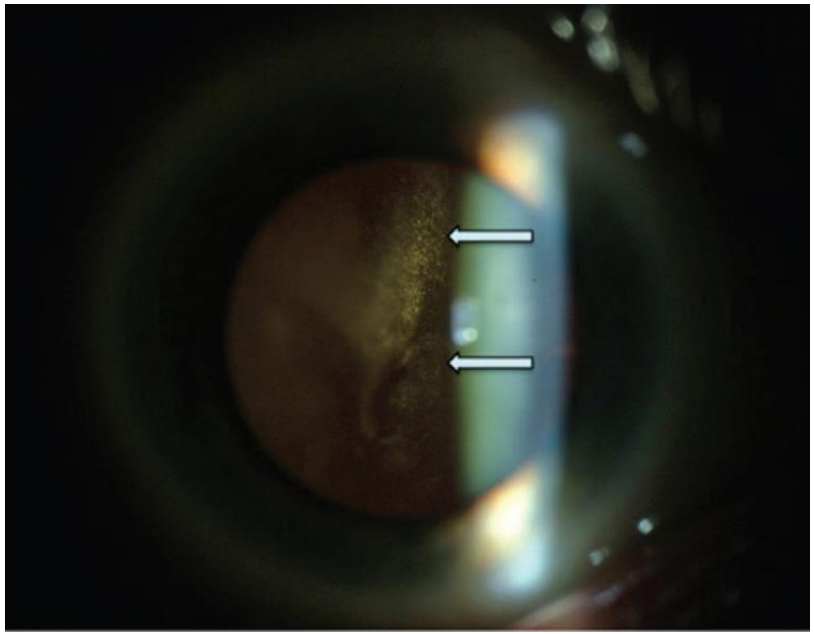
From: Batchelor TT, Buchbinder BD, Harris NL. Case records of the Massachusetts General Hospital, A 32 year old woman with difficulty walking, headache and nausea. *N Engl J Med* 2005; 352: 185-194

PCNSL: appearance on MRI

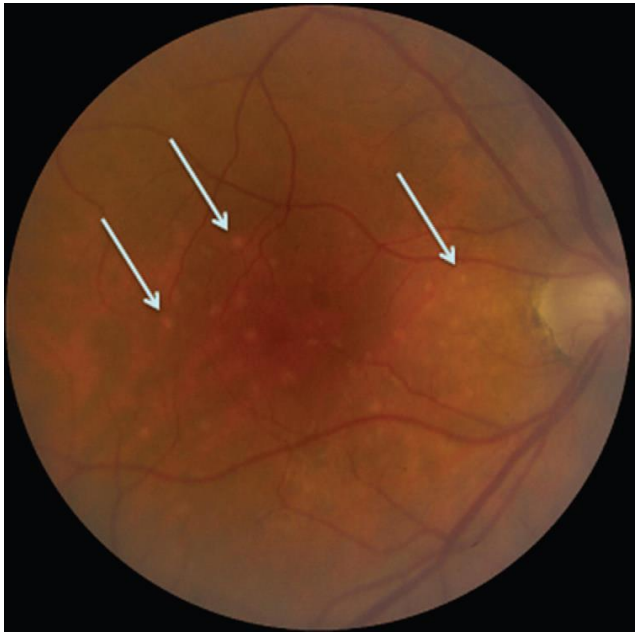


From: Batchelor TT, Buchbinder BD, Harris NL. Case records of the Massachusetts General Hospital, A 32 year old woman with difficulty walking, headache and nausea. *N Engl J Med* 2005; 352: 185-194

PCNSL: slit lamp and fundoscopy



Binocular slit-lamp examination reveals numerous infiltrating cells (arrows) behind the lens in the vitreous.



Fundoscopy of same patient. There are many small, round, yellow-orange lesions (arrows) at the retinal pigment epithelium level in the deep retina.

PCNSL: sites of disease

Site	Frequency (%)
Brain hemispheres	38
Thalamus/basal ganglia	16
Corpus callosum	14
Periventricular region	12
Cerebellum	9
Eyes	5-20
Meninges	16
Spinal cord	1
Spinal nerves	<1

Ferreri, Blood 2011

Difference in Survival Outcome of Primary Central Nervous System Lymphoma By Histologic Types

- SEER data on 4,375 adult (≥18 yrs) patients diagnosed with PCNSL between 1998- 2014

Pathology	Number	Frequency
DLBCL	3,091	70,7%*
Follicular lymphoma	83	1,9%
Peripheral T-cel lymphoma	64	1,5%
Marginal zone lymphoma	63	1,4%
Burkitt lymphoma	27	0,6%
Small lymphocytic lymphoma	22	0,5%
Hodgkin lymphoma	13	0,3%
Other/unclear	1,012	23,1%
Total	4,375	100,0%

* 92% of those with defined histology

Dai Chihara et al. Blood 2017;130:4137

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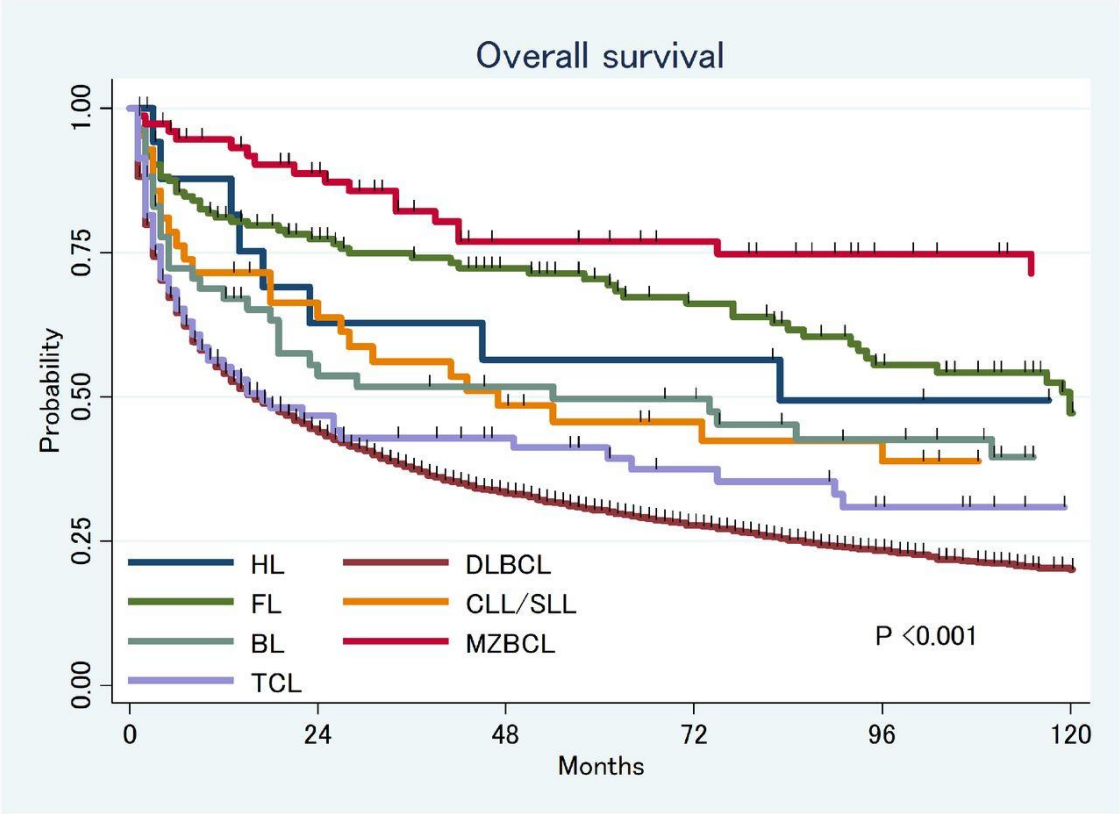
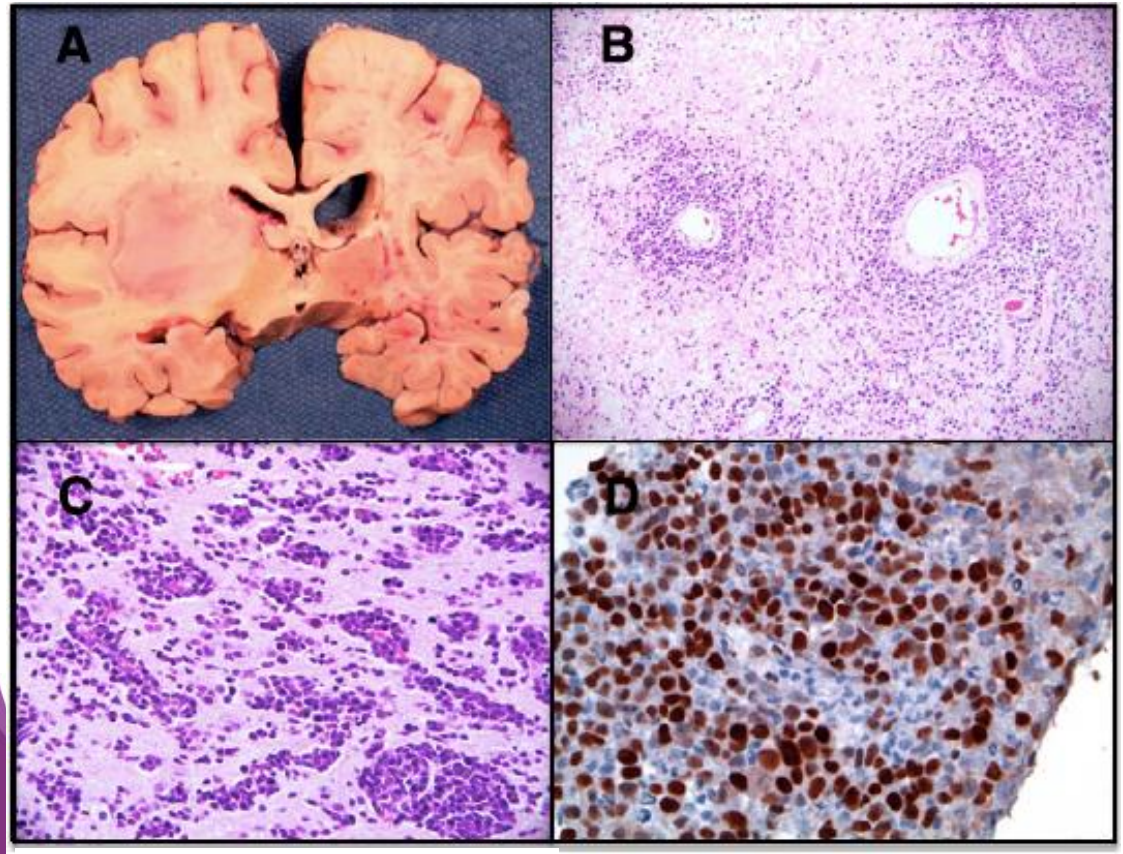
Difference in Survival Outcome of Primary Central Nervous System Lymphoma By Histologic Types



Dai Chihara et al. Blood 2017;130:4137

PCNSL: pathology



(A) DLBCL involving the left parietal lobe and basal ganglia exhibits marked mass effect, subependymal spread, and invasion of the lateral ventricle at relapse, upon progression with HD-MTX and rituximab-based chemotherapy. (B) DLBCL cells exhibiting an **angiotropic** growth pattern in a diagnostic specimen of PCNSL (H&E stain) (C) Invasive growth of DLBCL cells along the cerebral vasculature in PCNSL (H&E). D) **High expression of MYC** by DLBCL cells in a diagnostic specimen of PCNSL, as demonstrated by immunohistochemistry

Rubenstein et al. Blood 2013

PCNSL: A unique treatment challenge

- Rapidly lethal if not treated or responsive
- **RT alone is effective**, but CRs are brief (median survival: 1 yr)

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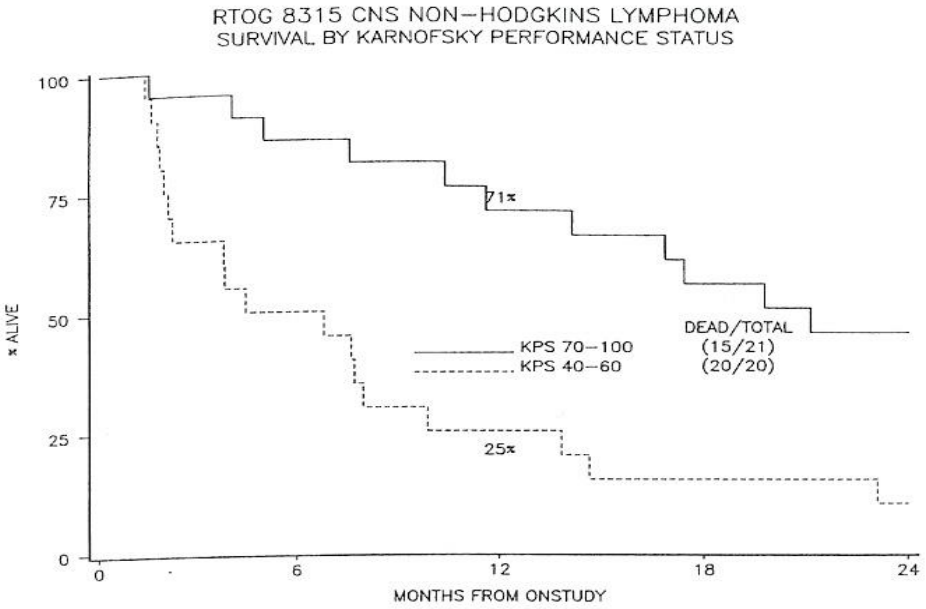
RTOG 83-15 WBRT alone

- 41 patients
- WBRT of 20 RT of 40 Gy + boost Gy t(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

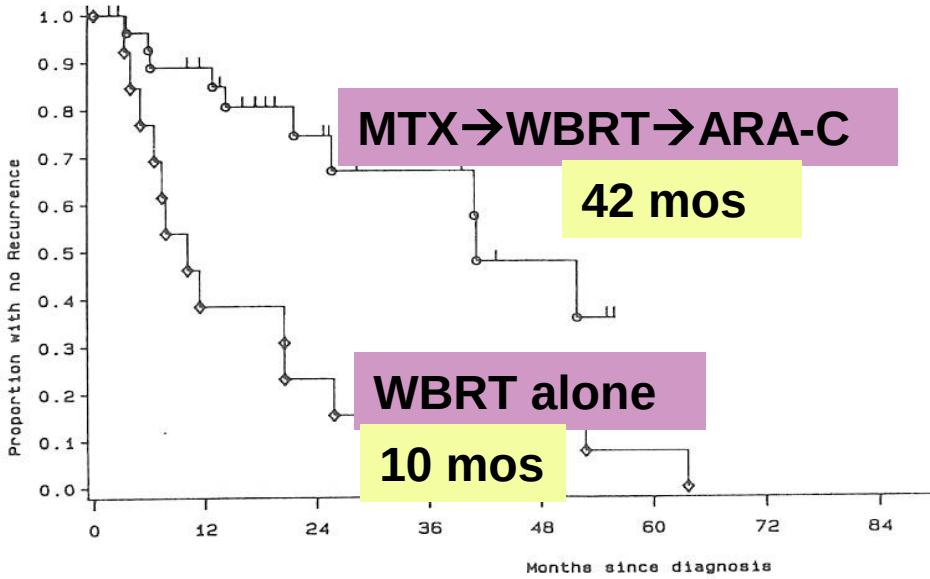


Nelson DF et al: IJROBP 1992; 23:9-17

Combined modality therapy for PCNSL

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

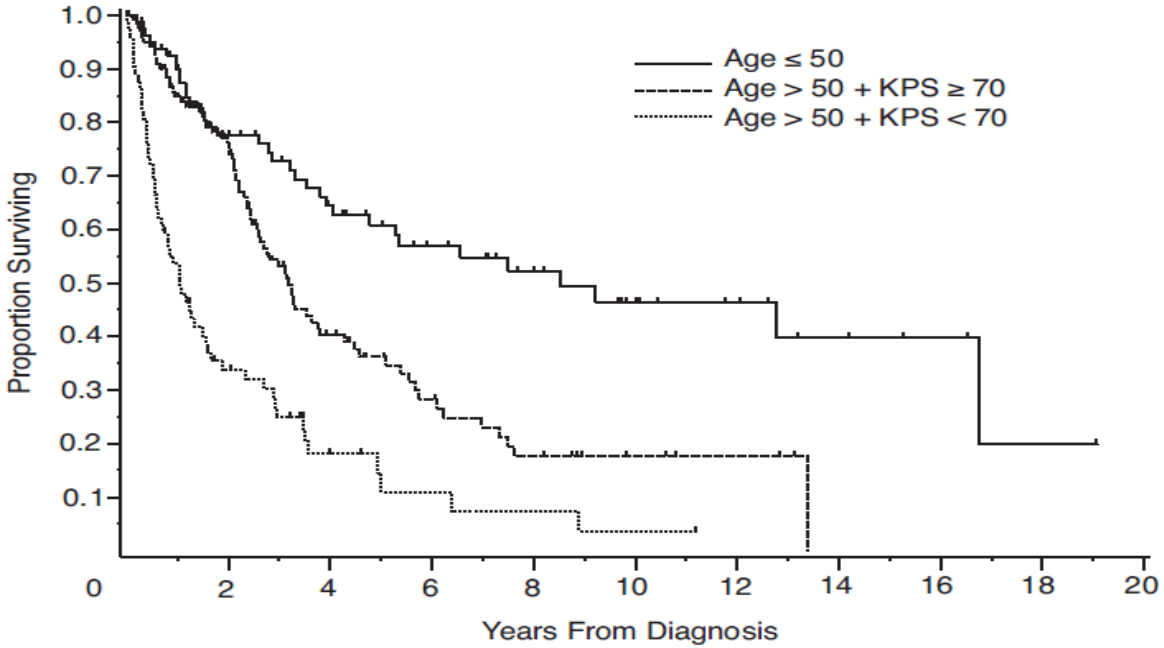
Fig 1. Outline of treatment protocol for PCNSL at MSKCC.



DeAngelis, JCO 1992

PCNSL: prognostic factors MSKCC

- Prognostic factors critical: age and KPS



Class	Median Overall Survival, y
1 (age ≤ 50 y)	8.5
2 (age > 50 y + KPS ≥ 70)	3.2
3 (age > 50 y + KPS < 70)	1.1

Abrey et al., JCO 2006

PCNSL: prognostic factors IEGSL

Prognostic Factor[a]	
Age > 60 y	
ECOG PS ≥ 2	
Elevated LDH	
Elevated CSF protein concentration	
Involvement of the deep structures of the brain	
Scores	**2-y Overall Survival, %**
0 or 1	80
2 or 3	48
4 or 5	15

Abbreviations: CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status.
Data were derived from Ferreri et al.[26]
[a] Each variable is assigned a value of 1 if it is present. The final score is the sum of these values.

Han, Cancer 2017

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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)
- Breakthrough for cure: introduction of high dose MTX
- Great concern: **radiation-related neurotoxicity**

➢ **Role of radiation is debated!**

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Delayed neurotoxicity in PCNSL

MSKCC Experience: 185 pts (1985-2000)

5-year cum inc neurotox: 24%

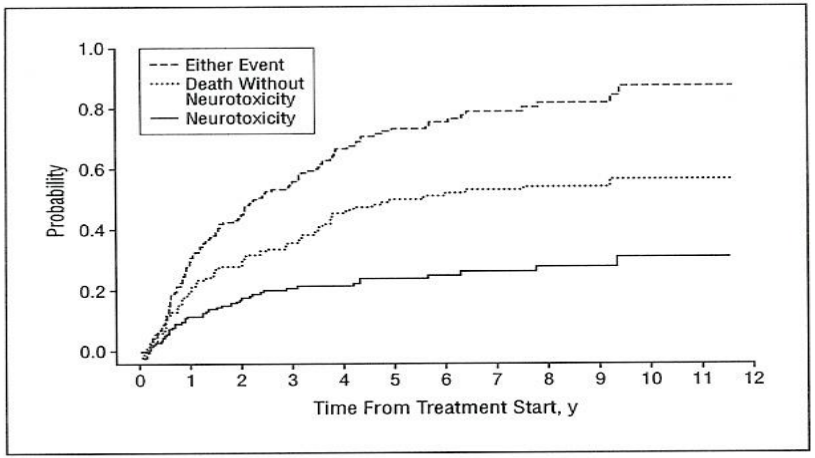

Figure 1. Incidence of neurotoxicity, death, and either neurotoxicity or death (either event).

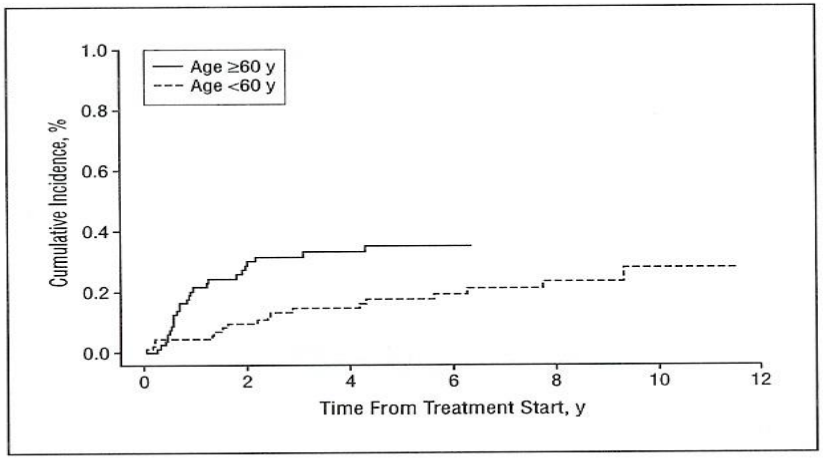

Figure 2. The incidence of neurotoxicity stratified by age, showing that although older patients are at a significantly higher risk, the development of neurotoxicity is also a concern in long-term survivors younger than 60 years.

Omuro et al, Arch Neurol. 2005; 62:1-6

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
  - Usually progressive, no treatment available
- Underlying mechanism unknown

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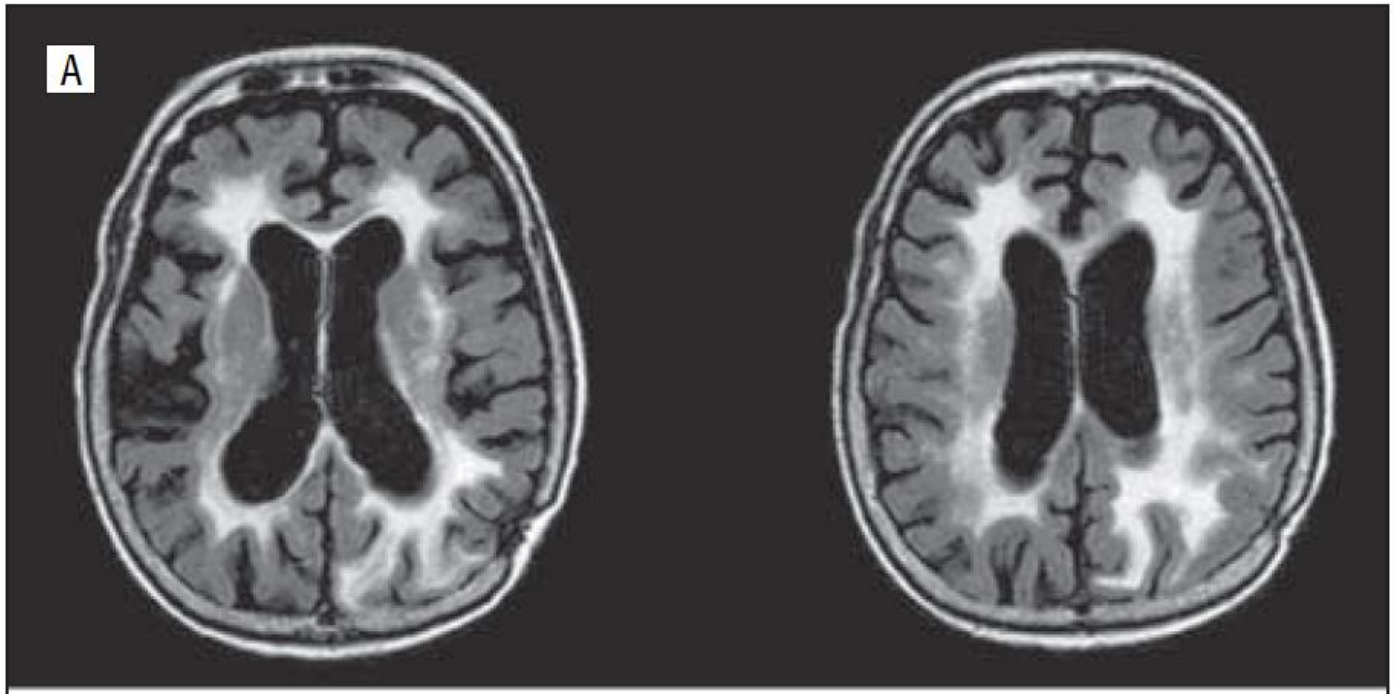
PCNSL: neurotoxicity



Magnetic resonance image from a 70-year-old patient with neurotoxicity showing **diffuse white matter changes** and **brain atrophy**

Omuro et al, Arch Neurol. 2005; 62:1-6

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*

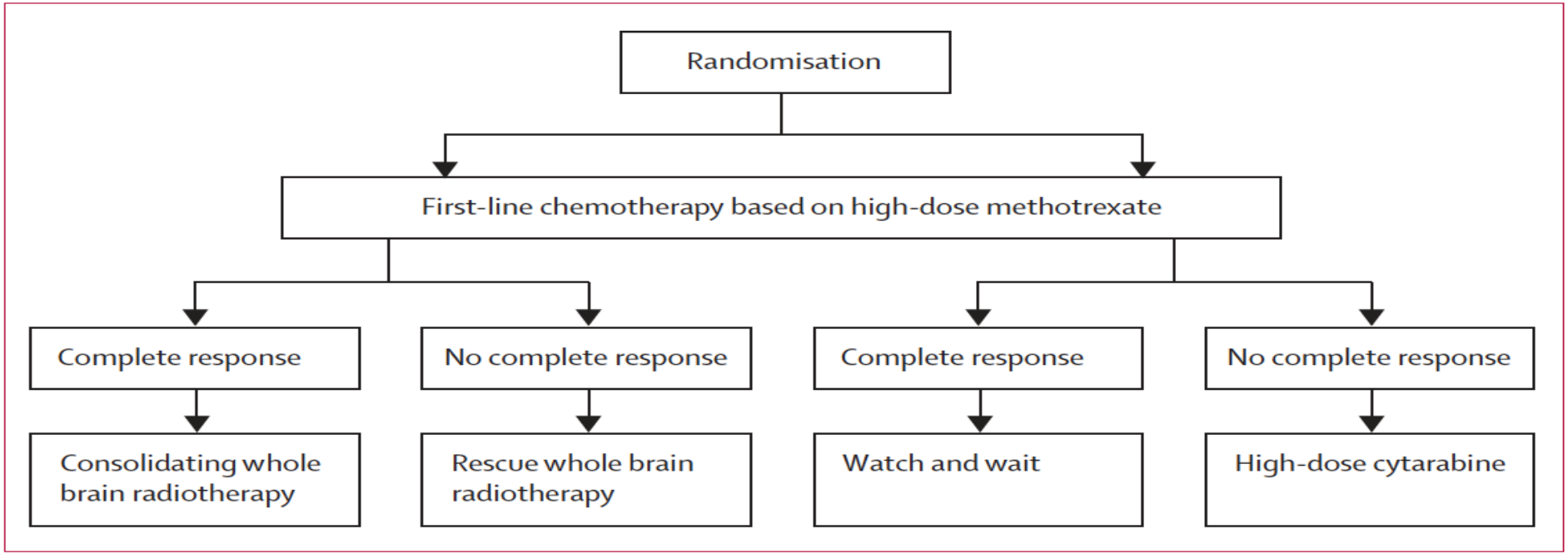
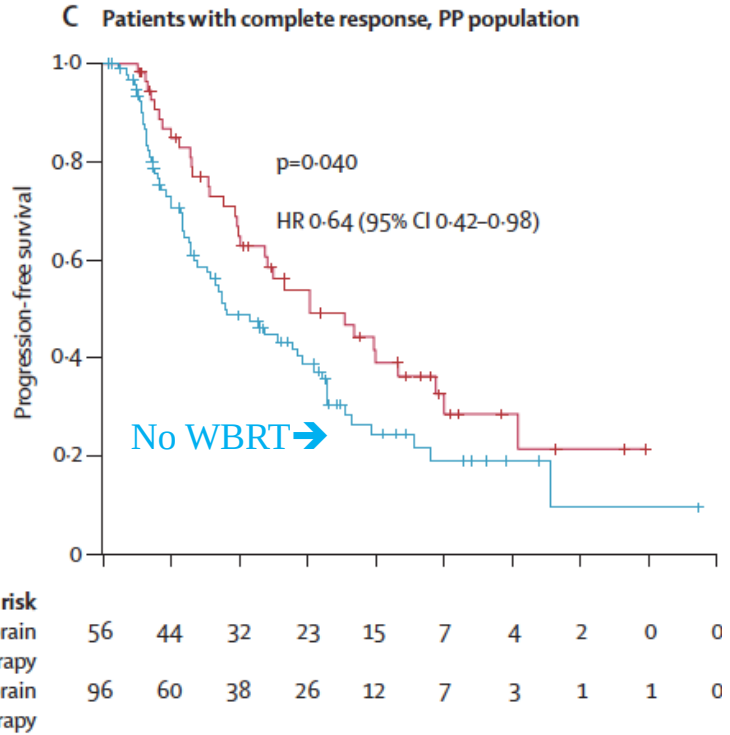
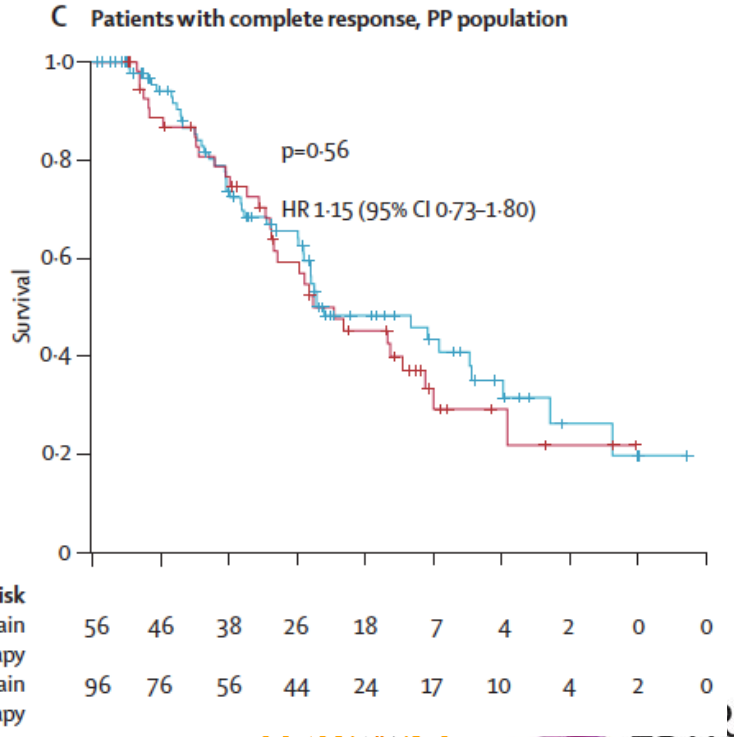


Figure 1: **Trial design**

Stratification by age and treatment center

High-dose methotrexate with or without WBRT for PCNSL (G-PCNSL-SG-1): PFS and OS for patients with CR (per protocol population





Thiel et al, Lancet Oncol 2010

High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

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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

Thiel et al, Lancet Oncol 2010

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Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial

Andrés J M Ferreri, Kate Cwynarski, Elisa Pulczynski, Christopher P Fox, Elisabeth Schorb, Paul La Rosée, Mascha Binder, Alberto Fabbri, Valter Torri, Eleonora Minacapelli, Monica Falautano, Fiorella Ilariucci, Achille Ambrosetti, Alexander Roth, Claire Hemmaway, Peter Johnson, Kim M Linton, Tobias Pukrop, Jette Sønderskov Gørløv, Monica Balzarotti, Georg Hess, Ulrich Keller, Stephan Stilgenbauer, Jens Panse, Alessandra Tucci, Lorella Orsucci, Francesco Pisani, Alessandro Levis, Stefan W Krause, Hans J Schmoll, Bernd Hertenstein, Mathias Rummel, Jeffery Smith, Michael Pfreundschuh, Giuseppina Cabras, Francesco Angrilli, Maurilio Ponzoni, Martina Deckert, Letterio S Politi, Jürgen Finke, Michele Reni, Franco Cavalli, Emanuele Zucca, Gerald Illerhaus, for the International Extranodal Lymphoma Study Group (IELSG)

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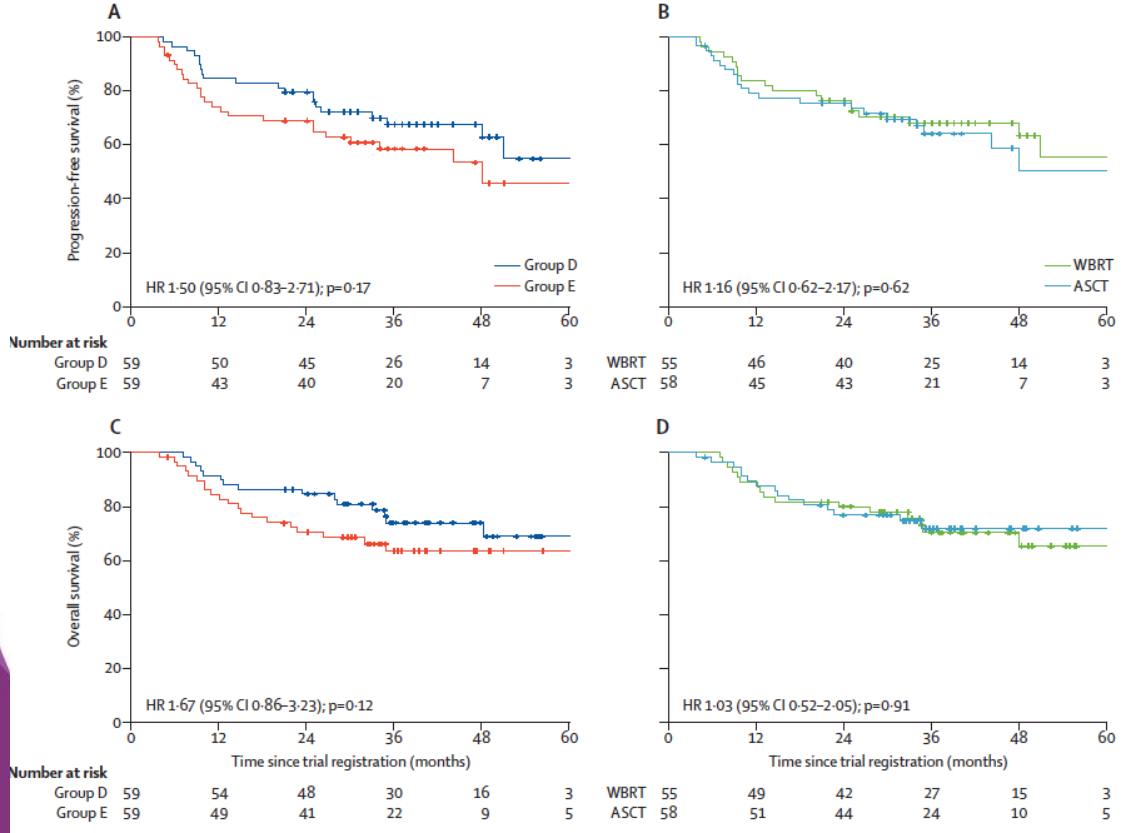
International Extranodal Lymphoma Study Group-32 phase 2 trial



WBRT and ASCT are both feasible and effective as consolidation therapies after high-dose MTX based chemoimmunotherapy in patients =<70 years with PCNSL .

The risks and implications of cognitive impairment after WBRT should be considered at the time of therapeutic decision.

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 entire treatment

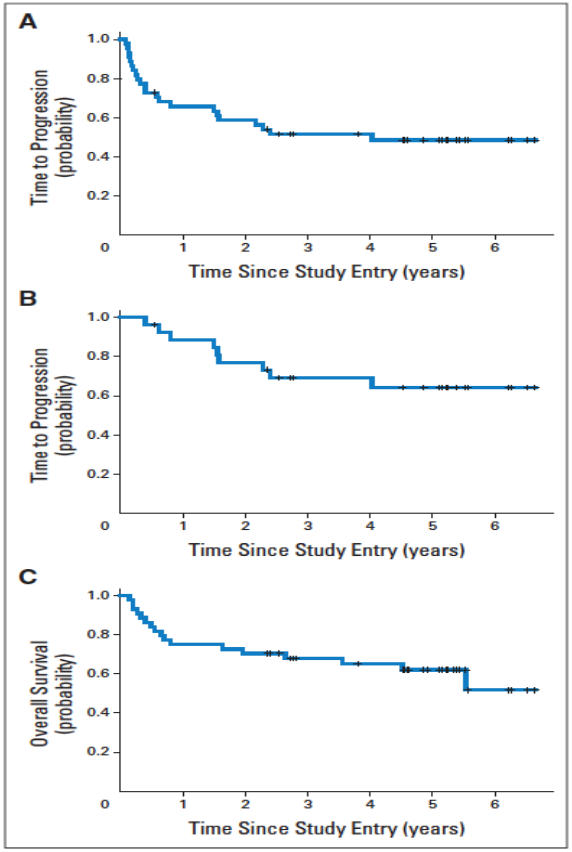
Remission Induction Therapy (4 cycles)

-> Start of CALGB 51101 Combination Chemotherapy Without Autologous Stem Ce in Treating Patients With Cer System B-Cell Lymphoma

Remission Induction T	
Day 1	Methotrexate
Day 2	Leucovorin 10
Day 3	Rituximab 37
Day 7-11	Temozolomi
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



Hypothesis MSKCC

Reduced-dose WBRT following effective immuno-chemotherapy will result in lower neurological toxicity while providing adequate disease control in all age groups

Chemotherapy schedule MSKCC

- **Day 1**
  - Rituximab 500 mg/m^2
- **Day 2**
  - MTX 3.5 gm/m^2
  - VCR 1.4 mg/m^2
  - Procarbazine 100 mg/m^2/d x 7 d. (cycles 1, 3, 5, 7)

X5 cycles (or X7, if PR)

- **Following WBRT**
  - ARA-C 3 gm/m^2 (2 cycles)

RT schedule

- **IF CR** after R-MVP X5 or X7 **→WBRT 2340 cGy/13 fx**
- **IF PR** after R-MVP X7 **→WBRT of 4500 cGy/25 fx**

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

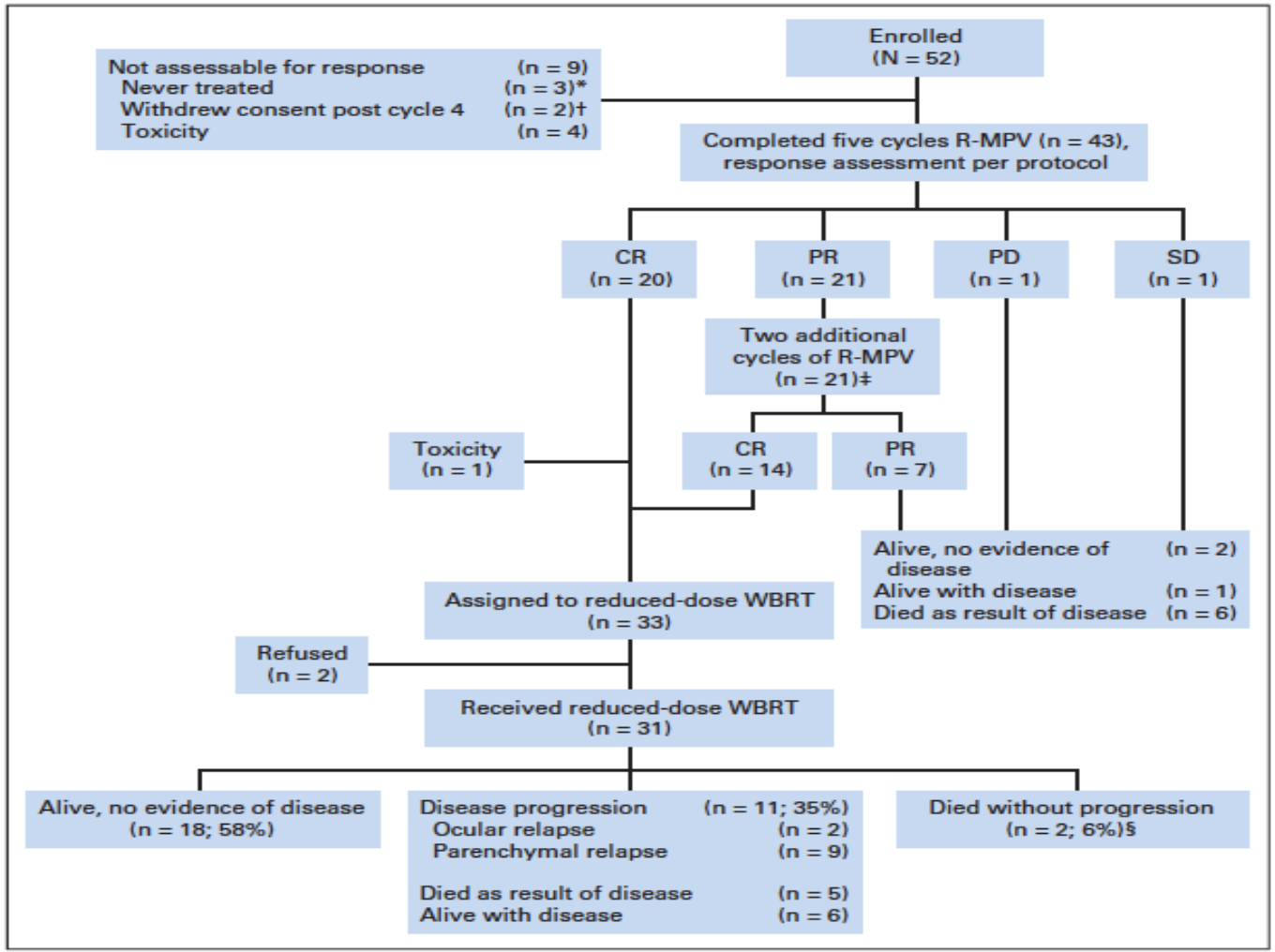
VOLUME 31 · NUMBER 31 · NOVEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

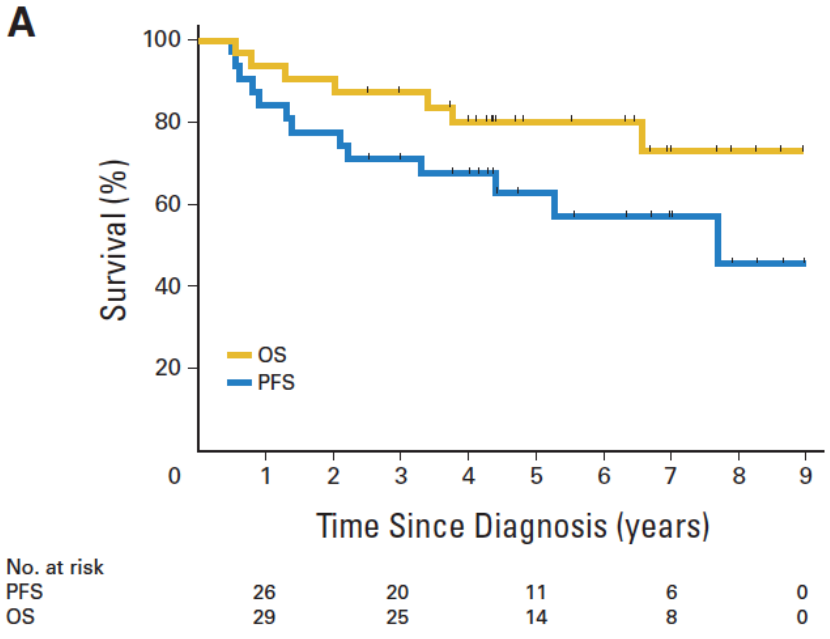
Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

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

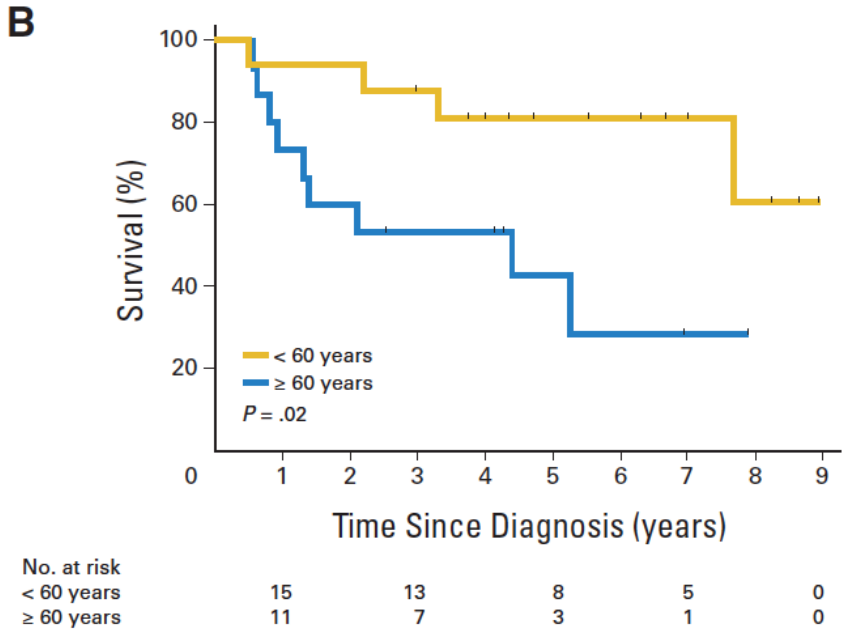

Enrolled
(N = 52)
Not assessable for response (n = 9)
Never treated (n = 3)*
Withdrew consent post cycle 4 (n = 2)†
Toxicity (n = 4)
Completed five cycles R-MPV (n = 43), response assessment per protocol
CR
(n = 20)
PR
(n = 21)
PD
(n = 1)
SD
(n = 1)
Two additional cycles of R-MPV
(n = 21)‡
Toxicity
(n = 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%)§

R-MPV followed by consolidation reduced-dose WBRT and cytarabine in newly diagnosed PCNSL: final results and long-term outcome

PFS and OS in patients who received WBRT (n=32)



PFS by age



Morris et al, JCO 2013

R-MPV followed by consolidation reduced-dose WBRT and cytarabine in newly diagnosed PCNSL: final results and long-term outcome

Exploratory neuropsychological evaluation (n=12)

- Baseline: cognitive impairment in several domains.
- After induction CT: significant improvement in executive and verbal memory
- Follow up: minor fluctuations were observed on memory performance over time. No evidence of depressed mood, and self-reported quality of life remained stable during the follow-up period

Morris et al, JCO 2013

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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

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RT in PCNSL: Field design

- **CTV**: Whole brain including meninges at level C1 and C2 and the posterior aspect of the eyes.
- In case of parallel opposed fields: set iso-center anteriorly and bisects the bony canthi (to reduce divergence in possible future match to ocular field).
- If the eyes were originally involved, both eyes should be included in their entirety in WBRT field.

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RT in PCNSL: Dose

Whole brain RT after chemotherapy:

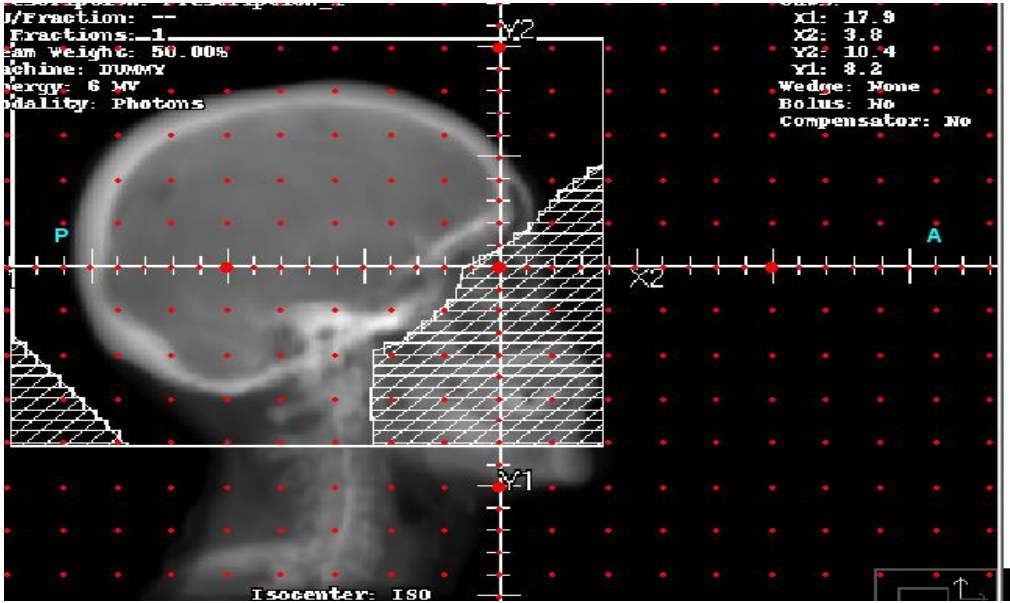
- CR: 23.4 Gy (1.8 Gy per fraction)
- PR/PD/relapse :
  - 36-45 Gy (1.5-1.8 Gy per fraction)
  - (Simultaneous integrated) boost: not recommended by experts but used in clinical trials i.e. HOVON 105

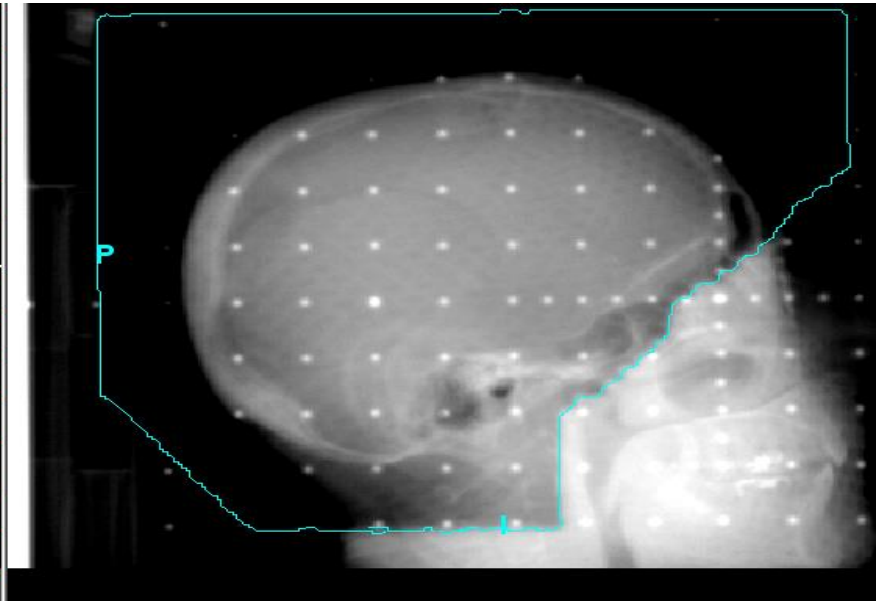
Primary whole brain RT for non-candidates for CT:

- 40-50 Gy (2 Gy per fraction)
- For palliation: 30-36 Gy (2-3 Gy per fraction)

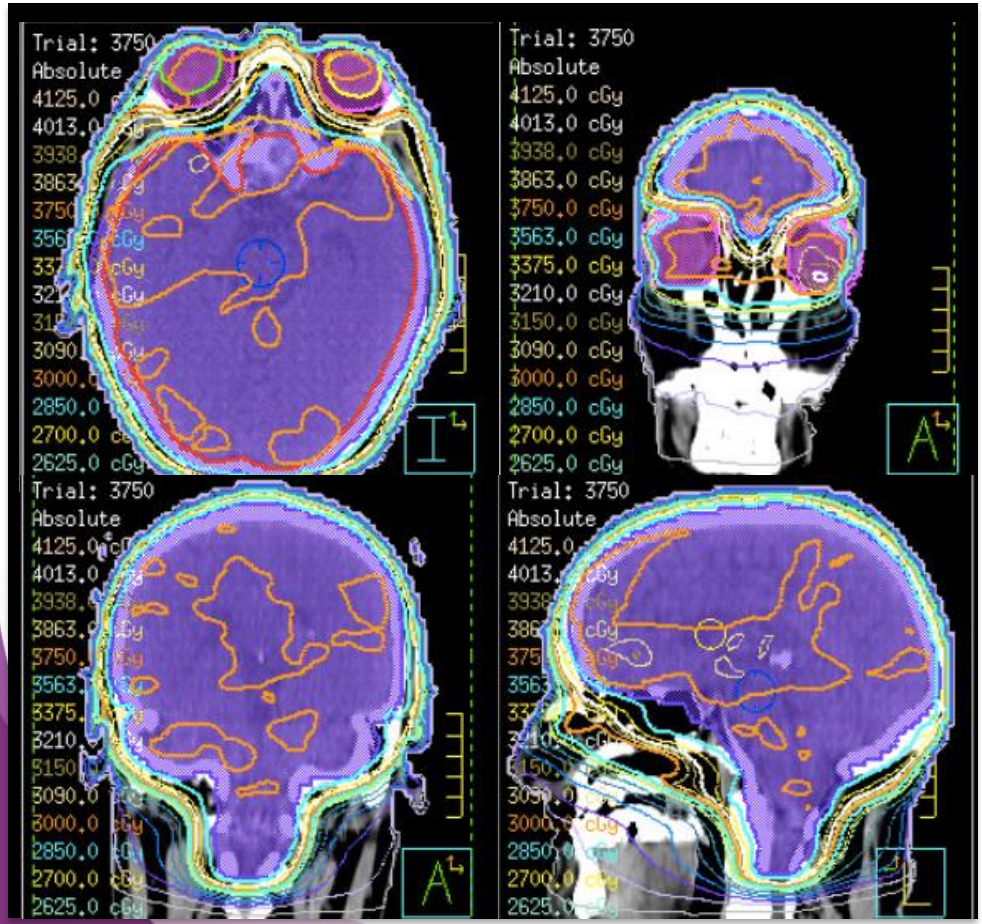
Milgrom&Yahalom, Leukemia and lymphoma 2015

Radiation fields





RT treatment plan including eyes



- Patient with CT refractory disease with multiple intracranial lesions and involvement of both eyes
- RT: brain+meninges at level C1-2+eyes 30 Gy/15 fx and SIB to brain+meninges 37.5 Gy/15 fx using VMAT 2 arcs

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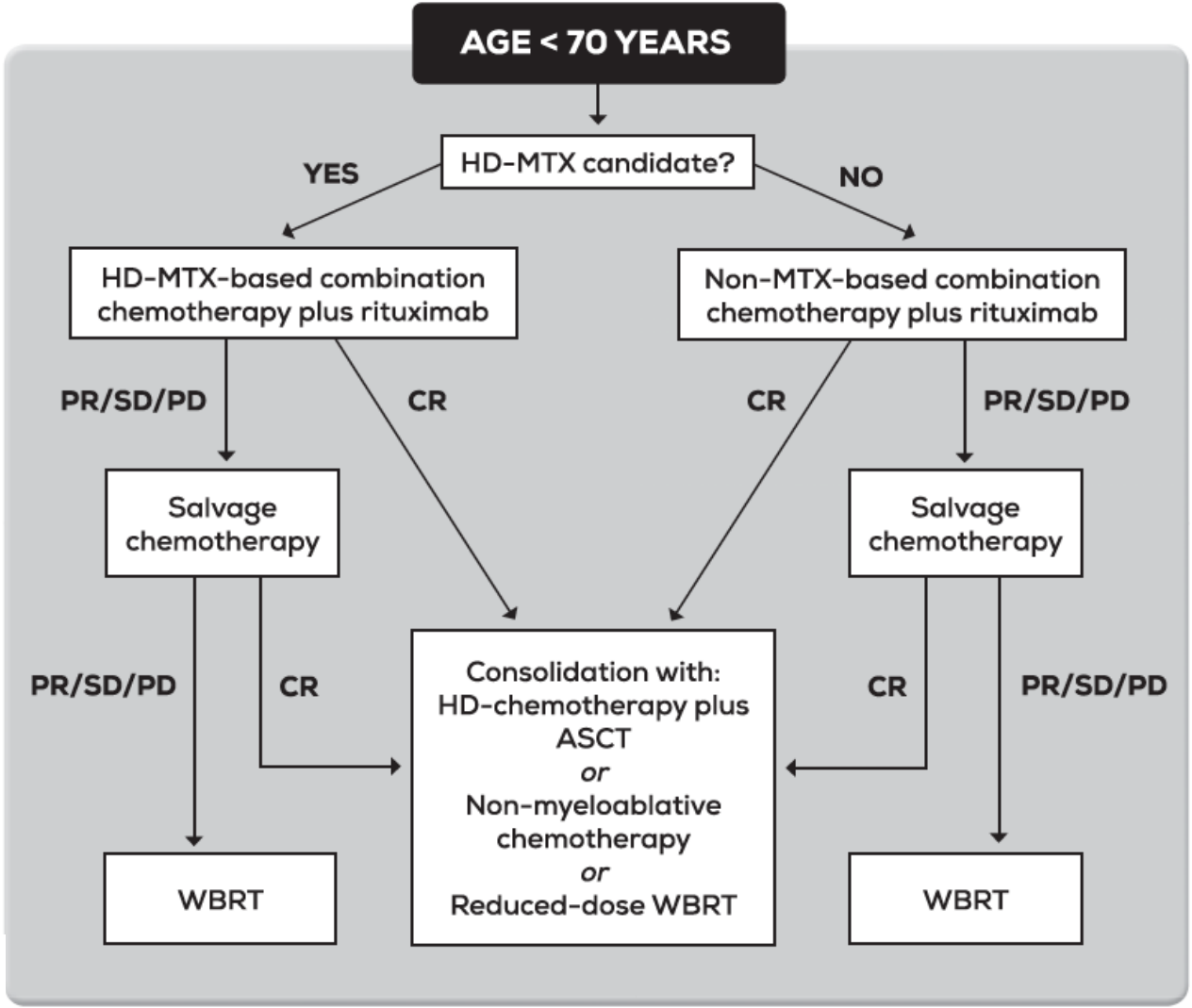

Han, Cancer 2017

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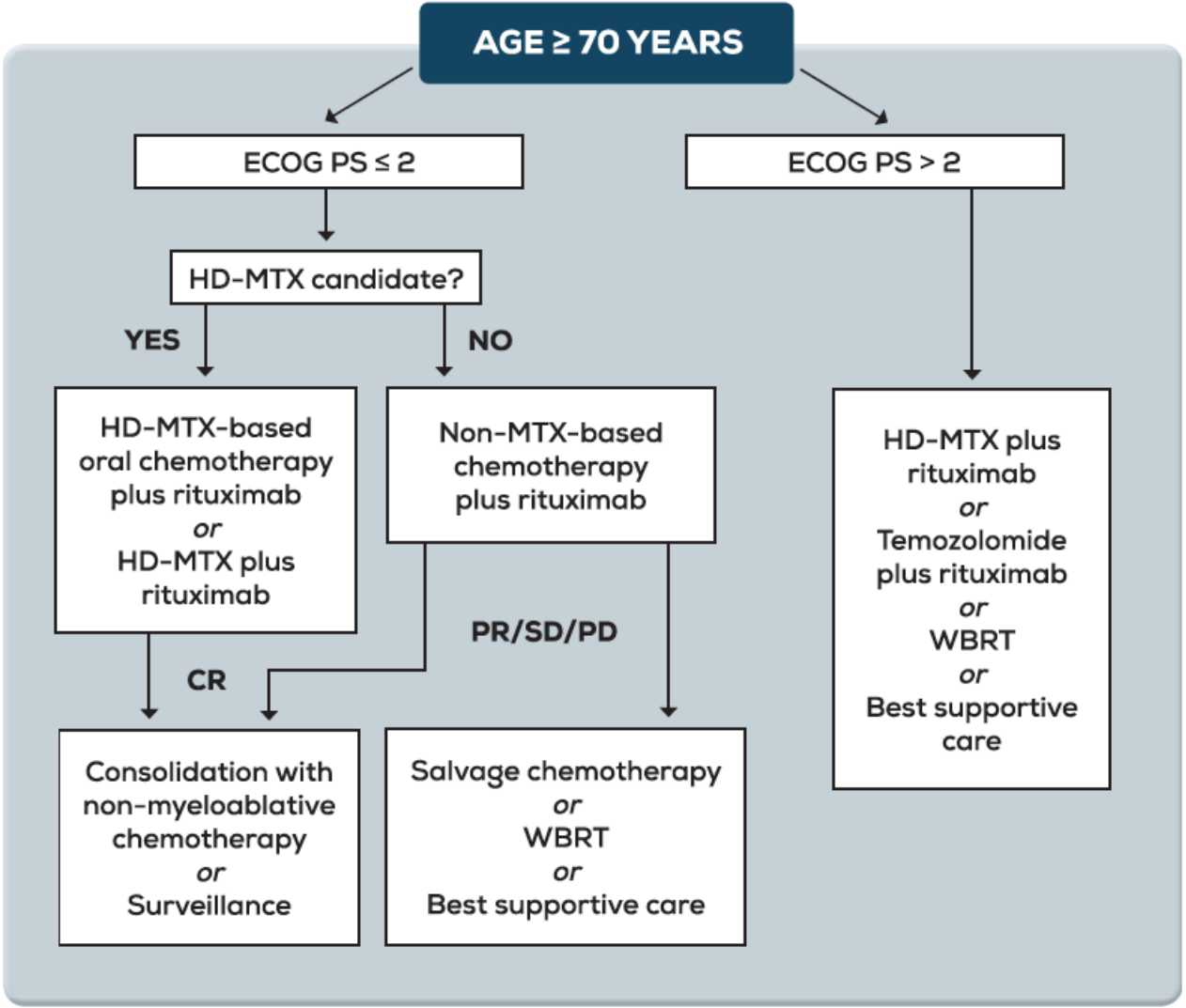

Han, Cancer 2017

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Follow-up schedule and assessments

Recommended Follow-Up Schedule	
Years 1 and 2	At completion of therapy
	Every 3 mo
Years 3-5	Every 6 mo
Years 6-10	Annually
Minimum Assessments at Each Follow-Up	
History	
Physical examination	
Cognitive evaluation (eg, IPCG battery or MMSE)	
Gadolinium-enhanced MRI of the brain (CT with contrast if MRI contraindicated)	
Optional as Clinically Indicated	
Ophthalmologic examination	
CSF analysis	

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; IPCG, International PCNSL Collaborative Group; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

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Intra ocular lymphoma

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Clinical presentation intra ocular lymphoma

- Patients may complain of vitreous floaters for 1–2 years before lymphoma is suspected
- 65% to 90% develop CNS involvement usually within 30 months

Treatment intra ocular lymphoma

- No standard treatment
- Options:
  - Local: radiotherapy or intra ocular chemo or immunotherapy
  - Systemic + local

Therapy	Efficacy	Toxicity
Ocular RT (30-40 Gy)	Rare local recurrence 60-95% RR; no impact on OS	Cataracts, dry eyes, retinopathy (mild)
HD-MTX	~50% sustained response, poor vitreous penetration	Mild
HD-MTX+ RT both eyes	100% CR	Cataracts, dry eyes, retinopathy
Intensive chemo (EA) +ASCT (TBC)	>50% response to EA; 6/10CR	Neurologic toxicity, hemorrhage, VOD
Intravitreal rituximab or MTX	Requires>6 injections to achieve CR; investigational	Conjunctival keratopathy, cataracts, optic atrophy, endophthalmitis

Rubenstein et al. Blood 2013

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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Questions?

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Extranodal lymphomas: Gastric

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

Primary extranodal lymphomas, occurrence

- Constitute about ½ of localized lymphomas (stage I-II)
- Constitute 20-25% of all non Hodgkin lymphomas (NHL)
- Most common sites:
  - Gastrointestinal tract
  - Skin
  - Waldeyer's ring
  - CNS
  - Salivary glands
  - Ocular adnexae

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Gastric lymphoma

Table I. Distribution of the main histological types (defined according to the criteria in the REAL classification) in 393 patients with a localised gastric lymphoma that were enroled in the German multicentre perspective study for gastrointestinal NHL (GIT NHL 02/96) (Koch *et al*, 2005).

Histological type	Frequency (%)
Diffuse large B-cell lymphoma	59
With MALT component	14
Without MALT component	45
MALT lymphoma of the marginal zone	38
Mantle lymphoma	1
Follicular lymphoma	0·5
Peripheral T-cell lymphoma	1·5

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Gastric MALT lymphoma

- Often associated with *H. pylori* gastritis (up to 90 %)
- Eradication of *H. pylori* results in regression of lymphoma in 70 %
- Median time to histologic response 5 months, PCR evidence of monoclonality may persist in 50 - 75 % (not an indication for further treatment)
- Relapse rate 15 % in 2 years, strict endoscopic follow-up with multiple biopsies required

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Extranodal marginal zone B-cell lymphoma (MALT-lymphoma)

- 45% in the GI tract
  - Stomach >80%
  - Colon/rectum 10%
  - Small intestine 8%
- 55% Non-GI
  - Eye/adnexae 20%
  - Lung 15%
  - Skin 15%
  - Salivary glands 13%
  - Female breast 6%
  - Soft tissue incl. heart 5%
  - Thyroid 5%
  - Others (GU, CNS, upper aerodigestive tract, liver/gall bladder/pancreas etc.) each < 5%

Partly based on Khalil O et al. Br J Haematol 2014; 165: 67-77 (SEER data)

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Gastric MALT lymphoma

- Patients predicted not to respond to *H. pylori* eradication:
  - *H. pylori* negative
  - invasion beyond the submucosa, evaluated by endoscopic ultrasound
  - t(11;18) translocation (present in up to 40 %)
- Involved site radiotherapy indicated for these patients and patients relapsing after *H. pylori* eradication

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Organ motion: Gastric Lymphoma

- CTV = stomach/perigastric nodes + involved nodes
- Sources of uncertainty
  - Respiratory motion: 4DCT + ITV or DIBH
  - Gastric contents: fasting, minimal oral contrast
  - Residual movement + set-up variation: PTV expansion
- Constraints: kidneys, heart, liver
  - 3DCRT, IMRT

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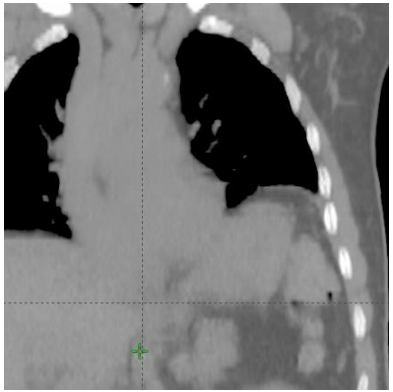
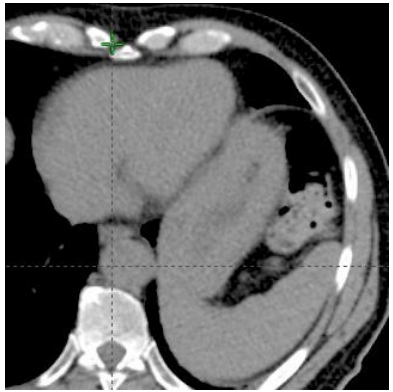
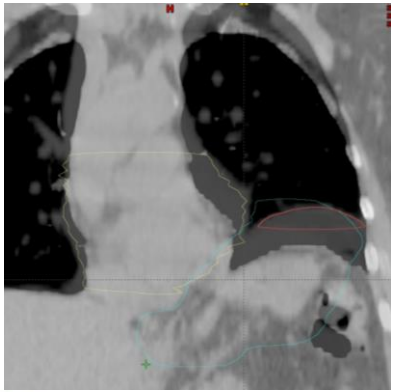
PATIENT A



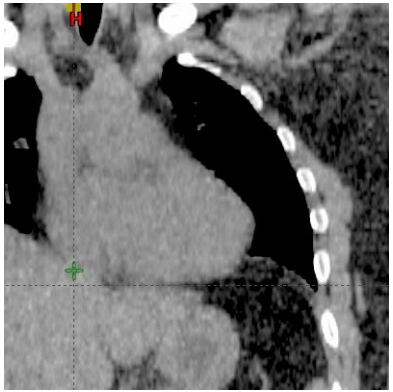
PATIENT A



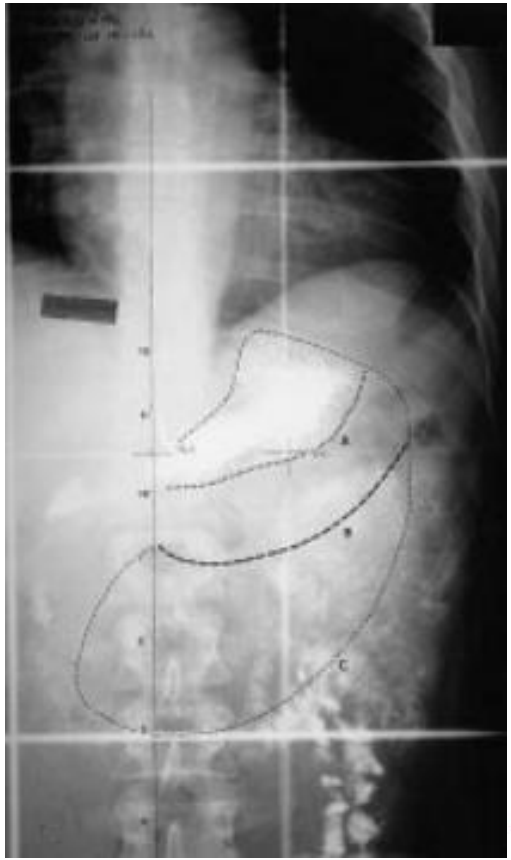
PATIENT A



PATIENT B



Variable gastric content



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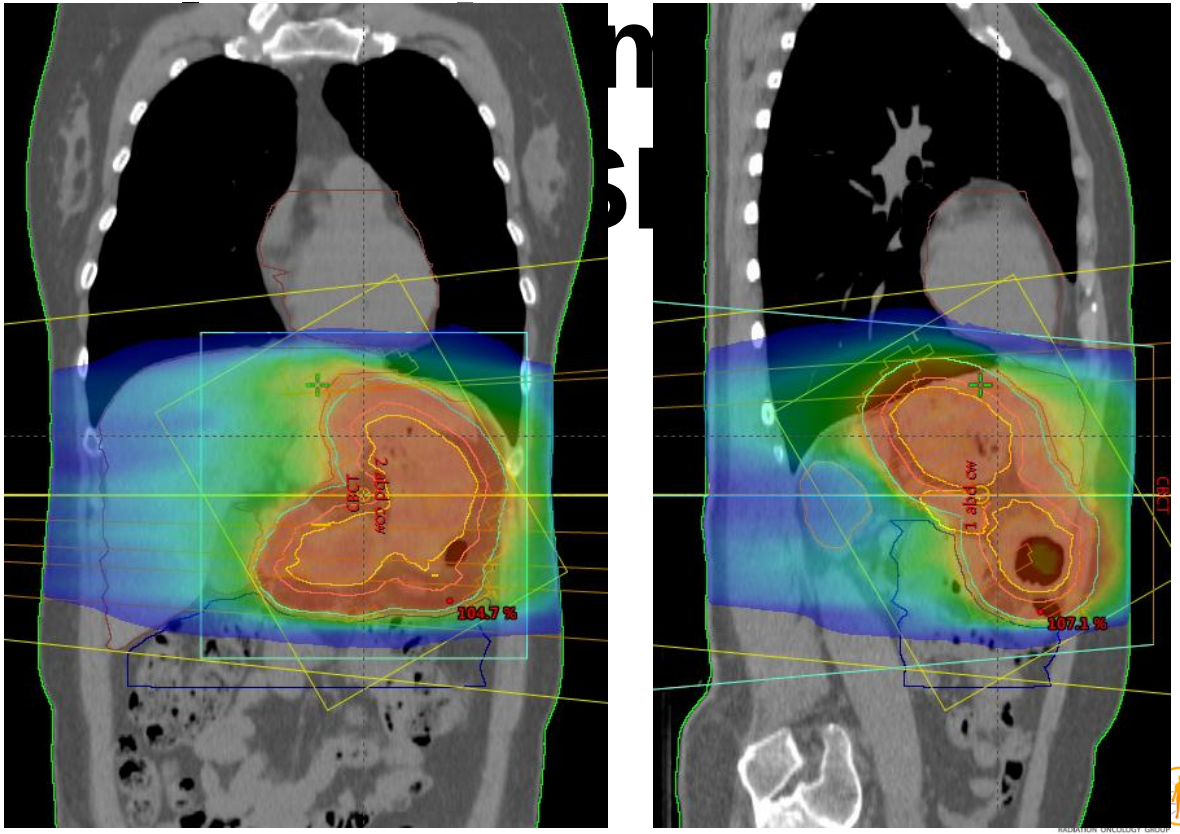
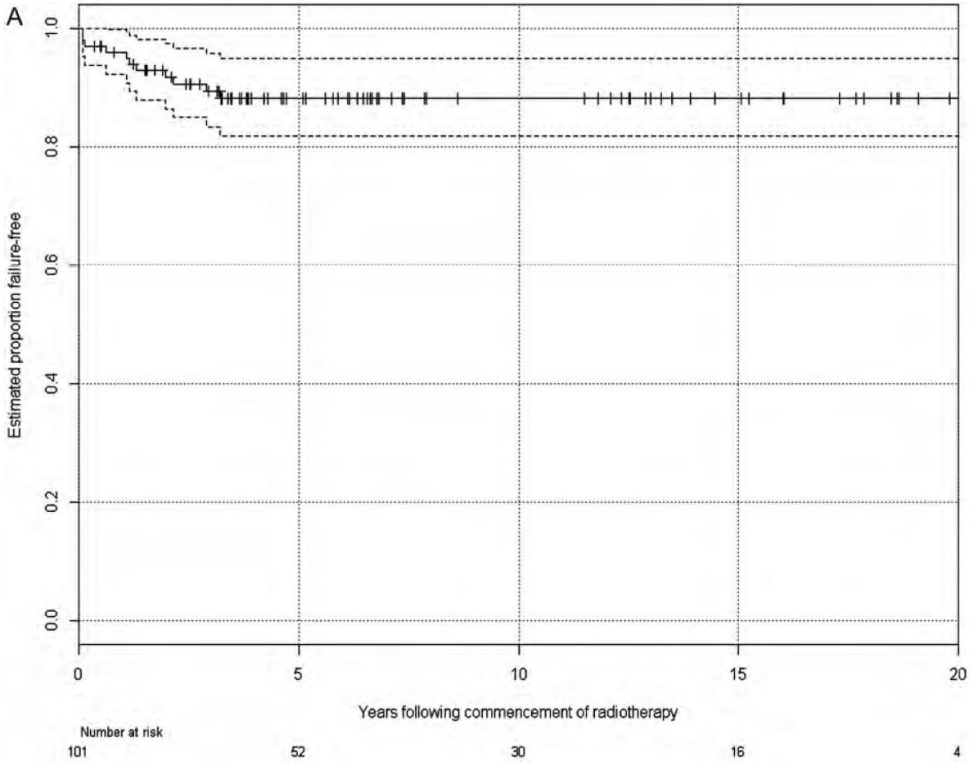
Gastric MALT



Gastric MALT lymphoma



Wirth A et al. Ann Oncol 2013; 24: 1344-51

Gastric lymphoma, ISRT

- Plan and treat patient fasting
- No or very little oral contrast at planning CT (we use a little water)
- Take into account breathing motion
  - 4D planning (margins, midventilation scan)
  - Deep inspiration breath hold
    - Reducing movement
    - Anatomic separation of target from critical normal structures (e.g., heart)

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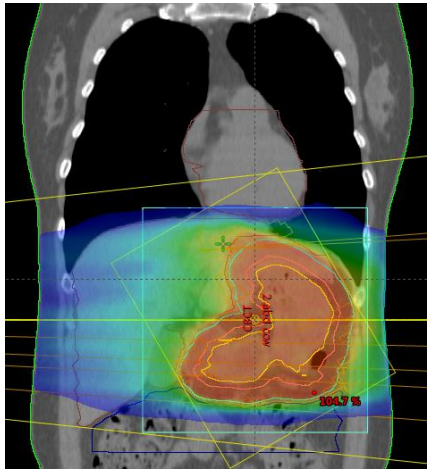
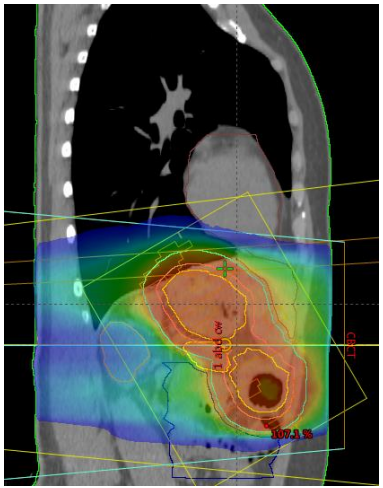
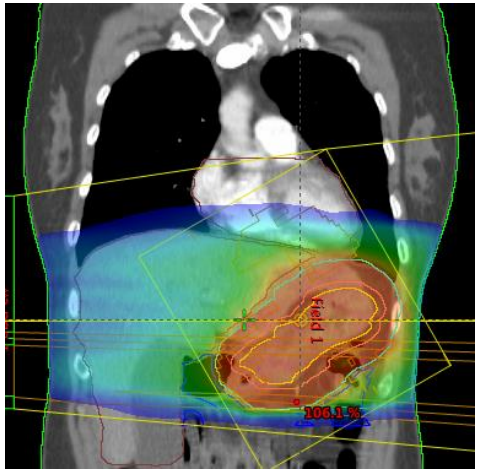
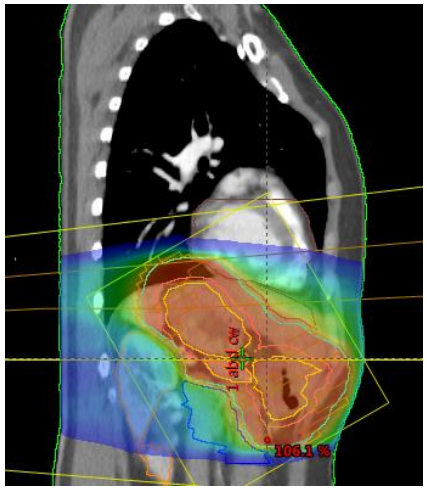
Deep inspiration breath hold

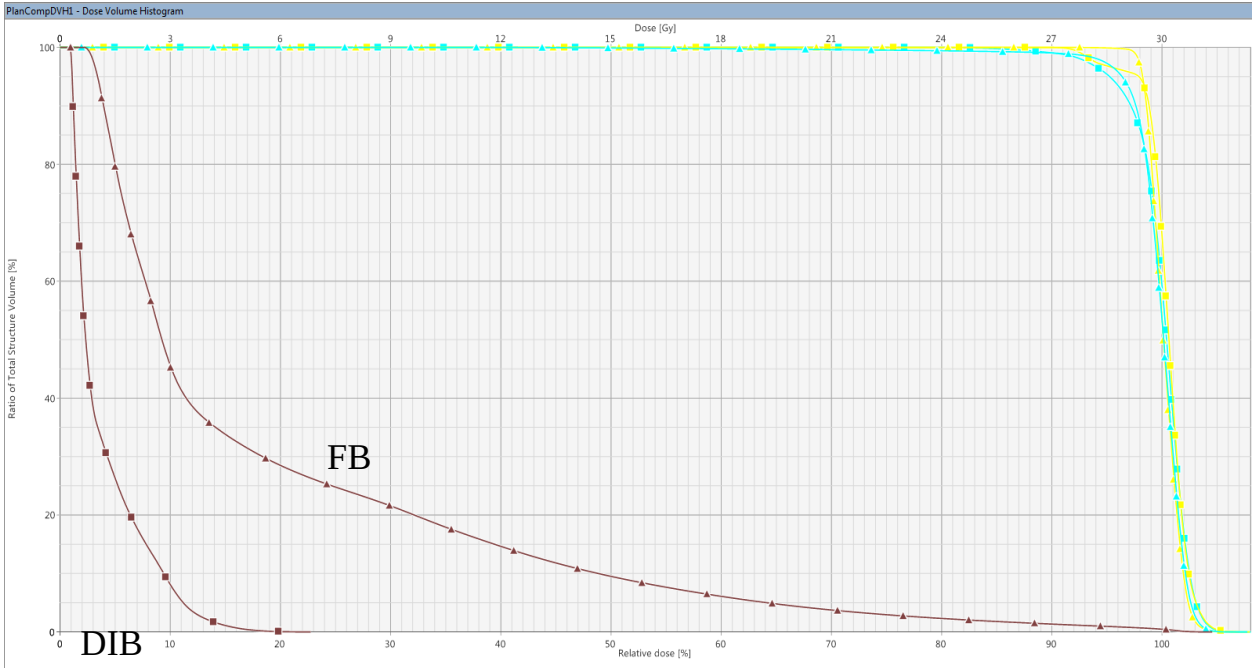




Free breathing

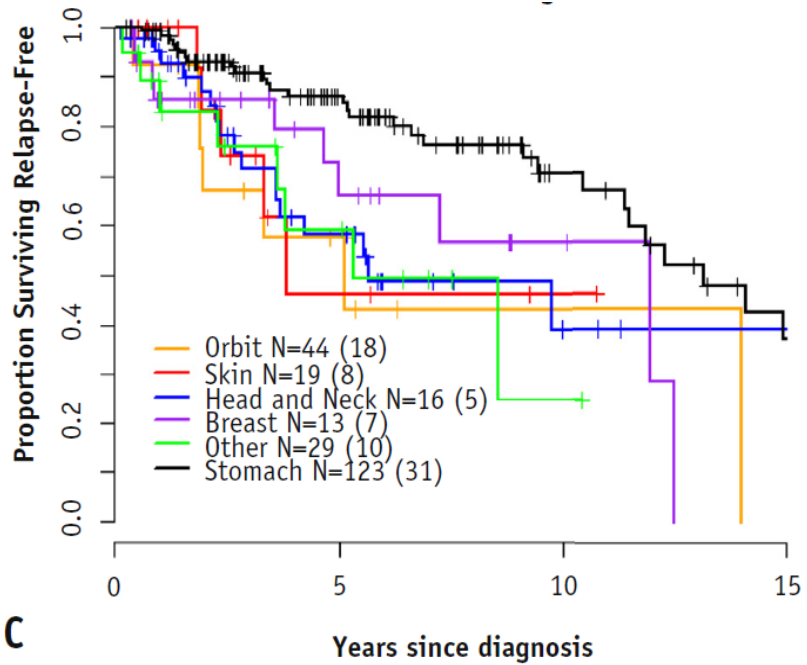


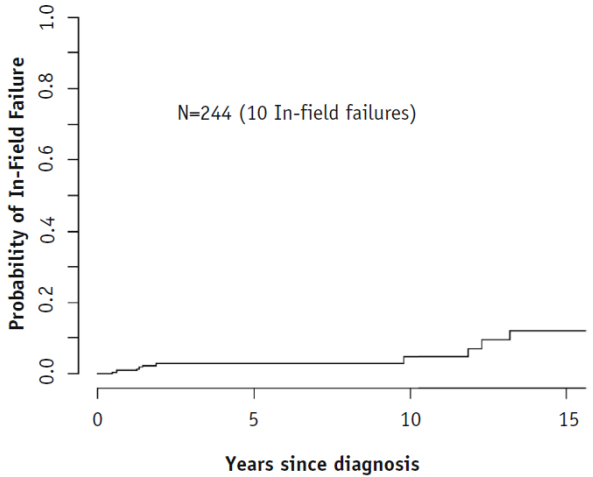




Mean heart dose:
FB: 4.5 Gy
DIBH: 0.9 Gy

244 pts treated with RT for early stage MALT lymphoma at MSKC





Teckie S et al. IJROBP 2015; 92: 130-7

Diffuse large B-cell lymphoma

- Around 40% are localized at diagnosis
- Around ½ of these are primary extranodal
- Treatment: R-chemo
- Followed by ISRT to 30 Gy if in CR after chemo, 40 Gy if residual disease
- 80% long term survival

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WWW.ESTRO.ORG/SCHOOL

Systemic approaches to early and advanced marginal zone lymphoma

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University of Southampton

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September 2016

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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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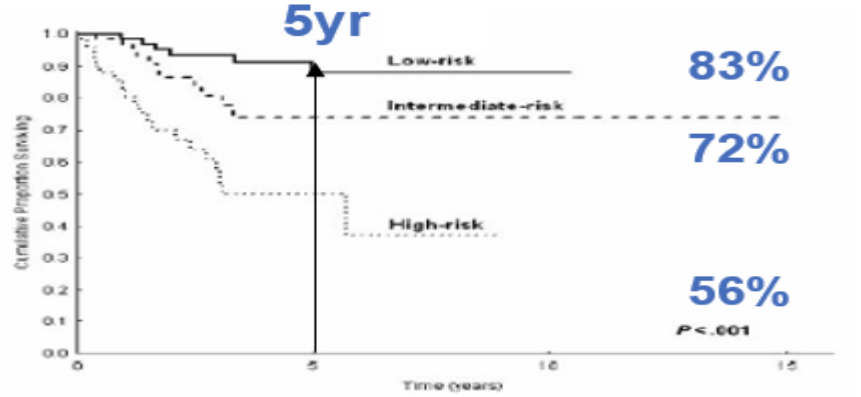
SMZL : LDH Hb=12 Albumin

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

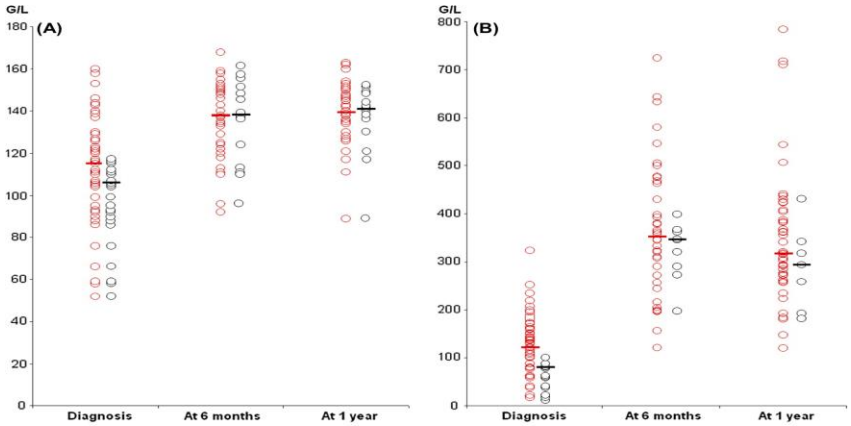
Many asymptomatic at diagnosis…watch and wait

If associated with HCV, then treat. May induce remission

More common HCV neg. Initiate therapy when nodal disease bulky, patient symptomatic or cytopenias

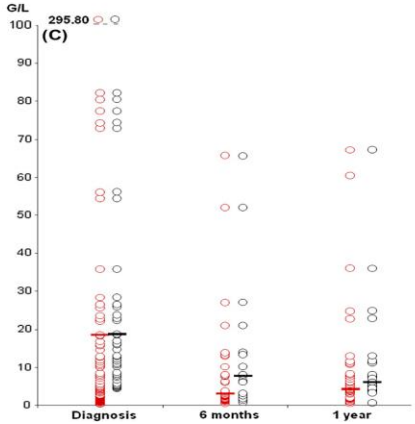
…..Splenectomy

Haemoglobin



Platelets

Lymphocytes



- Clearly improves haematological parameters
- Symptomatic improvement
- Associated morbidity

Lenglet et al 2014

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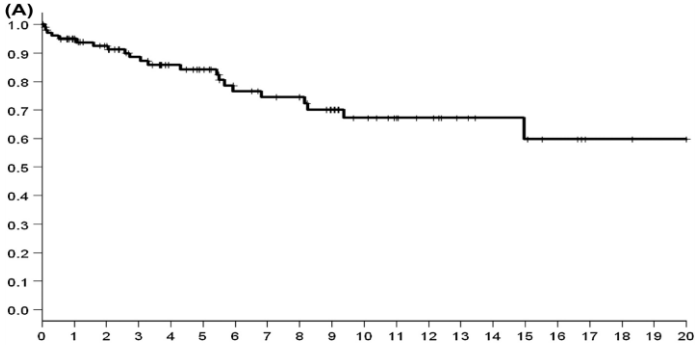
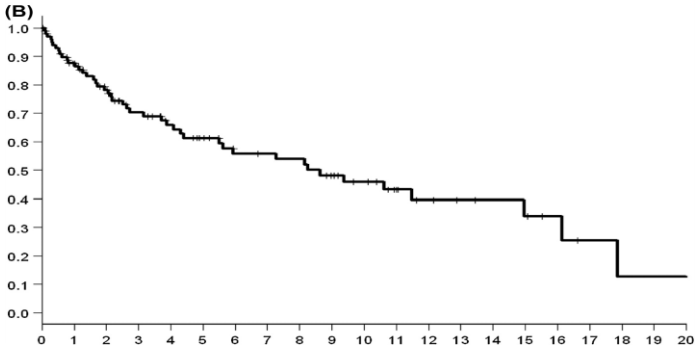
OS



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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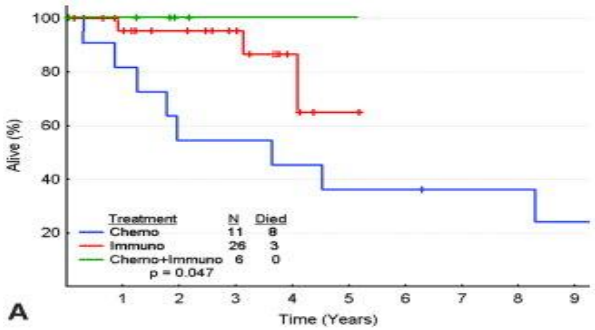
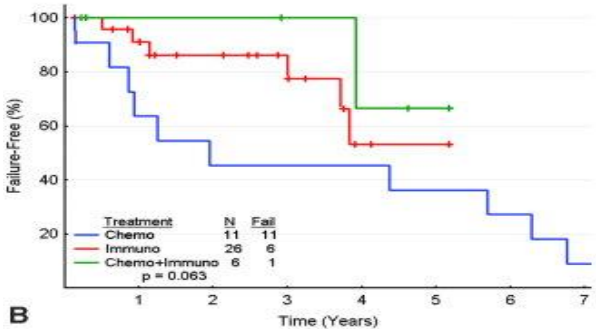
Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone

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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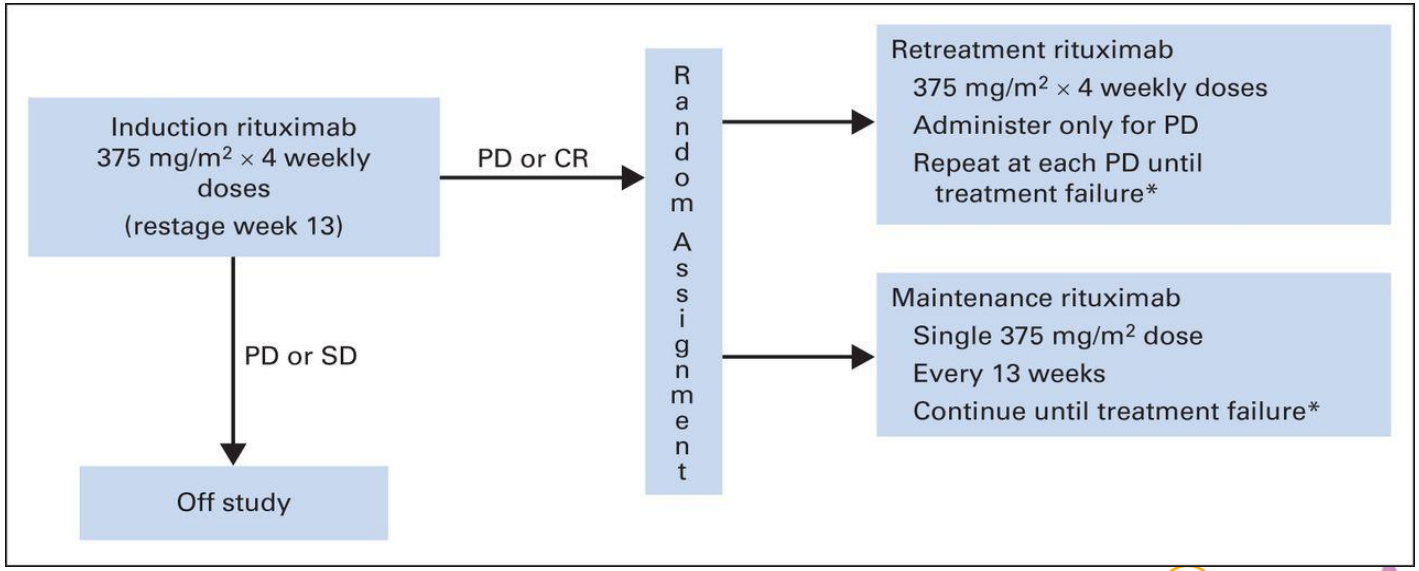
RESORT trial

Rituximab Extended Schedule or Re-Treatment Trial

N=289. Previously untreated low burden



Brad S. Kahl et al. JCO **2014;32:3096-3102**

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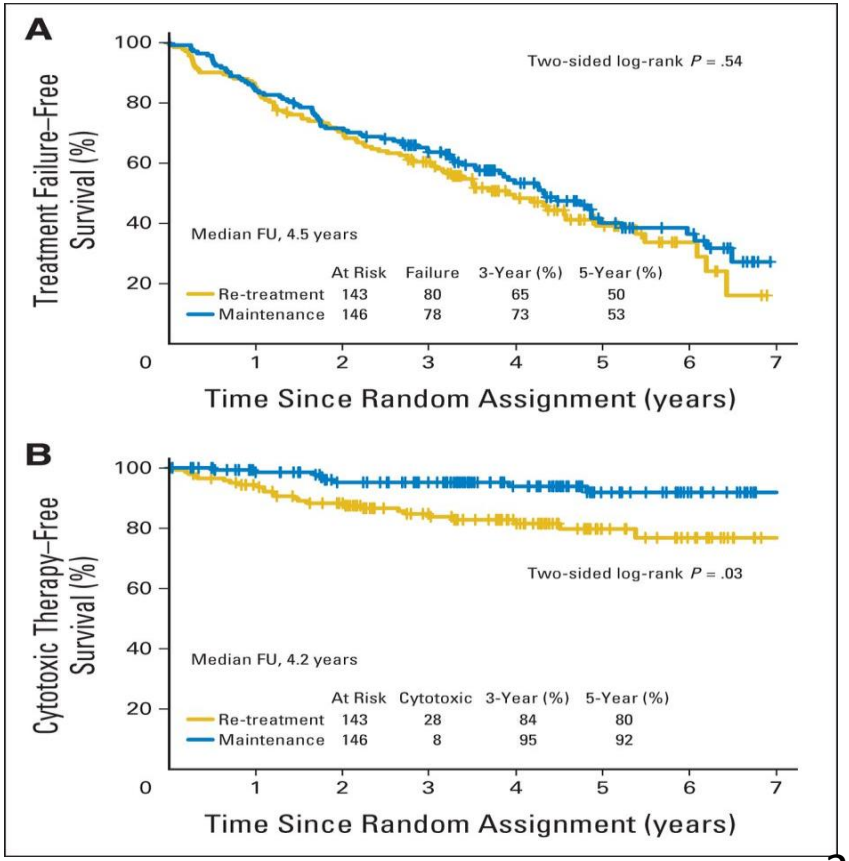


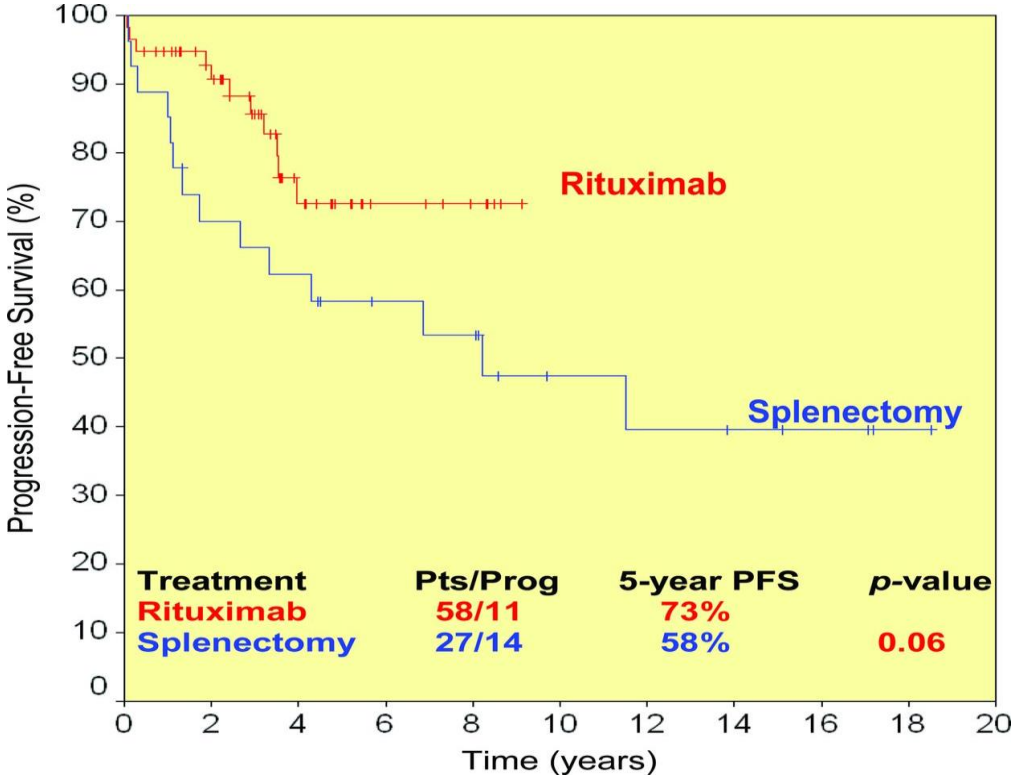
Time to treatment failure

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

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

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

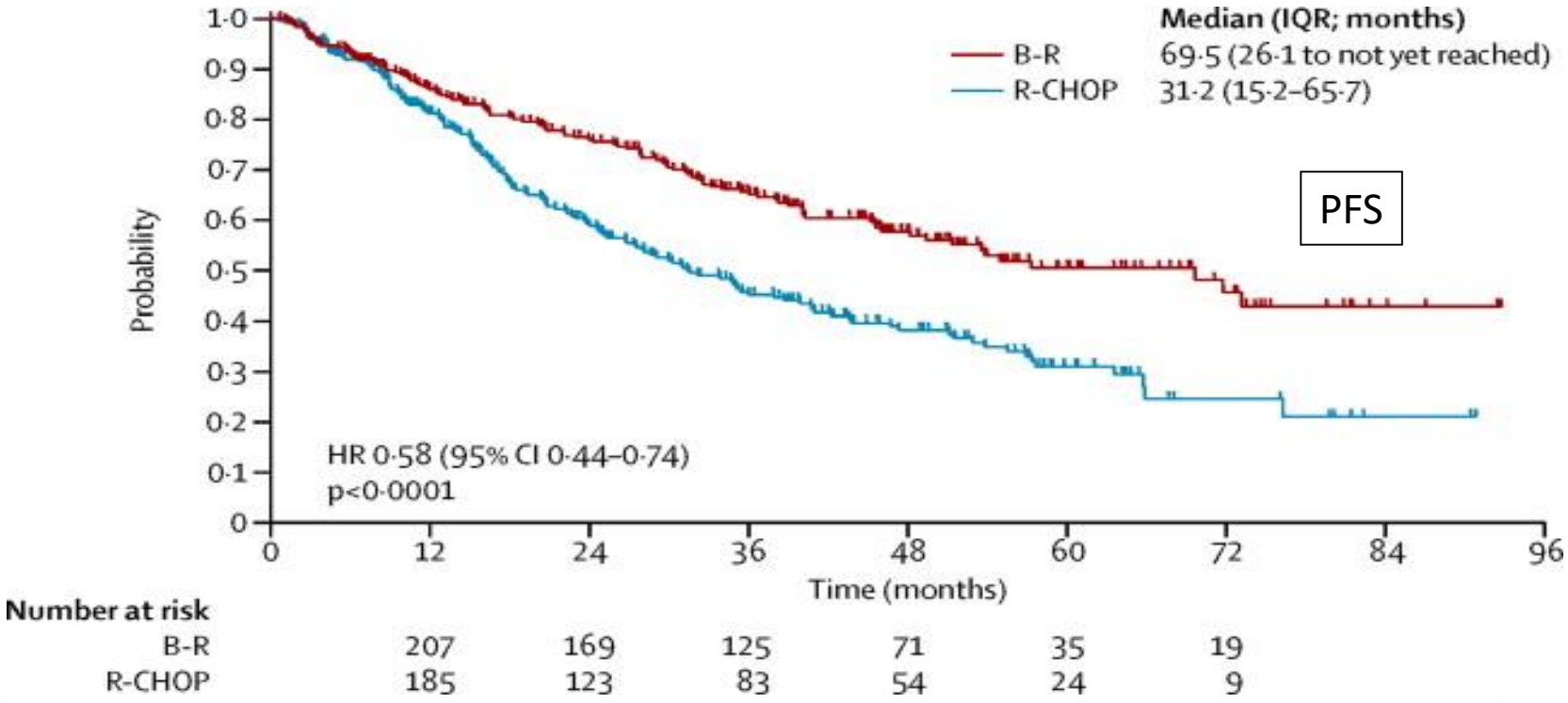
Primary objective

- **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

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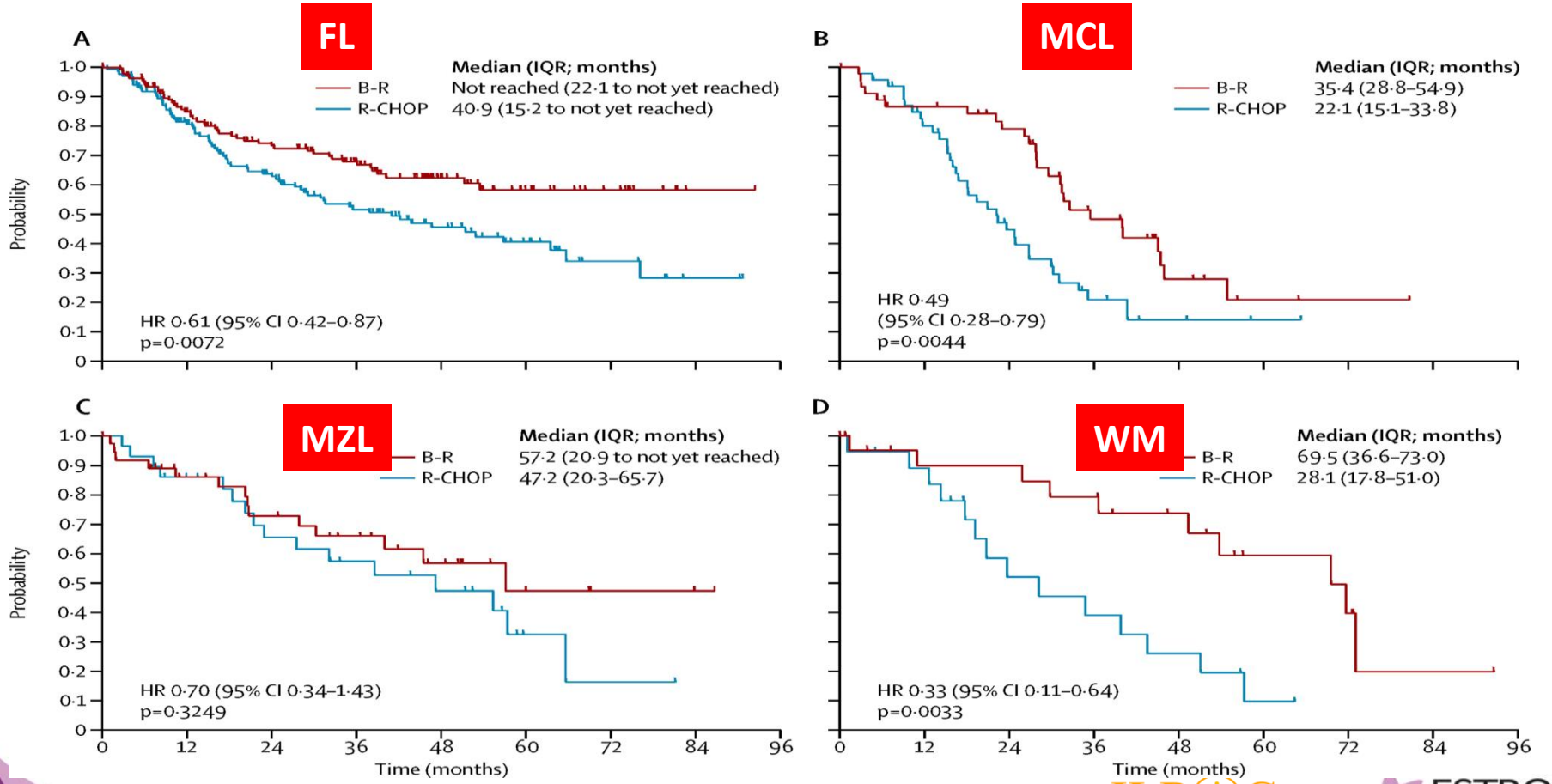
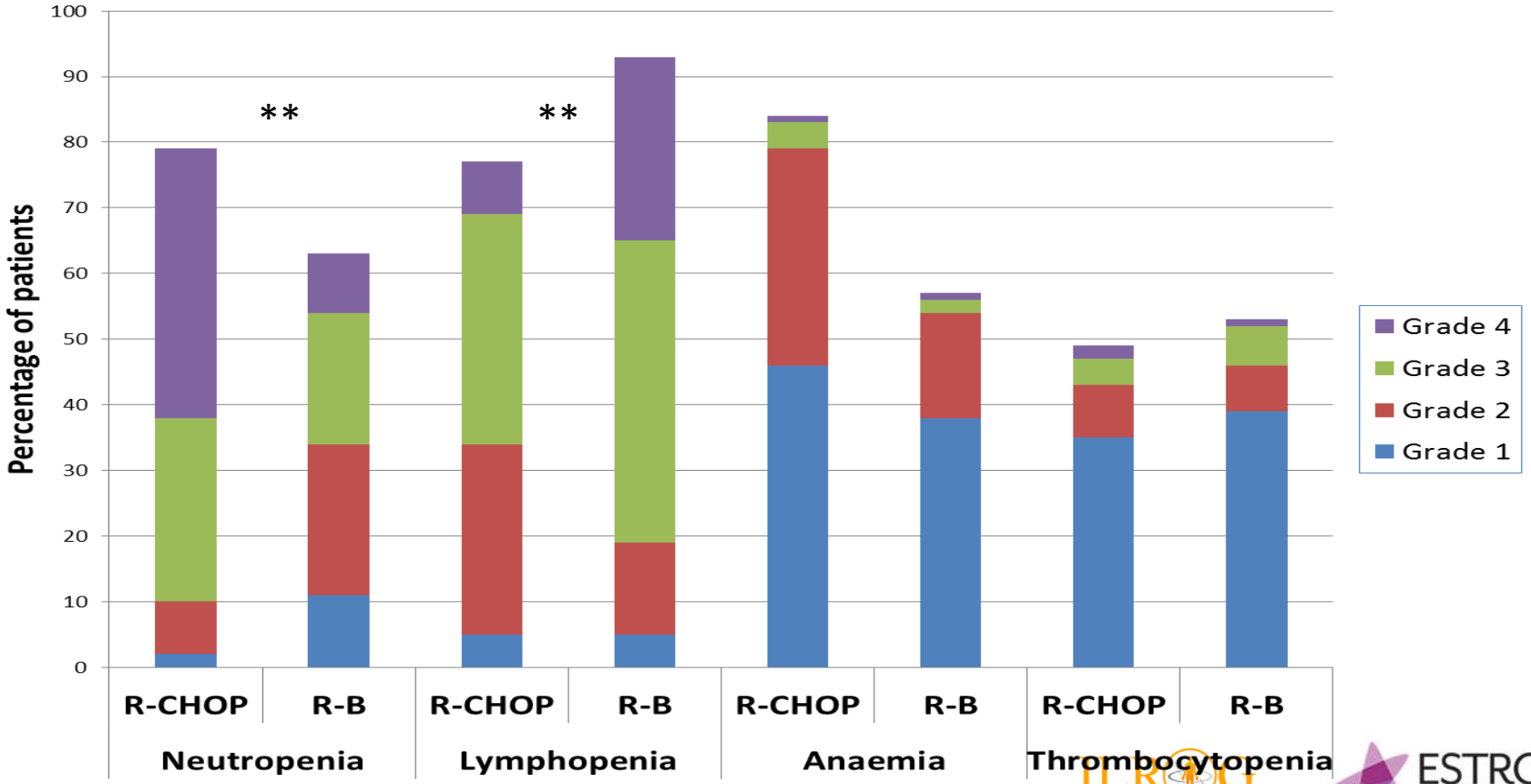


Progression Free Survival

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

Two years Rituximab maintenance vs. observation after first line treatment with Bendamustine plus Rituximab in patients with Marginal Zone Lymphoma (MZL): results from the StiL NHL7-2008 *MAINTAIN* trial

Results of a prospective, randomized, multicentre phase 2 study

(a subgroup study of the StiL NHL7-2008 *MAINTAIN* trial)

Mathias Rummel, Michael Koenigsmann, Kai Chow, Wolfgan Knauf, Christian A. Lerchenmuller, Christoph Losem, Martin Goerner, Bernd Hertenstein, Thomas Decker, Arnold Ganser, Tobias Gaska, Mich. Heike, Elisabeth Lange, Rudolf Weide, Wolfgang Willenbacher, Alexander Burchardt, Frank Kauff, Juergen Barth, Axel Hinke, Richard Greil on behalf of the **StiL Study group indolent Lymphomas,** Austria and Germany

StiL NHL 7-2008: Rationale

- Bendamustine plus Rituximab (B-R) is an established 1st-line treatment in low-grade lymphomas including Follicular lymphoma (FL), Waldenström, Small Lymphocytic Lymphoma (SLL) and Marginal Zone Lymphomas (MZL)

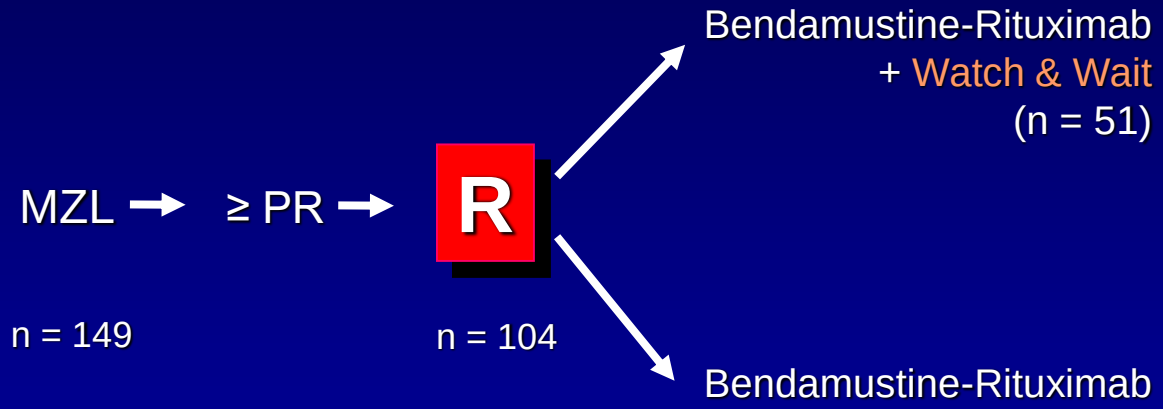
- Rituximab (R) maintenance improves PFS after R-chemoimunotherapy in FL
  - PRIMA trial, randomized to that effect
  - BRIGHT trial, not randomized, R was given at investigator's discretion
  - StiL MAINTAIN trial, not randomized, historical control to StiL NHL1

- No randomized data available for R-maintenance in MZL, thus, the role of 2 years R-maintenance after R-chemo is unclear in MZL

- R-maintenance as an attempt to further prolong disease control after B-R

B-R + Watch & Wait vs. B-R + 2 years Rituximab

StiL NHL 7-2008 - MAINTAIN



StiL
Studiengruppe indolente Lymphome

Response rates following B-R induction

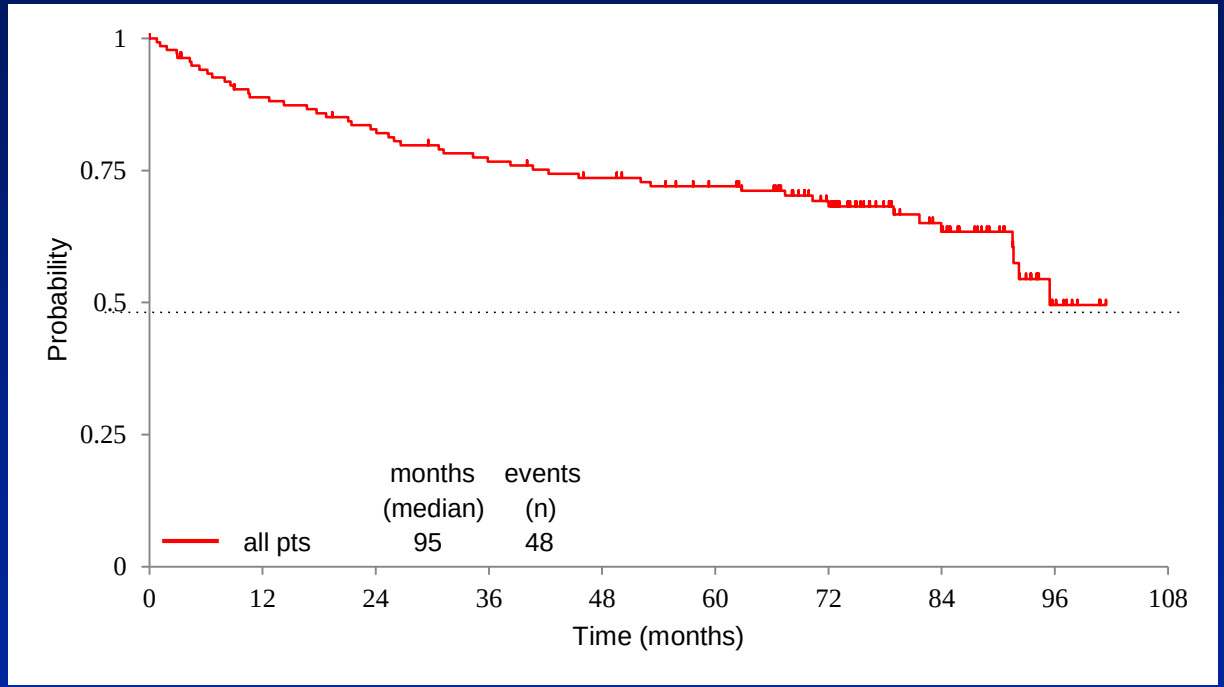
119 patients evaluable for response evaluation

ORR	108 (91%)
CR	23 (19%)
PR	85 (71%)
SD	4 (3%)
PD	7 (6%)
Early death	5 (3%)

MJR

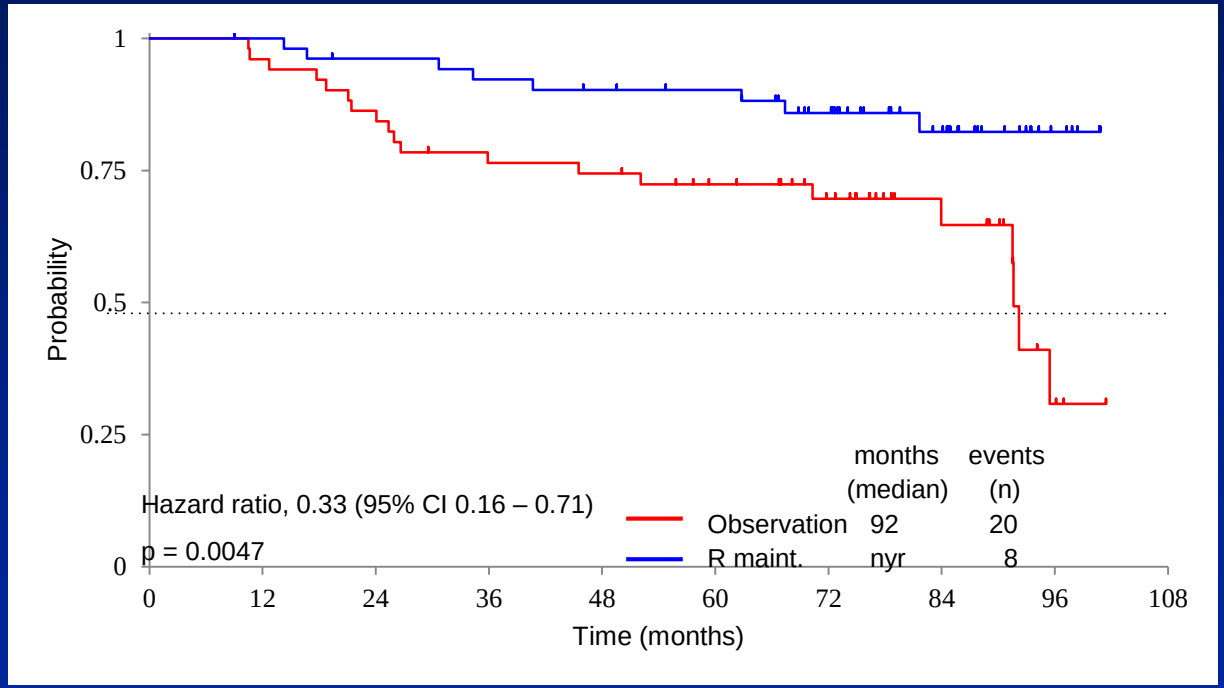
PFS all patients (IIT)

(78 months median follow-up)



Pts at risk									
all pts.	137	118	109	100	94	86	66	38	8

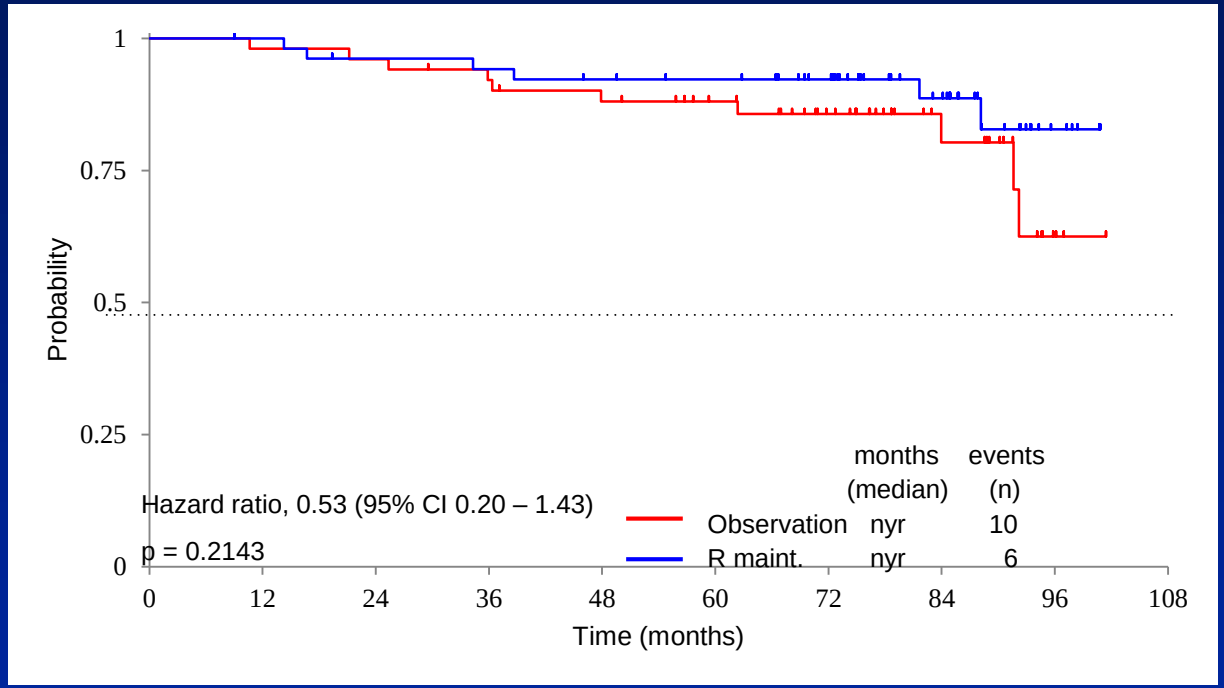
Progression free survival (78 months median follow-up)



Pts at risk									
Observ.	51	49	44	38	37	32	25	13	3
R maint.	53	52	49	47	45	43	35	22	5

Overall survival

(78 months median follow-up)



Pts at risk									
Observ.	51	50	49	46	43	38	29	15	3
R maint.	53	52	49	48	46	44	38	24	5

Toxicity grade 3/4 per patient during induction

	observation (n = 51)	2 yrs R (n = 53)	not rand (n = 33)	all patients (n = 137)
GOT / GPT /GGT	1 (2%)	-	1 (3%)	2 (1%)
Other lab. anomalies	2 (4%)	4 (8%)	4 (12%)	10 (7%)
Infections	1 (2%)	3 (6%)	4 (12%)	8 (6%)
Pneumonia	1 (2%)	1 (2%)	1 (3%)	3 (2%)
Cardiac events	-	2 (4%)	2 (6%)	4 (3%)
Gastrointestinal	1 (2%)	3 (6%)	2 (6%)	6 (4%)
Inflammation	-	-	1 (3%)	1 (1%)
sepsis	-	1 (2%)	1 (3%)	2 (1%)
kidney / urogenital	-	2 (4%)	1 (3%)	3 (2%)
Allergy	-	-	3 (9%)	3 (2%)
Chill / fever	5 (10%)	1 (2%)	4 (12%)	10 (7%)
fatigue	-	-	1 (3%)	1 (1%)

Conclusions

- 2 years R-maintenance prolonged PFS after B-R with a HR 0.33
- No difference in overall survival between R-maintenance and observation
- We selected patients who may not be suitable for R-maintenance by excluding those with toxicity or events from randomization
- This study confirmed the high anti-lymphoma activity of B-R even in MZL
- B-R followed by R-maintenance is a very effective treatment approach for patients with nodal and splenic MZL

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

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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

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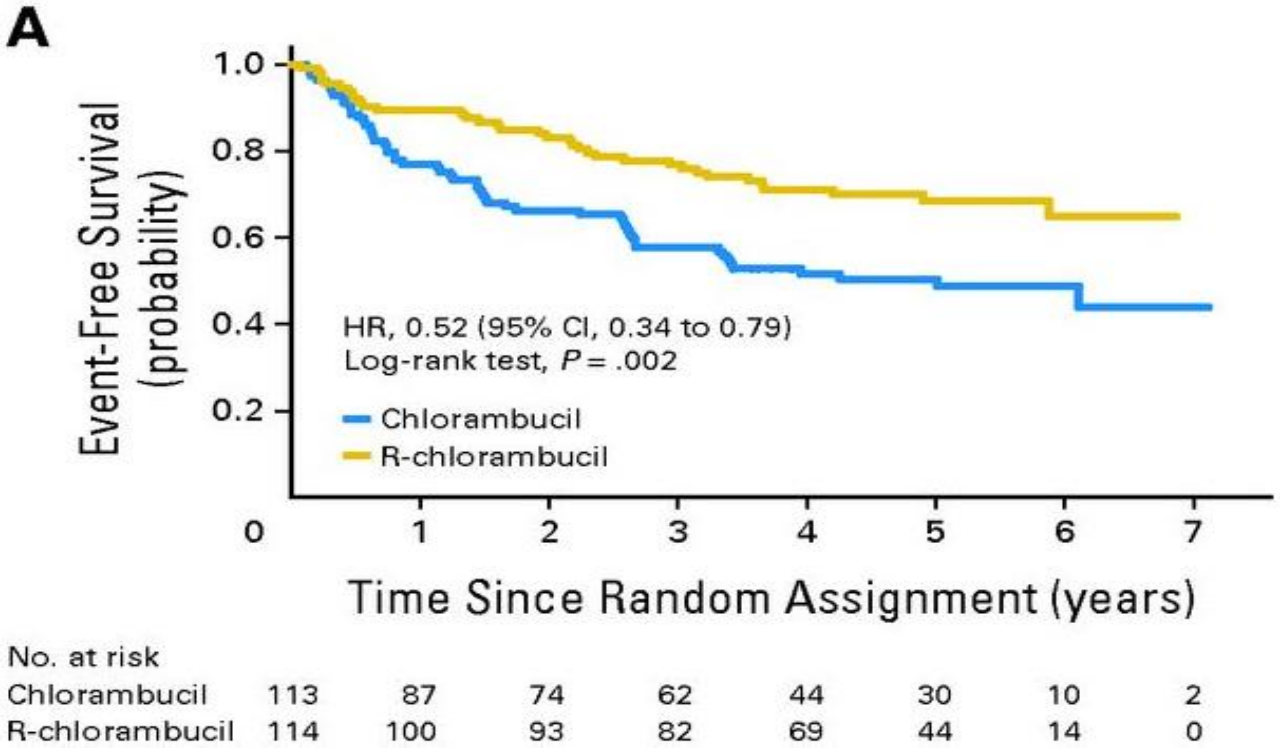
Event-free survival



Emanuele Zucca et al. JCO 2013;31:565-572

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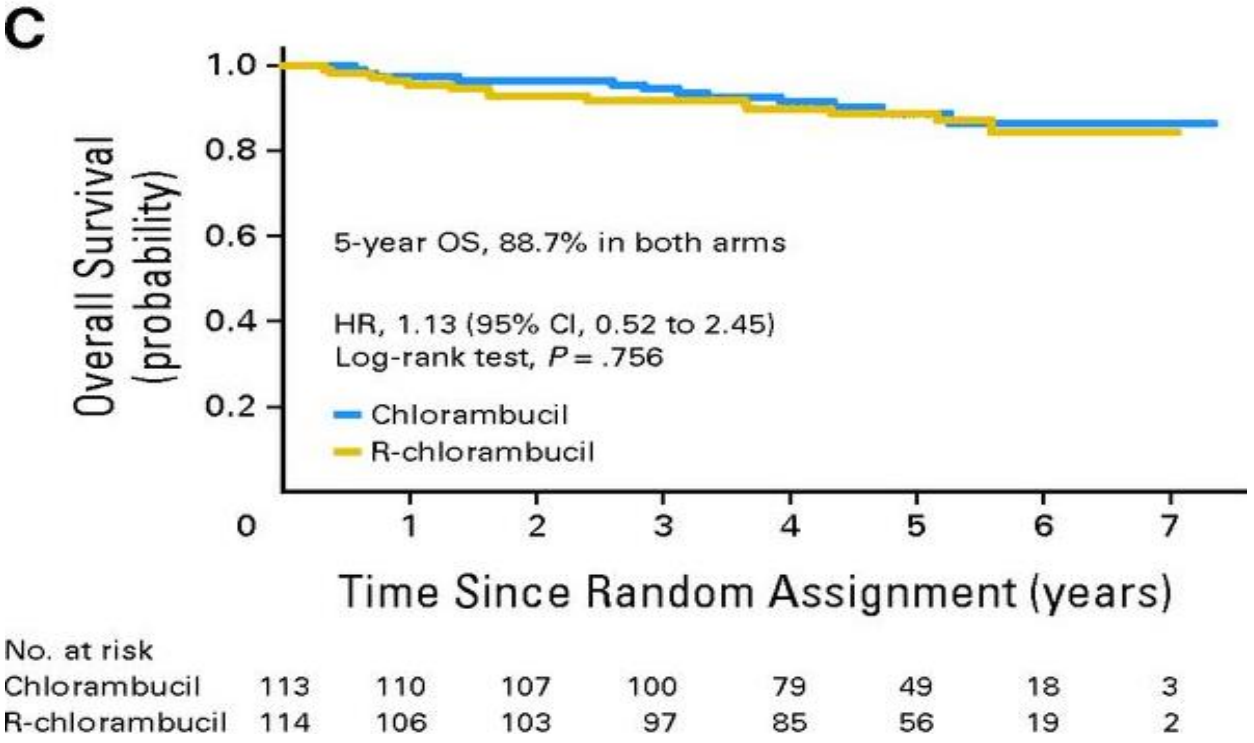
Overall survival.



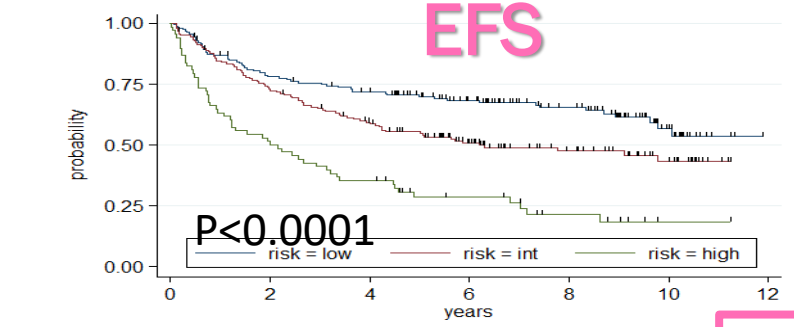
Emanuele Zucca et al. JCO 2013;31:565-572

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

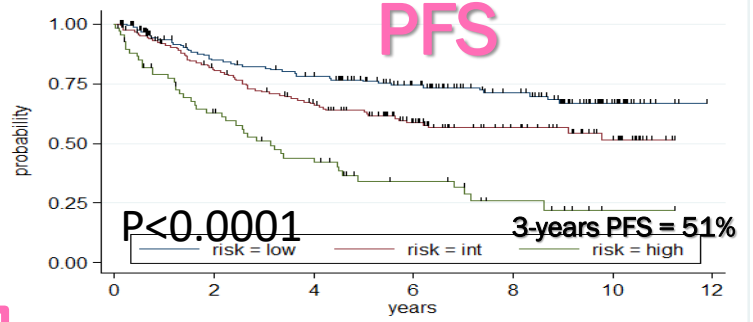
EFS



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

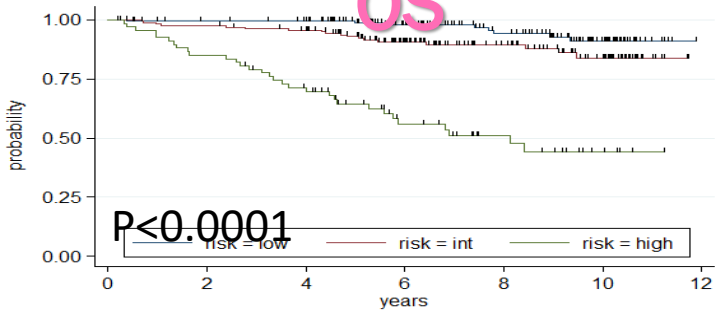


er at risk

sk = 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

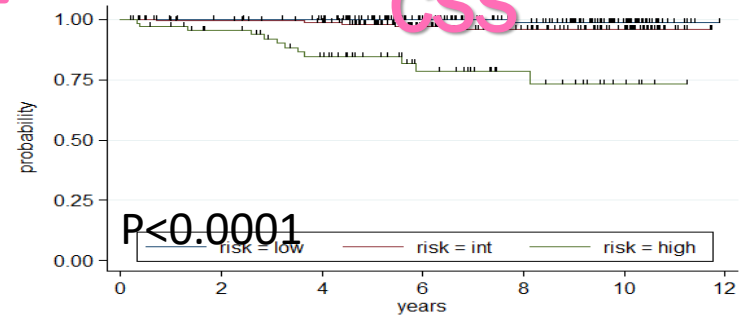
OS



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

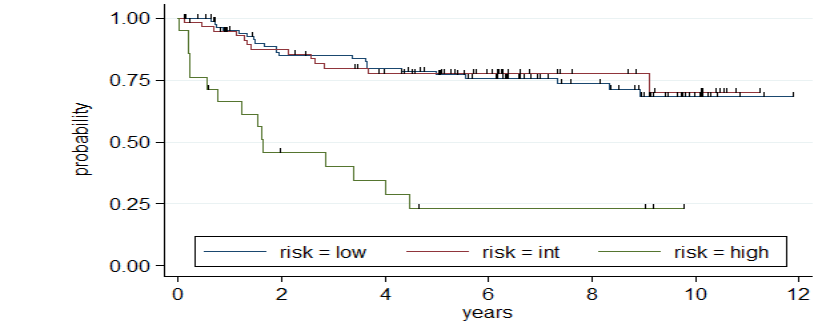


Number at risk

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

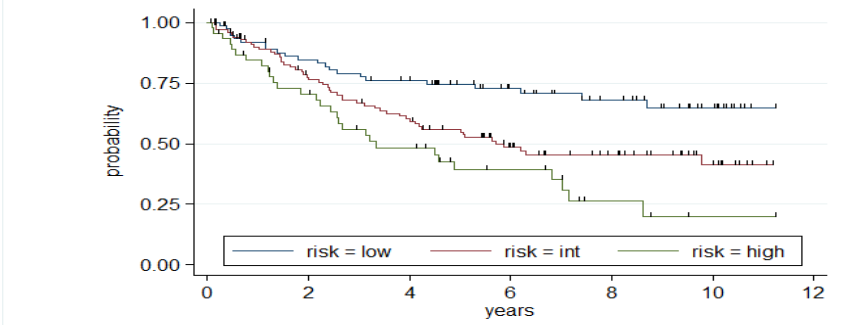
PFS by MALT prognostic score

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



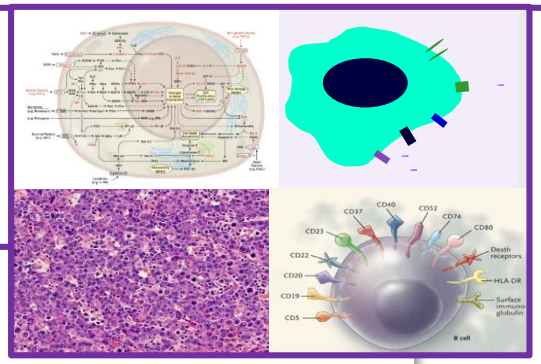
Number at risk							
risk = low	78	59	50	34	24	11	0
risk = int	104	73	56	34	23	9	0
risk = high	47	30	19	11	4	1	0

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

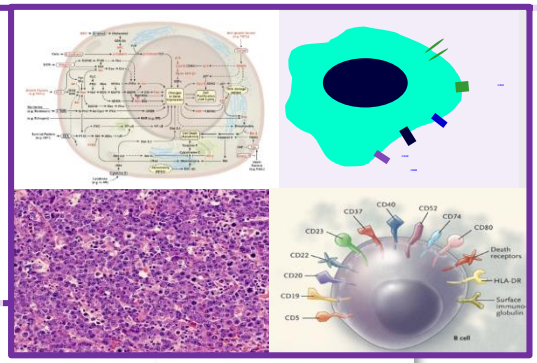
Lenalidomide

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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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
Vorinostat
Panobinostat

PKC inhibitors
Enzastaurin

Aurora kinase inhibitors

Nedd8-activating enzyme inhibitor
MLN4924

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

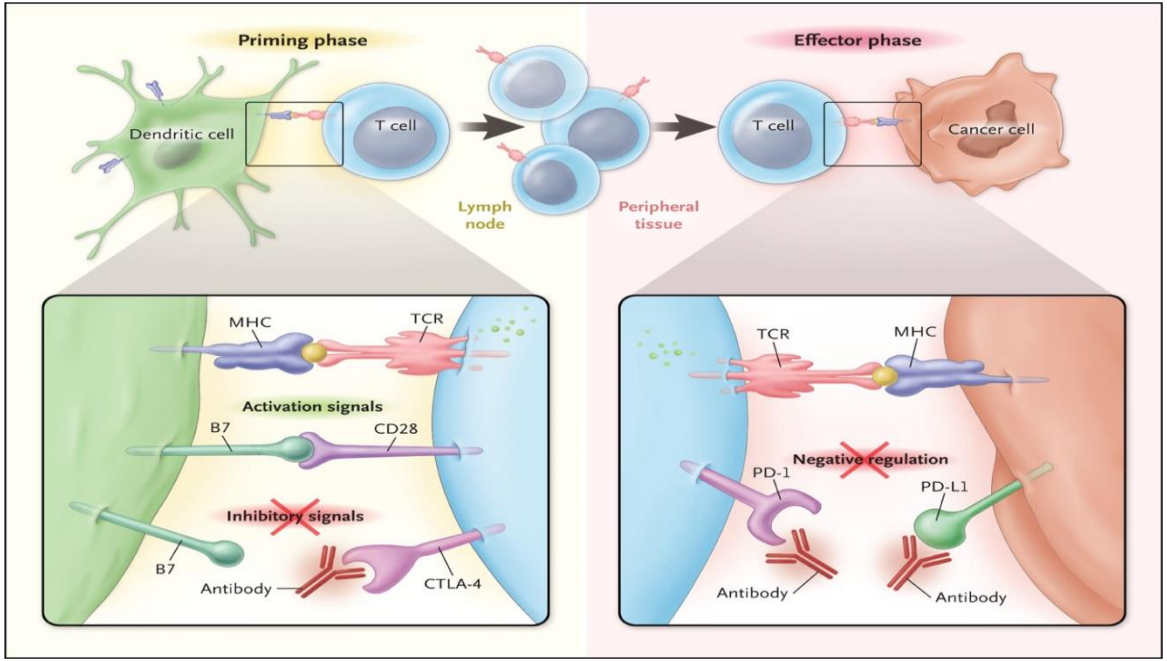
Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

%	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

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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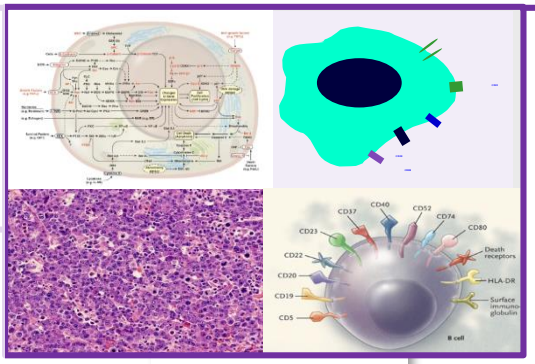

Surface markers

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  - GA-101
- **Anti CD40 moAb**
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- **Anti CD22**
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  - Inotuzumab Ozogamicin
  - polatuzumab

Pathways

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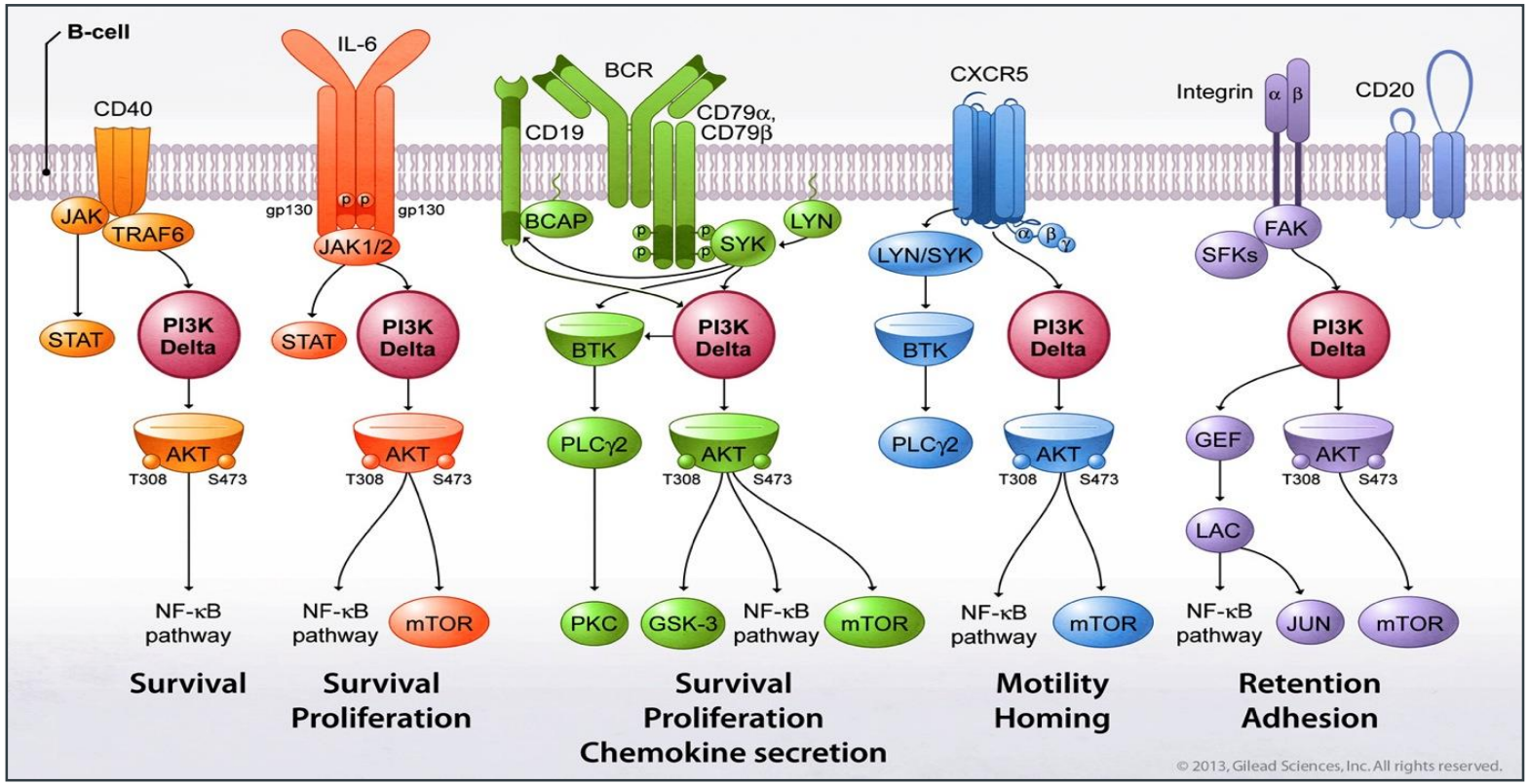
  - Temsirolimus
- **PI3k inhibitor**
  - idelalisib
  - copanlisib
  - duvelisib
- **Btk inhibitor**
  - Ibrutinib + others
- **Hsp 90 inhibitors**
  - KW 2478
- **HDAC inhibitors**
  - Vorinostat
  - Panobinostat
- **PKC inhibitors**
  - Enzastaurin
- **Aurora kinase inhibitors**
- **Nedd8-activating enzyme inhibitor**
  - MLN4924

PI3Kδ Inhibition Impacts Multiple Critical Pathways in iNHL



Idelalisib is highly selective for PI3Kδ isoform

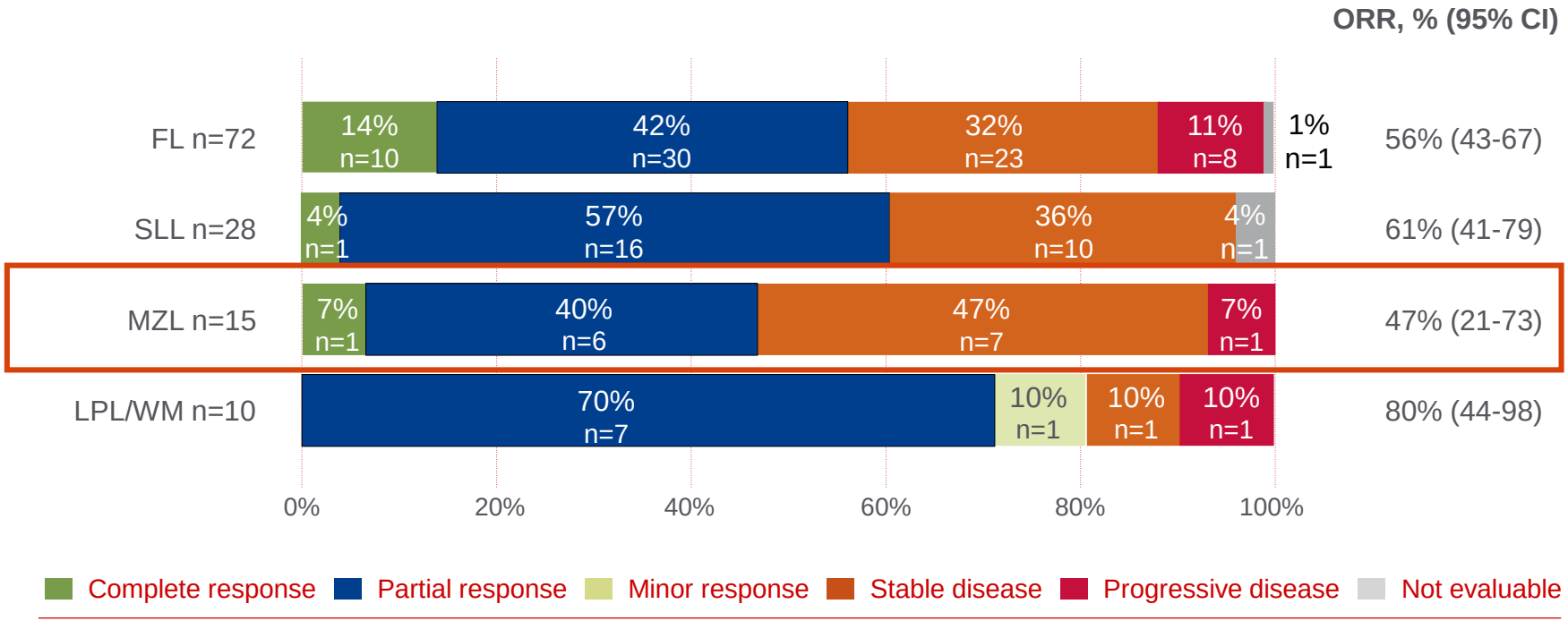
Class I PI3K isoform[1]

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]

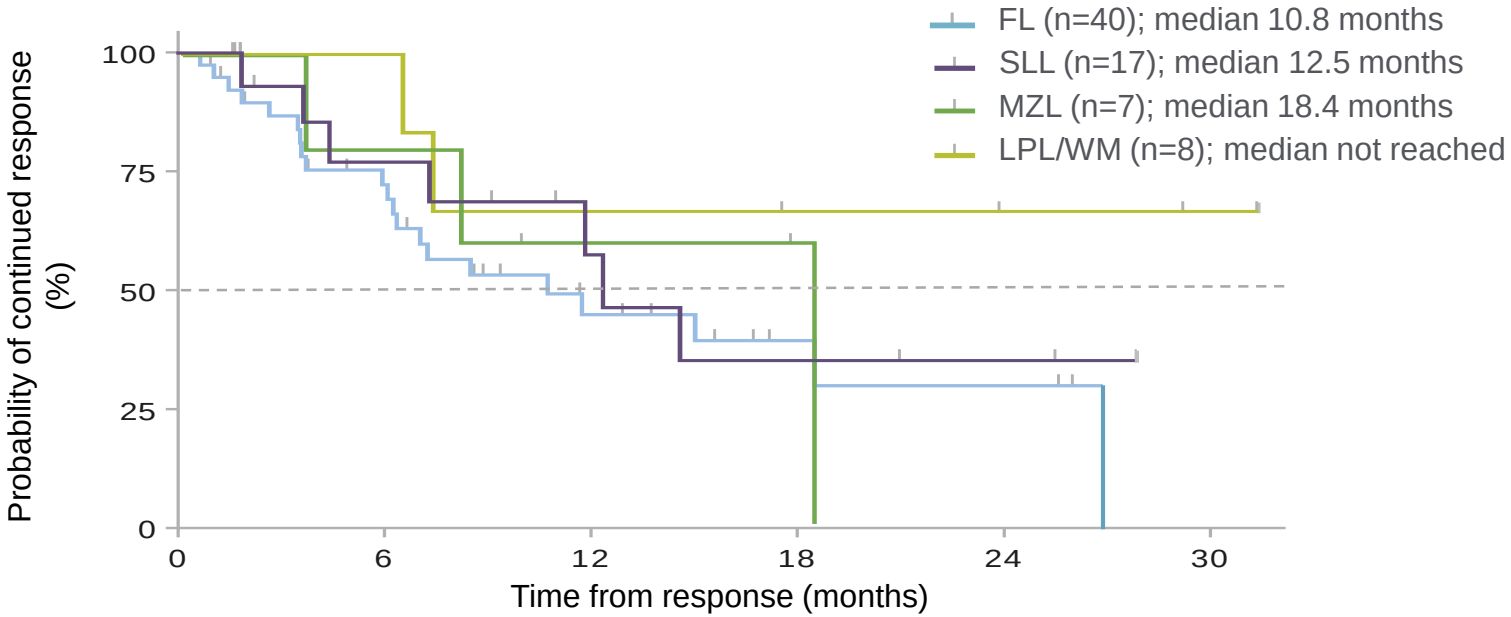
1. *Lannutti BJ, et al. Blood 2011;117:591-4;*
2. *Flinn IW, et al. Blood 2014;123:3406-13*;

Overall response rate 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

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)

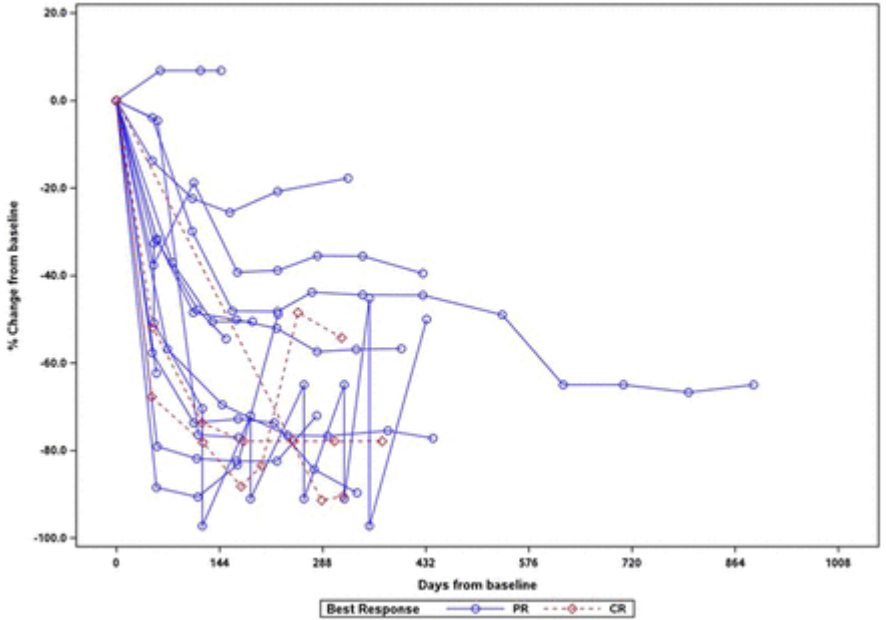
INHIBITORS OF PI3K

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

Copanslisib

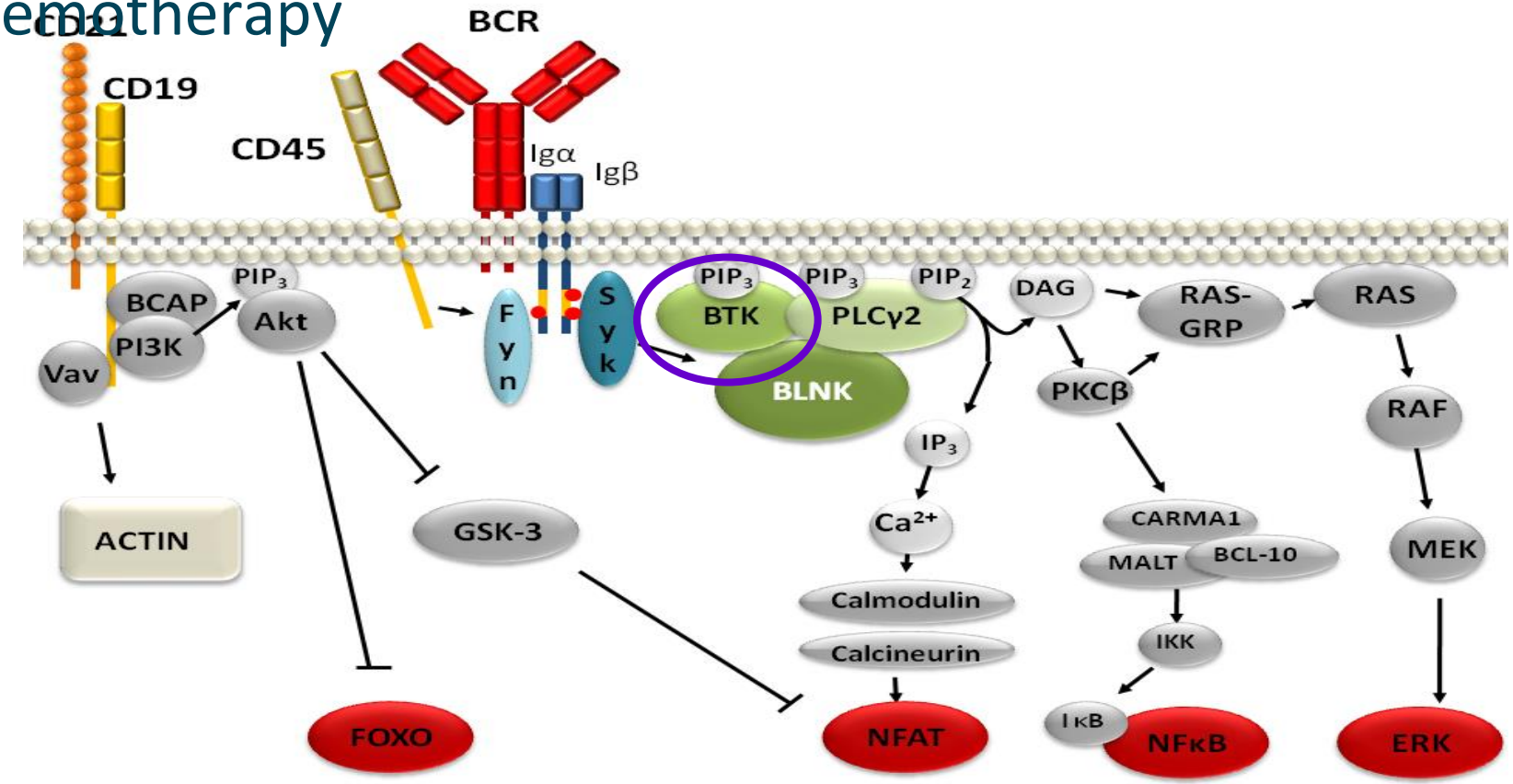
n=23
ORR 70%
CR 31%

Median duration of response not met. 85% at 10 months



Dreyling 2017

B-cell receptor signalling. ..Inhibit and spare the chemotherapy

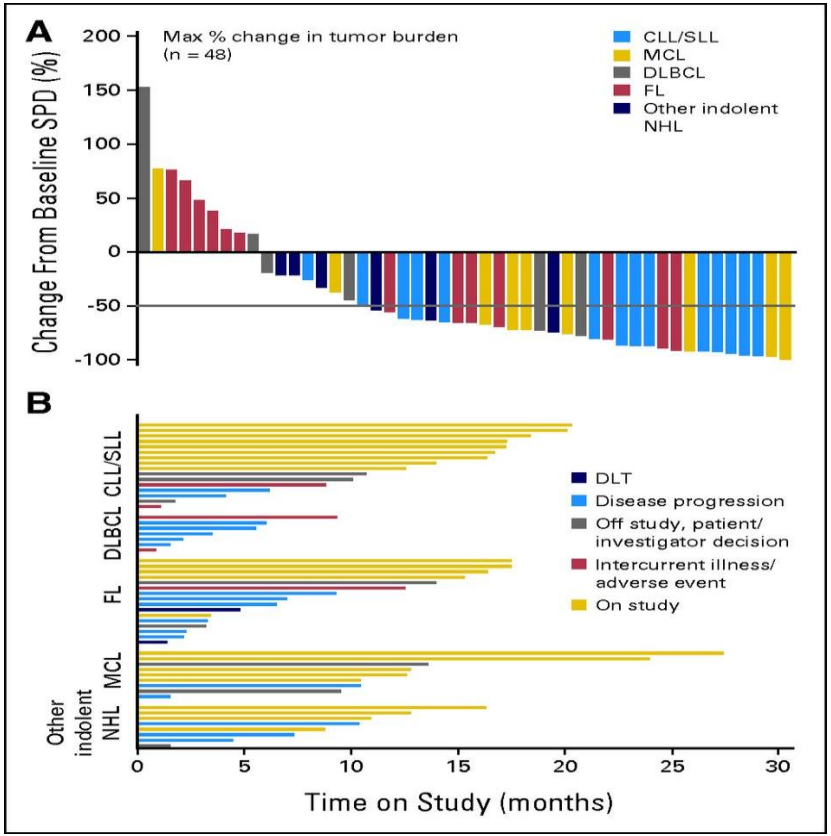


Ibrutinib in B-cell lymphoma

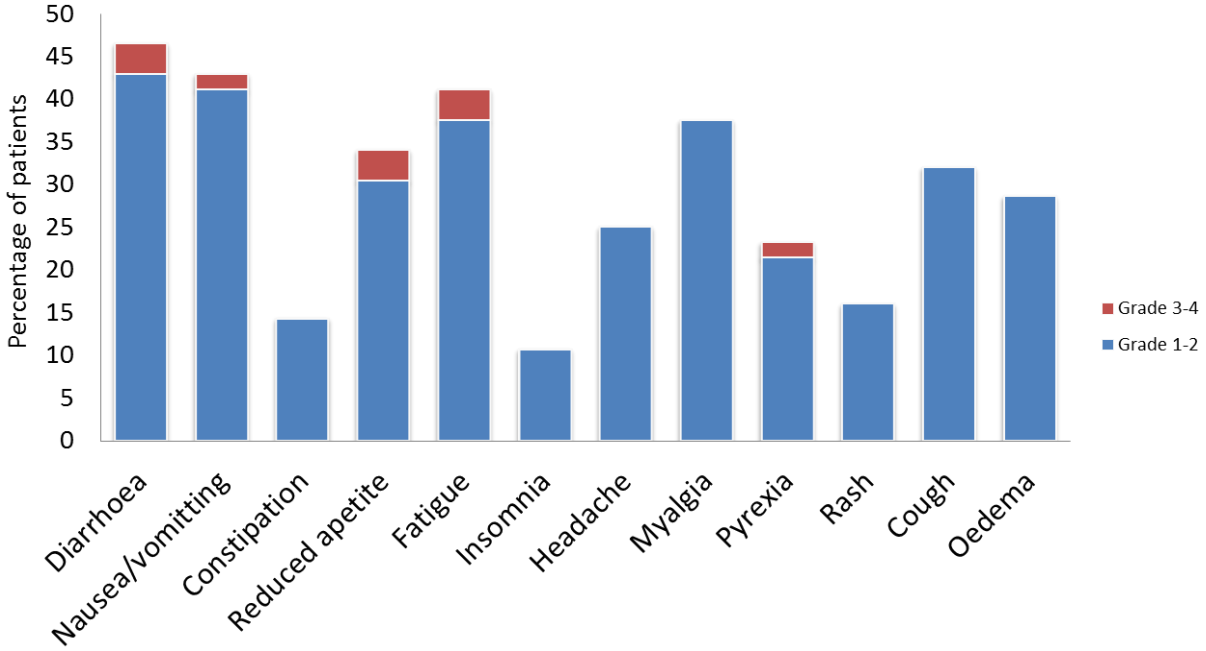
	Responders (n/N)
Mantle cell	7/9
CLL/SLL	11/16
FL	6/16
DLBCL	2/7
WM	3/4
ORR	**60%**

N=56. Median 3 (1-10) prior therapies

Advani R H et al. JCO 2013;31:88-94



Toxicity



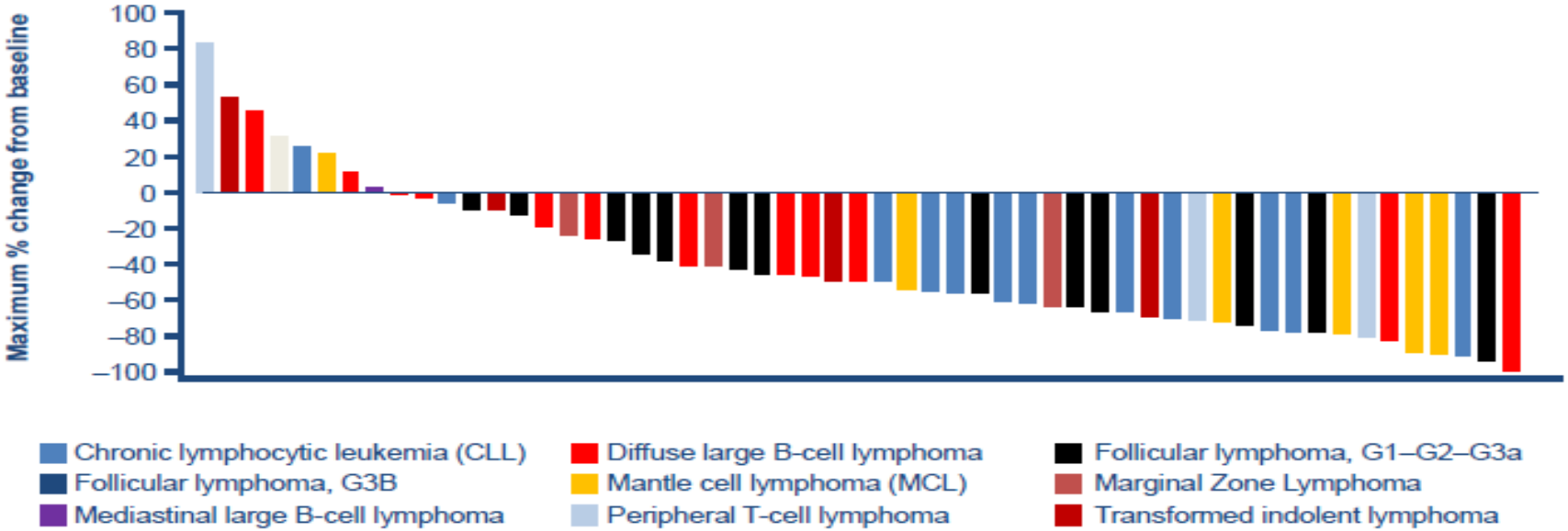
Grade ≥3 haematological toxicity:
Neutropenia 13%, thrombocytopenia 7%;
anaemia 7%
No decrease in Igs

Advani R H et al. JCO 2013;31:88-94

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

Obinutuzumab: Putative mechanism(s) of action

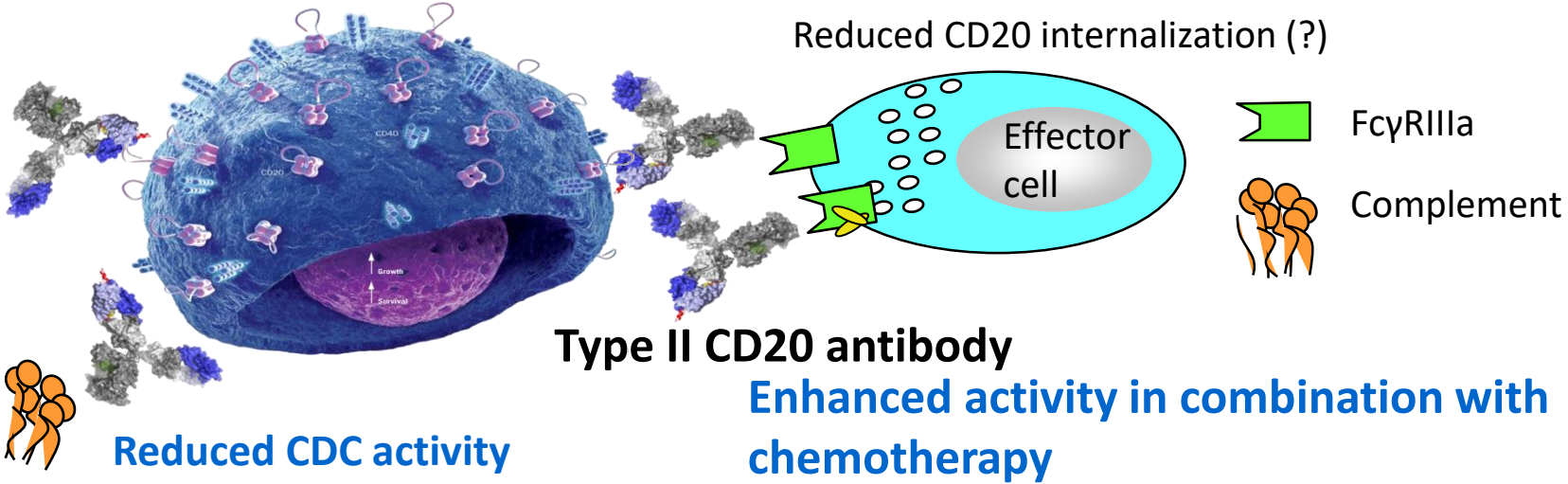
Increased direct cell death

Type II antibody & elbow-hinge modification

Increased ADCC

Higher affinity to the 'ADCC receptor' FcγRIIIa (GlycoMab TM technology) &

Reduced CD20 internalization (?)



Type II CD20 antibody

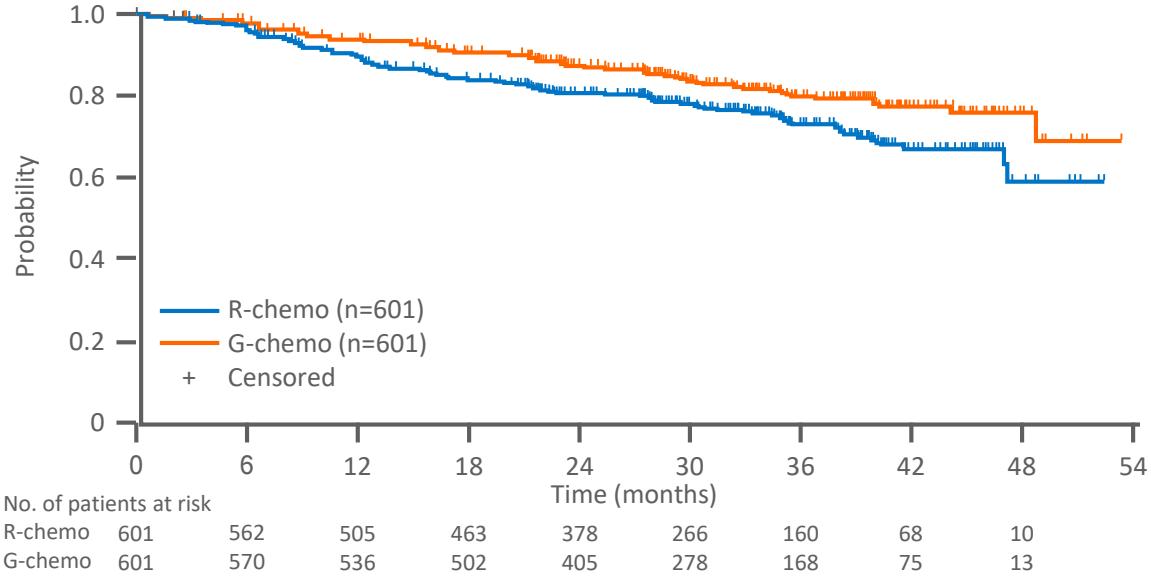
Reduced CDC activity

Type II antibody

Enhanced activity in combination with chemotherapy

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity

Primary endpoint of investigator-assessed PFS



PFS by investigator	R-chemo (n=601)	G-chemo (n=601)
Events, n (%)	144 (24.0)	101 (16.8)
Median PFS, months (95% CI)	NE (47.1, NE)	NE (NE, NE)
Stratified HR (95% CI), p value	0.66 (0.51, 0.85), p=0.0012	
3-year PFS, % (95% CI)*	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)

Median follow-up: 34.5 months

- GALLIUM met its primary endpoint demonstrating a 34% reduction in the risk or PD/relapse or death for G-chemo vs R-chemo in FL patients, a statistically significant and clinically meaningful difference

*7% difference in 3-year PFS between the two arms was as expected; both arms performed better than protocol assumptions
CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; NE, not estimable; PD, disease progression; PFS, progression-free survival

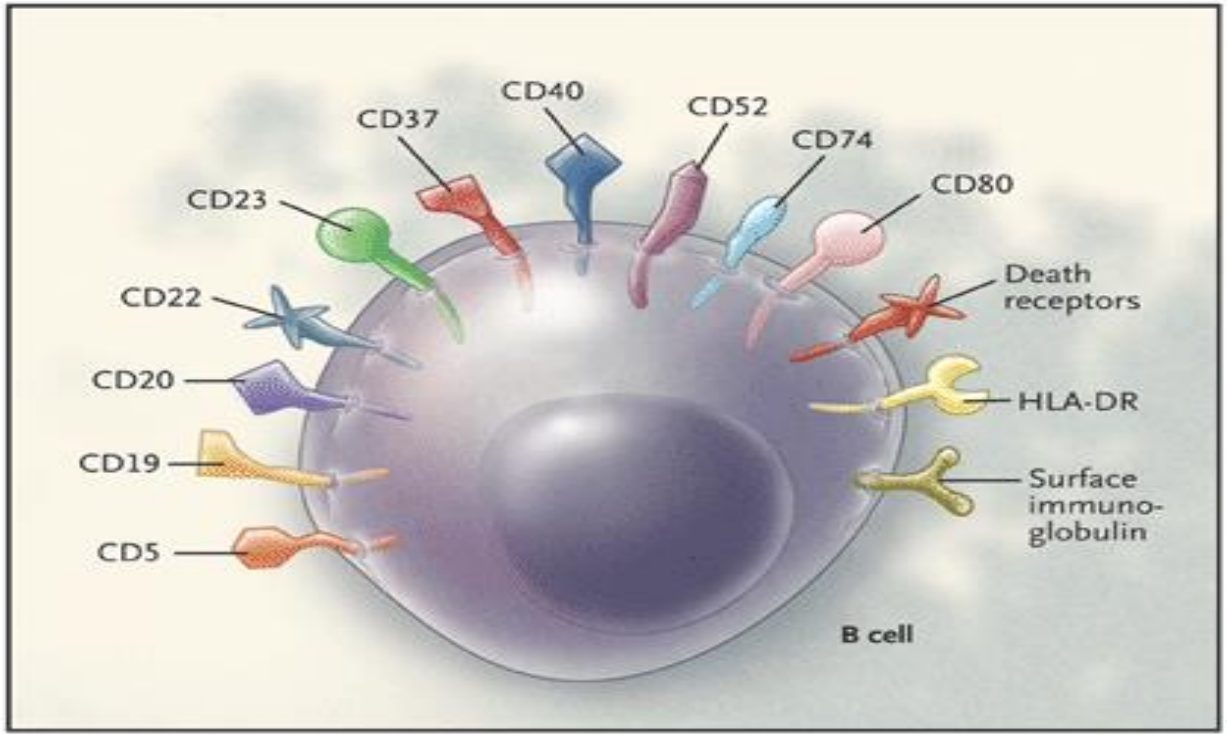
Marcus R, et al. N Engl J Med 2017;377:1331–44

Median observation time (range), months*	37.0 (0.6–54.4)	40.8 (0.2–52.8)
Number of PFS (INV) events (%)	21 (21.2)	26 (27.1)
HR for PFS (INV), G vs R (95% CL), p-value†	0.82 (0.45, 1.46), p=0.49	
HR for other time-to-event endpoints, G vs R (95% CL), p-value†		
PFS (IRC)‡	0.83 (0.46, 1.51), p=0.55	
Overall survival	0.90 (0.45, 1.81), p=0.78	
Time to new anti-lymphoma treatment	0.85 (0.48, 1.50), p=0.57	
Response at EOI by CT (INV)		
CR, n (%)	16 (16.2)	18 (18.8)
ORR, n (%)	82 (82.8)	78 (81.3)

Safety (all randomised MZL pts who received at least one dose of study drug)§

Number (%) of pts reporting at least one event	G-chemo(n=101)	R-chemo(n=93)
AEs	101 (100)	93 (100)
Grade ≥3 AEs	83 (82.2)	72 (77.4)
Neutropenia	46 (45.5)	34 (36.6)
Febrile neutropenia	4 (4.0)	9 (9.7)
Thrombocytopenia	10 (9.9)	3 (3.2)
Leukopenia	5 (5.0)	8 (8.6)
Infusion-related reactions	8 (7.9)	11 (11.8)
Pneumonia	10 (9.9)	3 (3.2)
Sepsis	5 (5.0)	5 (5.4)
Pyrexia	8 (7.9%)	2 (2.2%)
Dyspnoea	7 (6.9%)	4 (4.3%)
SAEs	65 (64.4)	48 (51.6)
Grade 5 (fatal) AEs	12 (11.9)	6 (6.5)
Infections and Infestations SOC	6 (5.9)	2 (2.2)

What about the other targets?



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 Lymphoma: Lung

Umberto Ricardi

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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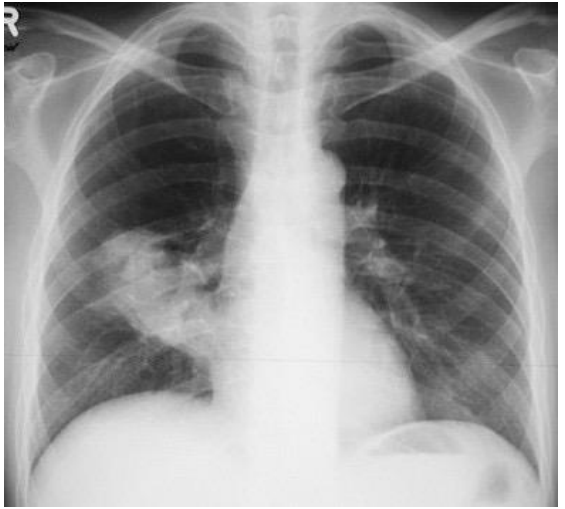
Background

- 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 (80-90%); DLBCL very rare (10%)

- 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



- 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

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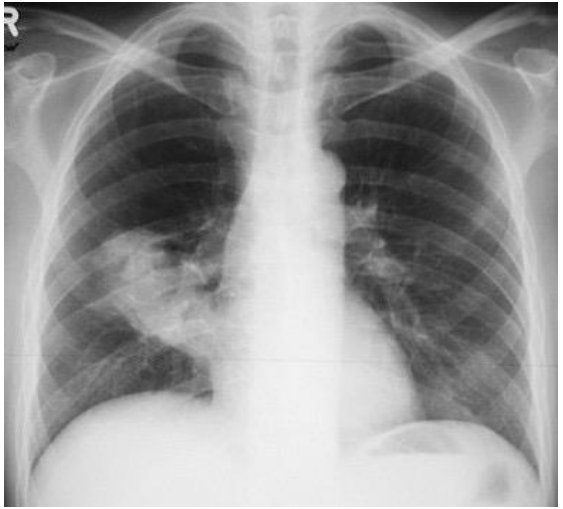
Background

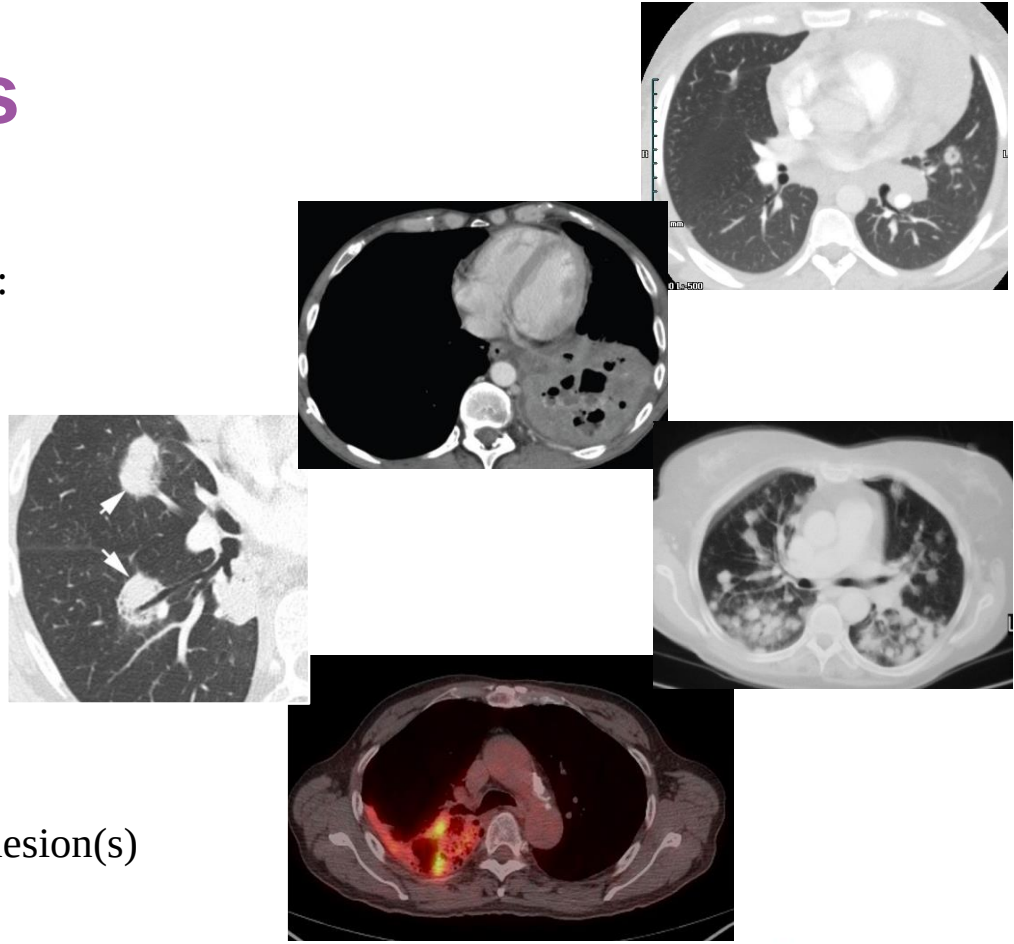
- MZL (bronchial associated lymphoid tissue lymphoma [BALT lymphoma]) may involve any element of the bronchial tree, often as an isolated lesion

- Surgery as first treatment: pulmonary lesion as a potential lung cancer

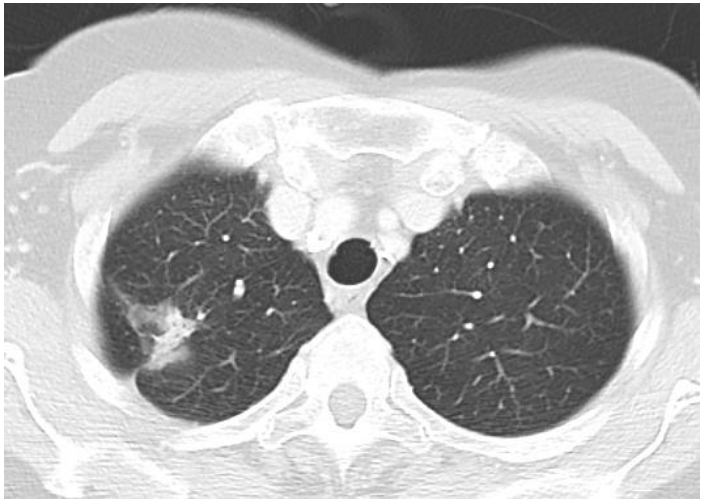
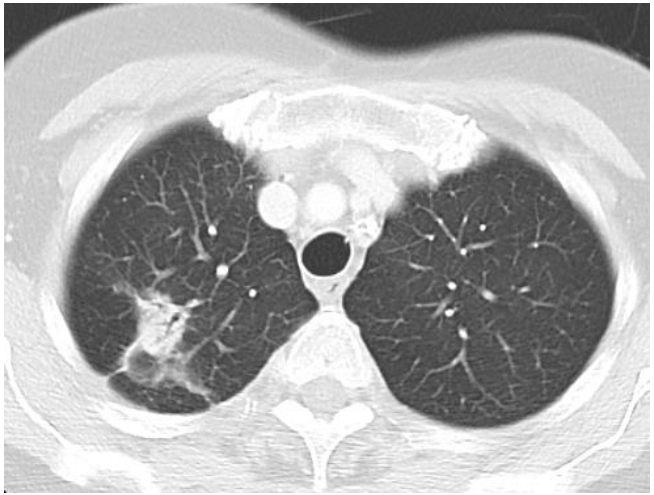
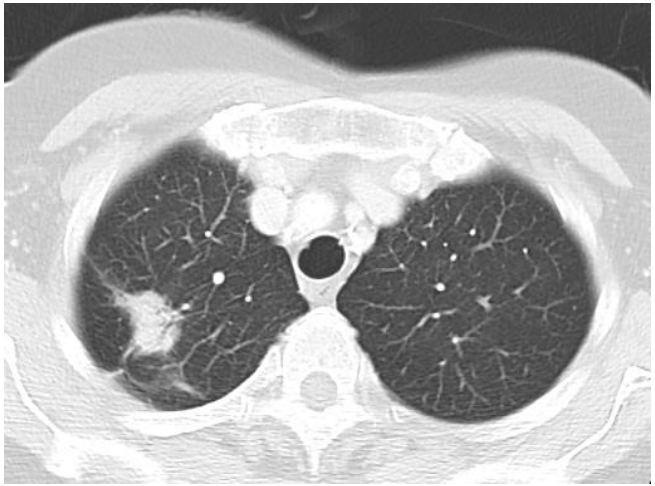
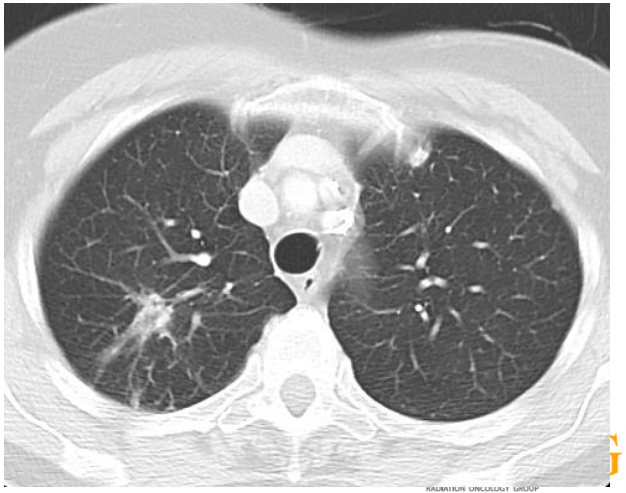


Diagnosis

- 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

Optimal treatment and prognostic factors are not well defined

- Surgery
- Watch and wait
- Chemotherapy
- Radiotherapy

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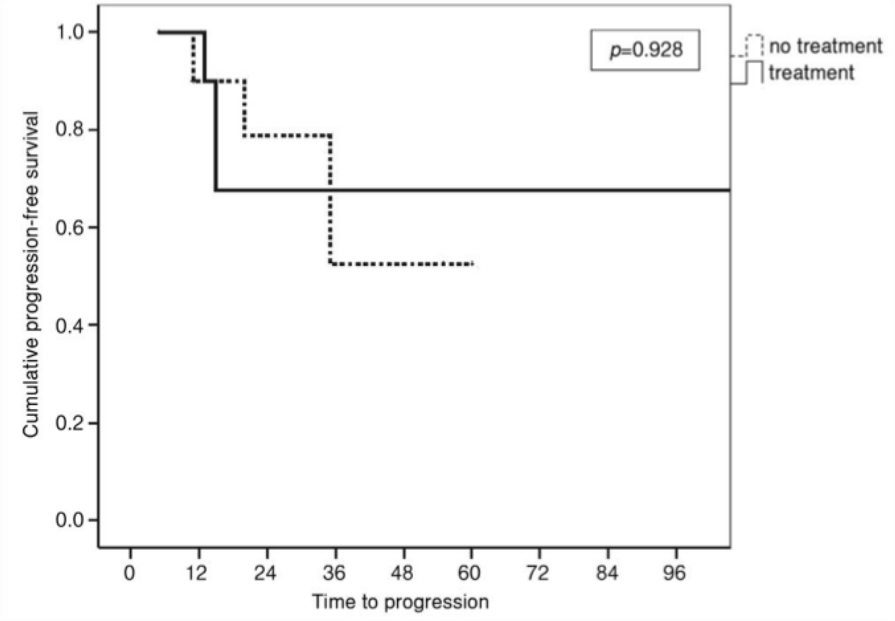
Does MALT Lymphoma of the Lung Require Immediate Treatment? An Analysis of 11 Untreated Cases with Long-term Follow-up



"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

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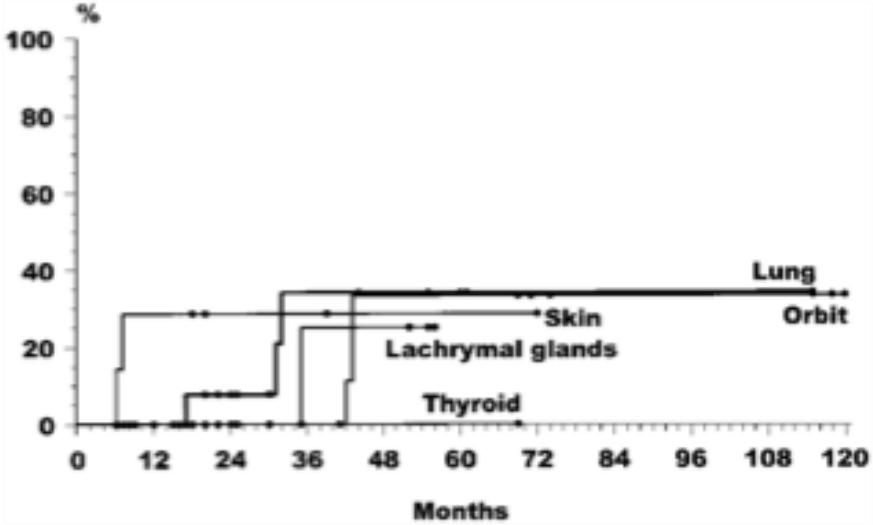
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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

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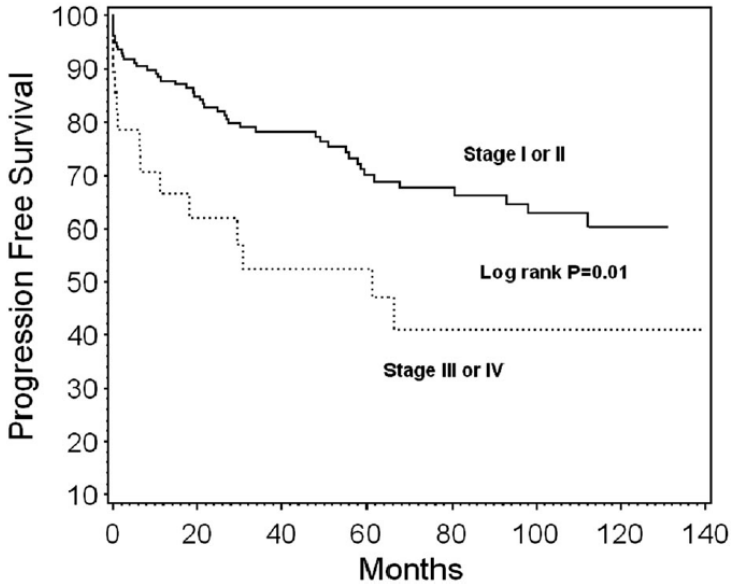
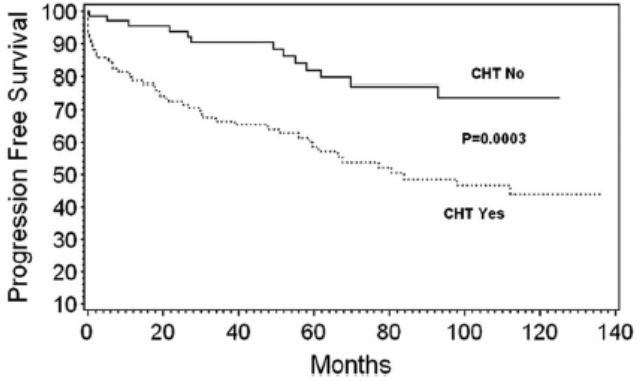
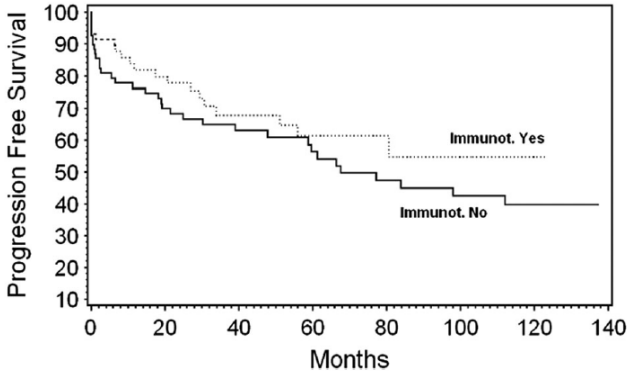
A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG)







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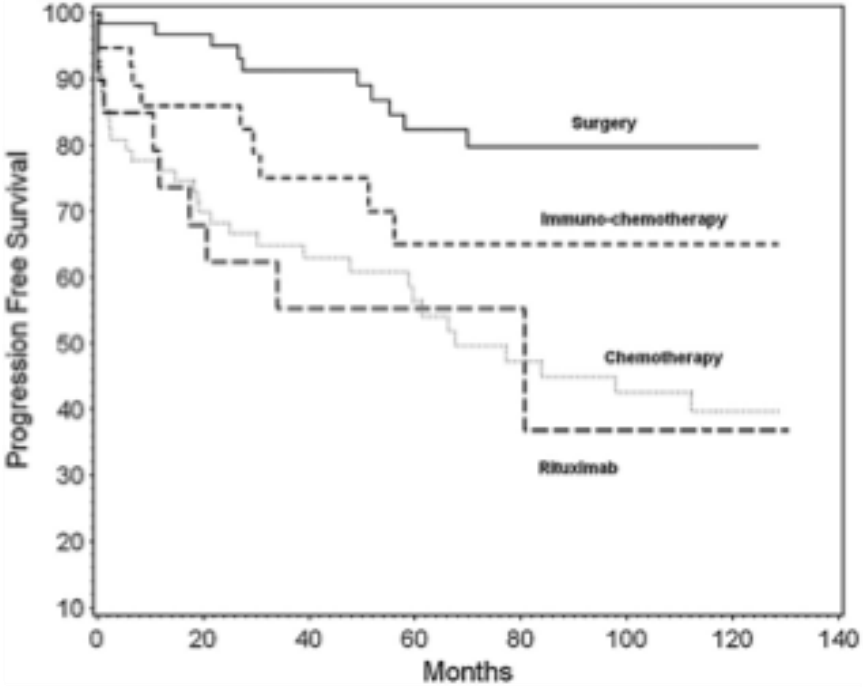

Conclusion:

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

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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Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 130–137, 2015

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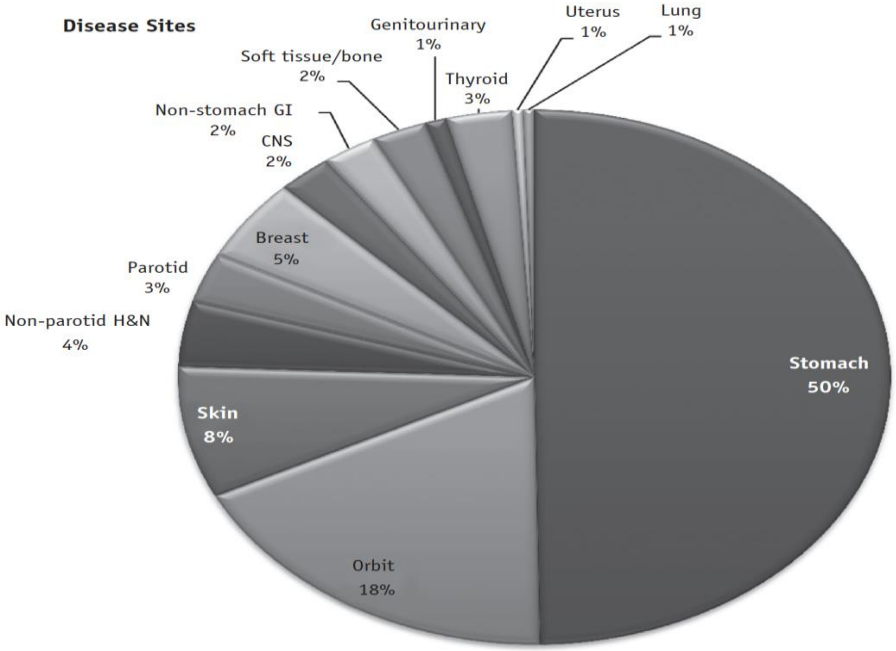
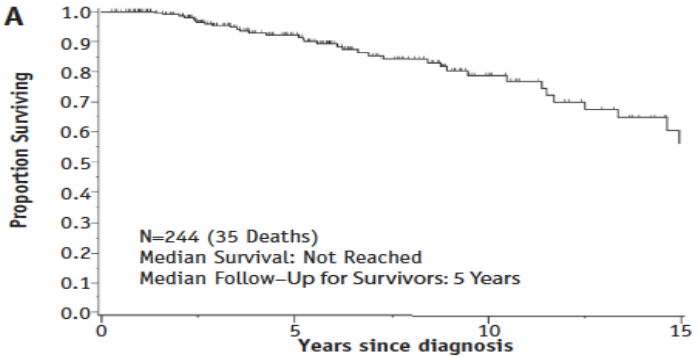
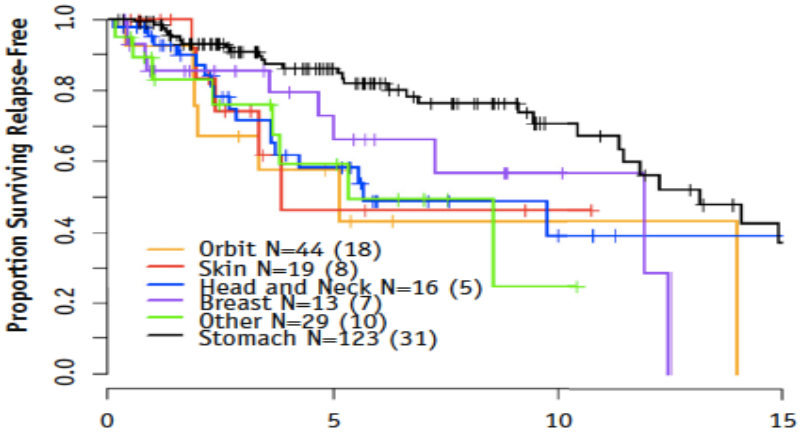
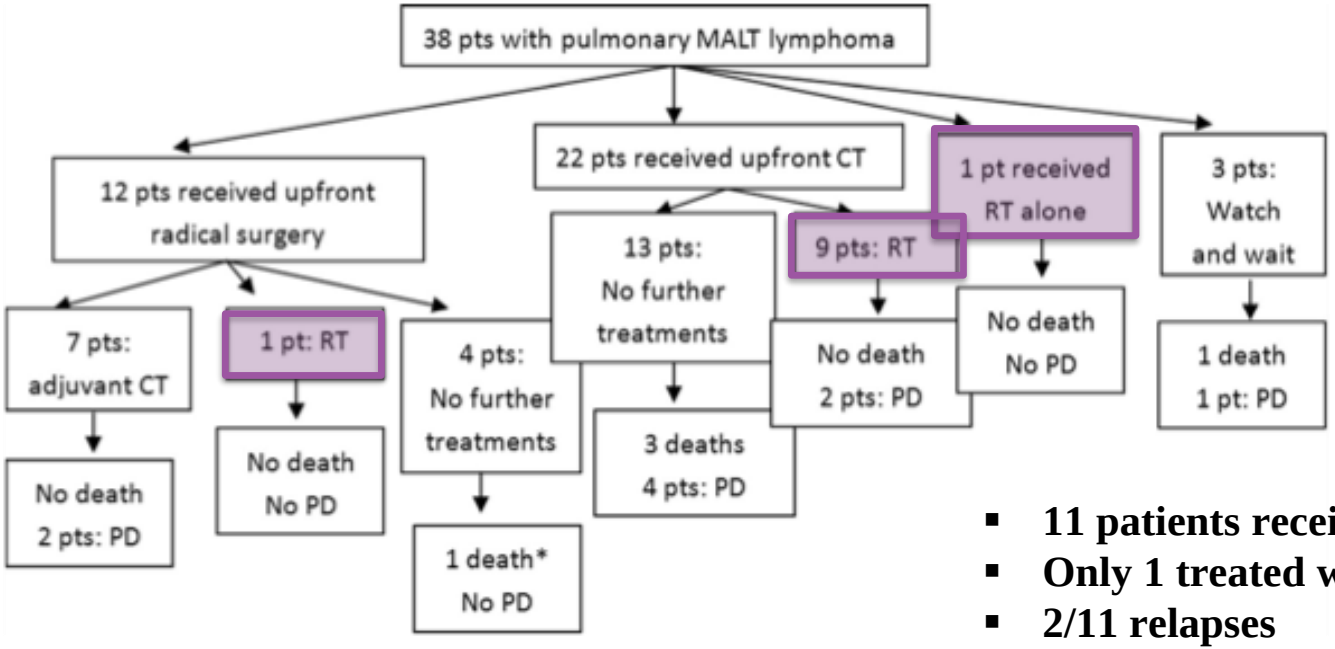






Radical surgery may be not an optimal treatment approach for pulmonary MALT lymphoma

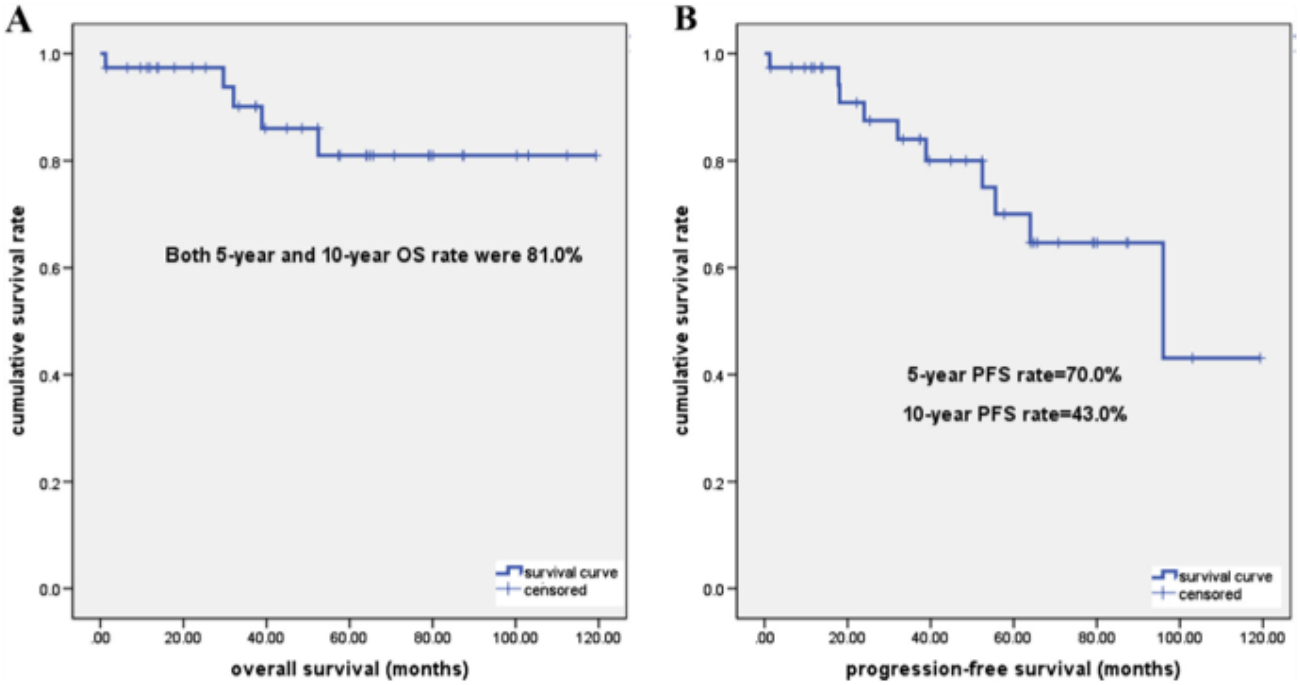


- **11 patients received RT**
- **Only 1 treated with RT alone**
- **2/11 relapses**
- **Median RT dose 30.6 (range 30-40 Gy)**

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

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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

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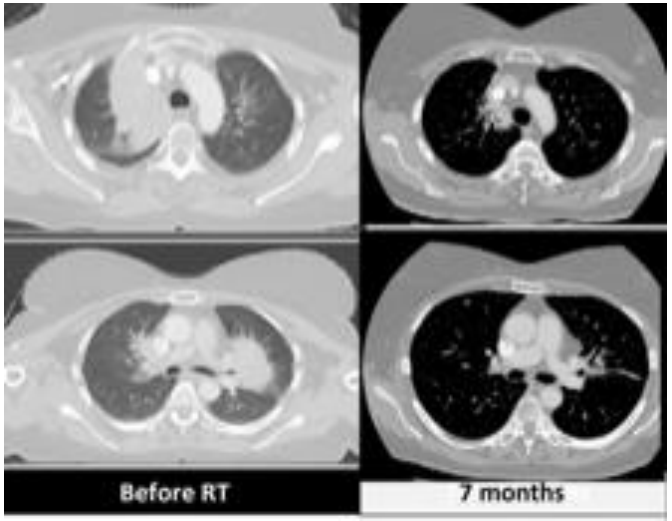
Low-Dose Radiation Treatment in Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma: A Plausible Approach? A Single-Institution Experience in 10 Patients

International Journal of Radiation Oncology biology • physics

BOOM-BOOM RADIOTHERAPY

Median follow up 56 months

4 Gy/2 fractions



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 24-25 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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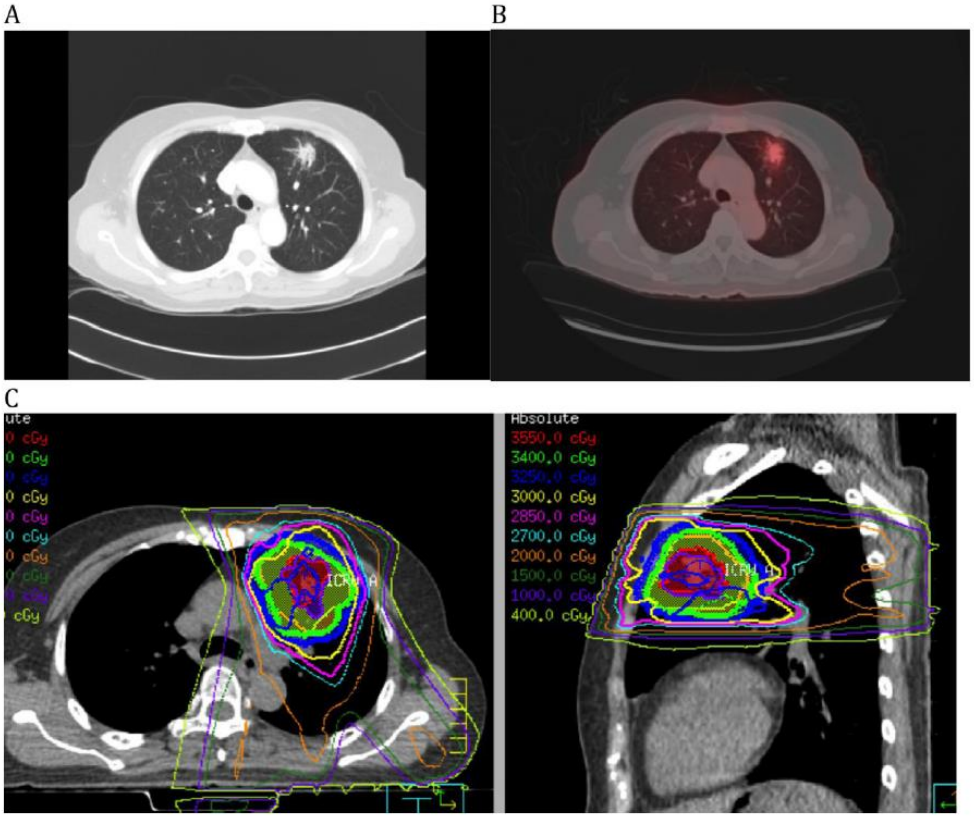
Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group



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

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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Extranodal lymphoma: Bone

Umberto Ricardi

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

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
- Slight preponderance of males over females (male/female ratio 1.5)

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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

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%

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

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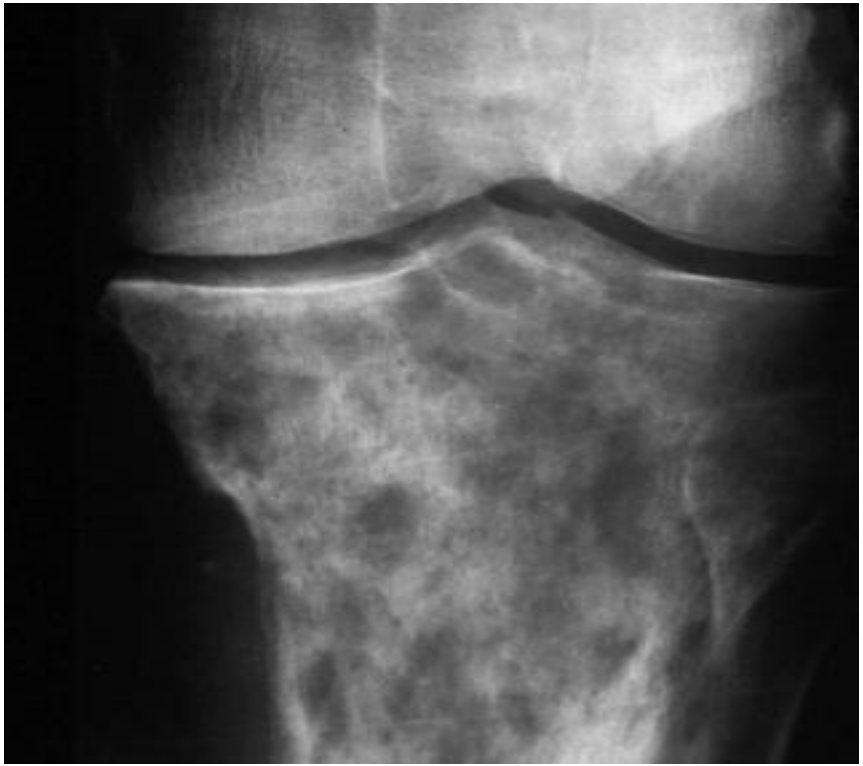
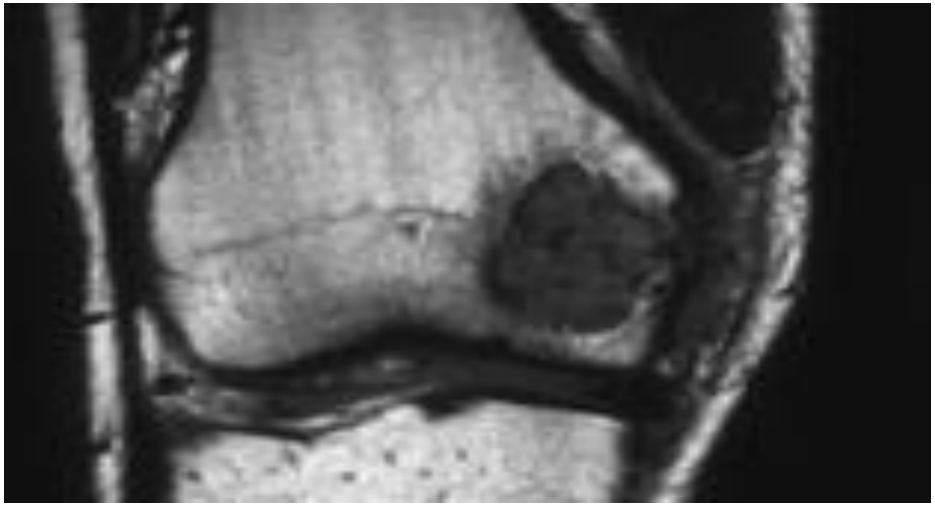
Radiographic findings

- **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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Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

U. Vitolo[1], J. F. Seymour[2], M. Martelli[3], G. Illerhaus[4], T. Illidge[5], E. Zucca[6], E. Campo[7] & M. Ladetto[8] on behalf of the ESMO Guidelines Committee*

Annals of Oncology 00: 1–12, 2016

Table 6. The International Extranodal Lymphoma Study Group (IELSG) staging system for DLBCL of the bone

Lymphoma extension	IELSG Stage
Single bony lesion	IE
Single bony lesion with involvement of regional lymph nodes	IIE
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)[a]	IVE
Disseminated lymphoma with at least one bony lesion	IV

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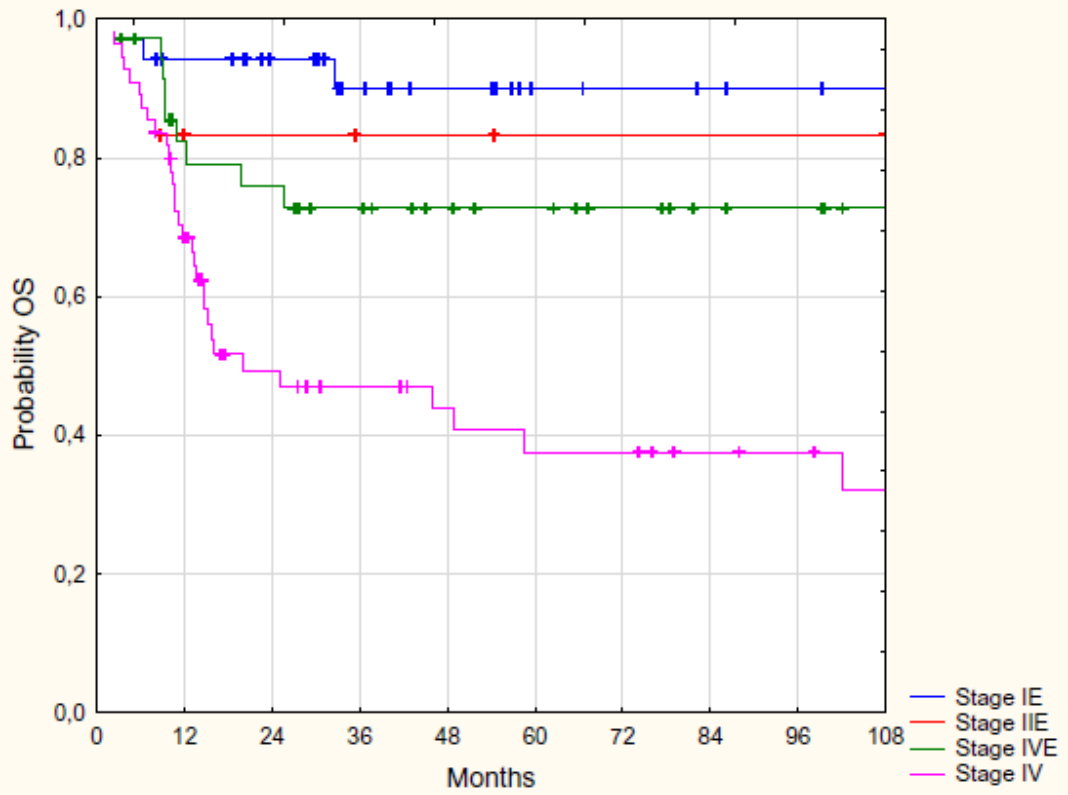
Prognosis according to stage



Messina et al, Cancer Treat Rev, 2015

DLBCL: combined modality treatment

- In aggressive DLCL, RT is used in combination with chemotherapy

- RT continues to have an important place in ensuring locoregional control and improving overall outcome in the combined modality treatment programs

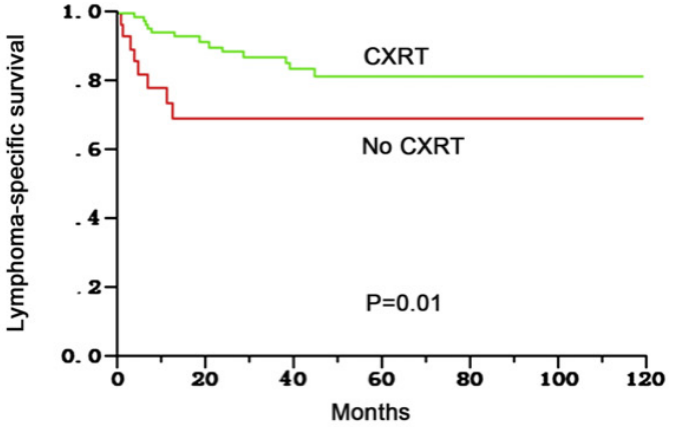
Treatment

- *Combined modality therapy:*

R-CHOP x 6, followed by RT

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

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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

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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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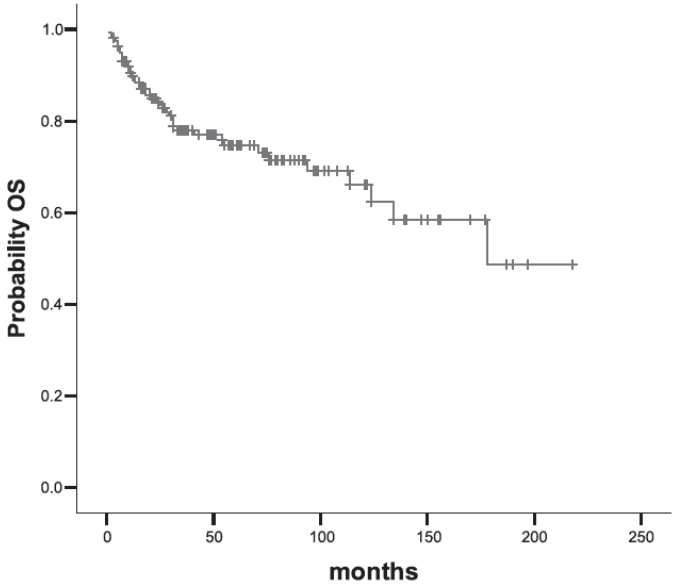

Table 4. Multivariate analysis

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			

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**

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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%

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Yahalom et al, IJROBP, 2015

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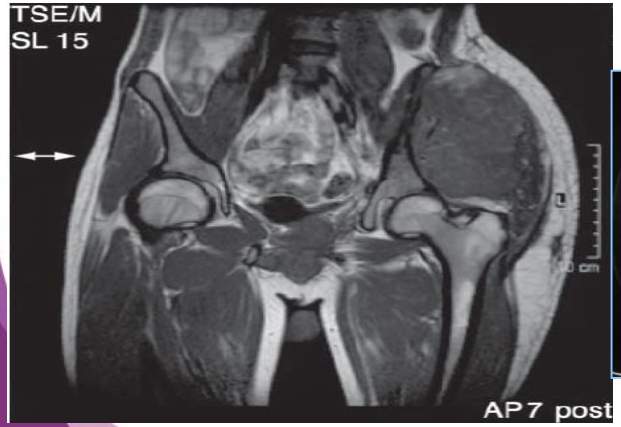
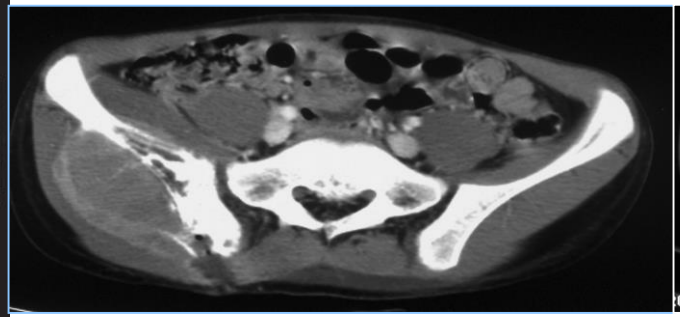
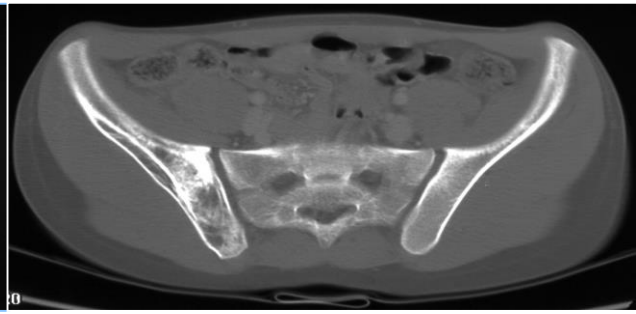
Radiation volumes

- 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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Considerations on RT dose

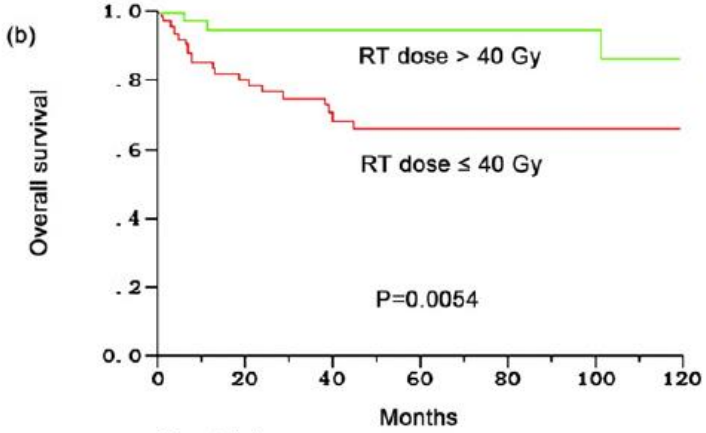
- Radiation dose depends on:
  - the size of the irradiated volume
  - the anatomical area
  - the response to primary chemotherapy

- 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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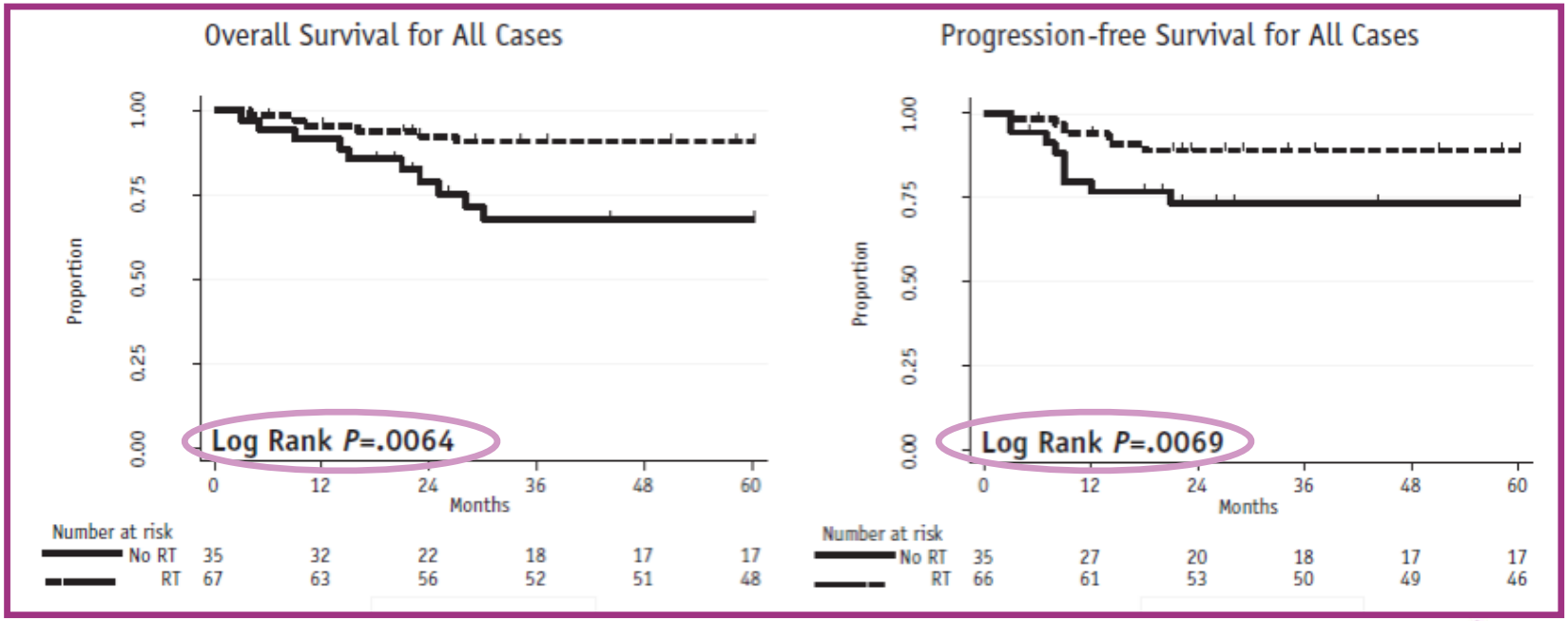
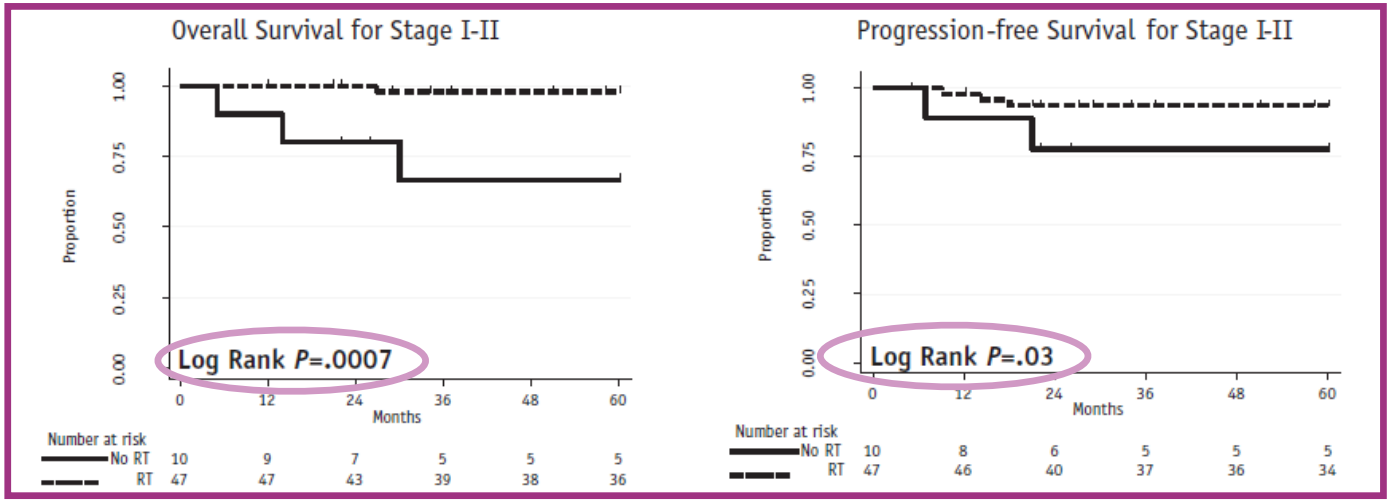
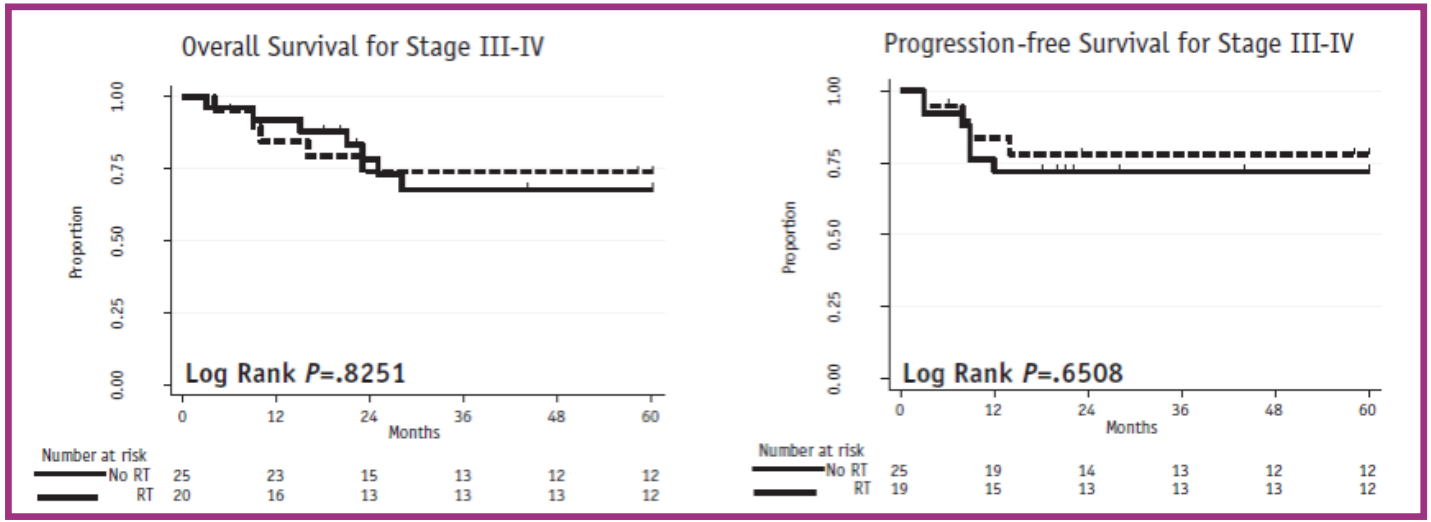
- 102 patients with primary bone DLBCL
- median age: 55 years (range, 16-87 years)
- most common site of presentation: long bones

- 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

Dose range is 30 to 40 Gy, depending on the certainty that a CR has been obtained with systemic treatment

After chemotherapy, complete regression of PET uptake may not be clear at the time of RT

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

Therapeutic issues

Long-term bone health preventive measures should also be taken into account in patients with primary bone lymphoma, including evaluation and treatment of any underlying osteoporosis, and/or vitamin D deficiency


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Myeloma:
Solitary & Disseminated

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

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Multiple myeloma

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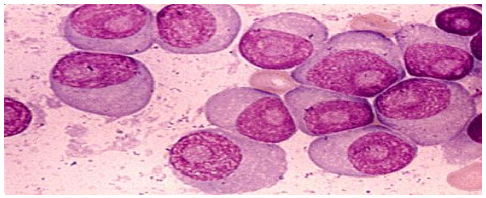
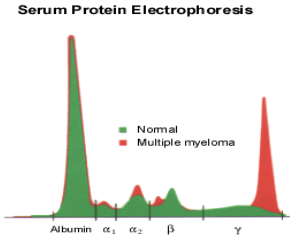


Multiple myeloma



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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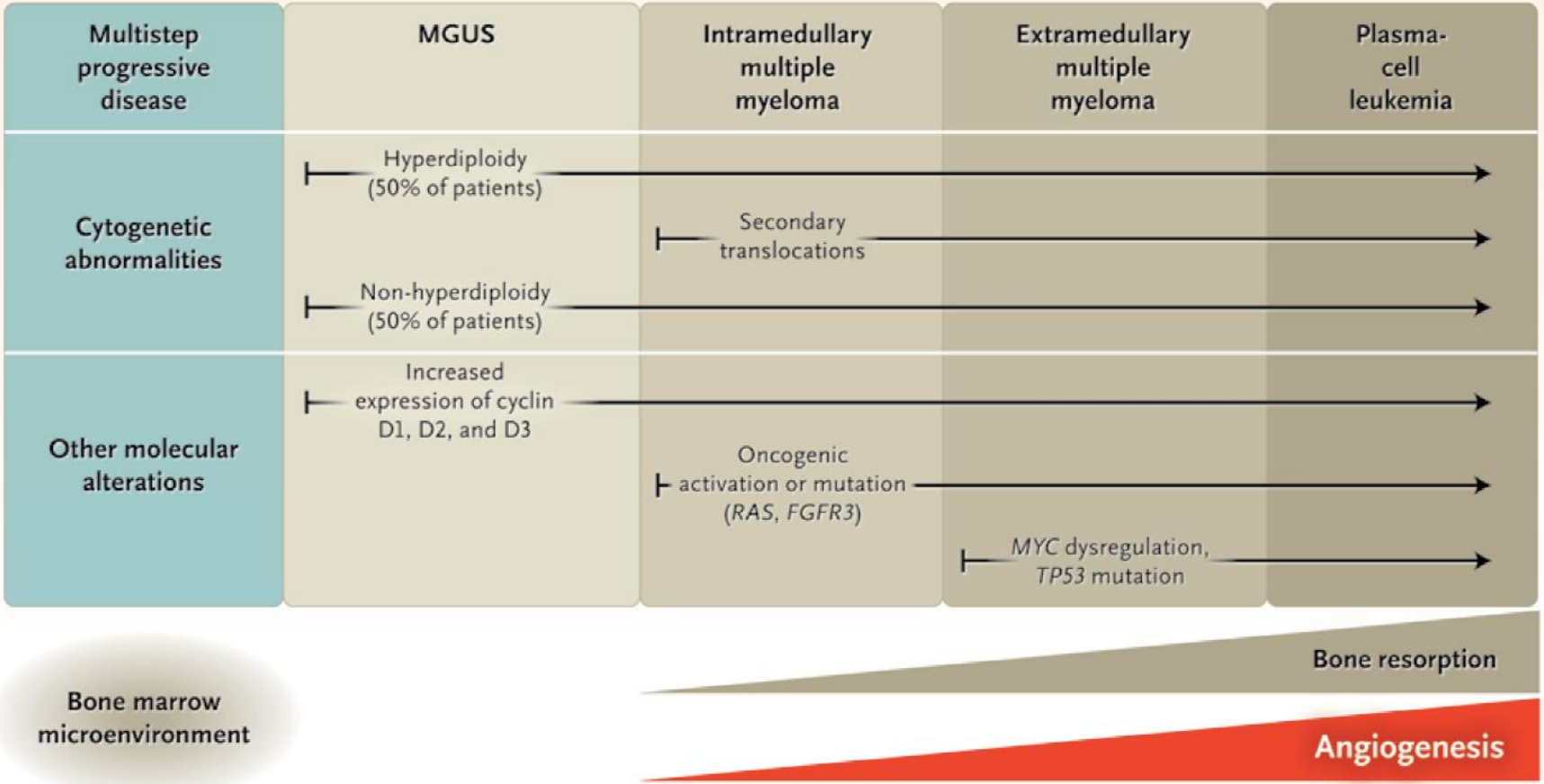
Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post-germinal-center B cells

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.**

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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

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

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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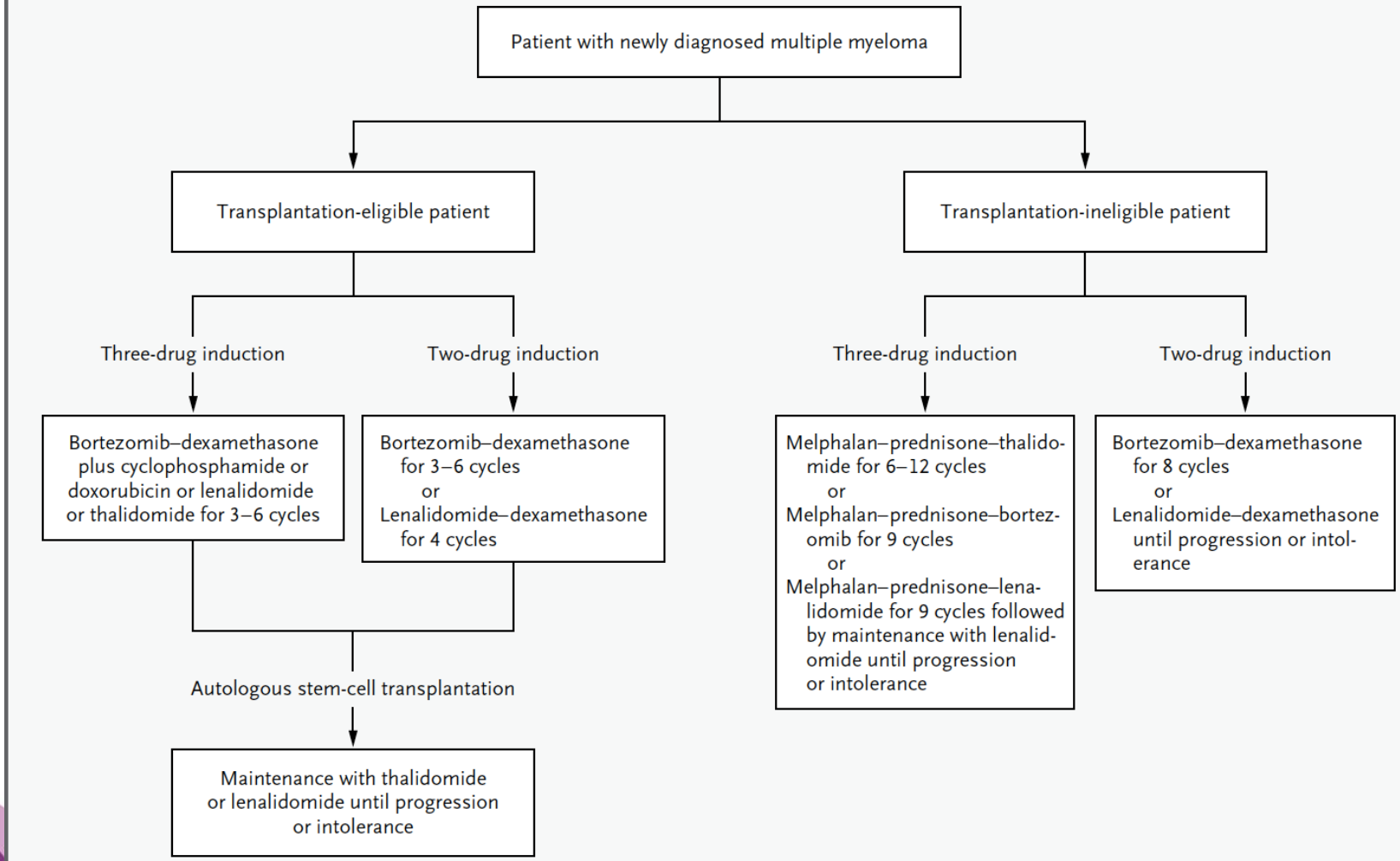
Treatment

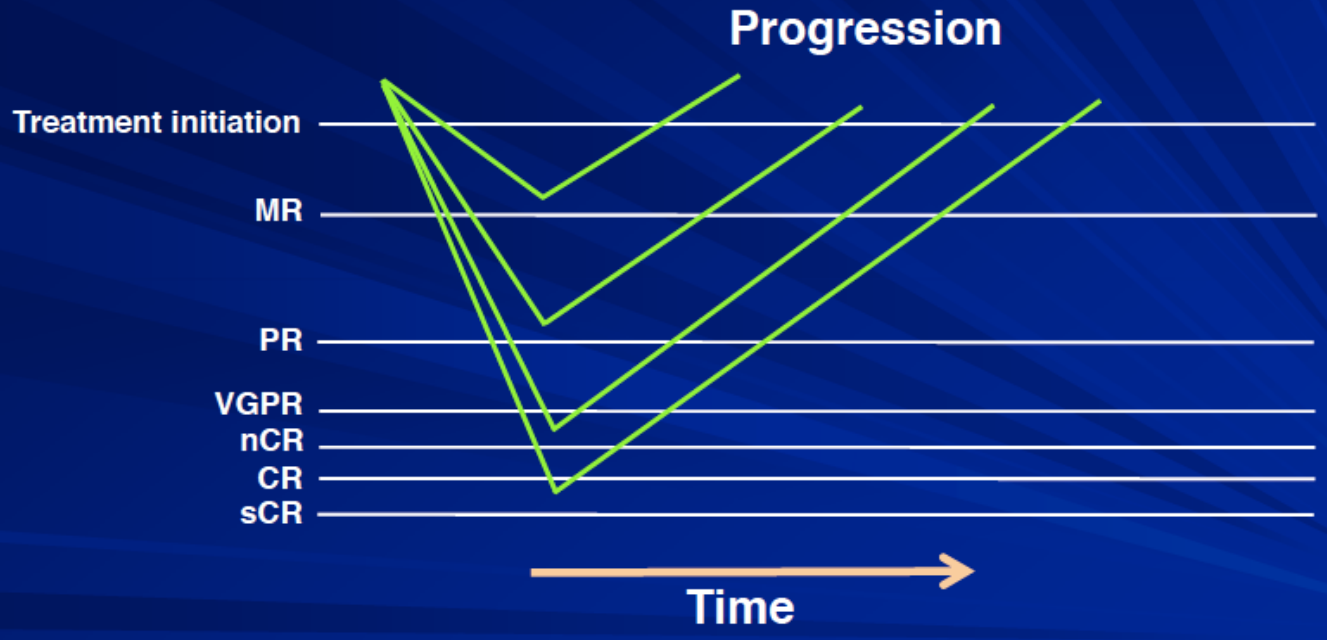
Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no benefit

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

Depth of response



Depth of response is related to TTP

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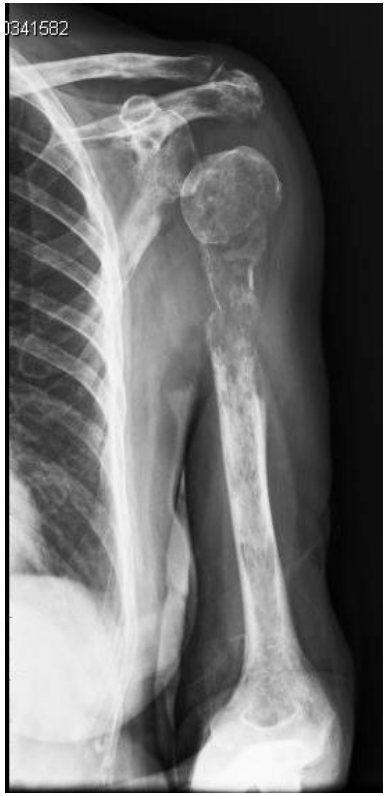
Role of Radiotherapy in MM

- 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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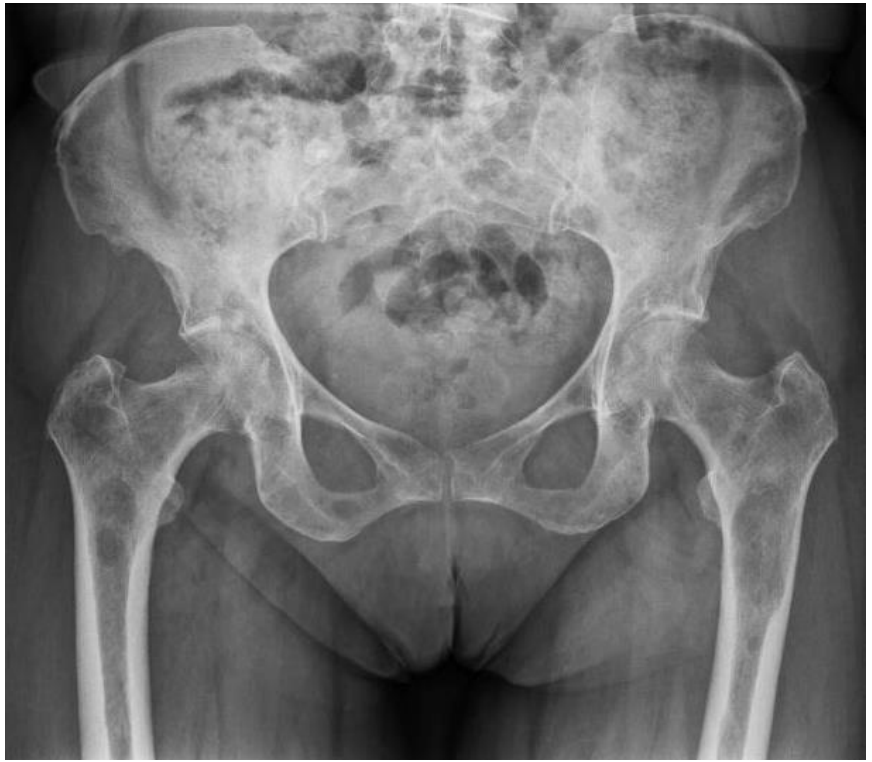

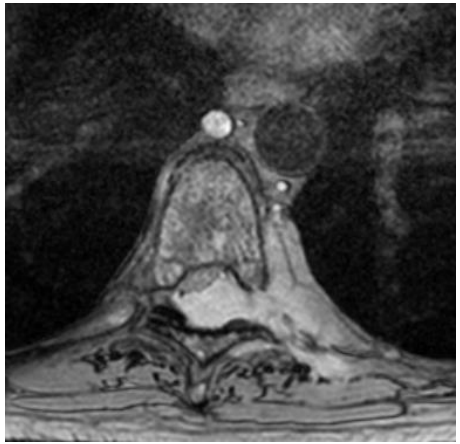

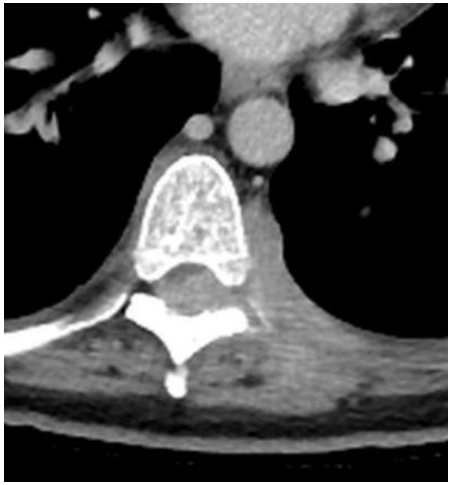

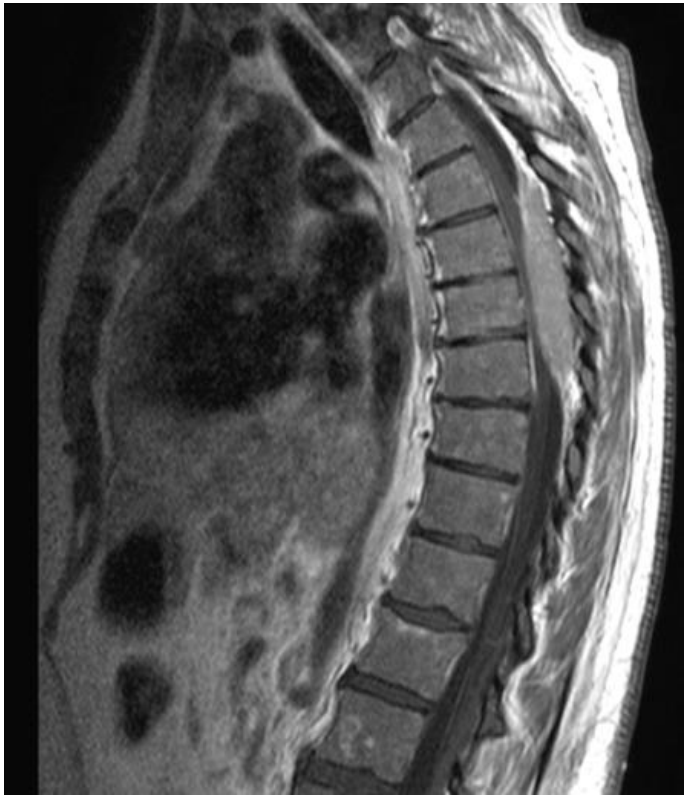

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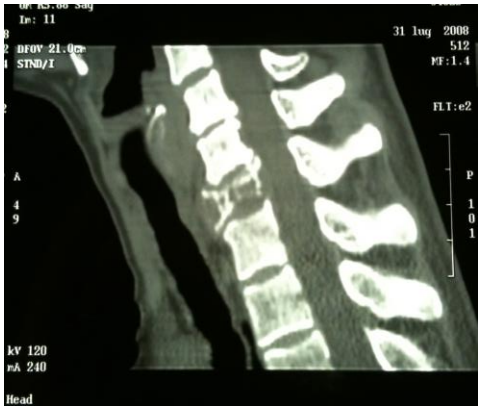
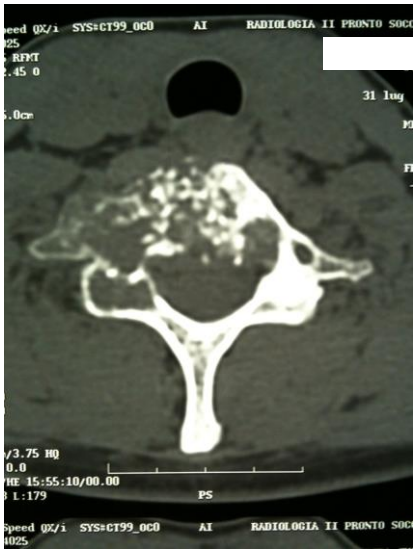
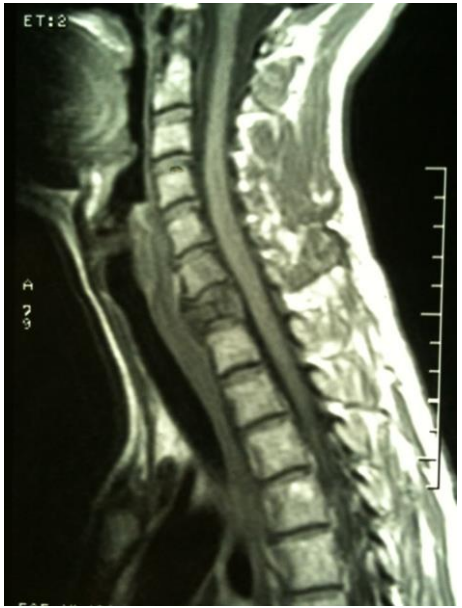
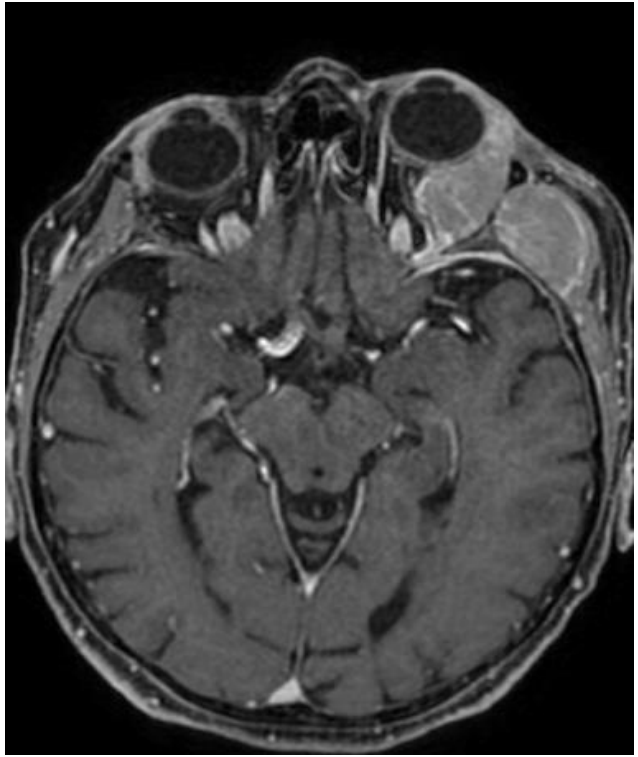
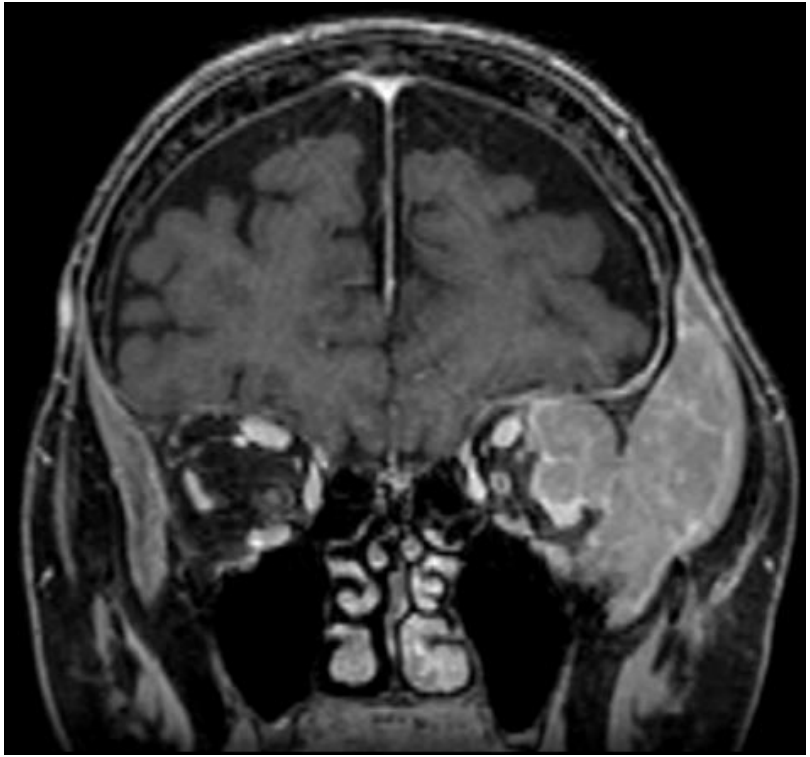
- solitary vertebral body lesion (C7) in MM



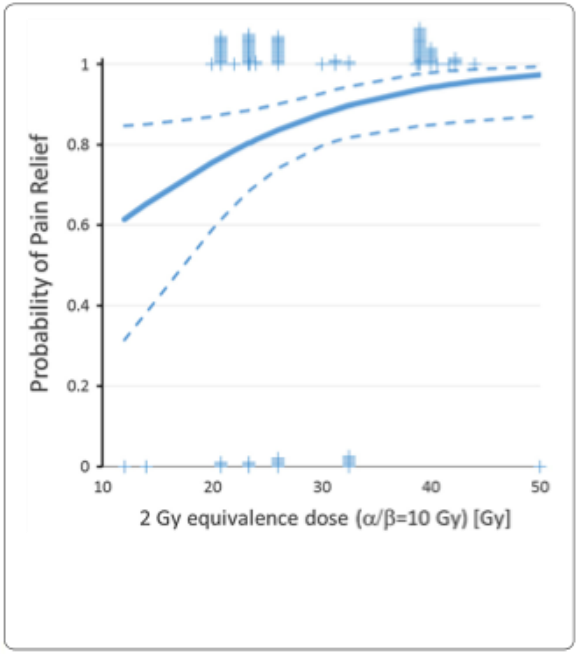








Effects of Radiotherapy in the treatment of multiple myeloma: a retrospective analysis of a Single Institution



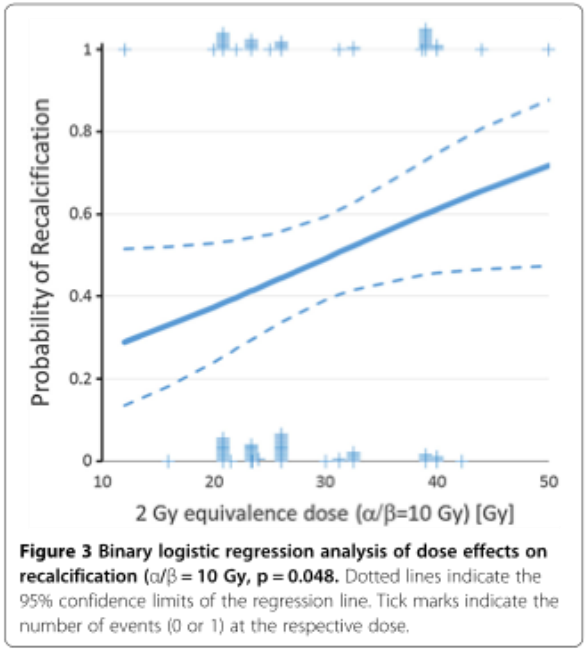
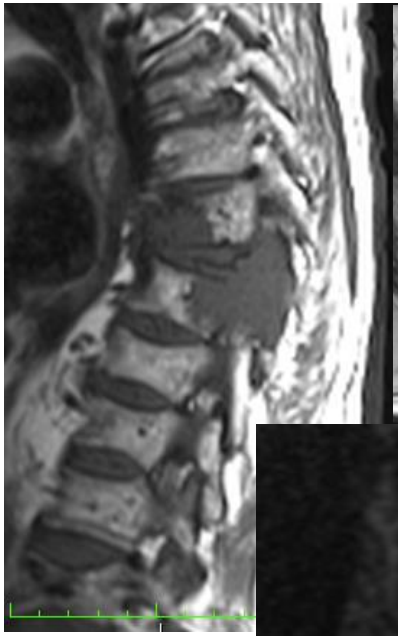
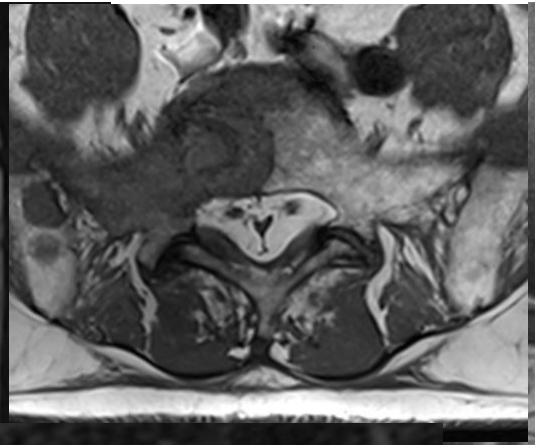
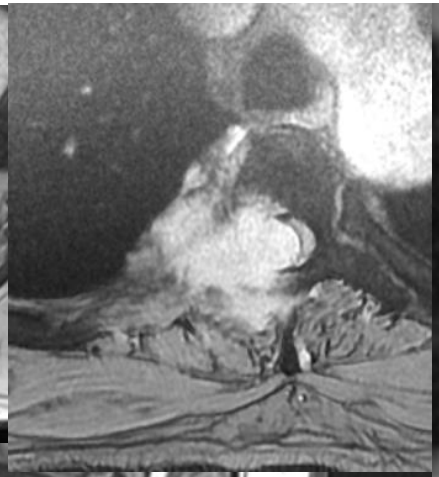
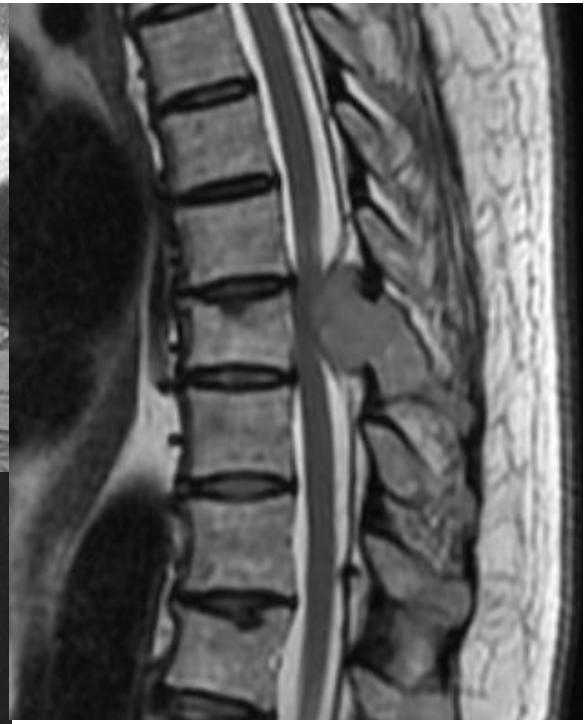
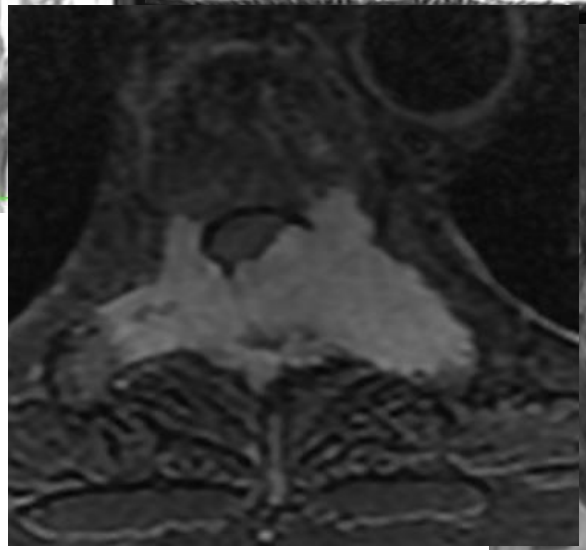
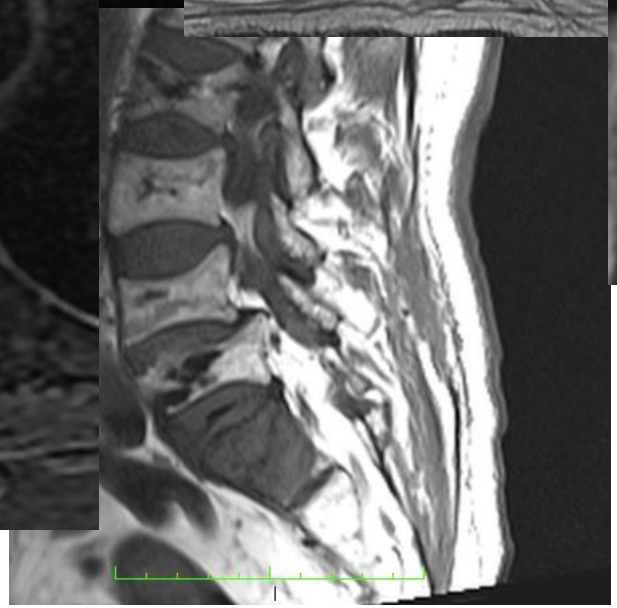


Figure 3 Binary logistic regression analysis of dose effects on recalcification (α/β = 10 Gy, **p = 0.048.** Dotted lines indicate the 95% confidence limits of the regression line. Tick marks indicate the number of events (0 or 1) at the respective dose.

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

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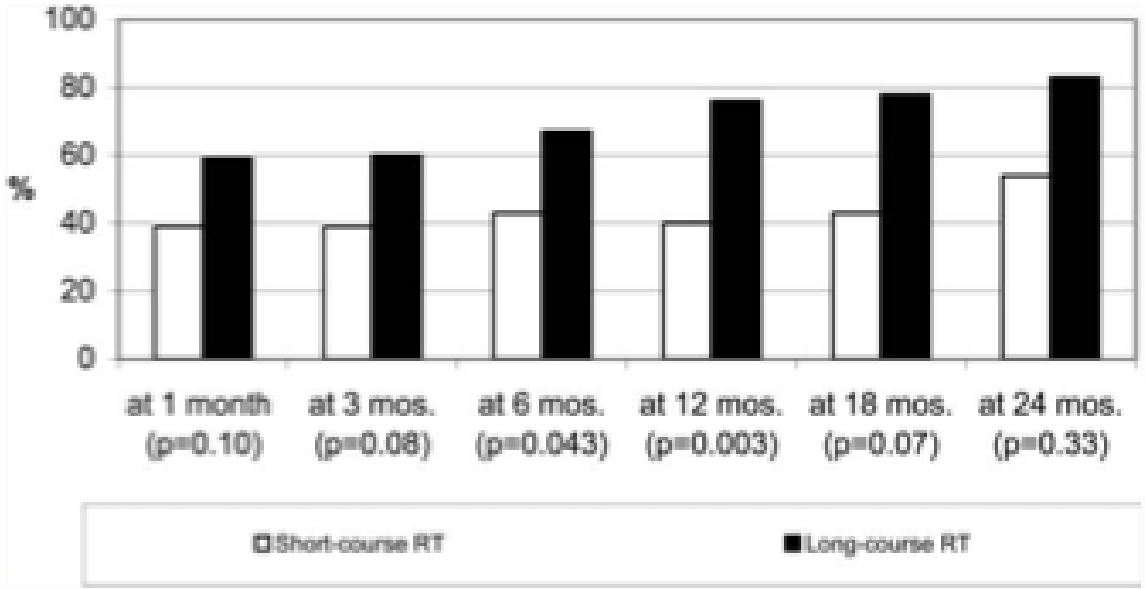
SHORT-COURSE RADIOTHERAPY IS NOT OPTIMAL FOR SPINAL CORD COMPRESSION DUE TO MYELOMA

IMPROVEMENT OF MOTOR FUNCTION AFTER RADIOTHERAPY



172 patients
1994-2004

Short course RT:

- 8 Gy in single fraction
- 20 Gy/5 fractions

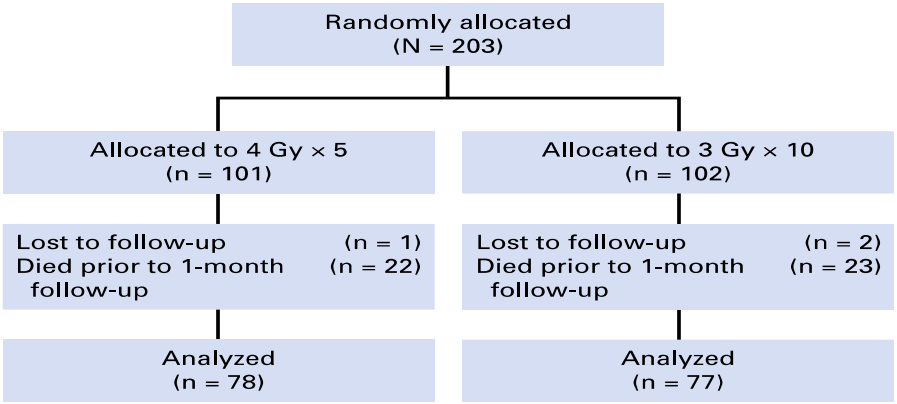
Long course RT:

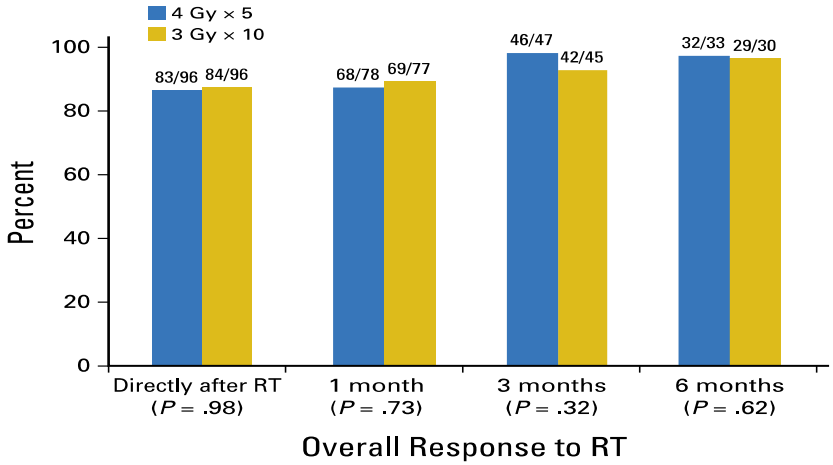
- **30 Gy/10 fractions**
- **37.5 Gy/15 fractions**
- **40 Gy/20 fractions**

Rades et al IJROBP 2006;64(5):1452-1457

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)





Rades et al. JCO 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

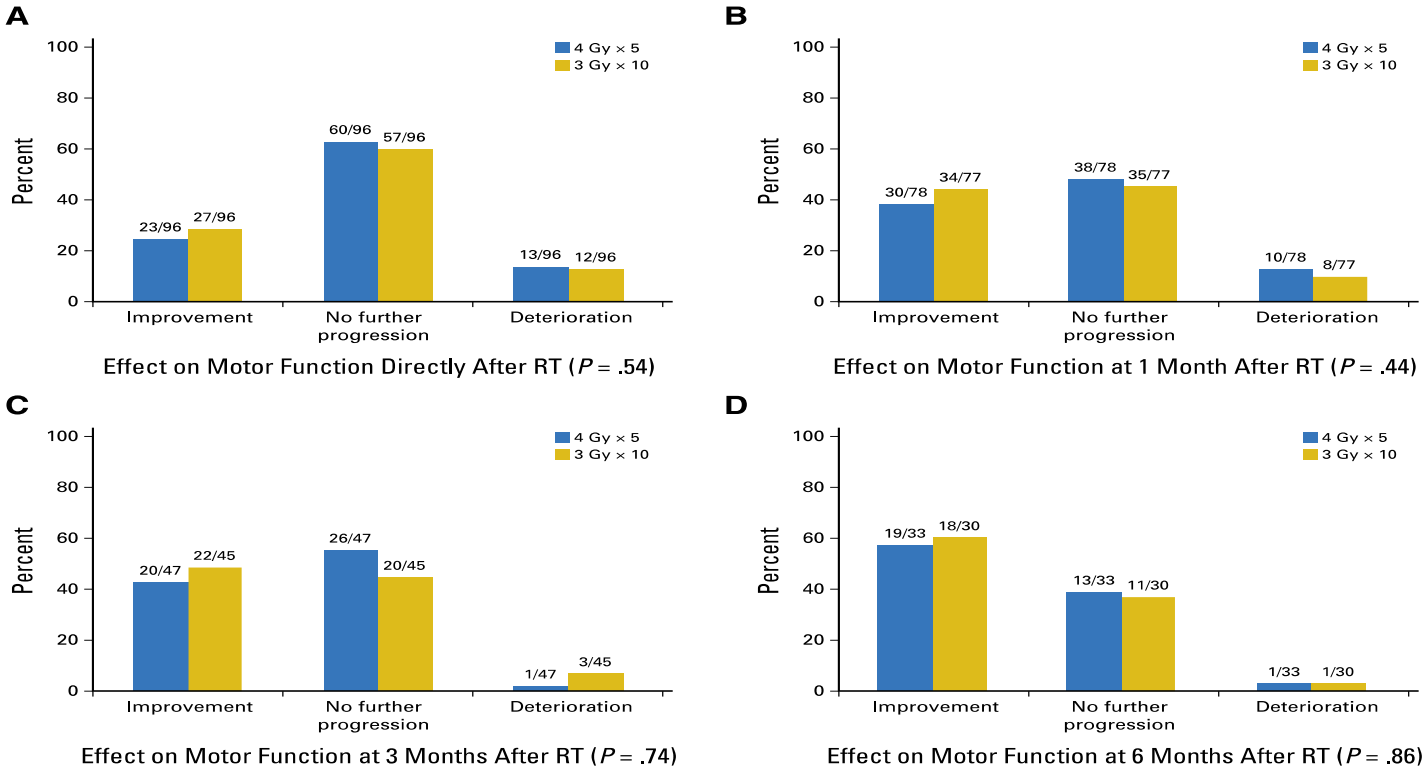
Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)

Table 1. Distribution of the Three Stratification Factors and Additional Characteristics

Stratification Factors and Additional Characteristics	Patients, n (%) 4 Gy × 5	3 Gy × 10	*P*
Stratification factor			
Ambulatory status before RT			
Ambulatory without aid (N = 52)	26 (25.7)	26 (25.5)	> .99
Ambulatory with aid (N = 65)	32 (31.7)	33 (32.4)	
Not ambulatory (N = 86)	43 (42.6)	43 (42.2)	
Time developing motor deficits before RT, days			
1-7 (N = 92)	46 (45.5)	46 (45.1)	> .99
8-14 (N = 53)	26 (25.7)	27 (26.5)	
> 14 (N = 58)	29 (28.7)	29 (28.4)	
Type of primary tumor			
Breast cancer (N = 32)	16 (15.8)	16 (15.7)	> .99
Prostate cancer (N = 32)	16 (15.8)	16 (15.7)	
Myeloma/lymphoma (N = 16)	8 (7.9)	8 (7.8)	
Lung cancer (N = 58)	29 (28.7)	29 (28.4)	
Other tumors (N = 65)	32 (31.7)	33 (32.4)	

Rades et al. JCO 2016

Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)



Rades et al. JCO 2016

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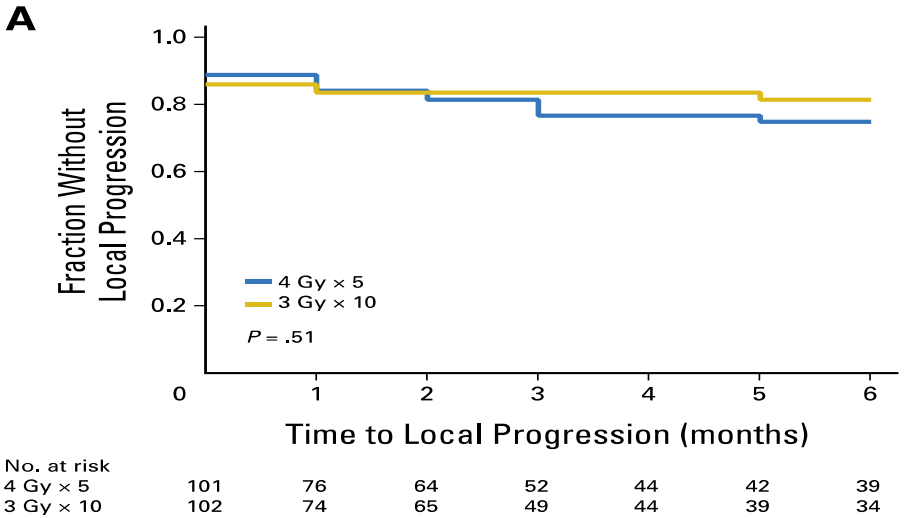
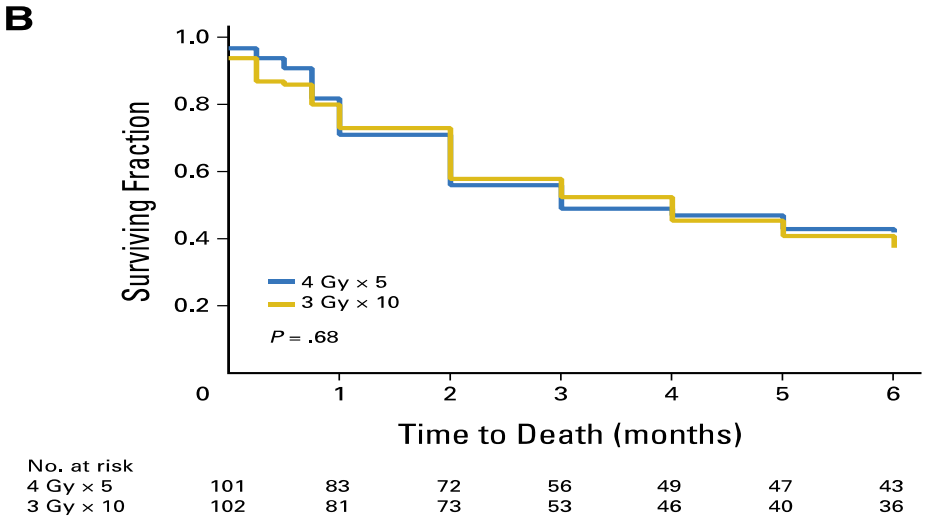




Rades et al. JCO 2016

Rades *et al. BMC Cancer* (2016) 16:292
DOI 10.1186/s12885-016-2325-y

BMC Cancer

RESEARCH ARTICLE Open Access

A predictive tool particularly designed for elderly myeloma patients presenting with spinal cord compression

Table 2 Characteristic significantly associated with overall survival in the Cox regression analysis and the corresponding scoring points based on the 1-year survival rates

	Scoring points
Age	
≤71 years	7
≥72 years	6
Myeloma type	
IgG	8
Others	5
ECOG-PS	
1–2	9
3–4	4
Ambulatory status prior to radiotherapy	
Ambulatory (with or without aid)	8
Not ambulatory	3

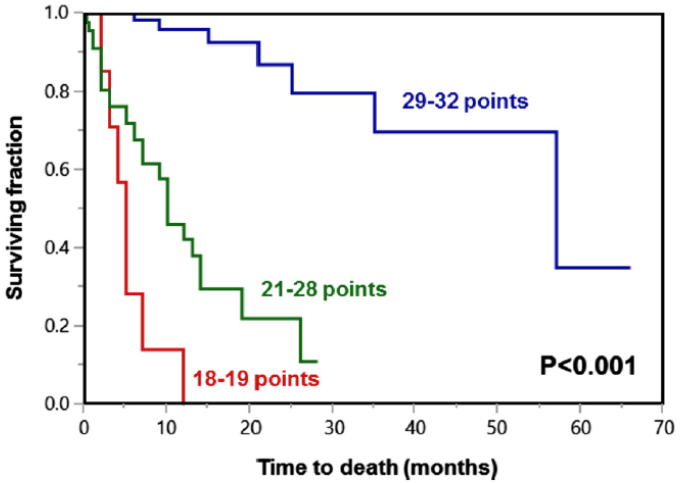


Fig. 2 Kaplan-Meier curves for the overall survival of the three prognostic groups 18–19 points, 21–28 points and 29–32 points

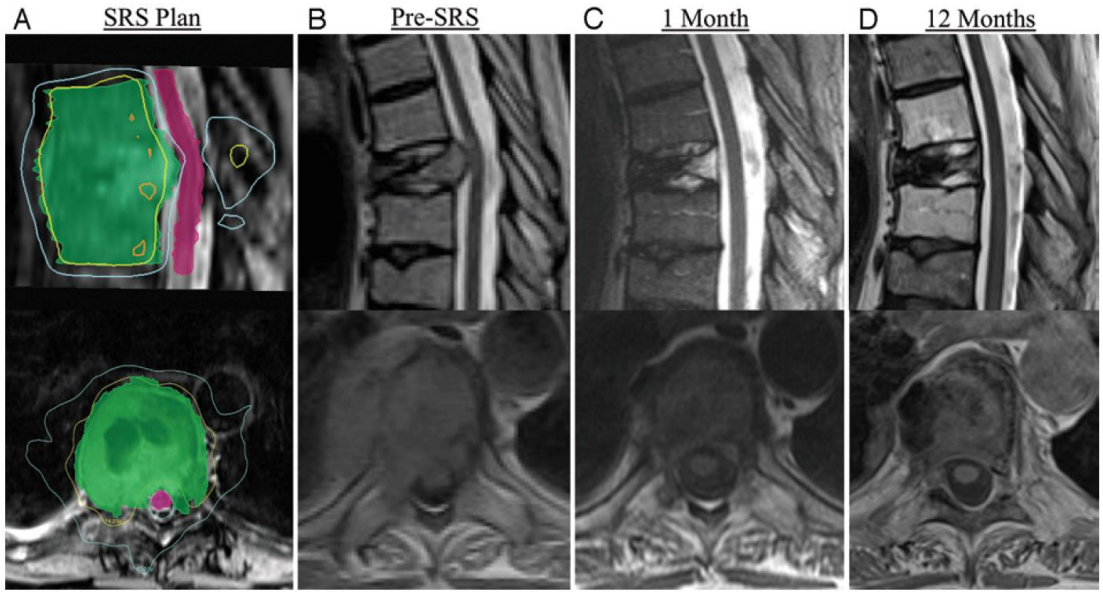
JNS SPINE

CLINICAL ARTICLE

J Neurosurg Spine 26:282–290, 2017

Spine stereotactic radiosurgery for the treatment of multiple myeloma

Jacob A. Miller, BS,[1] Ehsan H. Balagamwala, MD,[2] Samuel T. Chao, MD,[2,3] Todd Emch, MD,[4] John H. Suh, MD,[2,3] Toufik Djemil, PhD,[5] and Lilyana Angelov, MD[3,6]



This study reports the largest series of myeloma lesions treated with spine SRS (14-16 Gy single fraction)

A rapid and durable symptomatic response was observed, with a median time to pain relief of 1.6 months

This response was durable among 85% of patients at 12 months following treatment, with 91% local control

SRS should be considered for patients with MM and limited spinal disease, myelosuppression
requiring “marrow-sparing” radiation therapy, or recurrent disease after EBRT

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Radiation Therapy for Solitary Plasmacytoma and Multiple Myeloma: Guidelines From the International Lymphoma Radiation Oncology Group

International Journal of Radiation Oncology biology • physics

www.redjournal.org

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Volume 101 • Number 4 • 2018

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MM Palliation with RT

- For bony sites, where the goal is limited to symptom relief: a hypofractionated regimen with a total dose of 8 to 30 Gy (eg, 8 Gy in 1 fraction, 20 Gy in 5 daily fractions, or 30 Gy in 10 daily fractions, delivered as 5 fractions per week). A single 8 Gy fraction is preferred for bone disease in patients with poor prospects for survival

- Alternatively, conventional fractionation: 20 to 30 Gy in 10 to 15 daily fractions, at 5 fractions per week. This approach may be preferred if RT volumes are large or for retreatment

- For epidural disease with spinal cord compression, or a bulky mass, when durable local control is desired: 30 Gy in 10 to 15 daily fractions, at 5 fractions per week

- Spinal radiosurgery may represent an interesting oppirtunity for highly selected patients (in a reirradiation scenario)

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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)

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 Bone Plasmacytoma Bone (SBP)** [mostly occurs in the bones of the axial skeleton]

- When in soft tissues (less common: 20 to 30% of cases), the lesion is called **Solitary Extramedullary Plasmacytoma (SEP or EMP)**, occurring mostly (80% of the time) in the head and neck region (nasal cavity, paranasal sinuses, nasopharynx)

- SBPs 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

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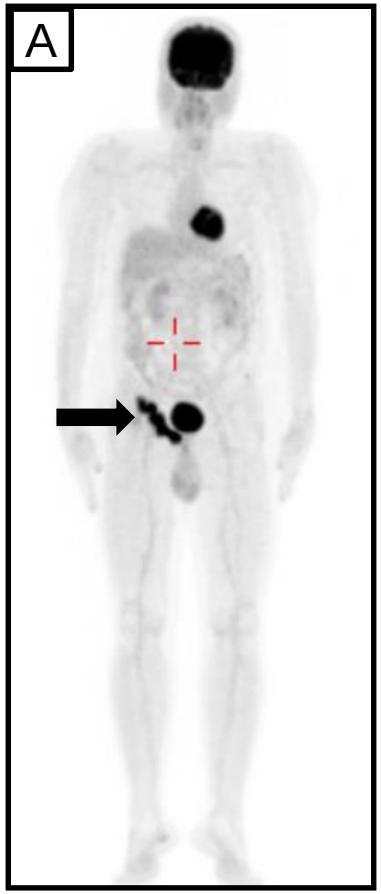

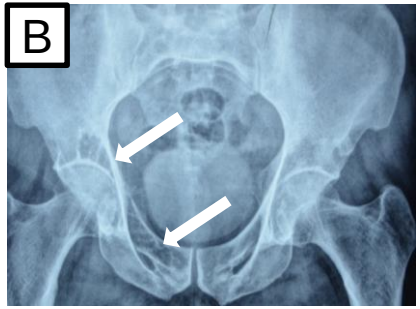

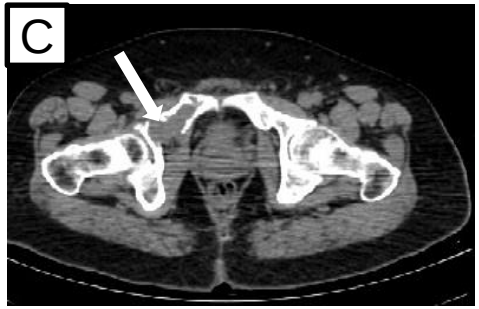

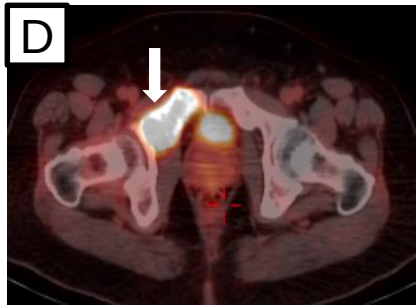

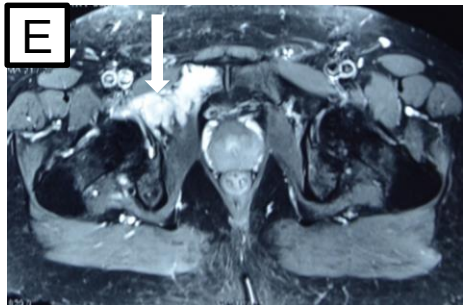

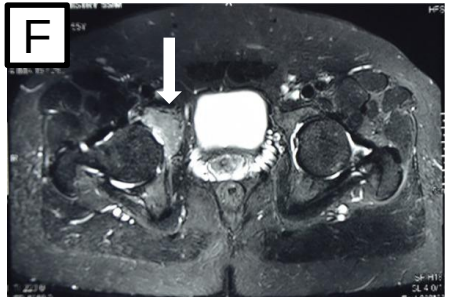

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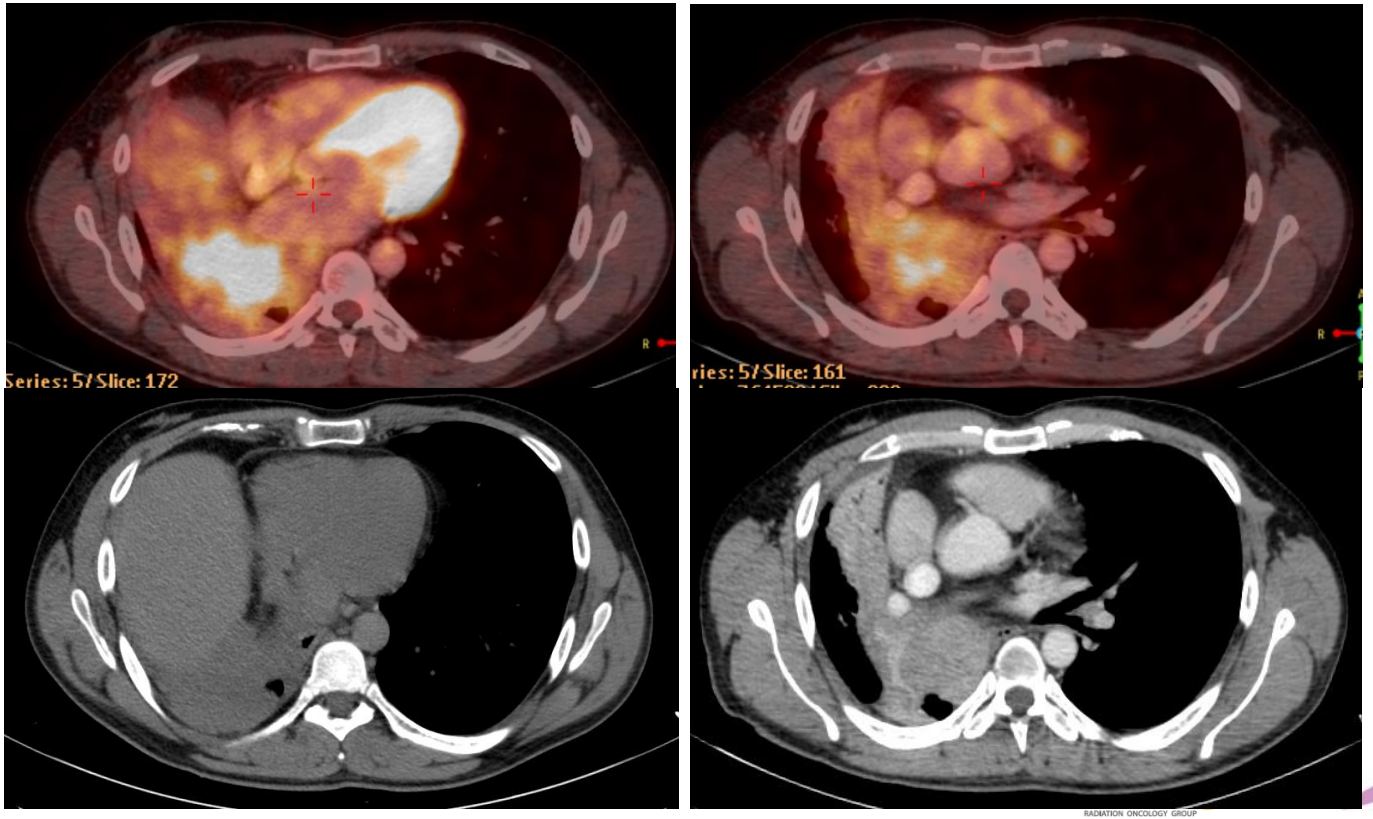
Bronchial plasmacytoma



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)

Solitary Plasmacytoma

Table 1 Diagnostic criteria for solitary plasmacytoma, as recommended by the International Myeloma Working Group (1). The diagnosis of solitary plasmacytomas is based on the exclusion of systemic plasma cell disorders.

Plasma cell disorder	Diagnostic criteria
Solitary bone plasmacytoma, or solitary extramedullary plasmacytoma	• Biopsy-proven solitary destructive lesion of bone or soft tissue mass of clonal plasma cells. • Absence of clonal plasma cells in bone marrow biopsy and aspirate. • Normal skeletal survey and magnetic resonance imaging (or computed tomography) of spine and pelvis (except for the primary solitary lesion) • If available positron emission tomography/computed tomography showing solitary lesion (2) • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) attributed to a plasma cell proliferative disorder
Solitary plasmacytoma with minimal marrow involvement	• As above but: • Clonal bone marrow plasma cells are detected but quantified to be $<10\%$

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- The updated 2017 International Myeloma Working Group guidelines consider PET/CT as a valuable tool in many indications, including the work-up of patients with MM, and in fact stated that PET/CT is mandatory to confirm a diagnosis of solitary plasmacytoma

- ILROG recommends that PET/CT should be performed as standard work-up for SP, particularly when whole body MRI is of limited availability

Solitary Bone Plasmacytoma

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

RT Dose Consideration for SP: ILROG consensus

The following dose guidelines are recommended (with 1.8-2 Gy daily fractions):

- **SBPs < 5 cm:** total dose 35 to 40 Gy (for small SBPs it is acceptable to prescribe 35 Gy, which is different from the National Comprehensive Cancer Network's recommendation of minimum total dose of 40 Gy)

- **SBPs ≥ 5 cm:** total dose 40 to 50 Gy

- **SEPs:** total dose 40 to 50 Gy (in cases of small, welldefined, or postexcision with positive margins, 40 Gy is acceptable)

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Radiation volumes

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 (other than the entire involved bone)

Prophylactic regional nodes irradiation is not necessary in SBP, 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

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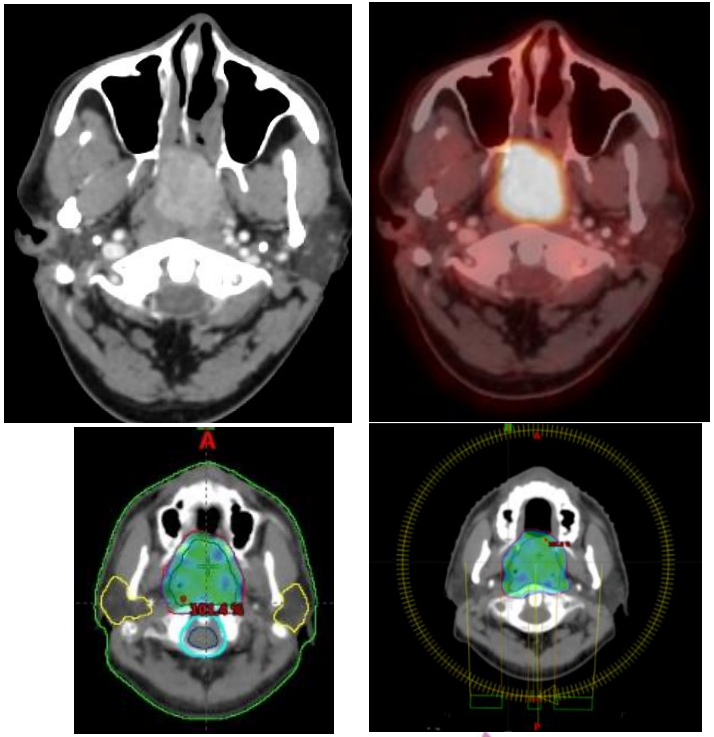
SEP: benefit of prophylactic nodal irradiation

With the advent of sophisticated imaging (MRI and PET/CT), the ILROG panel consensus is that elective lymph node coverage is not required for SEP, unless there is persuasive clinical evidence to indicate a high risk of nodal involvement, such as very bulky primary disease or proximity to the primary lesion when nodal coverage will not increase the treatment toxicity in a significant way



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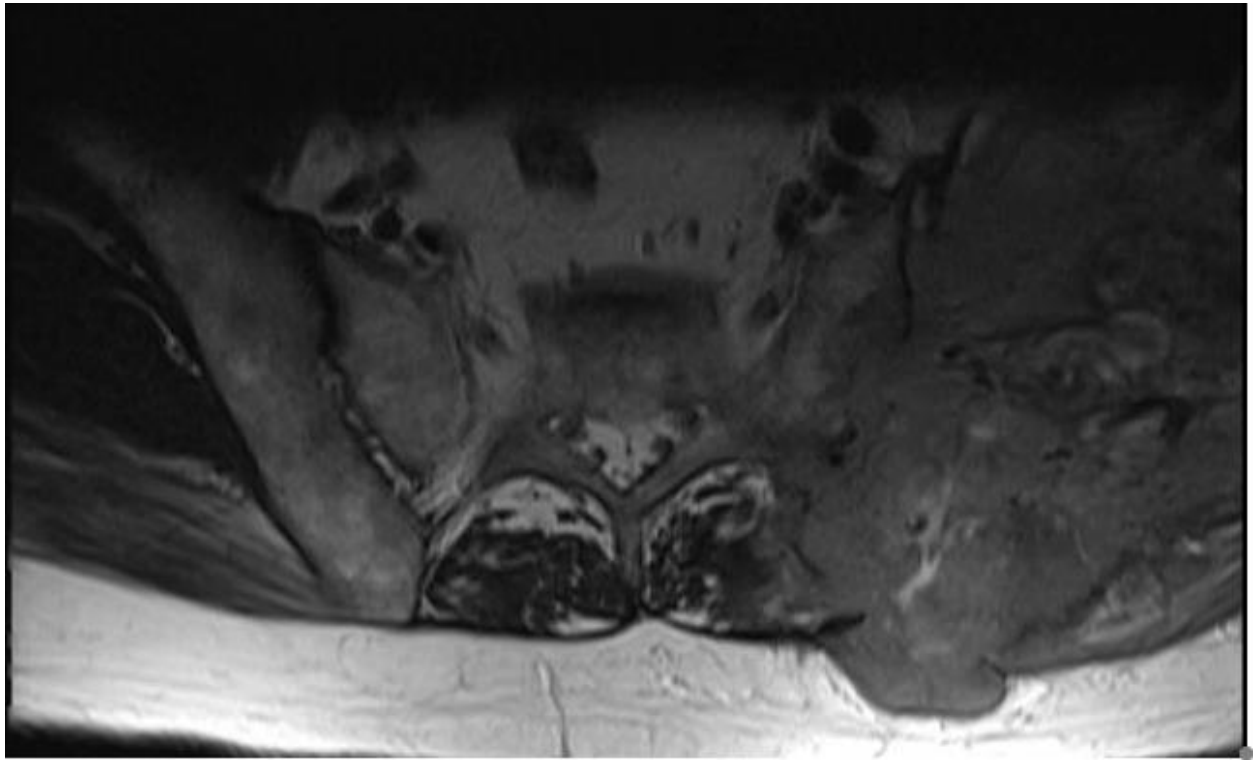

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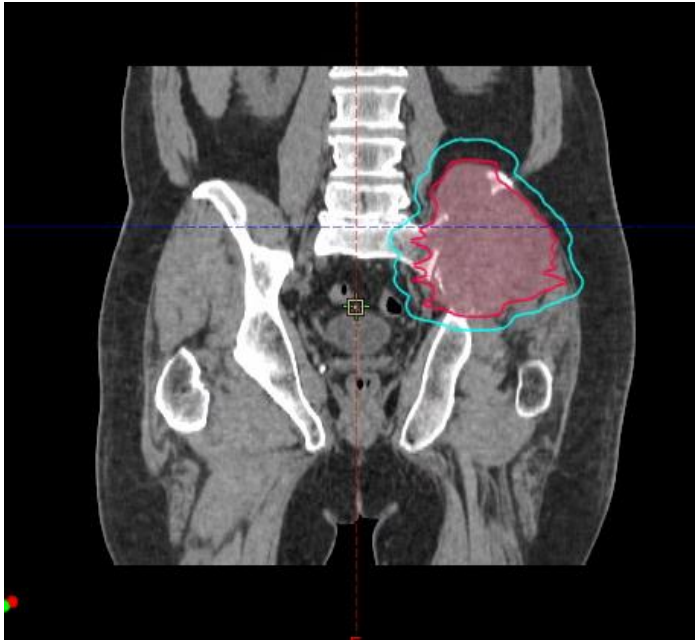

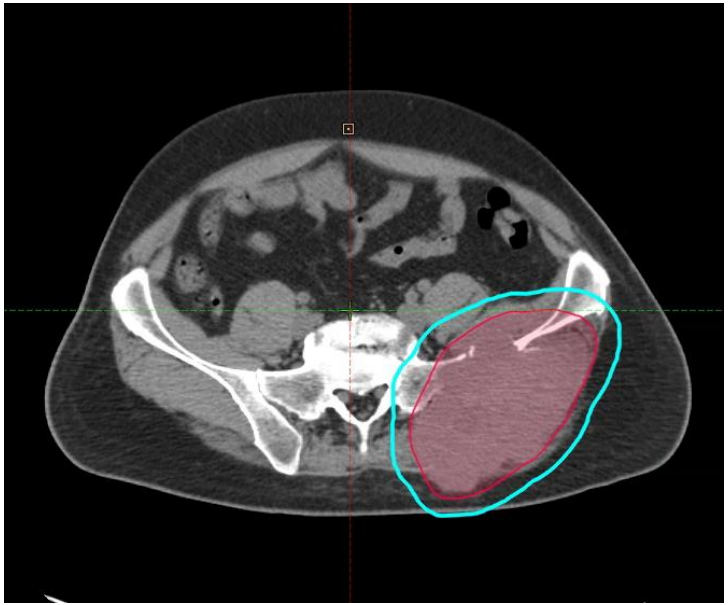

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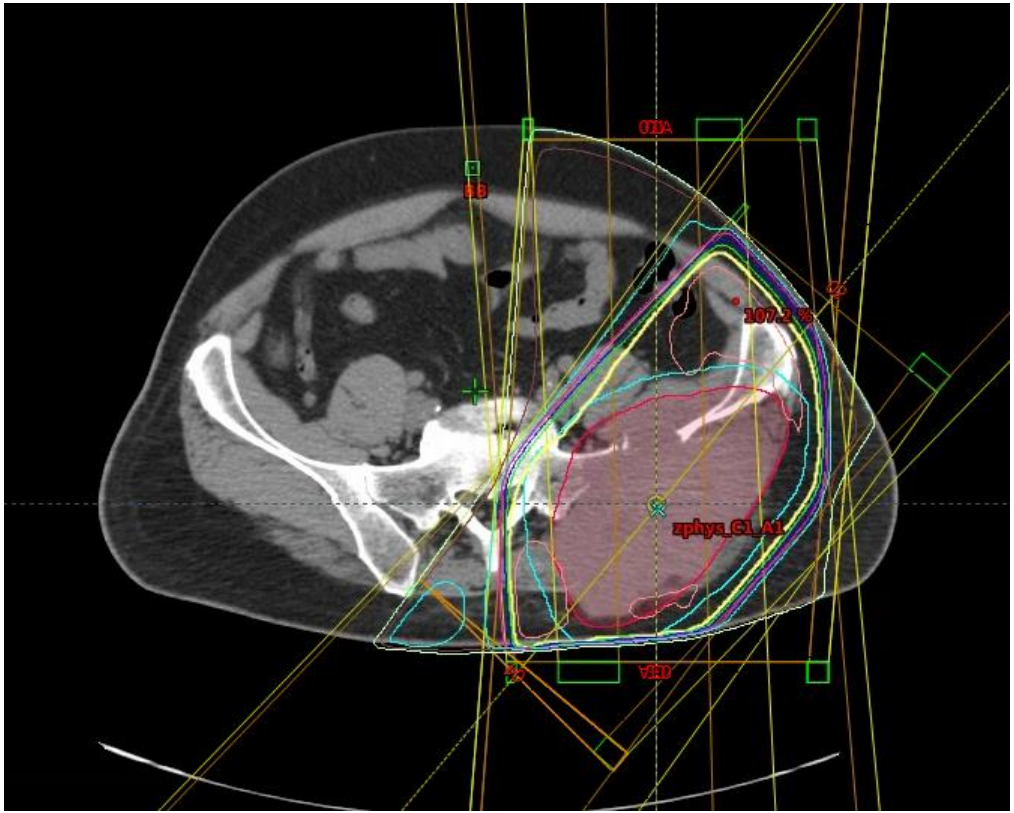
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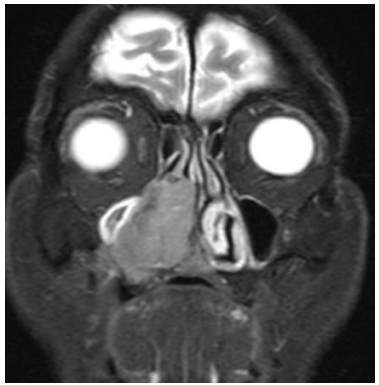
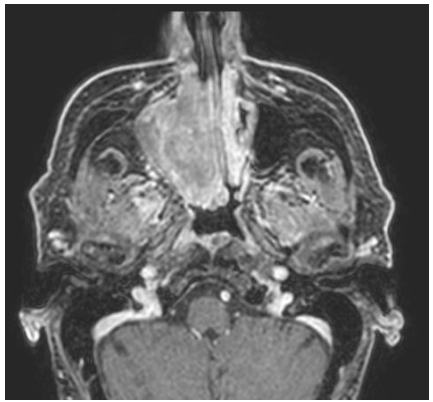
Extramedullary plasmacytoma

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)





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MULTI-INSTITUTIONAL ANALYSIS OF SOLITARY EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK TREATED WITH CURATIVE RADIOTHERAPY

67 patients

1983-2008

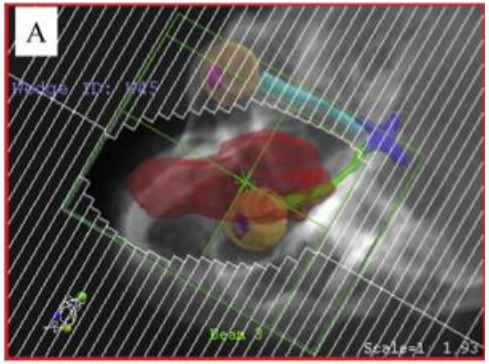
Japanese cohort

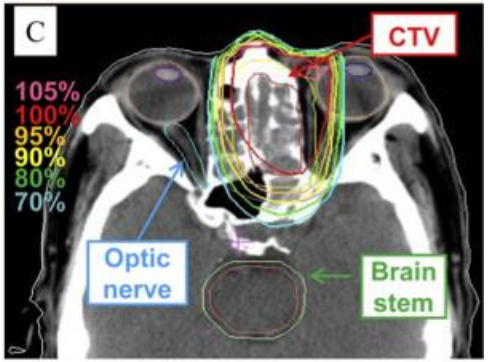
Median RT dose 50 Gy

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

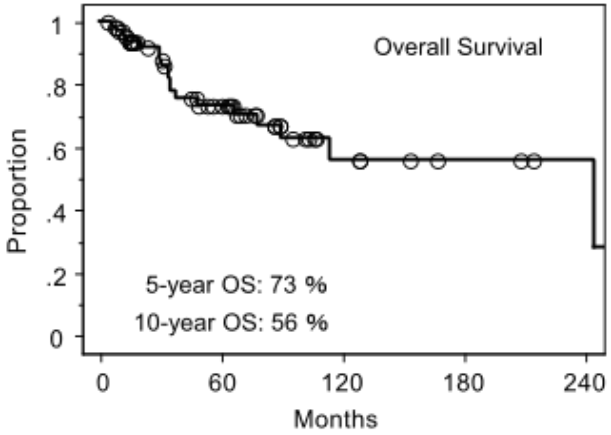
* median age, median tumor size.





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



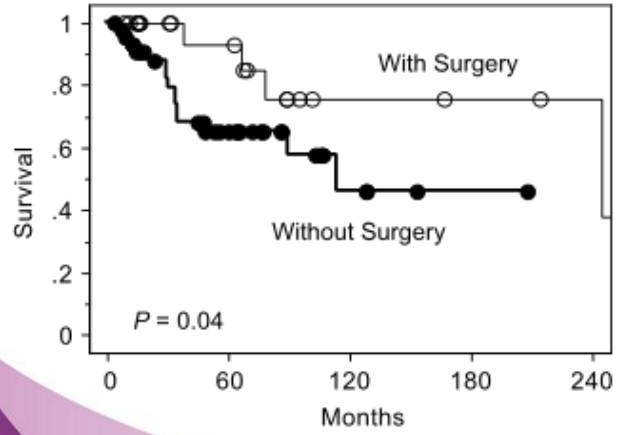


Table 5. Prognostic factors for overall survival

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

Patterns of failure:

- local recurrence
- development of MM
- development of new bony 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 worse 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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Management of SP (SBP and SEP)

- SBPs have a high risk of progression to MM (65 to 84% in 10 years)
- In contrast, SEPs have a lower risk of progression to MM (10 to 30% over 10 years), but have a slightly higher risk of local recurrence
- Currently, the standard of care for SBP and SEP is definitive local RT, as it provides excellent local control (85 to 90%) that may translate into a durable remission and even cure

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- “Adjuvant” systemic treatments are not of convincing benefit in SBP and EMP

Future directions

- The addition of adjuvant novel agents to RT, such as proteasome inhibitors or immunomodulatory drugs (eg, lenalidomide), is a theoretically attractive approach, both in enhancing local control and possibly eradicating subclinical disease in patients with SP to prevent the development of systemic MM

- Preliminary data suggest feasibility and effectiveness of a combined approach

- This approach will be under active investigation in the United Kingdom in a phase 3 study, examining the potential role of lenalidomide with dexamethasone in improving progression-free survival

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Imaging in the Management of Lymphoma

George Mikhaeel

Professor of Radiation Oncology, King's College London, UK

Consultant Clinical Oncologist, Guy's & St Thomas' NHS Trust, London

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Guy's Cancer

Outline

- Staging & Response assessment: Lugano Criteria–2104.
- What is after Lugano?
- Optimal use of imaging for RT

Staging & Response Criteria

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

What is new in Lugano Classification?
(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.

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

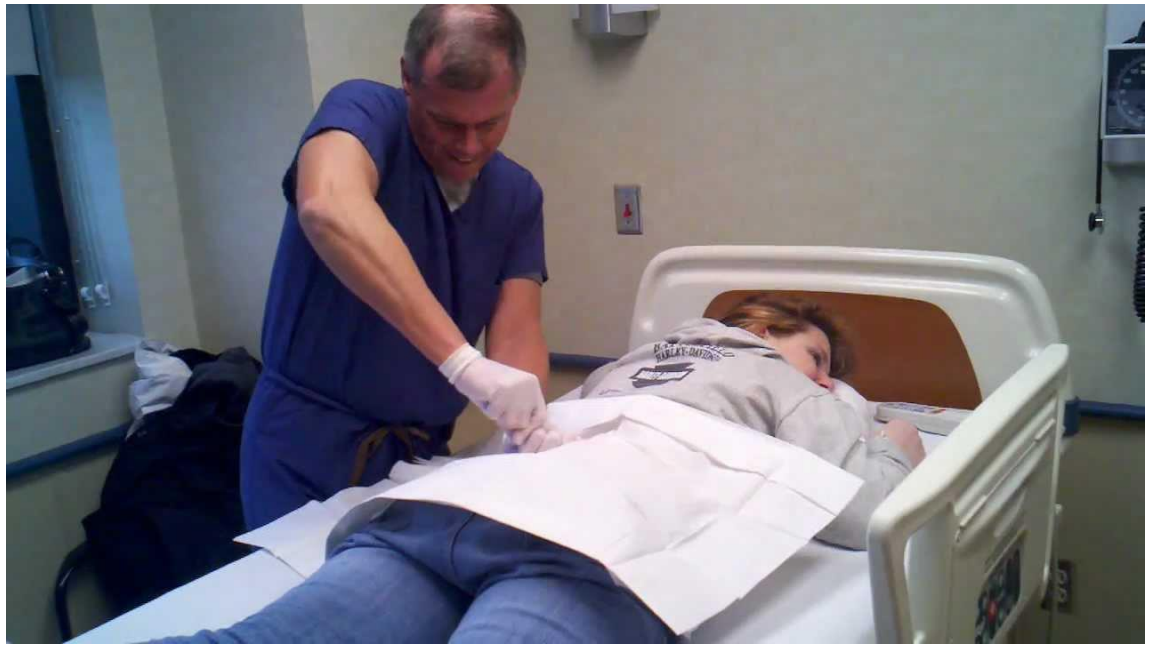
	Histology and numbers of patients included in studies	Percentage FDG-avid
B-cell	Hodgkin lymphoma (n = 489)	97 - 100
	Diffuse Large B cell lymphoma (n = 446)	97 - 100
	Follicular lymphoma (n = 622)	91 - 100
	Mantle cell lymphoma (n = 83)	100
	Burkitt lymphoma (n = 24)	100
	Lymphoblastic lymphoma (n = 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
T-cell	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

SLL / CLL
EN MZL / MALT

Some cutaneous
T-cell

Modified from Weiler-Sagie et al. JNM 51: 25-30, 2010

Bone Marrow Biopsy

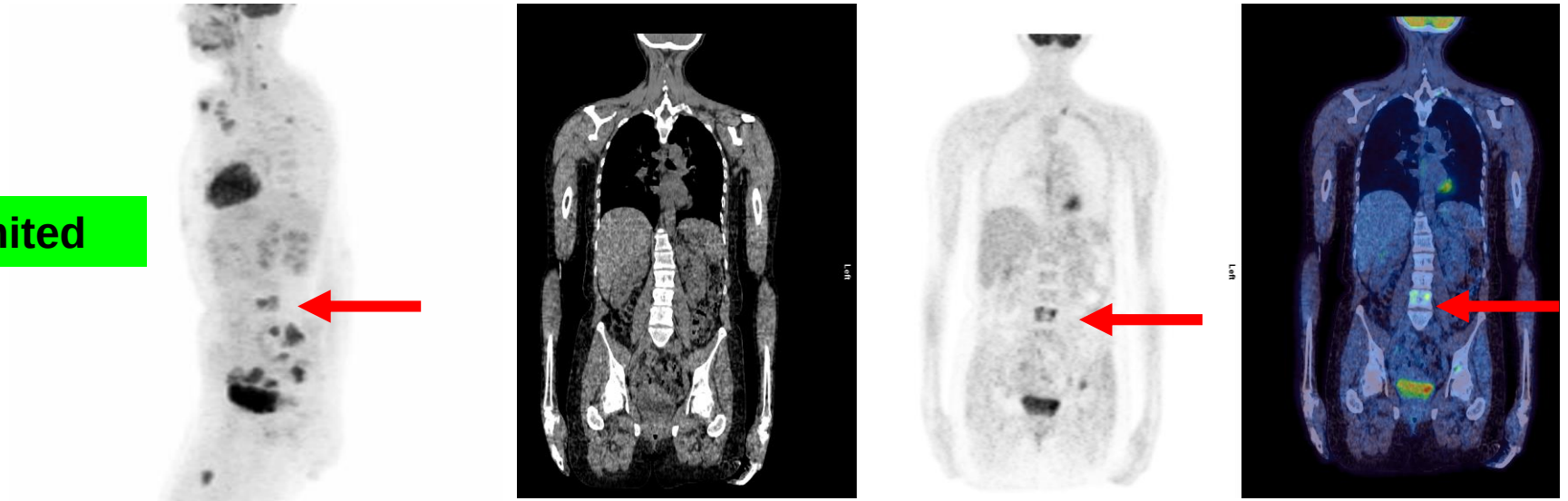


'As a cancer survivor I can tell you this procedure hurts like no other and generally all doctors downplay the pain'.

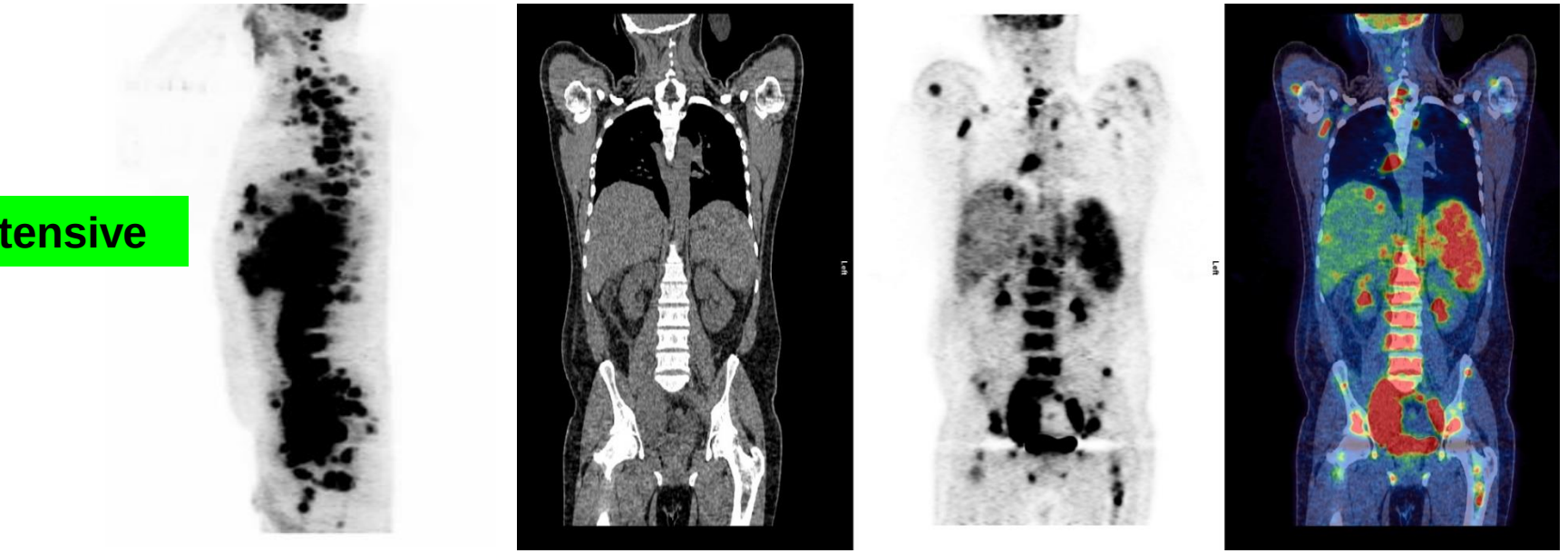
(You Tube posted 2011)

BM Involvement

Limited

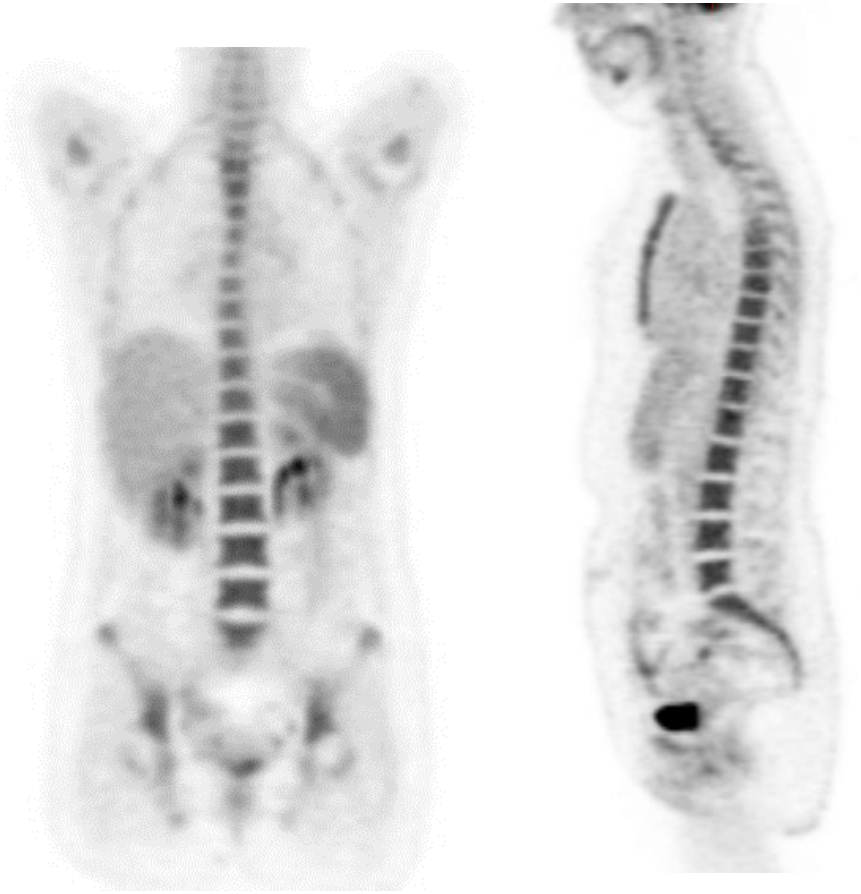


Extensive

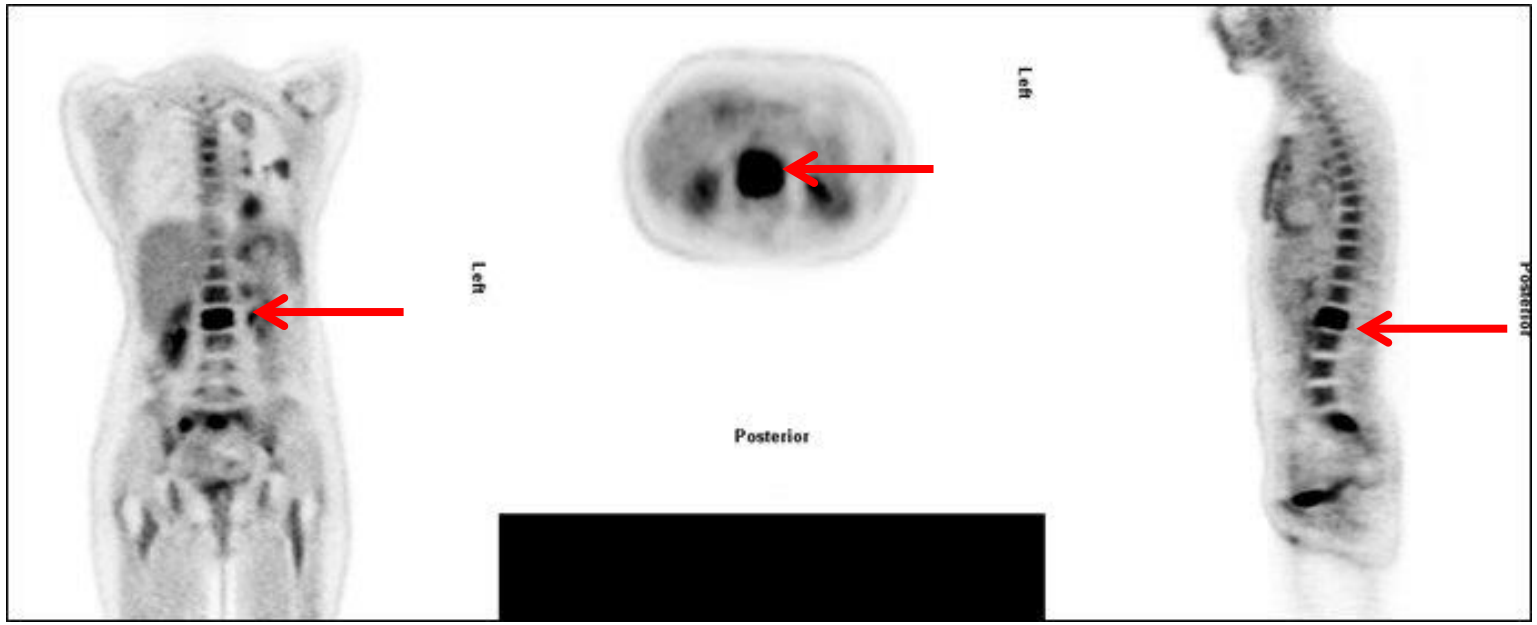


Interpretation of DIFFUSE marrow uptake

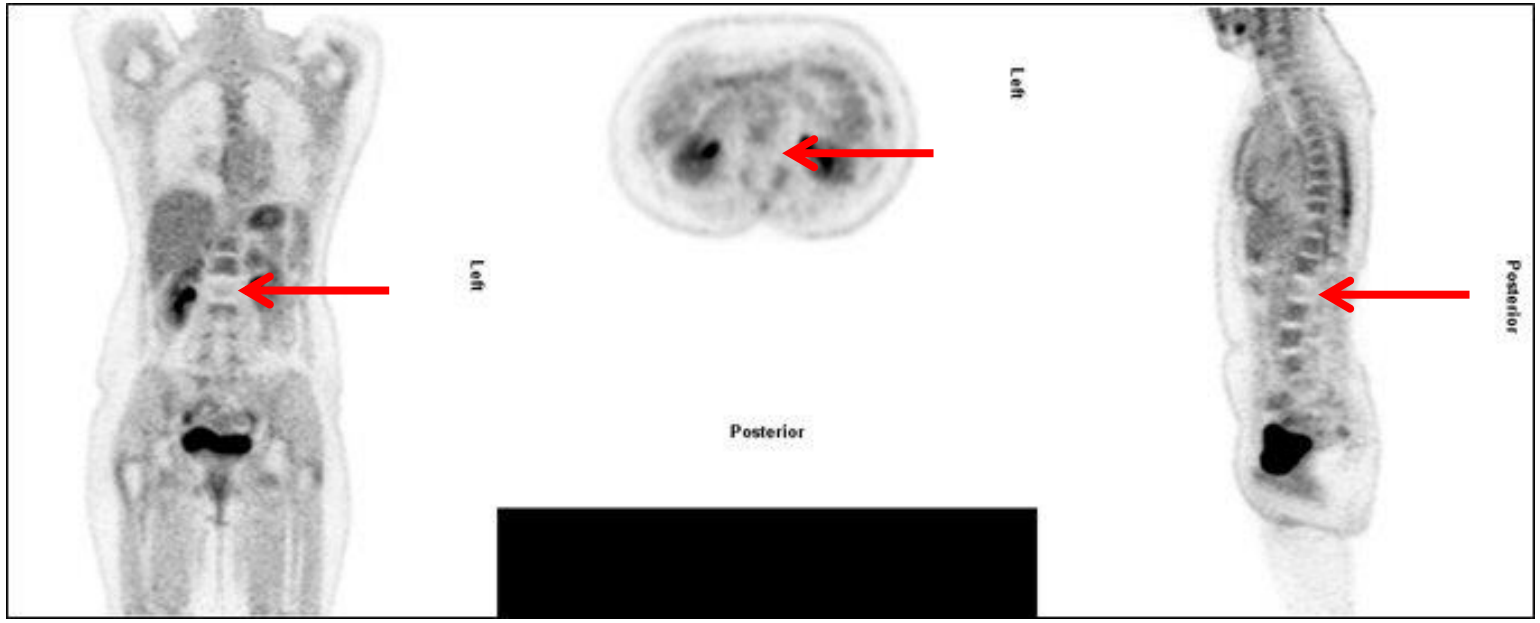
- indicates hyperplasia in HL
- occurs with chemotherapy & GCSF
- can indicate BMI or hyperplasia in DLBCL



Baseline



Response



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]

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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 %)

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 %)

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 BM involvement 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

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?

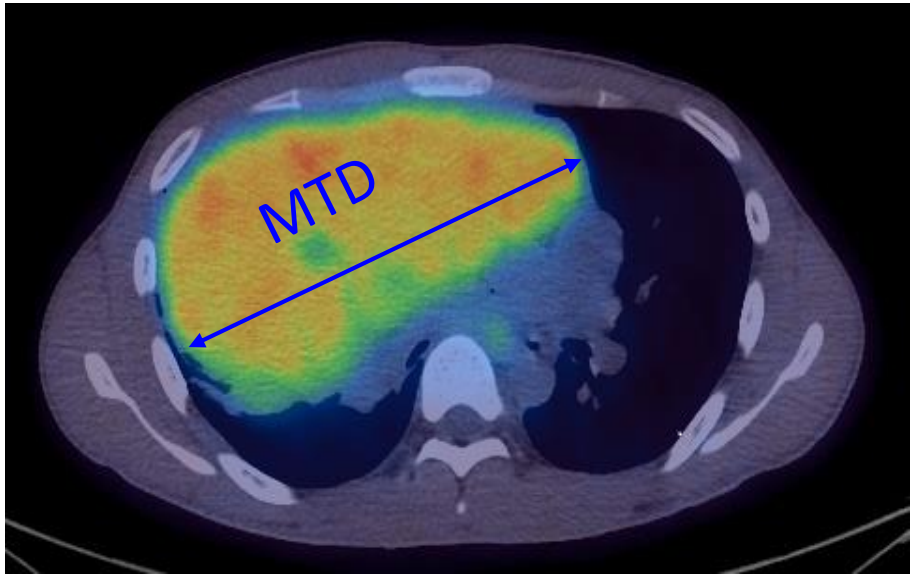
- Maximum tumour dimension (MTD) on CT should be recorded at staging*

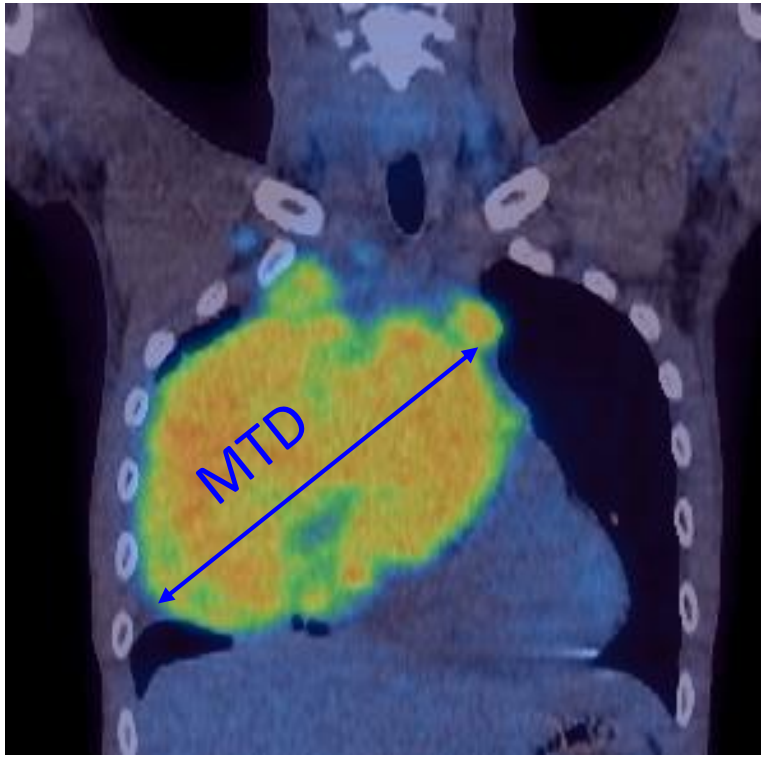
  * *Term X need no longer be used*

- Methods of Volumetric Measurement of total tumour volume should be explored

Maximum Tumour Dimension (MTD)

longest dimension in transverse & longitudinal planes

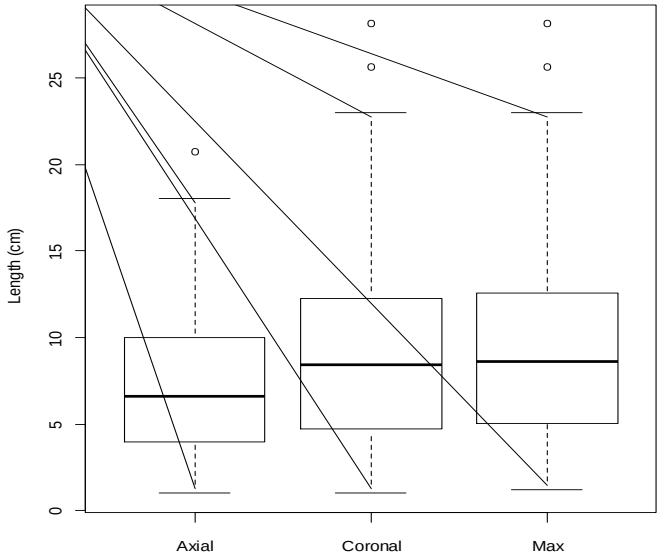


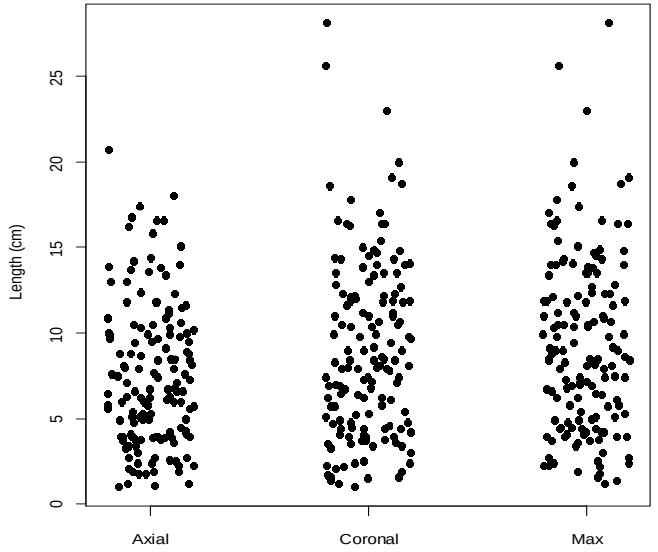


- PET: metabolic tumour volume (MTV) defined by total volume of tumour with uptake ≥2.5 SUV.

Max Tumour Dimension (147 DLBCL pts)

MTD (cm)	Transverse	longitudinal
Mean	7.5	9.0
Median	6.6	8.4
Range	1.0 – 20.7	1.0 – 28.1

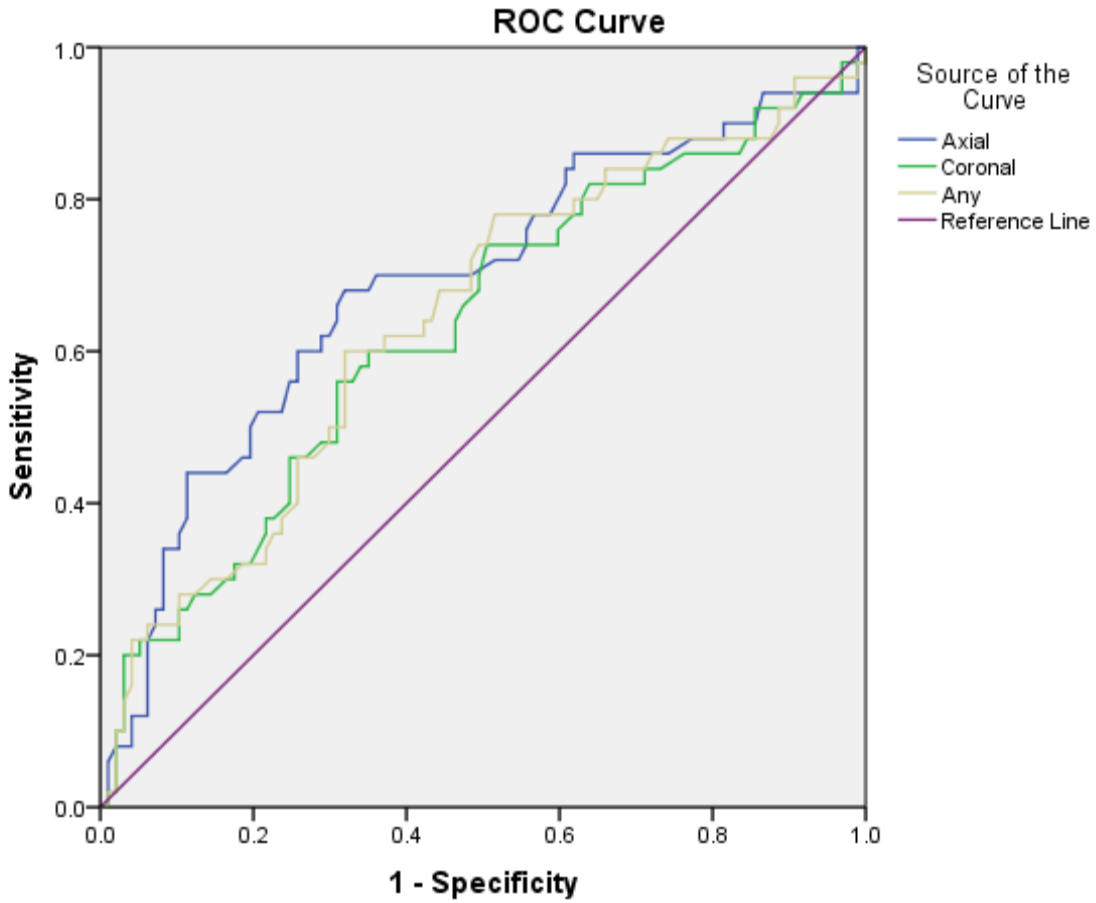




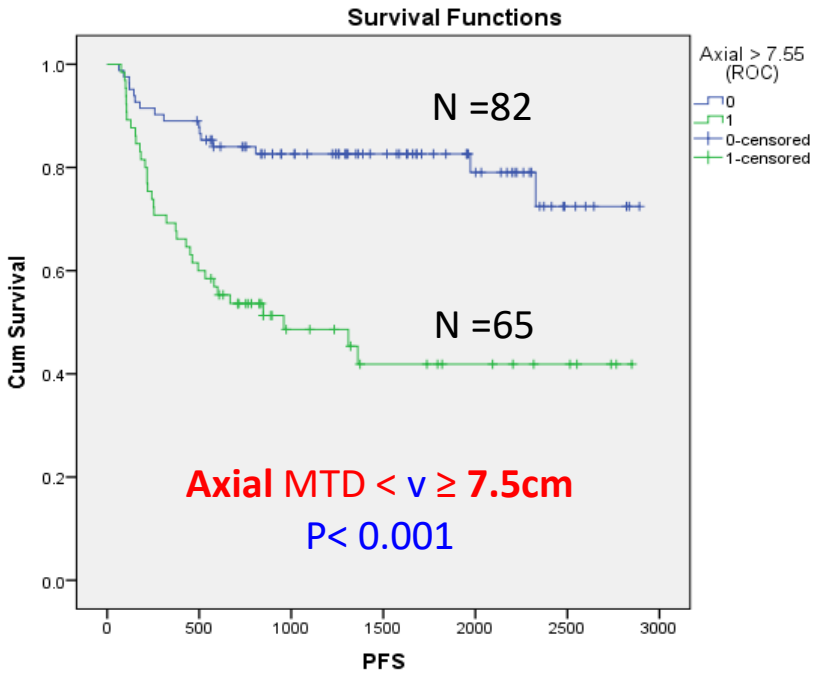
Longitudinal MTD greater > transverse MTD in 108 patients (73.5 %).

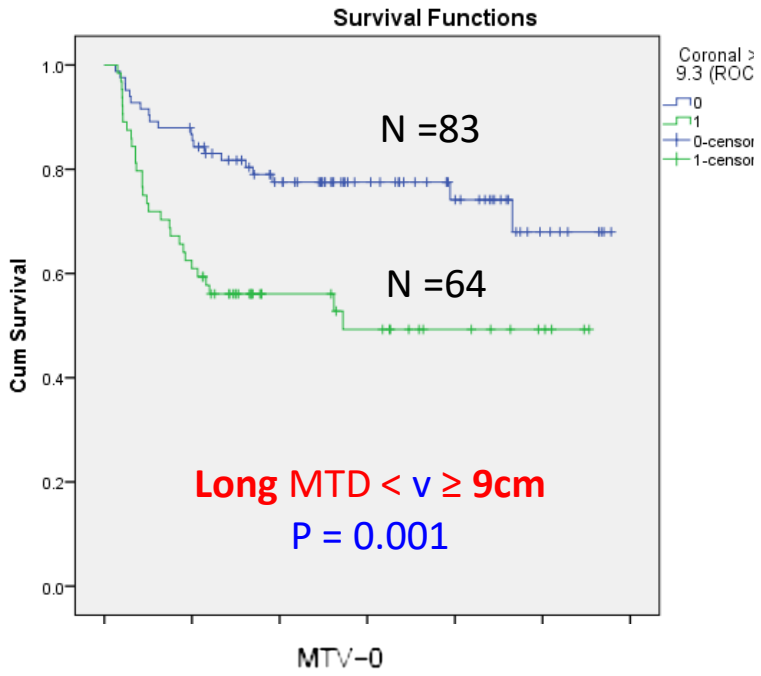
Mikhaeel ASTRO 2015

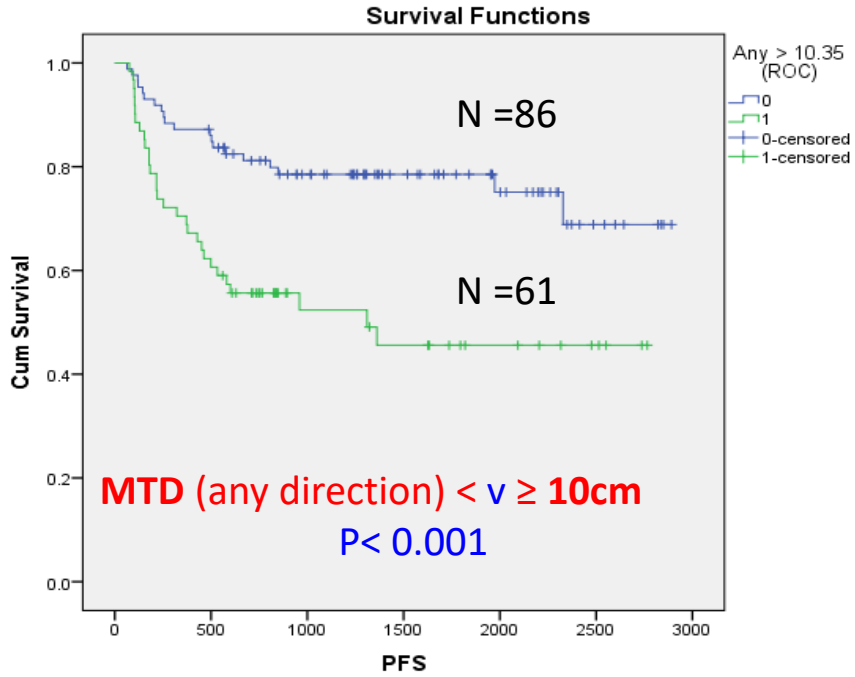
MTD
best cut-off
to predict PFS



	Optimal Cut off (cm)	Sensitivity	Specificity
Axial	7.55	.68	.68
Coronal	9.3	.60	.65
Any direction	10.35	.60	.68







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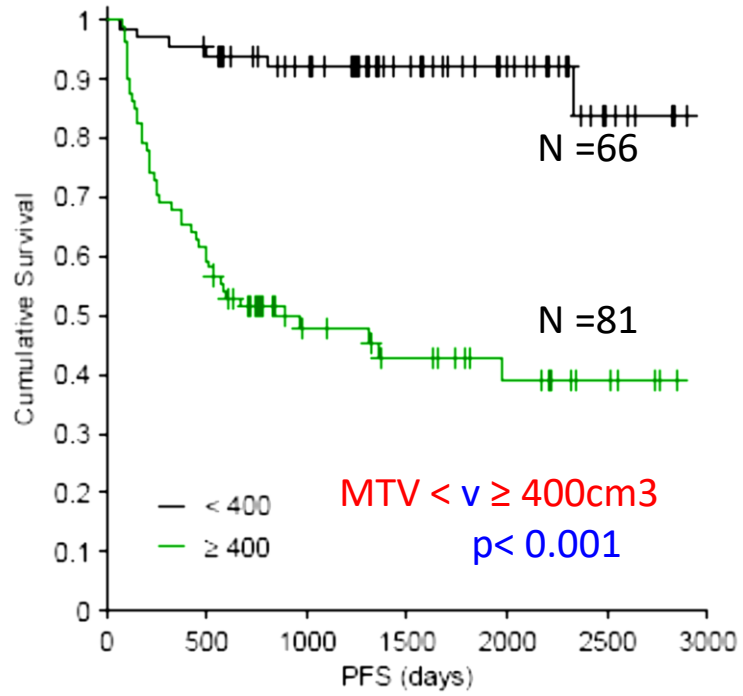


Mikhaeel ASTRO 2015

ARTICLE

Definition of bulky disease in early stage Hodgkin lymphoma in computed tomography era: prognostic significance of measurements in the coronal and transverse planes

Anita Kumar,[1] Irene A. Burger,[2] Zhigang Zhang,[3] Esther N. Drill,[3] Jocelyn C. Migliacci,[1] Andrea Ng,[4] Ann LaCasce,[5] Darci Wall,[6] Thomas E. Witzig,[7] Kay Ristow,[7] Joachim Yahalom,[8] Craig H. Moskowitz,[1] and Andrew D. Zelenetz[1]

[1]Lymphoma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [2]Department Medical Radiology, University Hospital Zurich, Switzerland; [3]Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [4]Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA; [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [6]Department of Hematology, Mayo Clinic, Rochester, MN, USA; [7]Department of Hematology, Mayo Clinic, Rochester, MN, USA; and [8]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

Haematologica 2016
Volume 101(10):1237-1243

ABSTRACT

Disease bulk is an important prognostic factor in early stage Hodgkin lymphoma, but its definition is unclear in the computed tomography era. This retrospective analysis investigated the prognostic significance of bulky disease measured in transverse and coronal planes on computed tomography imaging. Early stage Hodgkin lymphoma patients (n=185) treated with chemotherapy with or without radiotherapy from 2000-2010 were included. The longest diameter of the largest lymph node mass was measured in transverse and coronal axes on pre-treatment imaging. The optimal cut off for disease bulk was maximal diameter greater than 7 cm measured in either the transverse or coronal plane. Thirty patients with maximal transverse diameter of 7 cm or under were found to have bulk in coronal axis. The 4-year overall survival was 96.5% (CI: 93.3%, 100%) and 4-year relapse-free survival was 86.8% (CI: 81.9%, 92.1%) for all patients. Relapse-free survival at four years for bulky patients was 80.5% (CI: 73%, 88.9%) compared to 94.4% (CI: 89.1%, 100%) for non-bulky; Cox HR 4.21 (CI: 1.43, 12.38) (P=0.004). In bulky patients, relapse-free survival was not impacted in patients treated with chemoradiotherapy; however, it was significantly lower in patients treated with chemotherapy alone. In an independent validation cohort of 38 patients treated with chemotherapy alone, patients with bulky disease had an inferior relapse-free survival [at 4 years, 71.1% (CI: 52.1%, 97%) *vs.* 94.1% (CI: 83.6%, 100%), Cox HR 5.27 (CI: 0.62, 45.16); P=0.09]. Presence of bulky disease on multidimensional computed tomography imaging is a significant prognostic factor in early stage Hodgkin lymphoma. Coronal reformations may be included for routine Hodgkin lymphoma staging evaluation. In future, our definition of disease bulk may be useful in identifying patients who are most appropriate for chemotherapy alone.

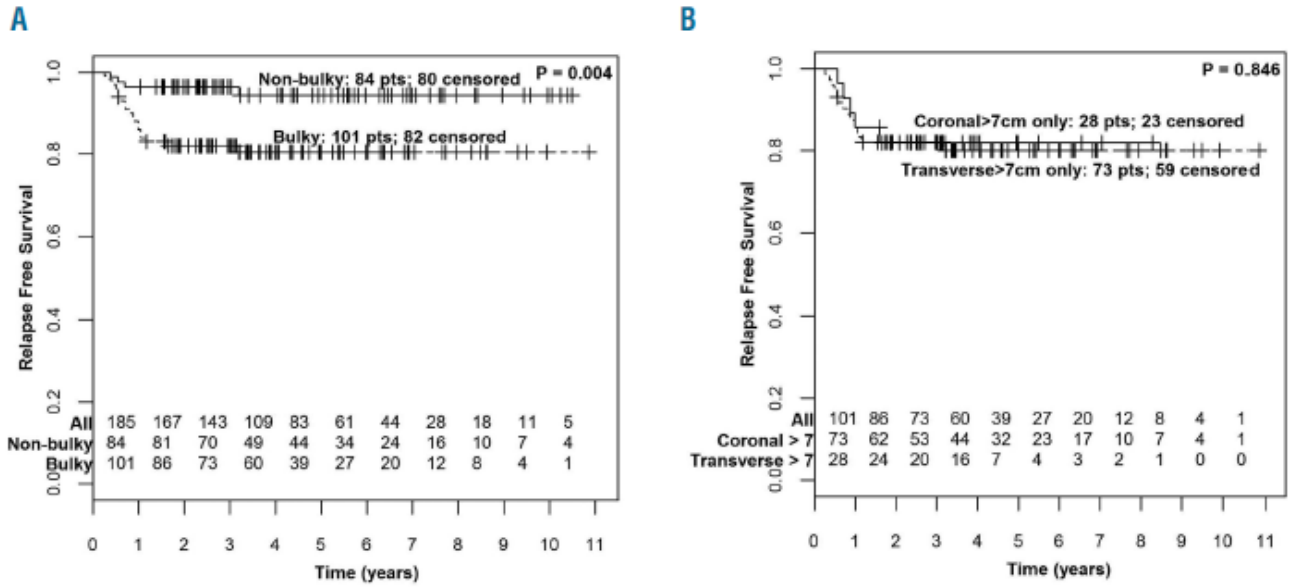


Figure 3. Relapse-free survival (RFS) by presence of bulky disease. (A) RFS for non-bulky *versus* bulky disease (transverse or coronal max diameter > 7cm). (B) RFS for coronal bulk alone (coronal max measurement > 7cm, transverse max, measurement ≤ 7cm) compared to traditional definition of bulk (transverse max, measurement >7cm).

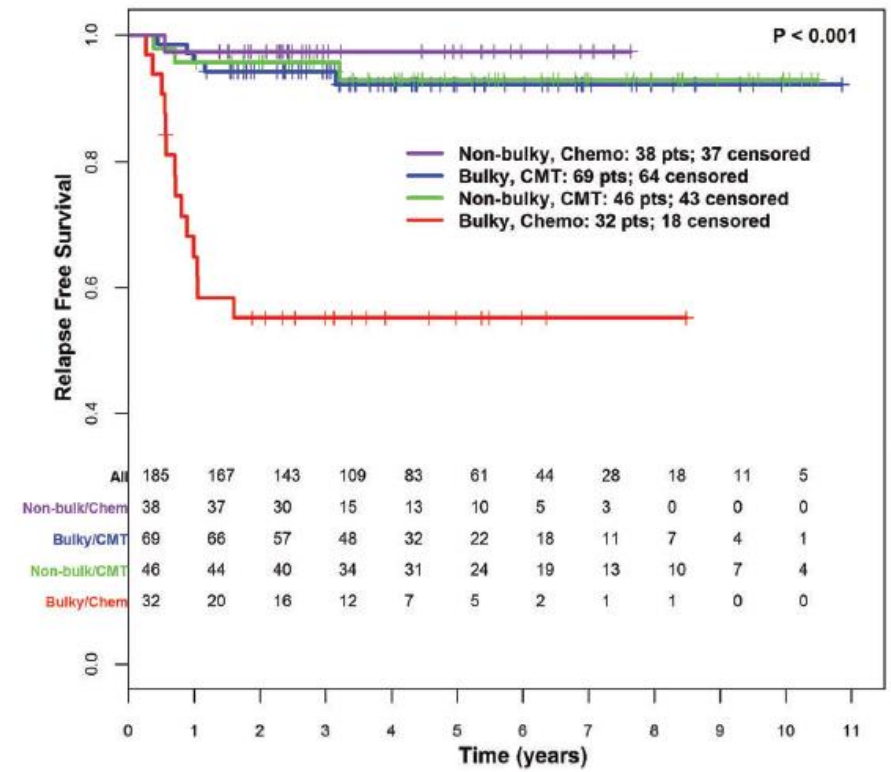


Figure 4. Relapse-free survival by presence of bulky disease (transverse or coronal max, diameter > 7cm) and treatment [chemotherapy alone (Chemo) *vs.* combined modality therapy (CMT)].

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.

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

Escalation De-escalation

Score 1 no uptake

Score 2 uptake ≤ mediastinum

Score 3 uptake > mediastinum but ≤ liver

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

Negative scan

Positive scan

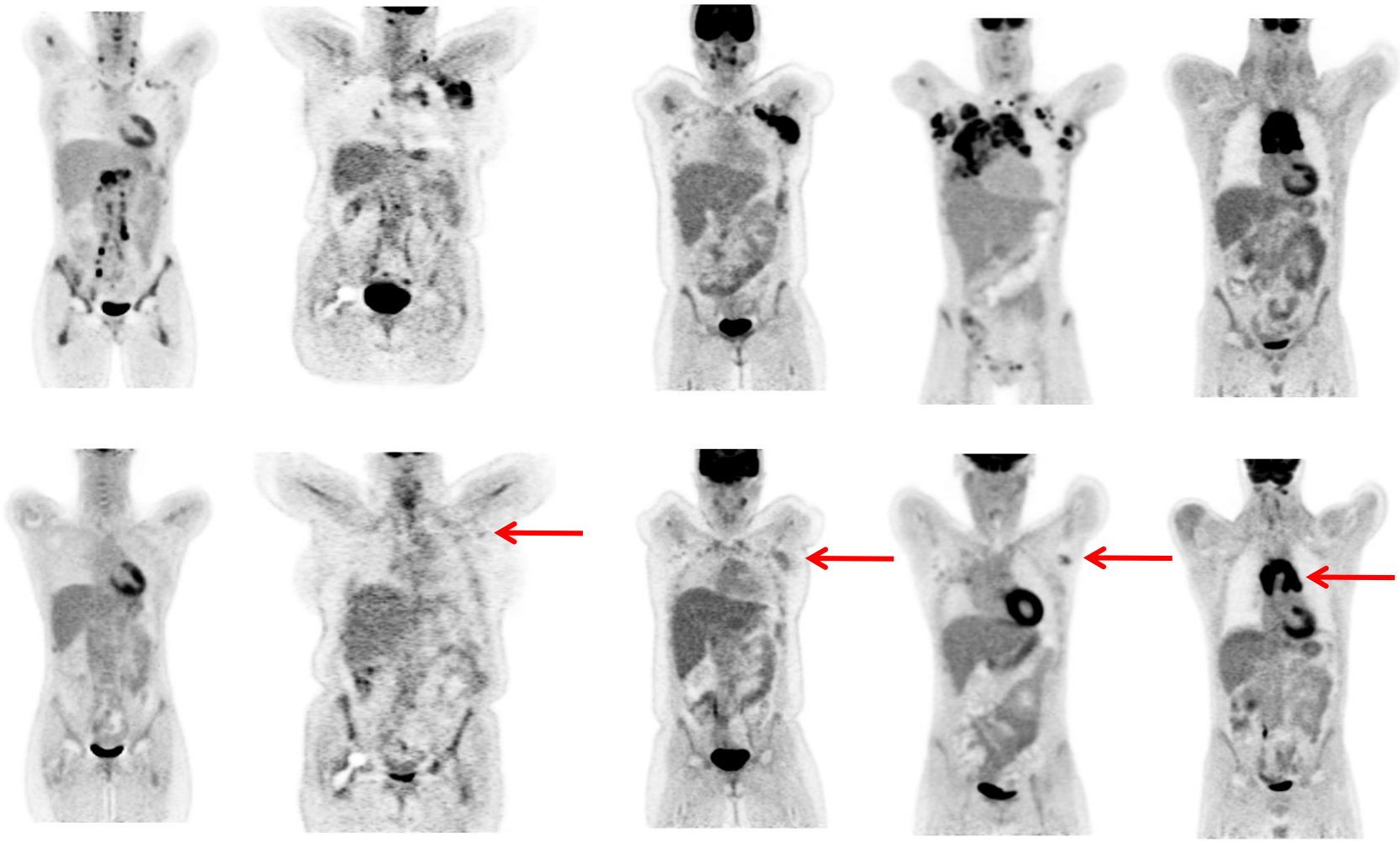
King's College London
& Guy's and St Thomas'
PET Centre

Deauville Score

King's College London & Guy's and St Thomas' PET Centre

Staging

Response

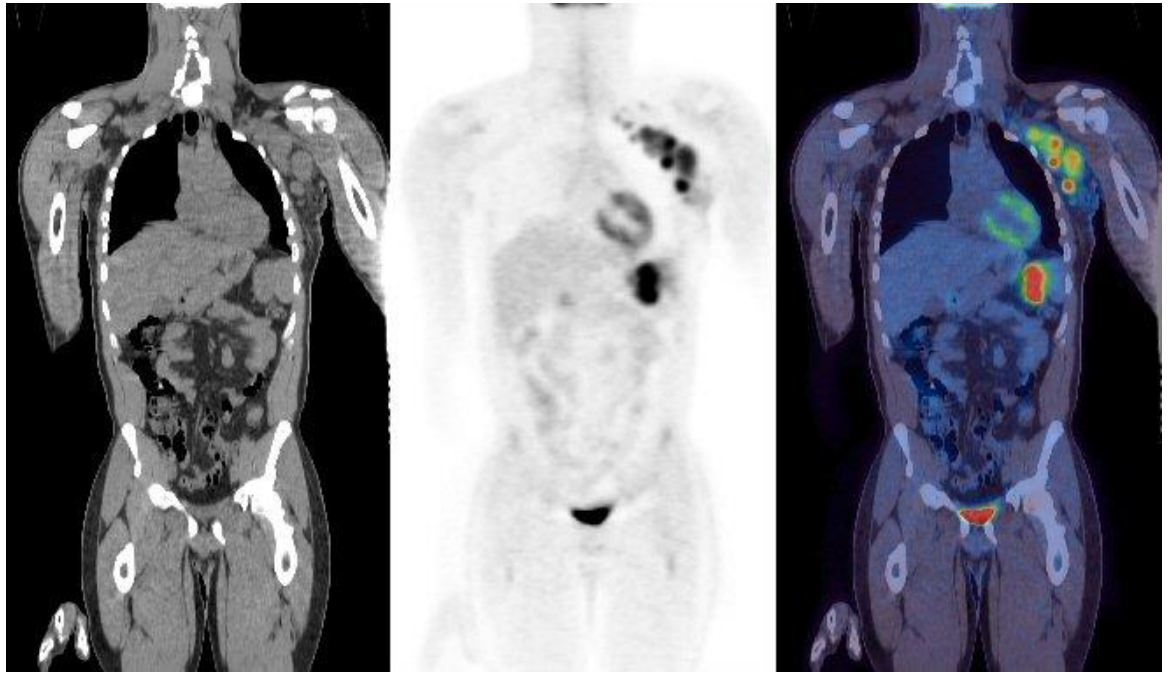


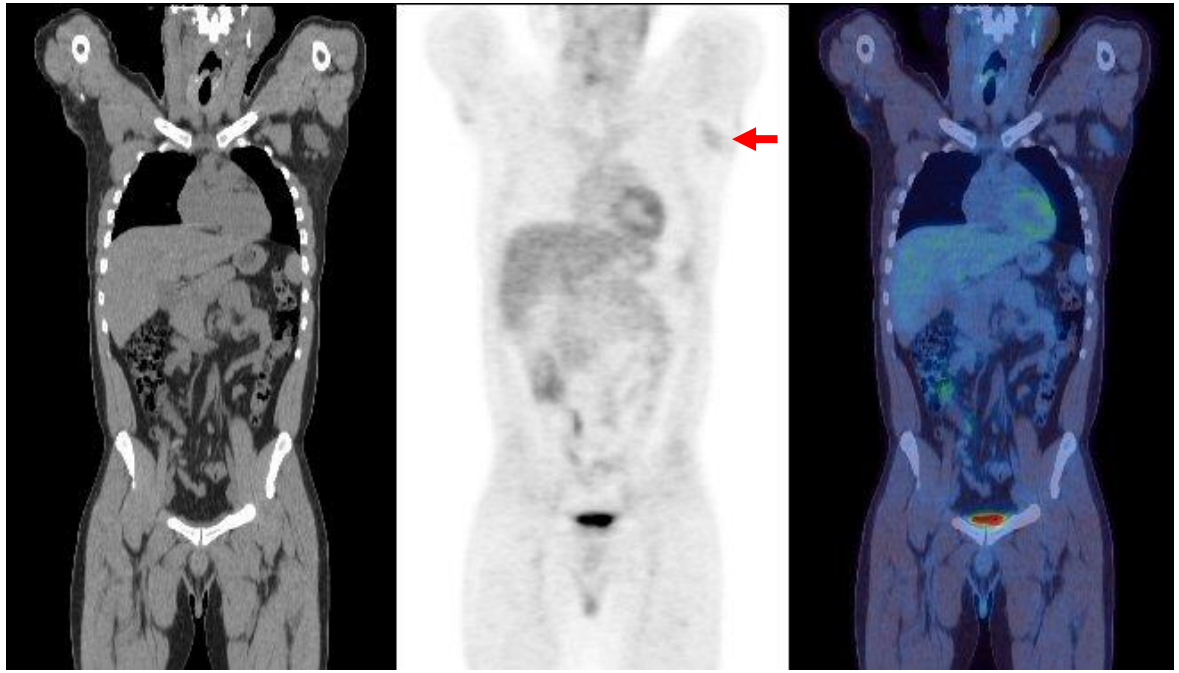
Score	1	2	3	4	5
	No uptake	FDG < MBP	FDG >MBP ≤ liver	FDG > liver	FDG >> liver

Score 3

Pre

Post

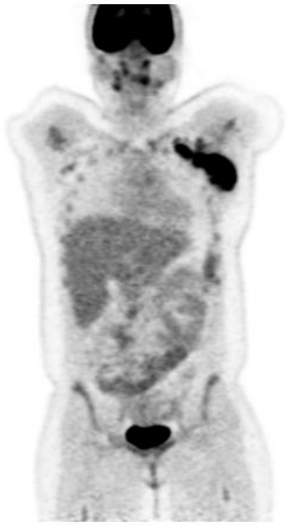


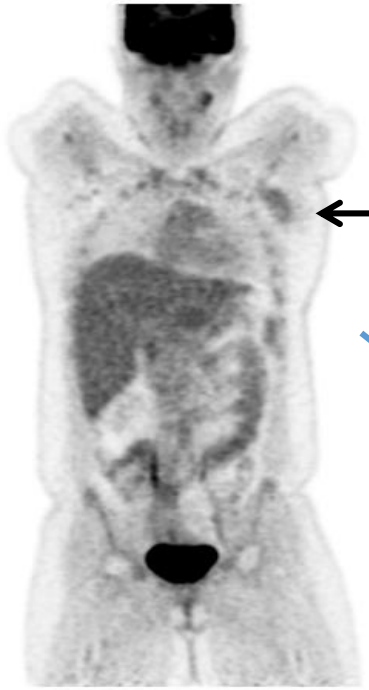


uptake > mediastinum

but < liver

Score 3 in trials





Early stage H10

Advanced stage RATHL

BEACOPP

+ INRT

Score 3

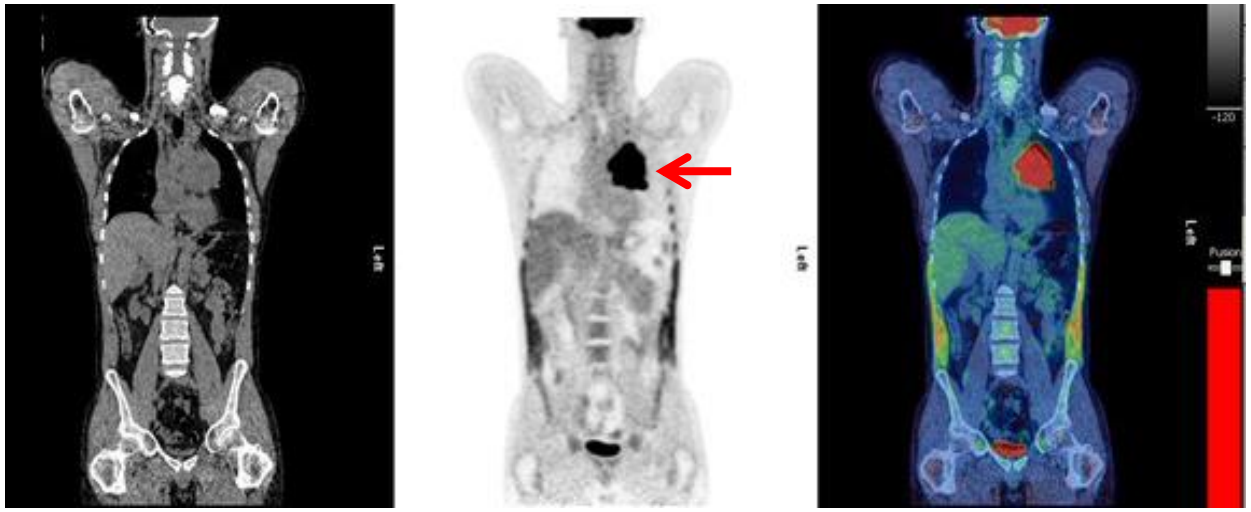
AVD – no Bleo

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
	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**

Baseline



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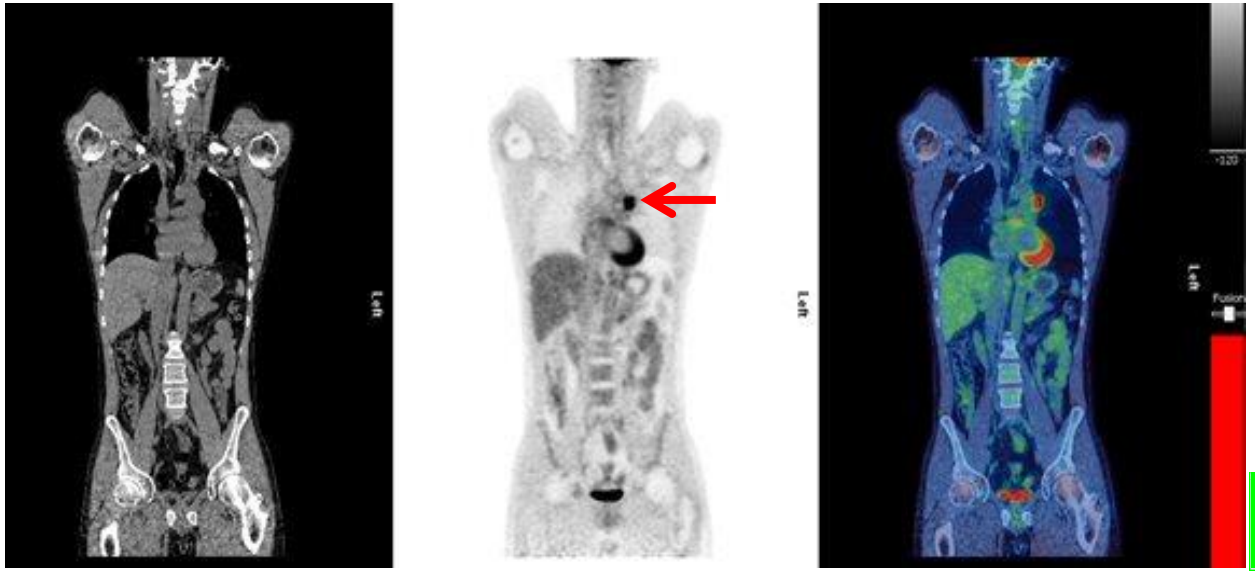
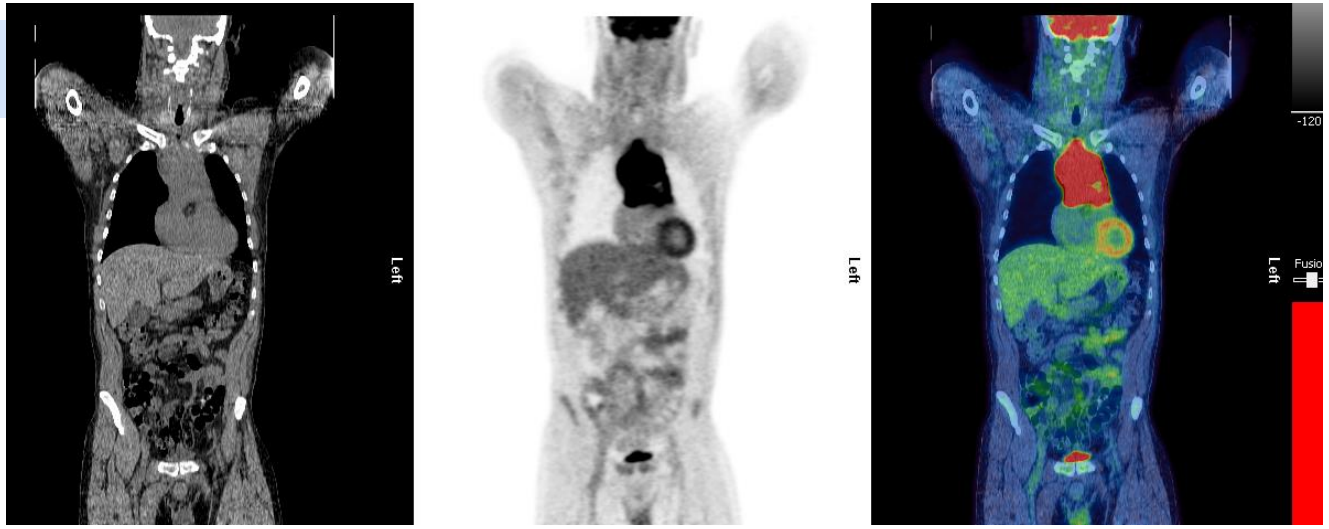


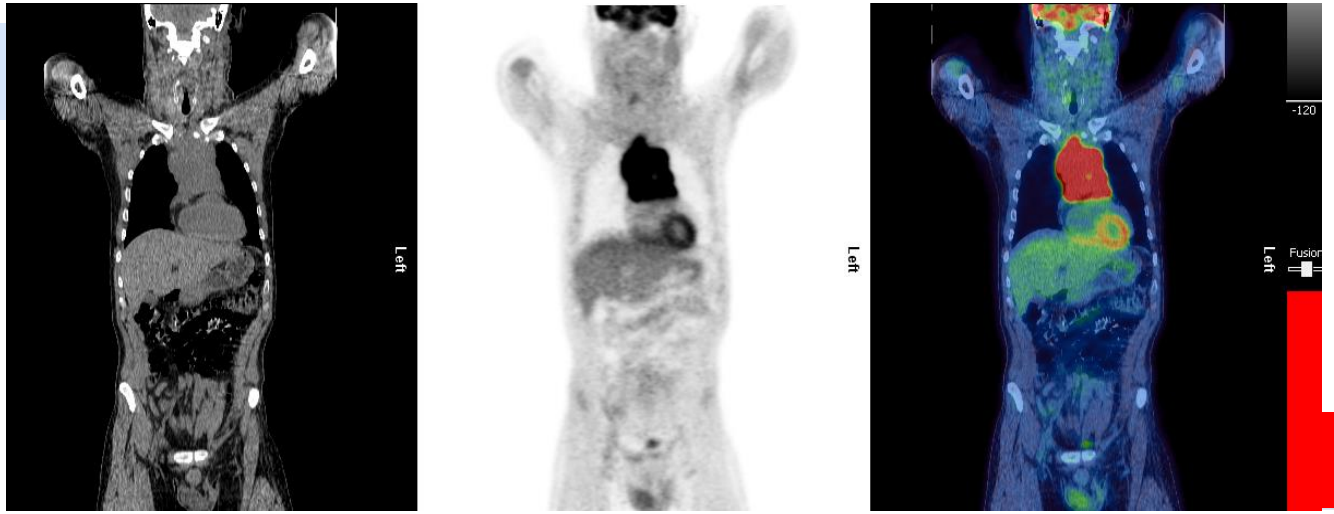
Score 5

PMR

Baseline

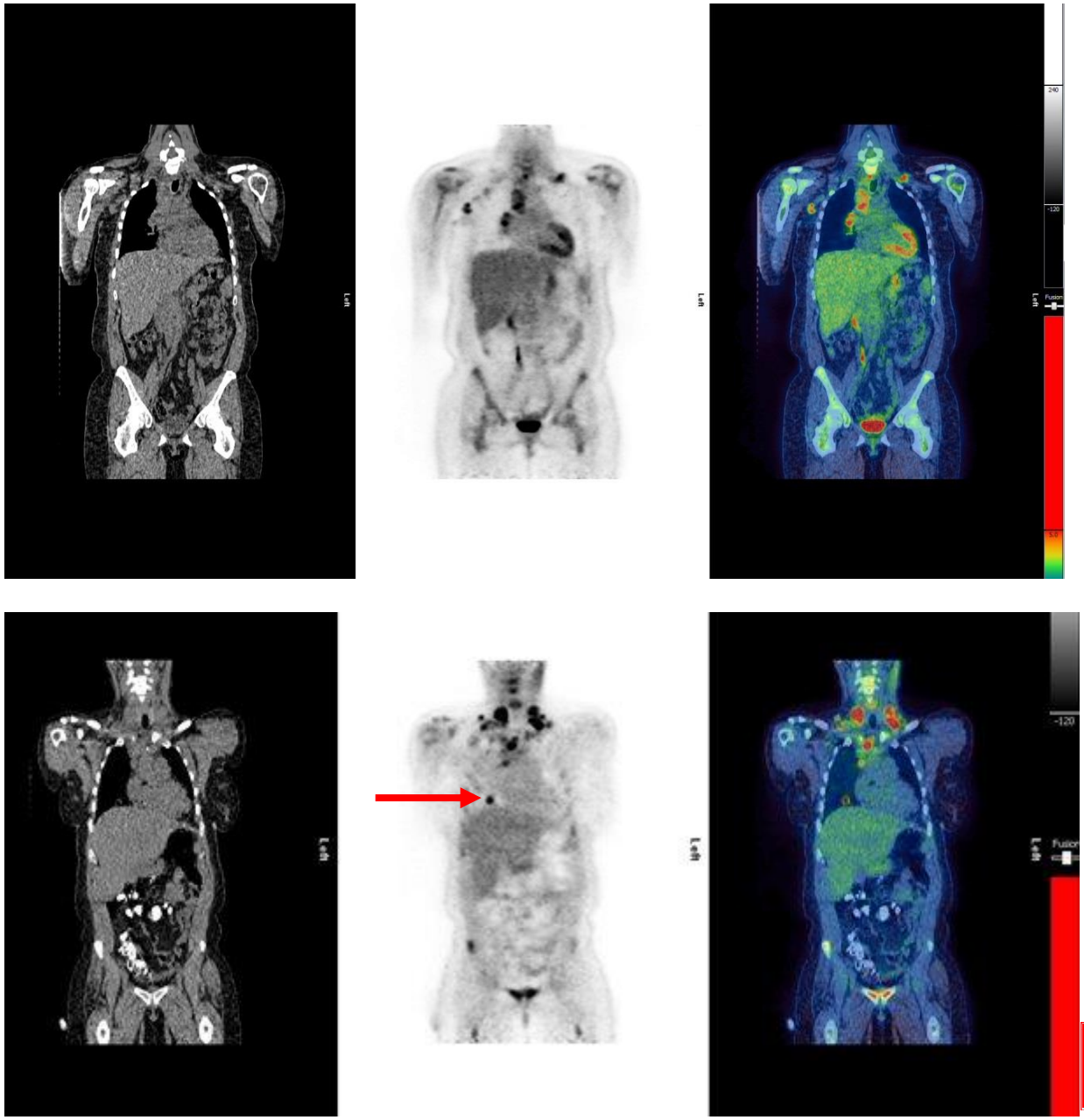


Response



Score 5

NMR



Score 5

PMD

Recommendation:
Residual metabolic activity

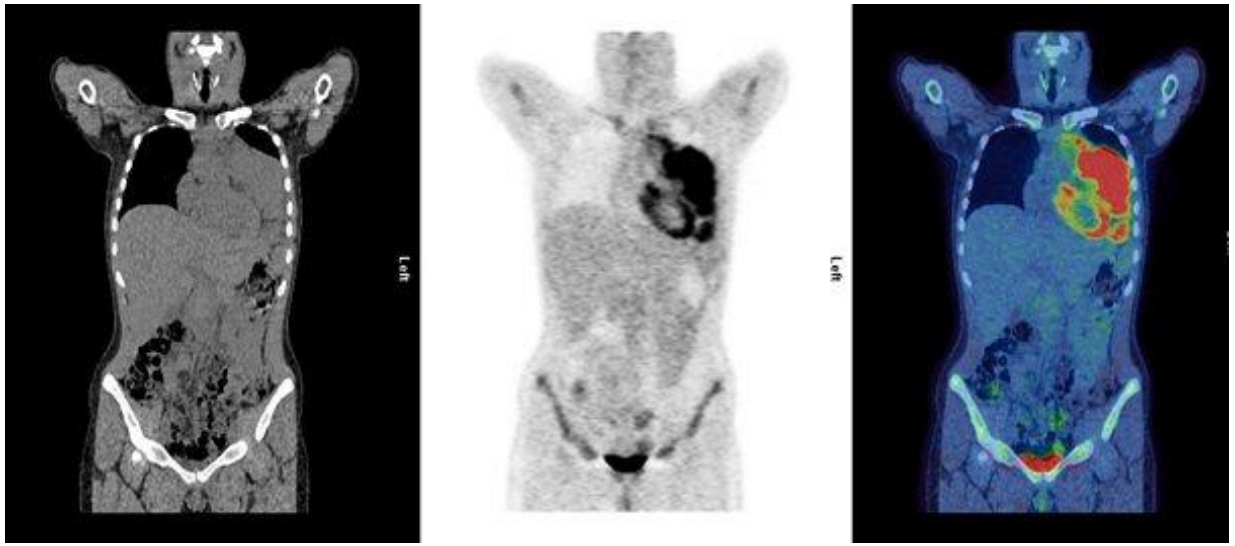
- Biopsy of residual metabolically active tissue is recommended if salvage treatment is considered

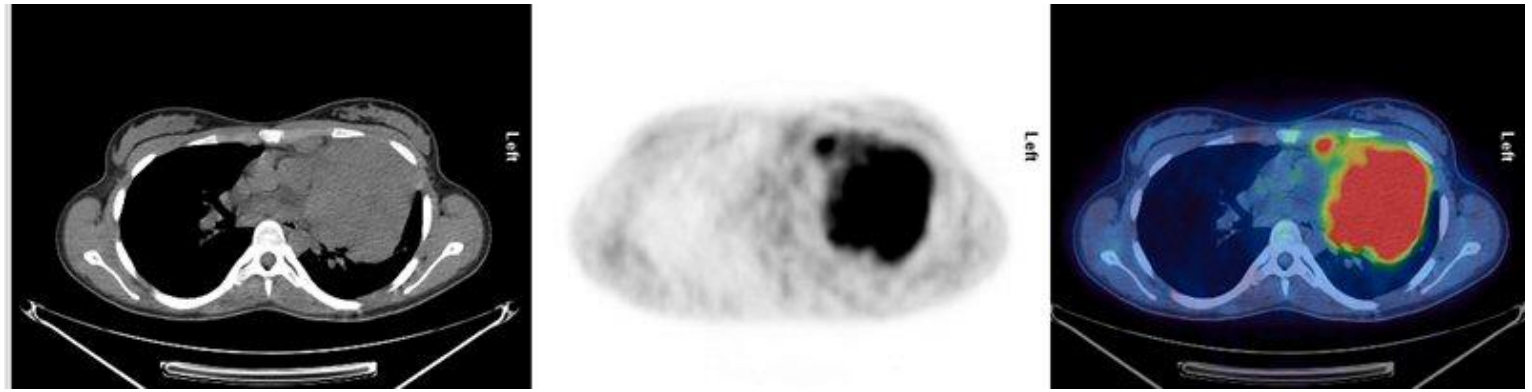
Or

- an interval scan where clinical likelihood of disease is low to decide on treatment (or not)

HL

Staging





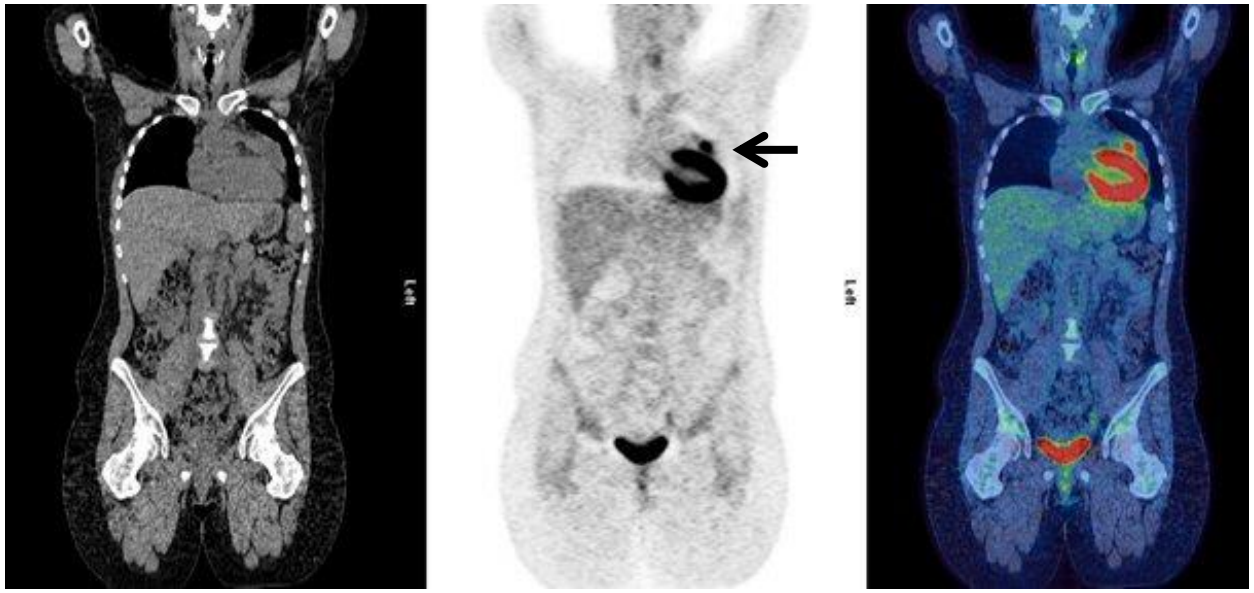
Mediastinal disease; left internal mammary

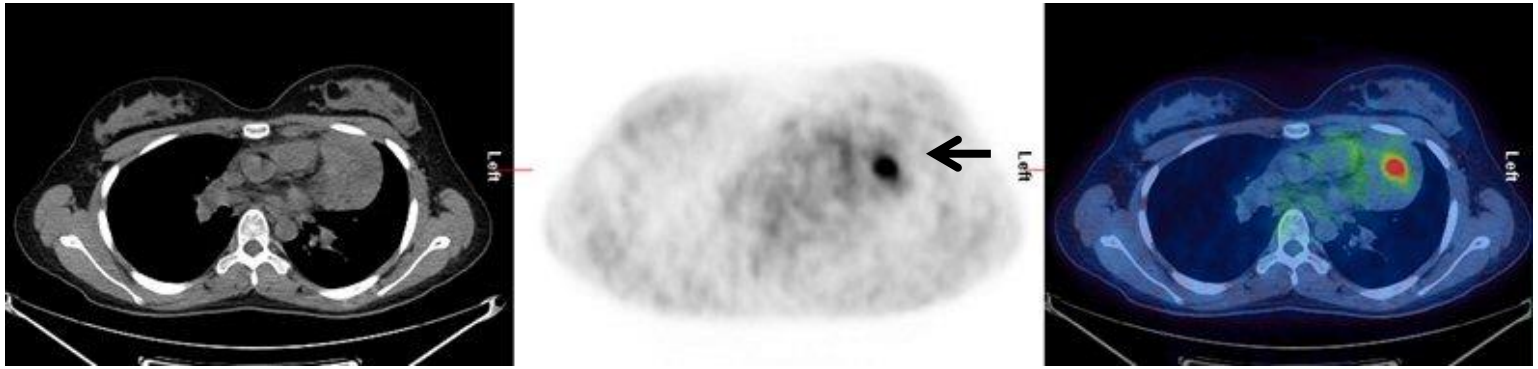
& paracardiac nodes Stage II

King's College London
& Guy's and St Thomas'
PET Centre

6 ABVD

PMR



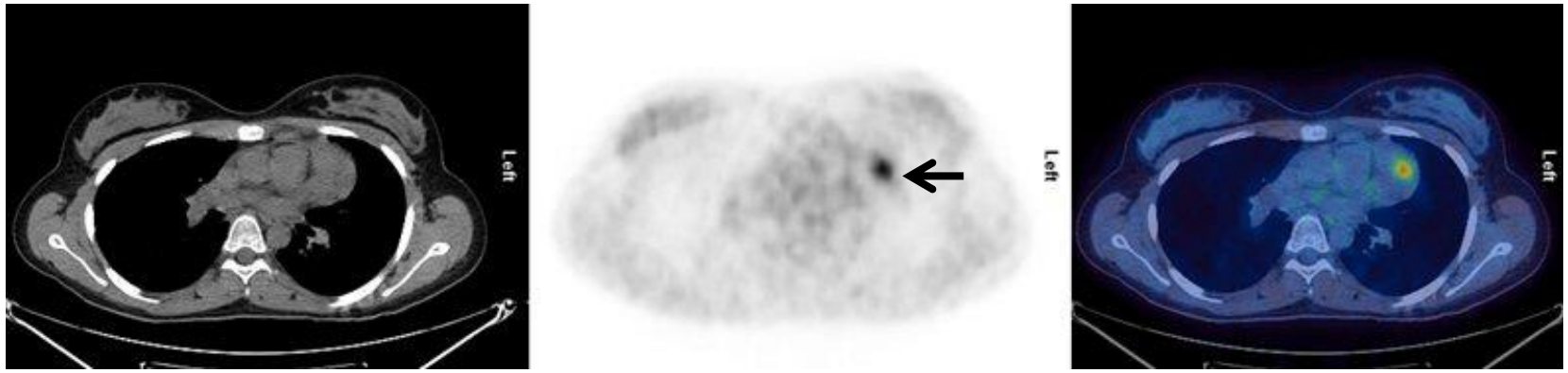


Residual uptake mediastinum > Liver
SUV 7.2 (more than 3 x liver) Score 5

King's College London
& Guy's and St Thomas'
PET Centre

3 months post chemo + IFRT

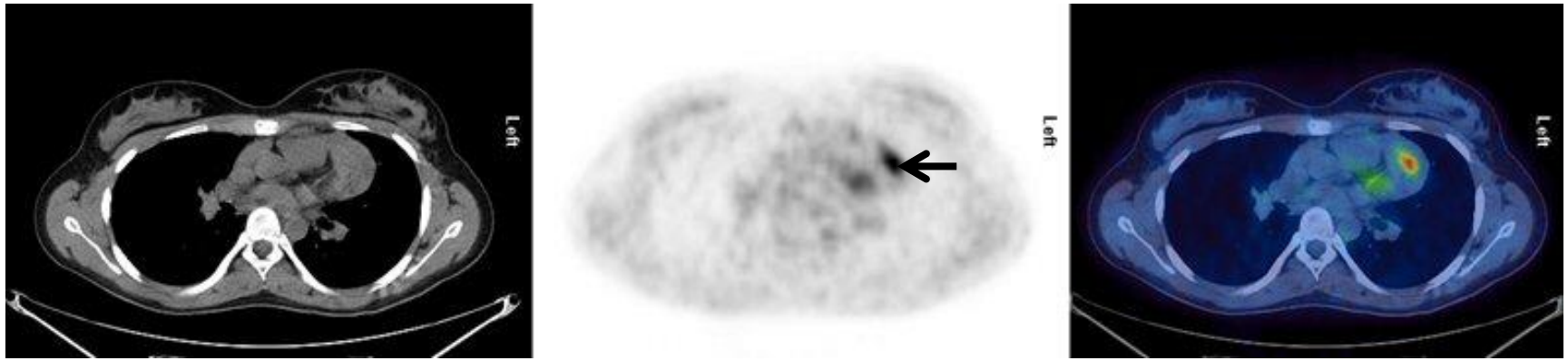
PMR



Residual uptake mediastinum > Liver

SUV 4.4 ; Score 4

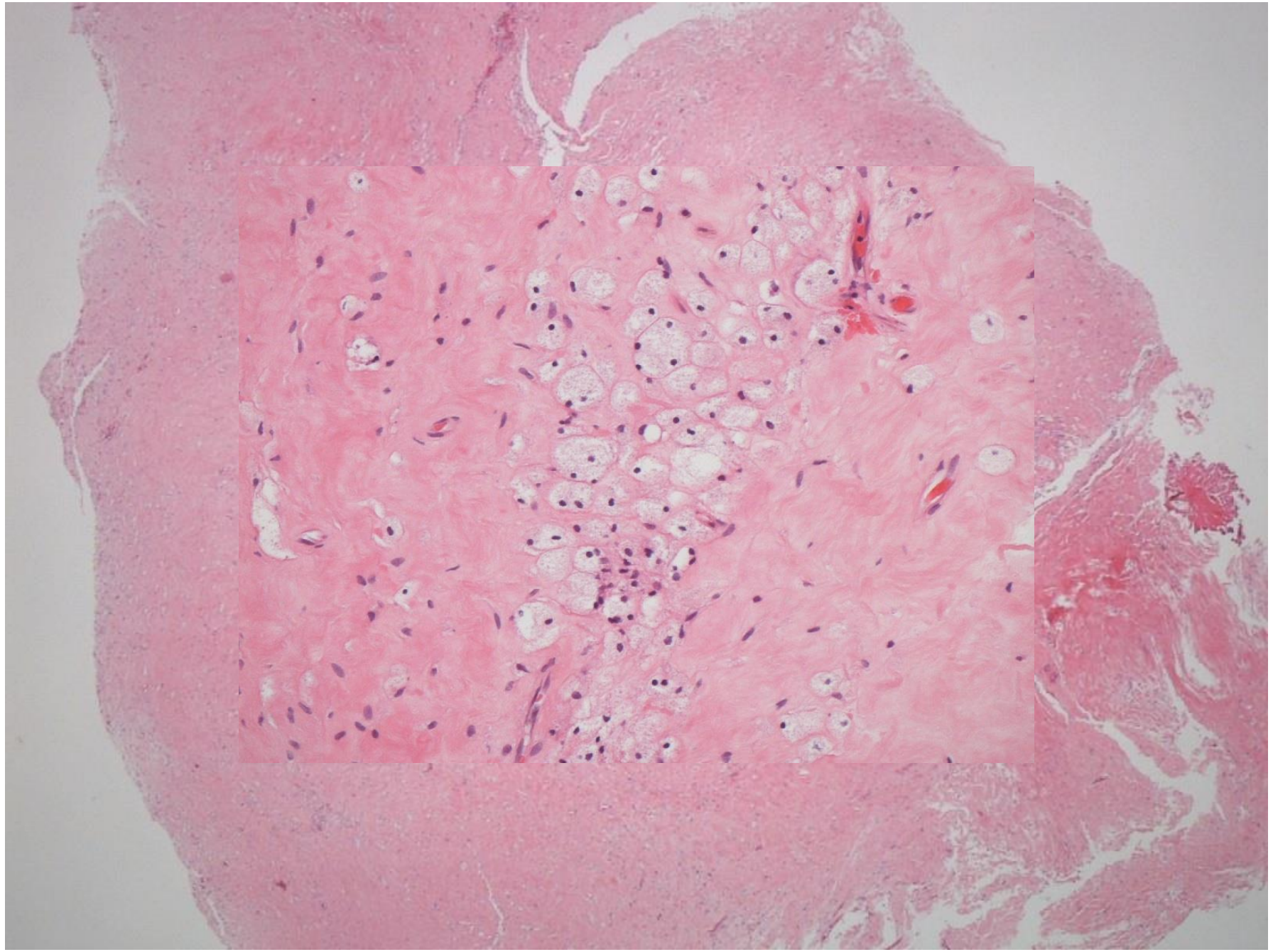
Interval scan 3 months



Residual uptake mediastinum > Liver

SUV 5.4 ; Score 4

King's College London & Guy's and St Thomas' PET Centre



- A positive PET scan often (but not always!) indicates residual lymphoma
- Treatment related inflammation can mimic disease especially in bulky masses
- Consider this where adequate treatment given for ‘good prognosis’ disease
- Biopsy of residual tissue should be considered prior to salvage whenever feasible

Follow up

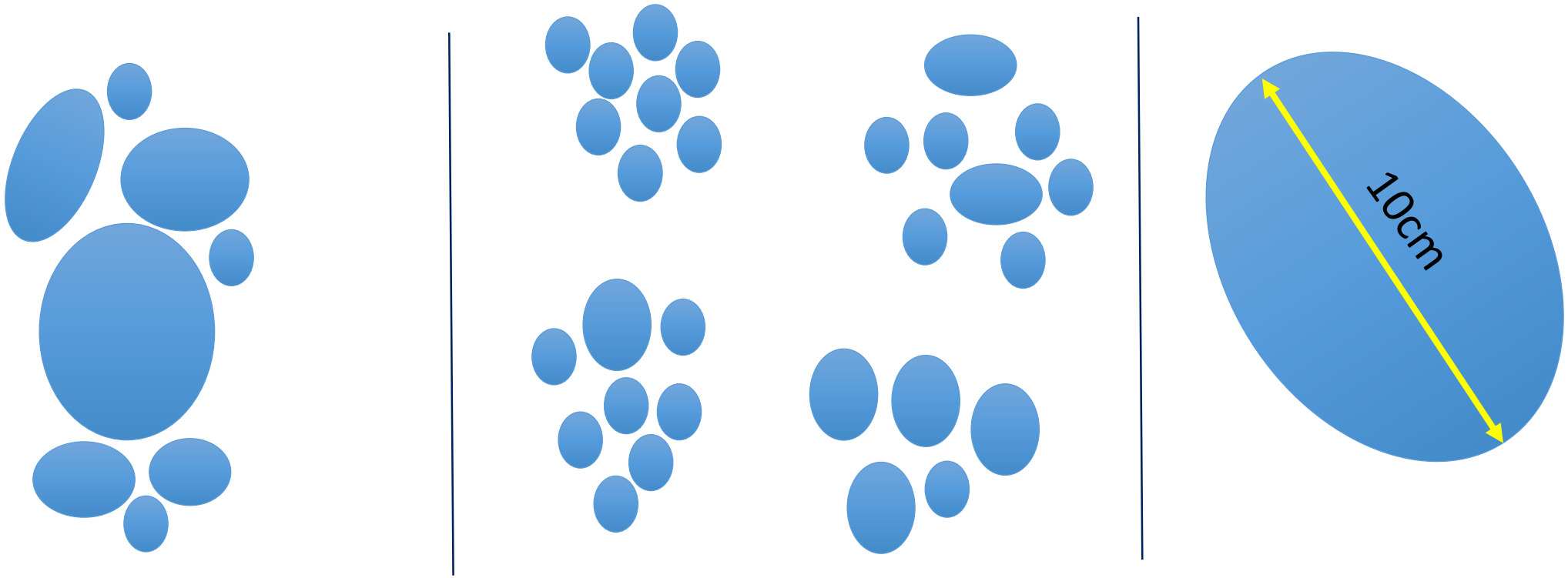
- Clinical judgement, history & examination are cornerstones of FU
- FU frequency is determined by histology, if patient is within a trial & clinical setting
- Frequency in curable lymphoma (eg HL, DLBCL) ↓ over time with ↓ likelihood of relapse
- Frequency of FU in other lymphoma (eg FL, MCL) ↑ over 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

What is next ?

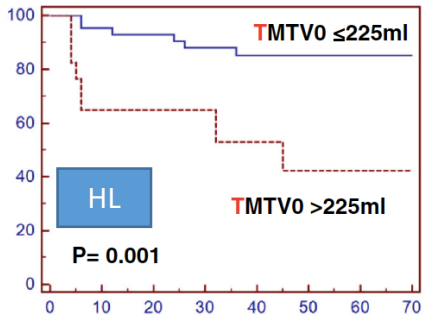
Metabolic Tumour Volume (MTV)

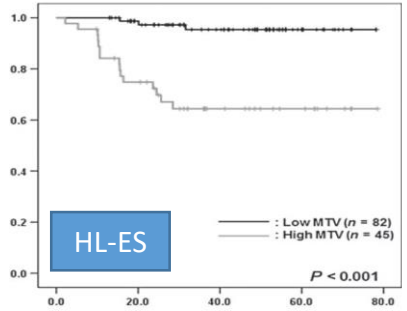
Metabolic tumour volume

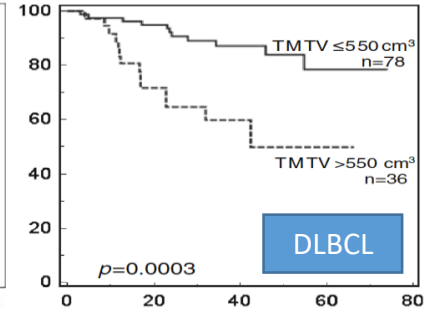
- Total volume of metabolically active tumour tissue, defined by FDG uptake above a specific threshold.
- More accurate representation of tumour burden

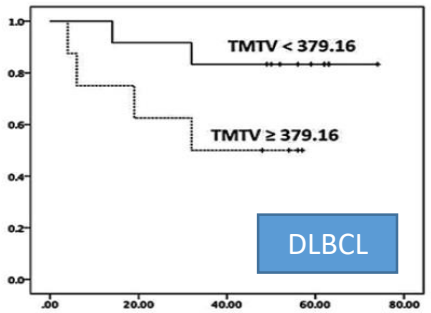


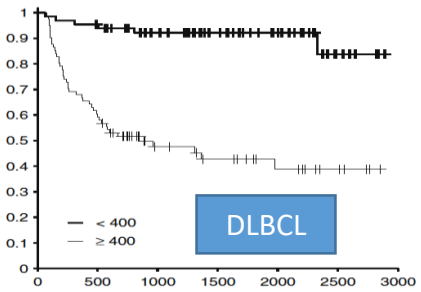
Baseline MTV and lymphoma outcome (PFS)

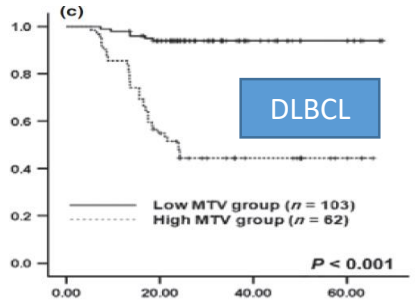


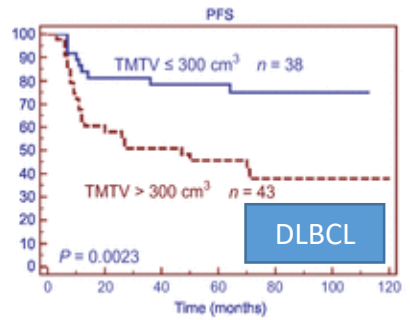


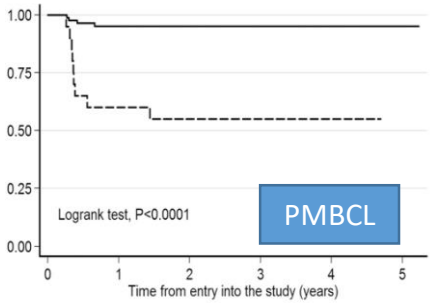


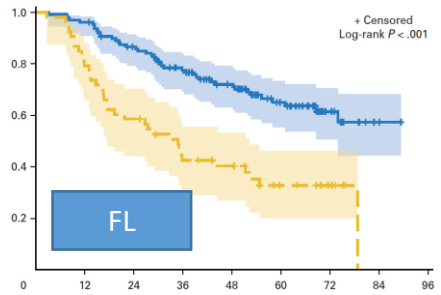


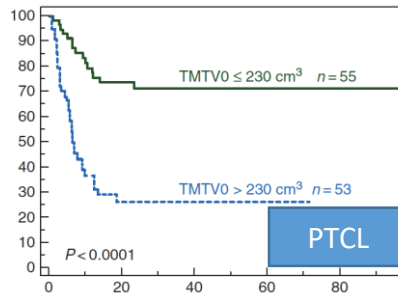


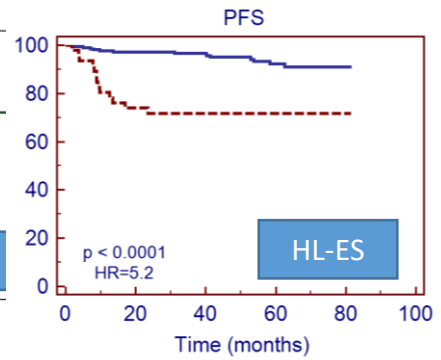


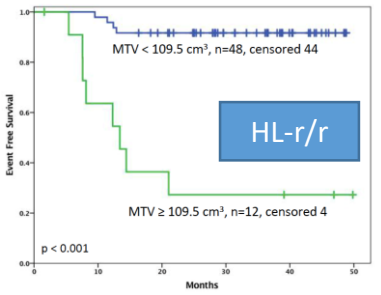












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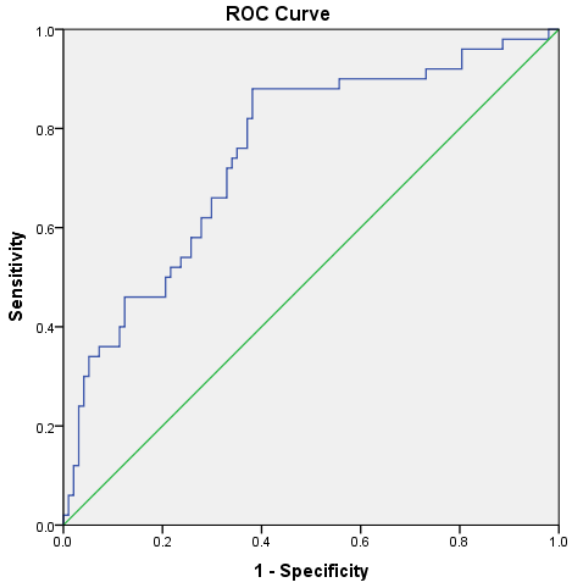
Moskowitz AJ: Blood 2017-06788877 [epub]

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-016-3315-7

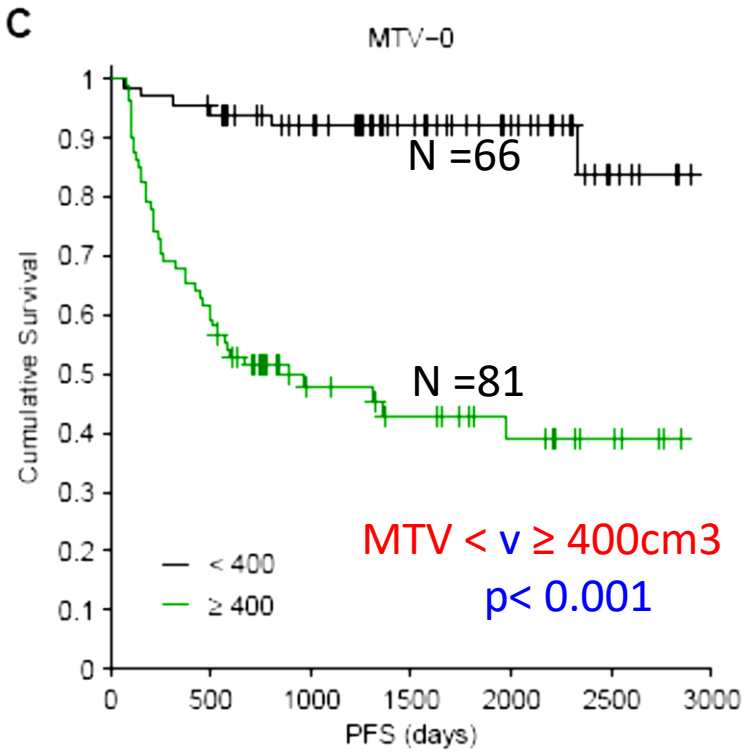
ORIGINAL ARTICLE

Combination of baseline metabolic tumour volume and early response on PET/CT improves progression-free survival prediction in DLBCL

N. George Mikhaeel[1] · Daniel Smith[1] · Joel T. Dunn[2] · Michael Phillips[2] · Henrik Møller[3] · Paul A. Fields[4] · David Wrench[4] · Sally F. Barrington[2]



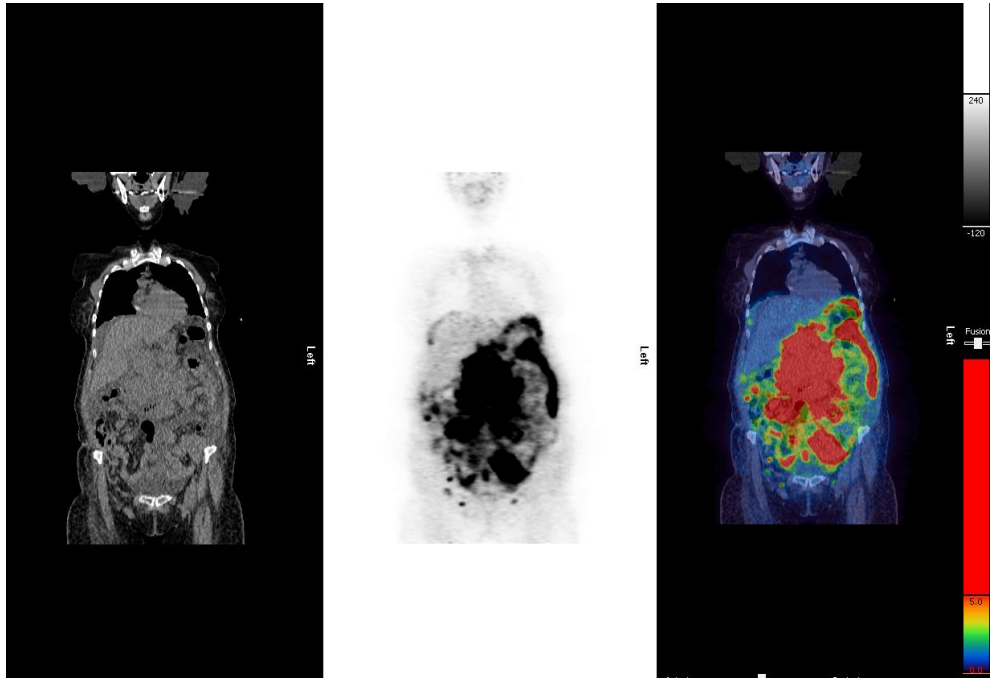
400 cm3



MTD

19.1cm

= high bulk

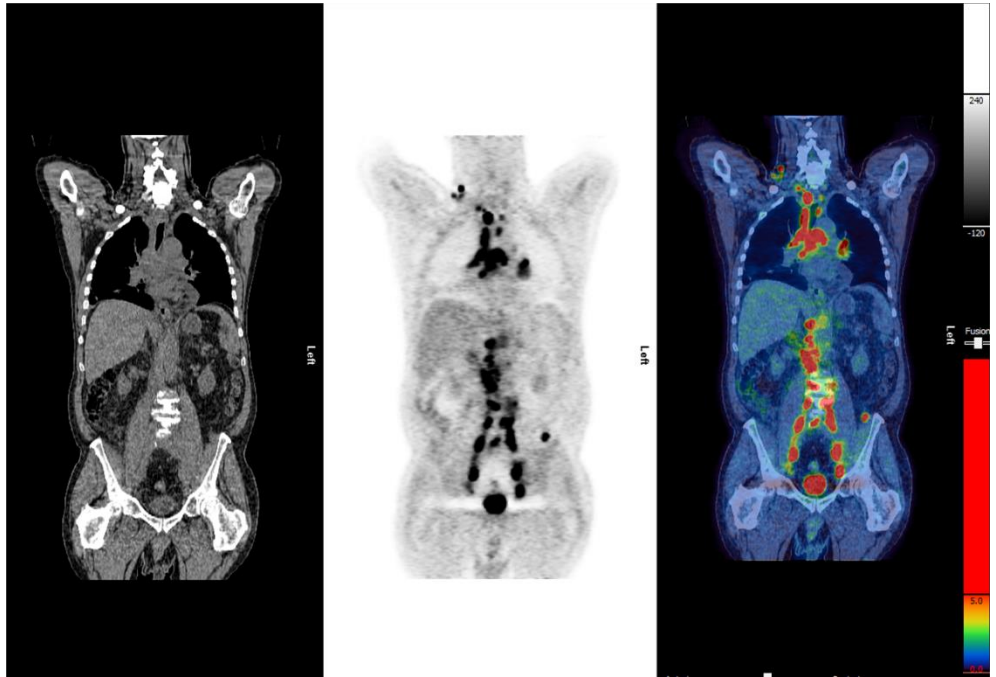


MTV

4616cm^3

5.7 cm axial
6.5 cm coronal

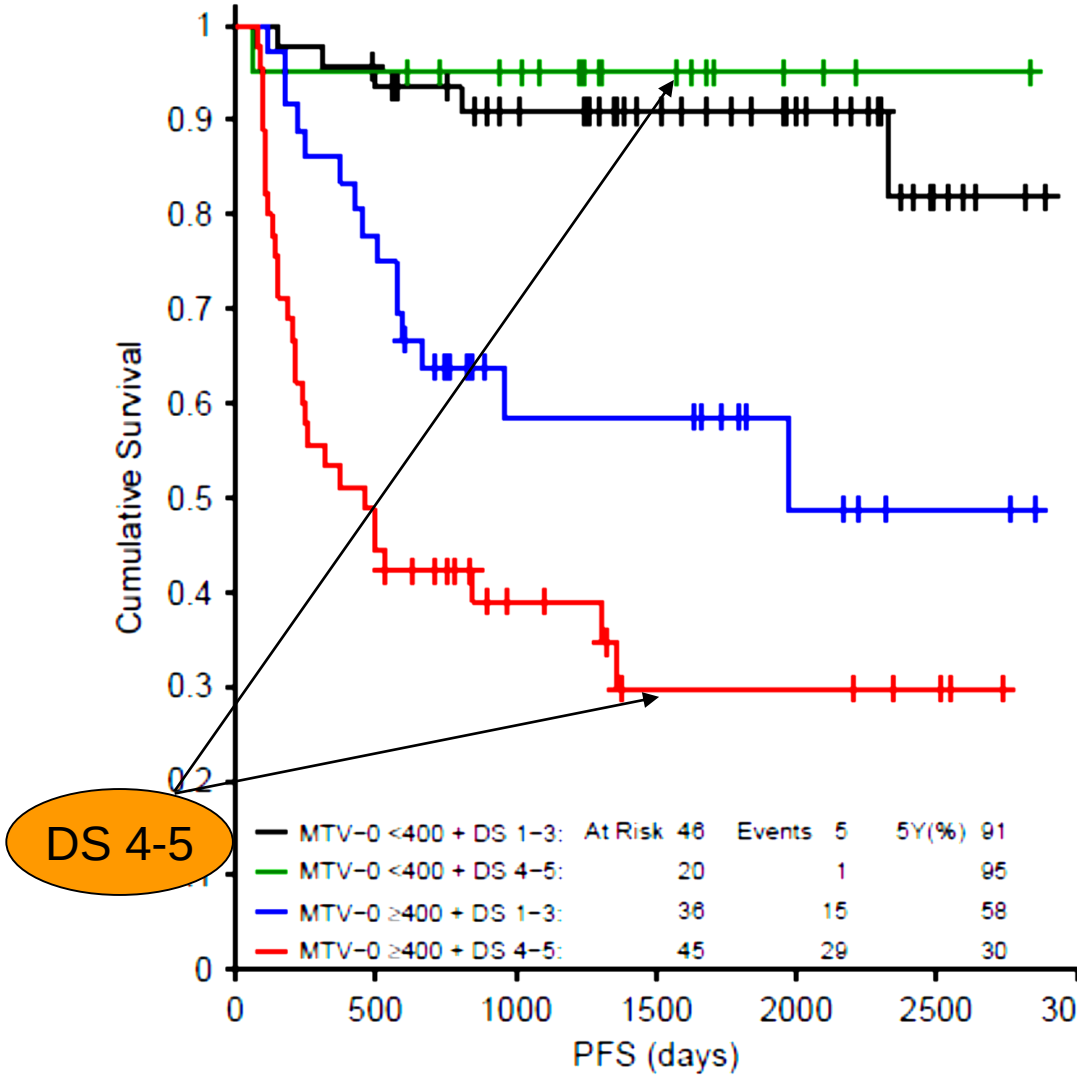
= low bulk



1422 cm^3

King's College London
& Guy's and St Thomas'
PET Centre

Baseline MTV + early response

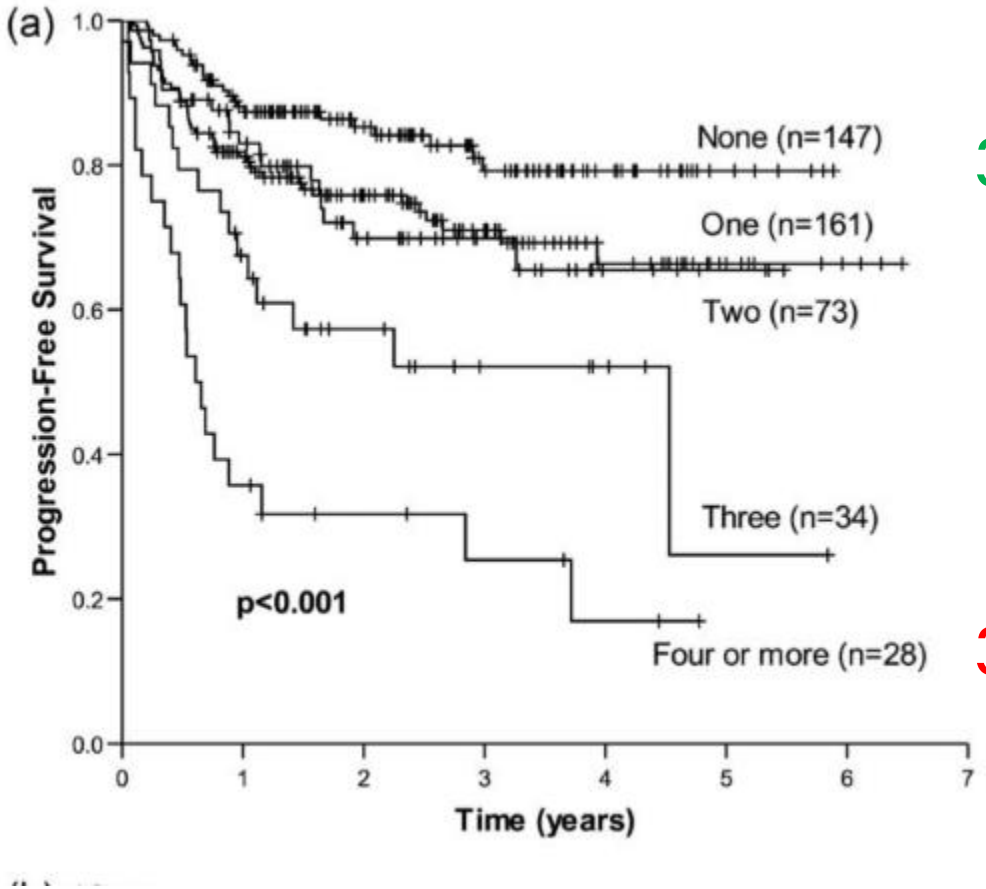


	At risk	Events	5y-PFS
MTV low+ DS 4-5	20	1	95%
MTV low+ DS 1-3	46	5	90.9%
MTV high + DS 1-3	36	15	58.5%
MTV high + DS 4-5	45	29	29.7%

Mikhaeel, EJNMMI 2016

Extra-nodal sites involvement

Number of EN sites on PET predicts prognosis

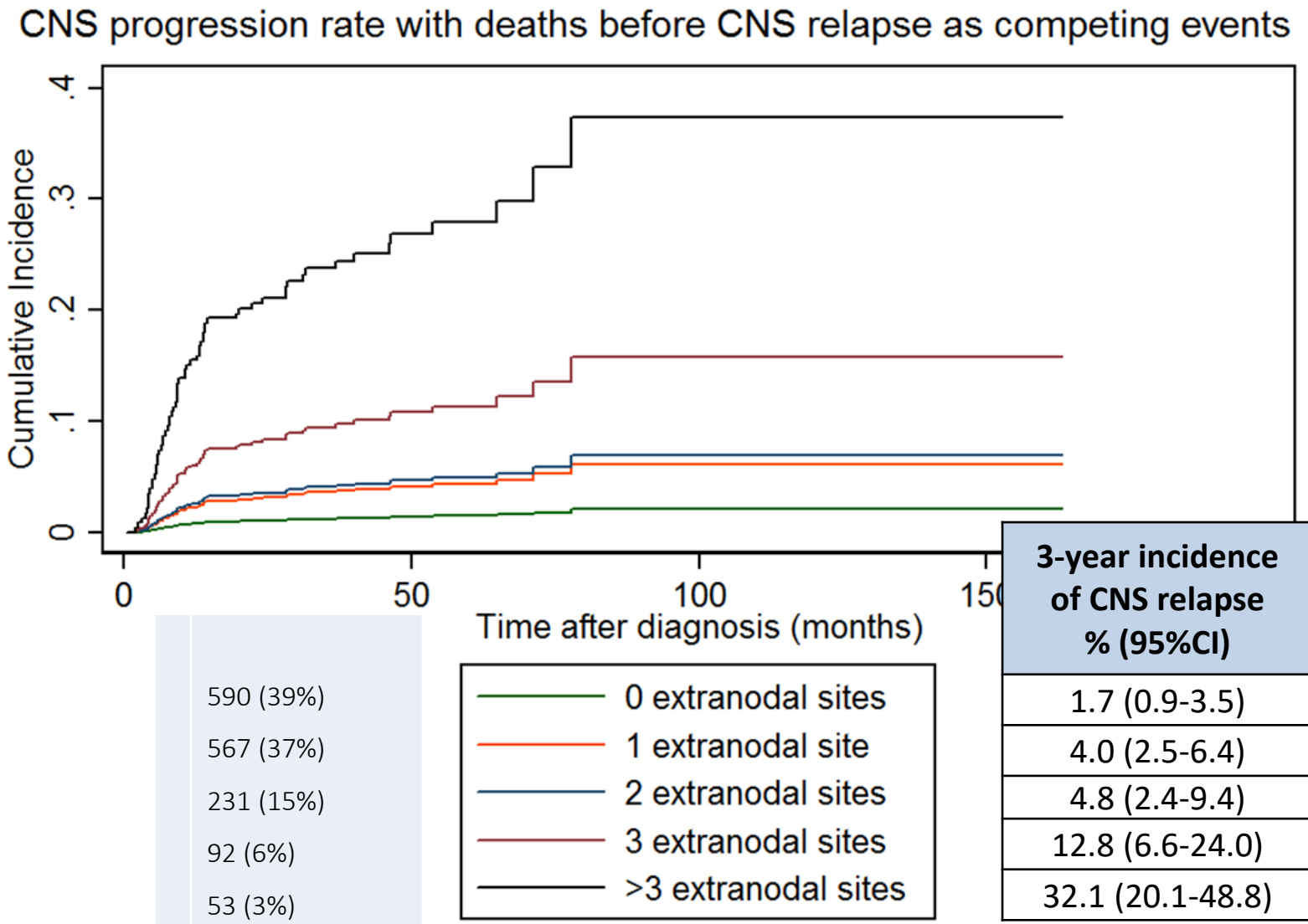


3y-PFS 79 %

3y-PFS 25 %

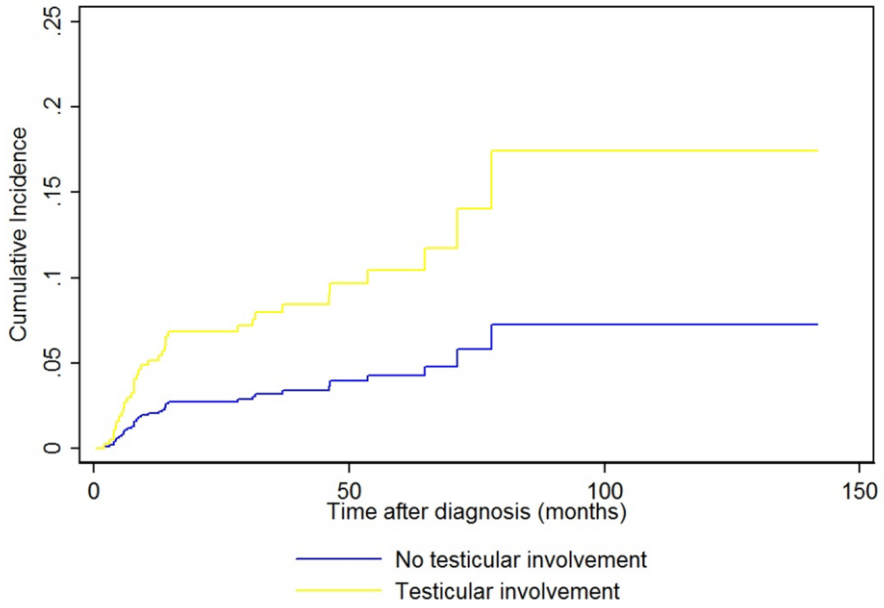
El-Galaly, Am J Hem 2015

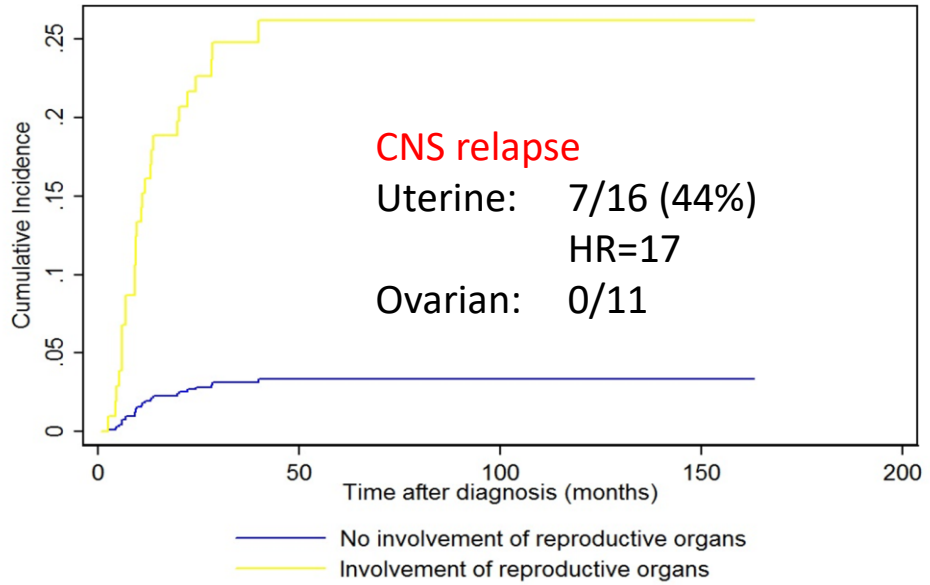
EN site involvement predicts CNS relapse risk



3-year incidence of CNS relapse % (95%CI)	Unadjusted hazard ratio HR (95% CI)
1.7 (0.9-3.5)	**1.0 (ref)**
4.0 (2.5-6.4)	**3.0 (1.3-6.7)**
4.8 (2.4-9.4)	**3.4 (1.3-8.5)**
12.8 (6.6-24.0)	**8.1 (3.1-20.9)**
32.1 (20.1-48.8)	**22.0 (9.0-53.6)**

Gynaecological organs involvement & CNS relapse



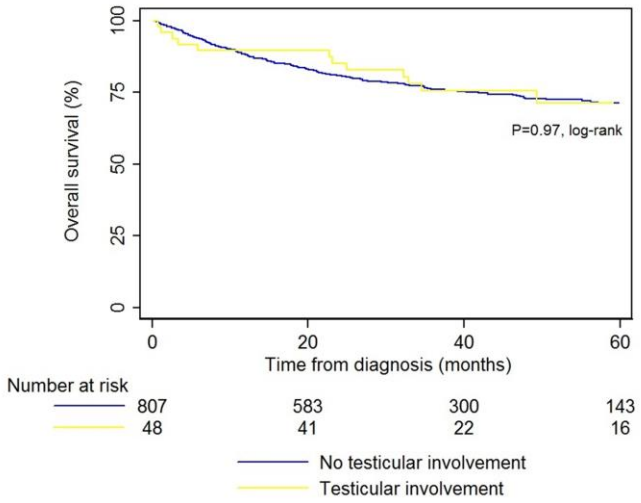


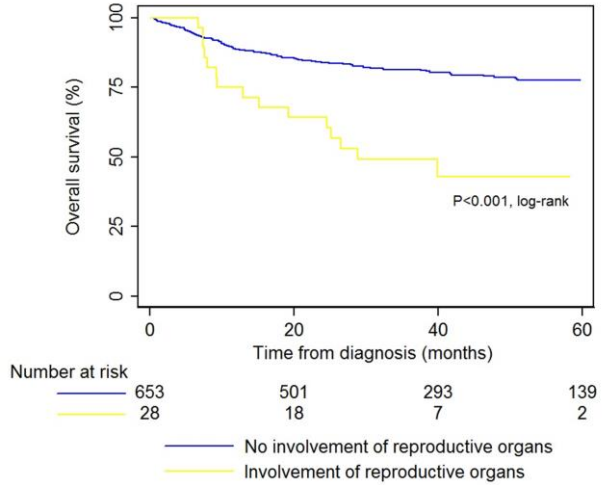
CNS relapse

Uterine: 7/16 (44%)
HR=17

Ovarian: 0/11

OS





qPET

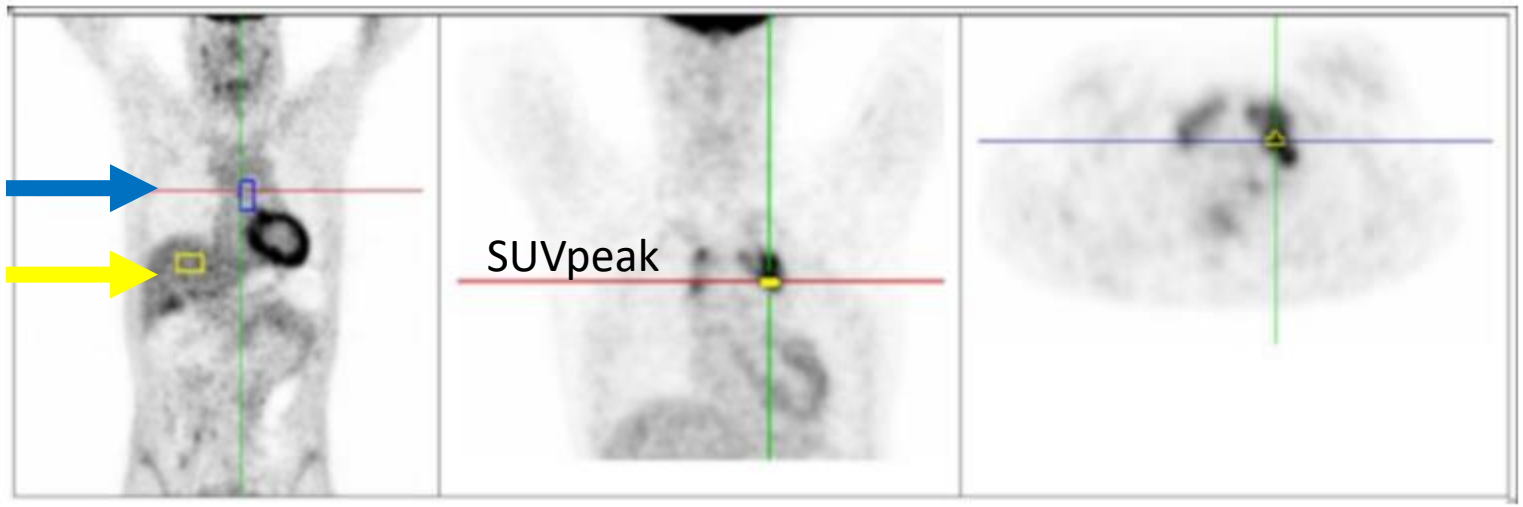
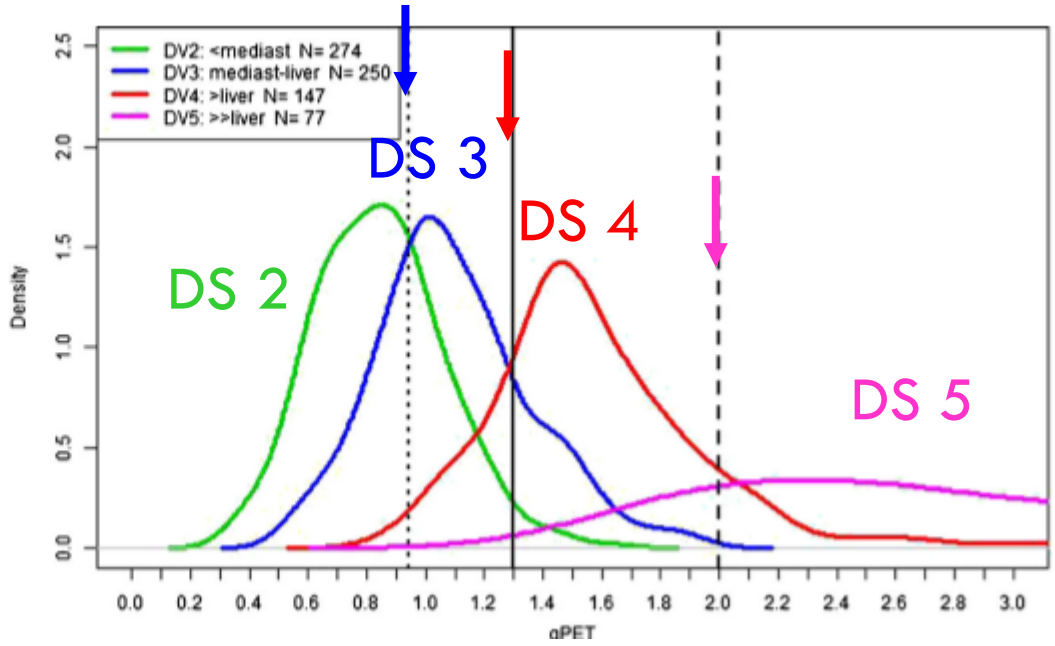


Fig. 2 **a** shows the densities, **b** the cumulative distribution functions of the qPET signals by visual Deauville categories. qPET thresholds discriminating between Deauville categories with roughly symmetric discrepancies are indicated: qPET = 0.95 (dotted line), qPET = 1.3 (solid line), qPET = 2.0 (dashed line) discriminate between Deauville categories 2 versus 3, 3 versus 4 and 4 versus 5, respectively



DS 3 qPET = 0.95

DS 4 qPET = 1.3

DS 5 qPET = 2.0

Hasenclever D et al EJNMMI 2014

Immunotherapy Response – LyRIC criteria

Perspectives

blood

Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy

Bruce D. Cheson,[1] Stephen Ansell,[2] Larry Schwartz,[3] Leo I. Gordon,[4] Ranjana Advani,[5] Heather A. Jacene,[6] Axel Hoos,[7] Sally F. Barrington,[8] and Philippe Armand[6]

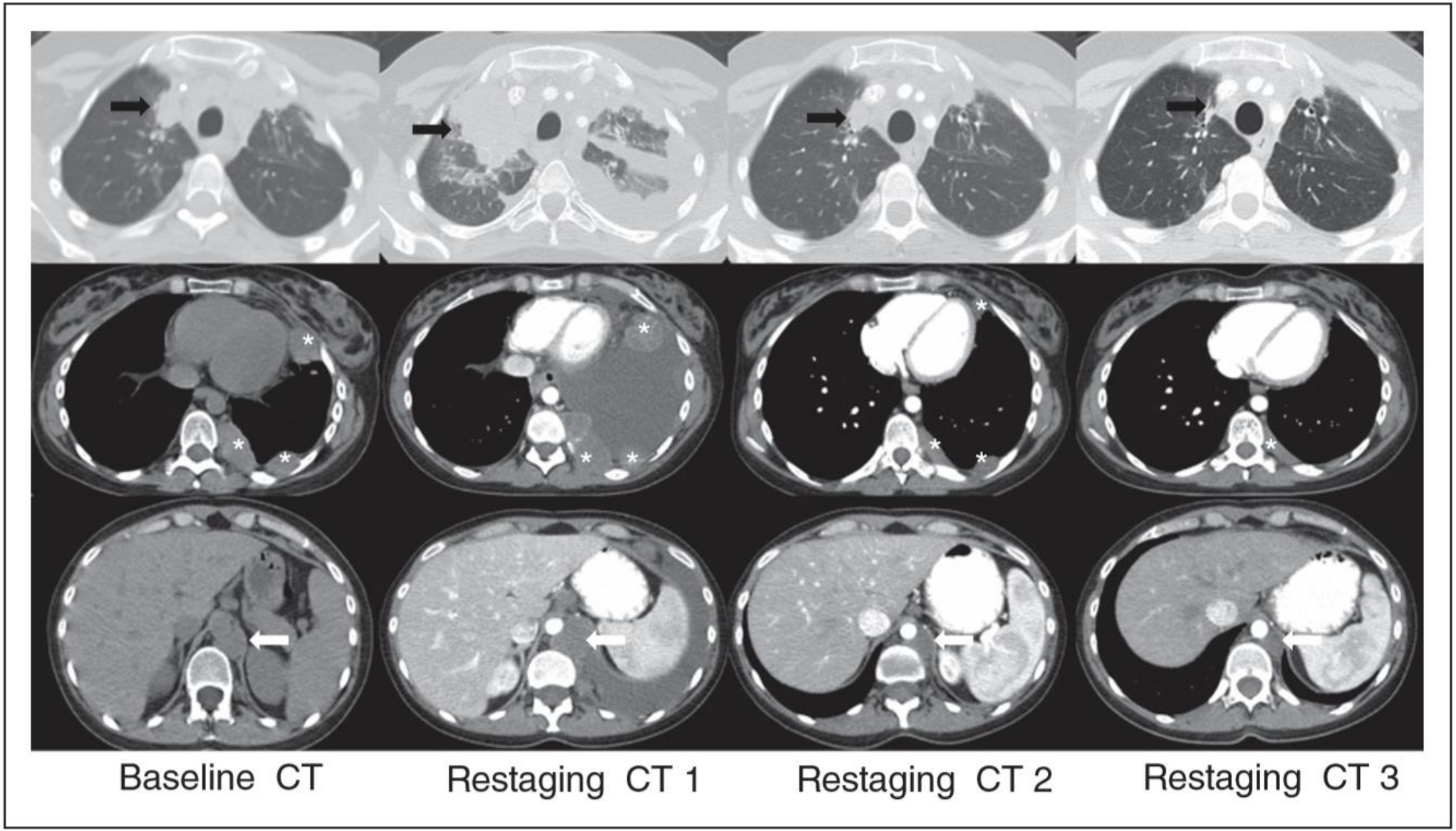
New Category: Indeterminate Response (IR)

Only with immunoRx

Provisional

IR 1, 2, 3

BLOOD, 24 NOVEMBER 2016 • VOLUME 128, NUMBER 21



Mediastinum

Pleura

Retrocrural

		3 weeks	7 weeks	13 weeks
SPD		+128%	-27%	-54%

LyRIC criteria: Indeterminate Response

Overall tumour burden INCREASE	↑ SPD ≥50% Up to 6 lesions	No Clinical Deterioration	1st 12 weeks	**IR 1**
No increased Overall tumour burden	↑ SPD ≥50% 1 or more lesions		Any time	**IR 2**
	↑ FDG 1 or more lesions	No ↑ in size or number		**IR 3**

Impact of PET on target definition

FDG-PET for target definition

- It makes sense to use the most accurate method

- RT has changed to smaller volumes (INRT or ISRT)
- 3D-conformal / IMRT dose is more conformal to target than AP/PA

- *Accurate definition of nodal involvement is essential*
- PET is essential for volumes less than IFRT & modern techniques

- ILROG guidelines

Effect of PET on TV definition

Table Studies examining the influence of information obtained from PET/CT scanning on lymphoma radiation therapy planning

Study (reference)	No. and lymphoma subtype	Type of study	Techniques of RT and PET/CT data interpretation	Findings
Lee et al, 2004 (61)	15 thoracic lymphoma (10 HL, 5 NHL)	Single center	AP-PA parallel opposed VAM	Median GTV (CT) = 29.4 cm^2 Median GTV (PET) = 7.9 cm^2
Hutchings et al, 2007 (62)	30 early-stage HL	Single center	IFRT VAM	Target volumes unchanged in 21, larger in 7 (median 17%), and smaller in 2 (8% and 30%)
Girinsky et al, 2007	30 early-stage supradiaphramatic HL	Single center	INRT SUV	Larger volumes with PET. PET showed avid nodes not shown on CT in 36% of cases. 25% of CT anatomic volume was PET avid
Terezakis et al, 2011 (63)	29 lymphoma and hematologic malignancies (21 NHL, 5 HL, and 3 plasma cell neoplasms)	Single center	IFRT SUV	Target volume changed in 23 of 32 treatment sites with PET data. PTV increased in 15 sites (median 11%) and decreased in 8 sites (median 20%)
Pommier et al, 2011 (64)	124 early-stage HL	Multicenter	IFRT VAM	With pre-RT PET information, RT was cancelled in 4.8% of cases, and treatment modifications occurred in 12.9% of cases

% change
na
30%
36%
72%
18%
18 - 72%

Yeoh & Mikhaeel. IJROBP 2012

Hodgkin Lymphoma

135 patients, H10 study, INRT

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Role of FDG-PET in the Implementation of Involved-Node Radiation Therapy for Hodgkin Lymphoma Patients

Théodore Girinsky, MD,* Anne Aupérin, MD, PhD,† Vincent Ribrag, MD,‡ Manel Elleuch, MD,§ Christophe Fermé, MD,‡ Guillaume Bonniaud, PhD,|| Claude Ruelle,¶ Jean-Louis Alberini, MD,# Aljosa Celebic,† and Véronique Edeline, MD#

Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1047–1052, 2014

How often does PET detect more nodes?

Table 1 Comparison between the number of lymph nodes and lymph-node areas per patient detected by CT scan and PET-CT before chemotherapy

Parameter	All CT scans	CT scan without IV contrast	CT scan with IV contrast	χ^2 test *P* value
No. of patients	135	88	47	
No. of patients with at least one additional LN detected by PET-CT	95	68	27	.016
(95% CI)	70.4% (61.9 - 77.9)	77.3% (67.1 - 85.5)	57.5% (42.2 - 71.7)	
No. of patients with at least one additional LN area detected by PET-CT	55	43	12	.009
(95% CI)	40.7% (32.4 - 49.5)	48.9% (38.0 - 59.7)	21.8% (13.9 - 40.3)	

Abbreviations: CI = confidence interval; CT = computed tomography; IV = intravenous; PET = positron emission tomography; LN = lymph node.

Girinsky IJROBP 2014; 89:1047

Impact of PET on target volume

Table 2 Impact of FDG-PET on the pre-chemotherapy GTV (cm^3) measured by CT scan and PET-CT before chemotherapy (134 patients)

Measure	Volume determination with CT scan	Volume determination with PET-CT	% increase*	Paired *t*-test *P* value
Mean (±SD)	501.1 (±331.7)	526.9 (±334.4)	8.8% (±24.0)	<.0001
Median (range)	452 (39 - 1972)	485 (44 - 2095)	1.9% (-36 to +184)	

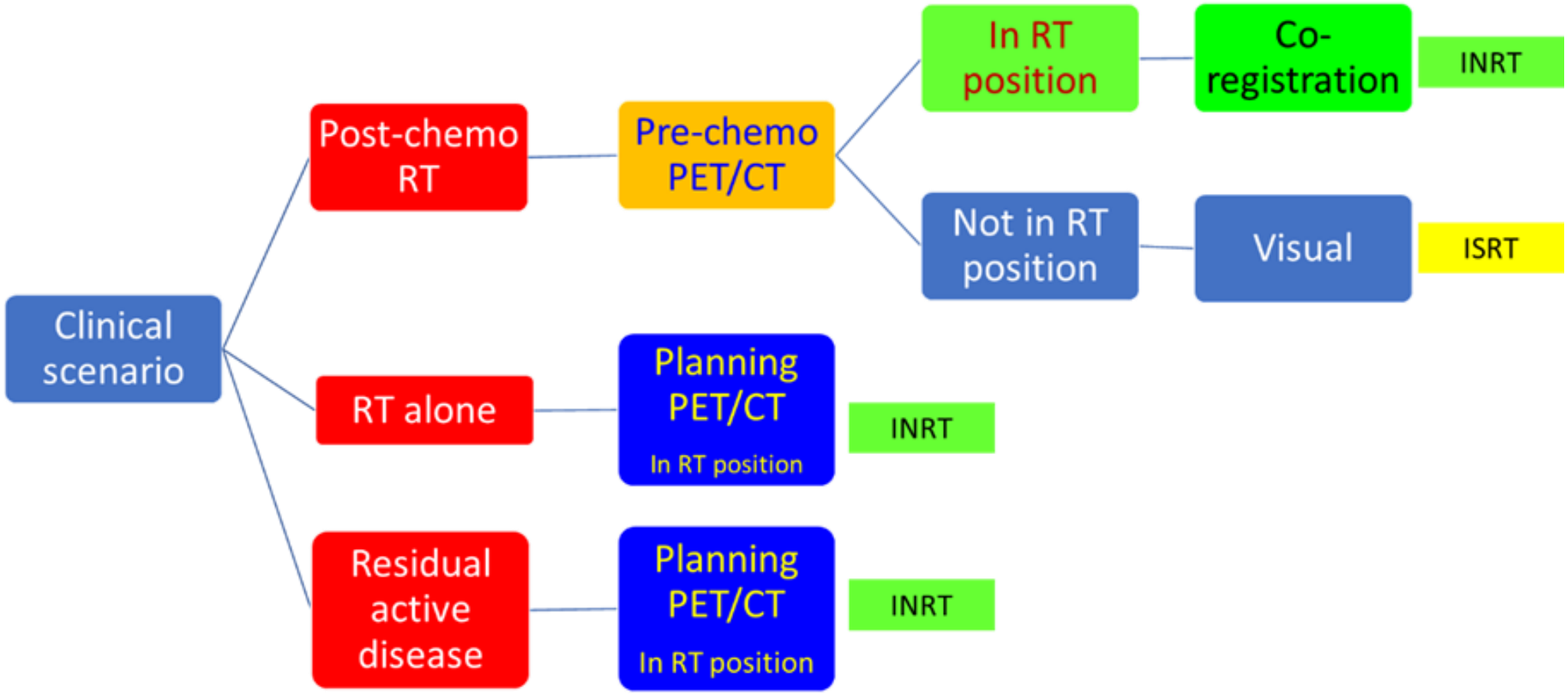
Abbreviations: CT = computed tomography; PET = positron emission tomography; GTV = gross tumor volume.
* In 87 of 134 patients (64.9%) there was an increase in the GTV idem than table 3 for presentation using PET. In 28 of 134 patients (20.9%) there was a decrease because the pre-chemotherapy gross tumor volume was smaller using PET.

Table 3 Impact of FDG-PET on post-chemotherapy CTV (cm^3) measured by conventional CT scan and PET-CT (115 patients)

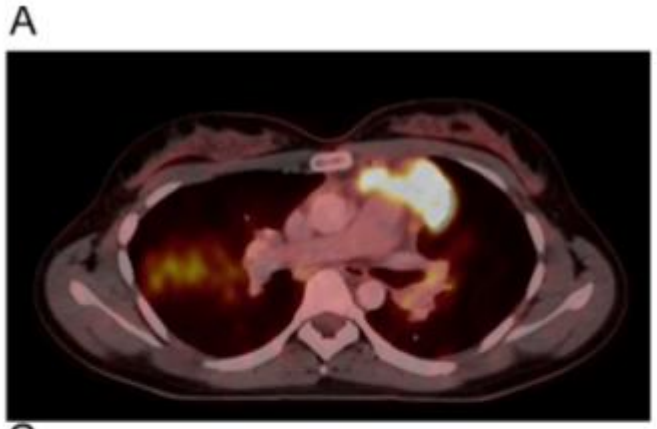
	post-chemotherapy CTV (115 patients)			
Measure	CT scan	PET-CT	% increase**	Paired *t*-test *P* Value
Mean (±SD)	327.2 (±155.2)	350.7 (±171.1)	7.1% (±13.5)	<.0001
Median (range)	317(33 - 873)	328 (33 - 968)	2.2% (-19 - +92)	

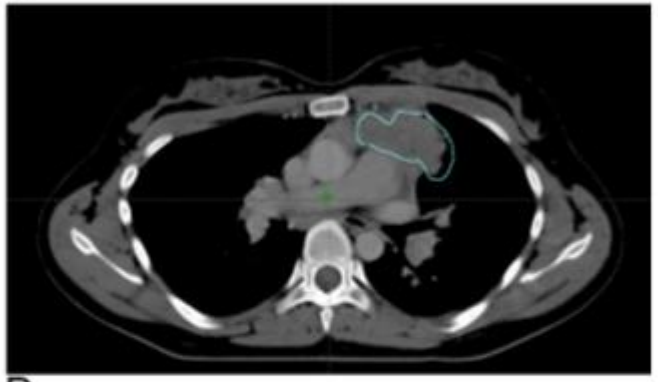
Abbreviations: CT = computed tomography; CTV = clinical tumor volume; PET = positron emission tomography.
** In 69 of 115 patients (60%) there was an increase in CTV using PET. In 7 of 115 patients (6.1%) there was a decrease in CTV using PET.

Girinsky IJROBP 2014; 89:1047

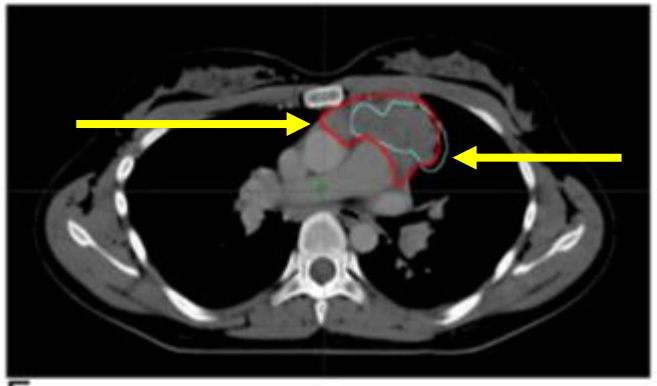

Clinical scenario
Post-chemo RT
Pre-chemo PET/CT
In RT position
Co-registration
INRT
Not in RT position
Visual
ISRT
RT alone
Planning PET/CT
In RT position
INRT
Residual active disease
Planning PET/CT
In RT position
INRT

Pre-chemo PET

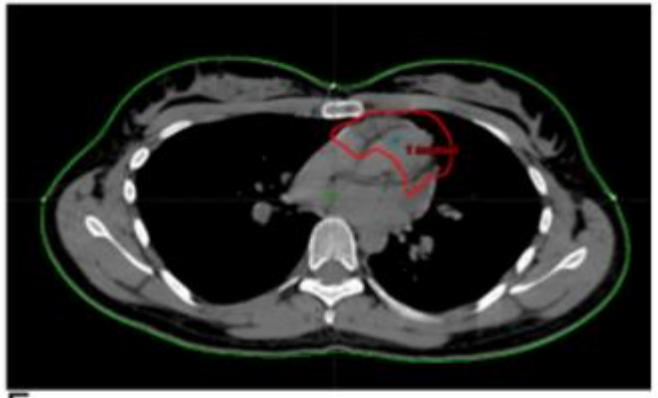




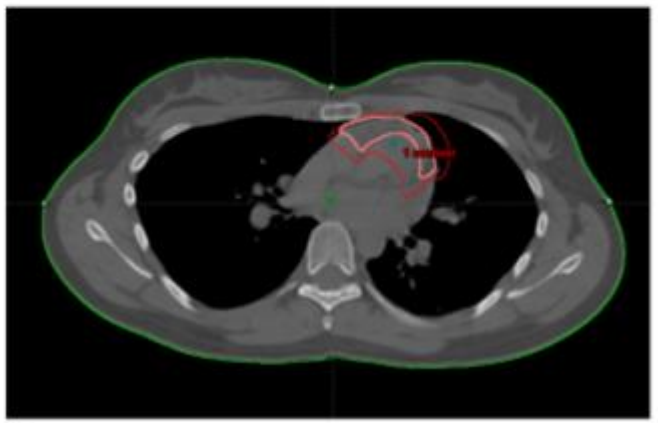
Pre-chemo PET-GTV



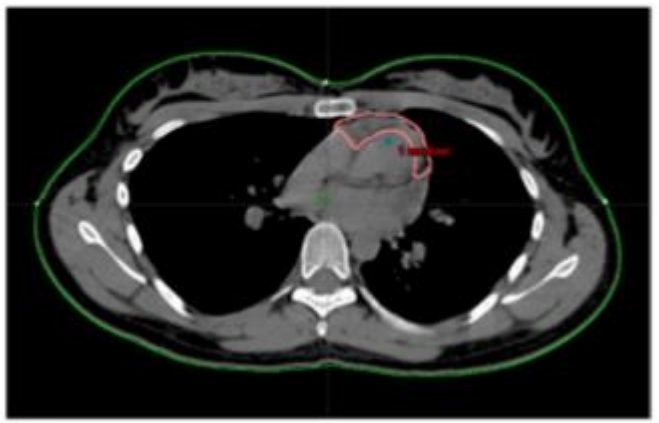
Pre-chemo CT-GTV



Pre-chemo GTV superimposed on post-chemo CT



Pre-chemo CTV excluding normal structures

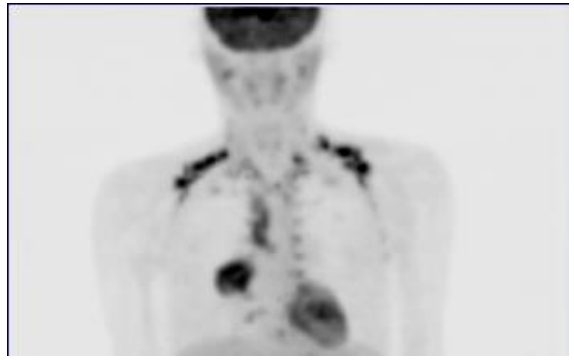


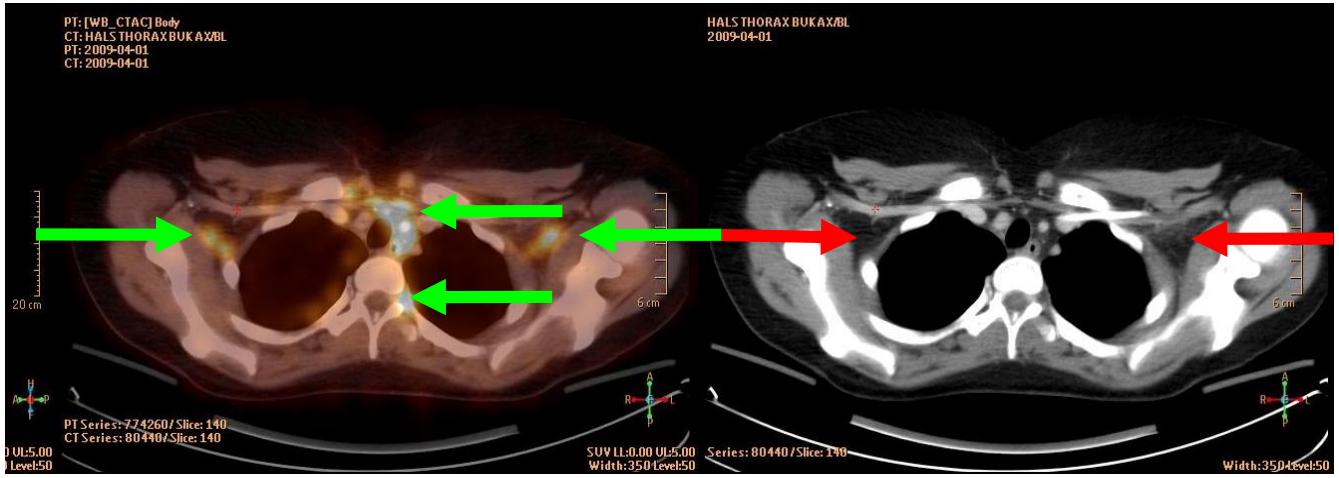
Illidge. IJROBP 2014 89: 49

Limitations of FDG imaging in Lymphoma

Physiological uptake – Brown Fat

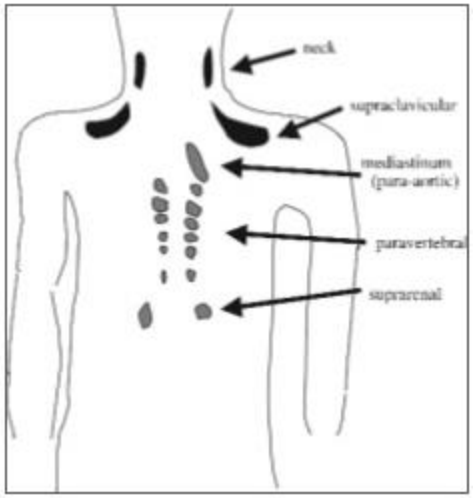
Brown fat





- Bilateral & Symmetrical
- More common in young age

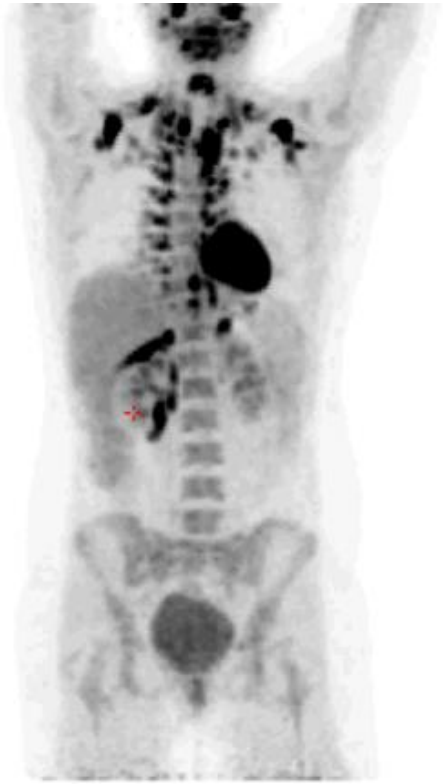
- Sites:
  - Neck
  - SCF/Axillae
  - Mediastinum
  - Para-vertebral



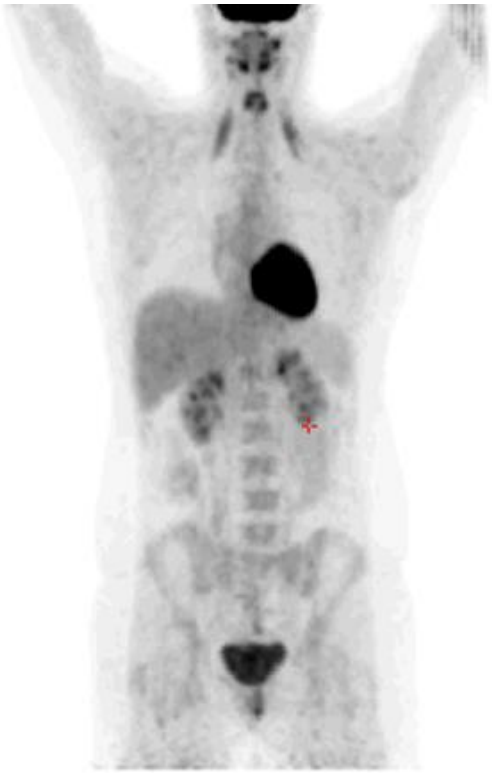
DD:

- No CT correlate

- Propranolol in difficult cases



31-year old female with DBLCL



after premedication with Propranolol

ILROG imaging guidelines (in preparation) – Images courtesy of Dr A Bresthlesen

Physiologic uptake - Head & Neck:

Tonsillar uptake

Head & Neck:

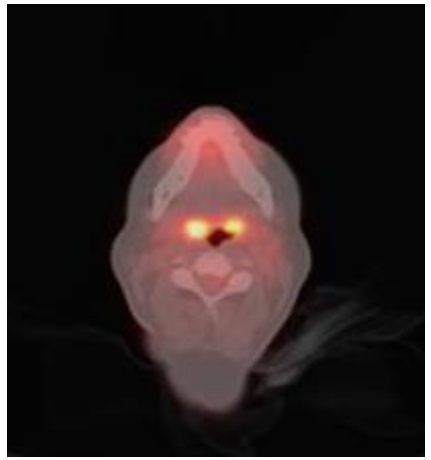
- NPX
- Tonsils
- Submandibular glands
- Parotids

DD:

- Symmetry
- History of URTI
- Pattern of disease
- Exam

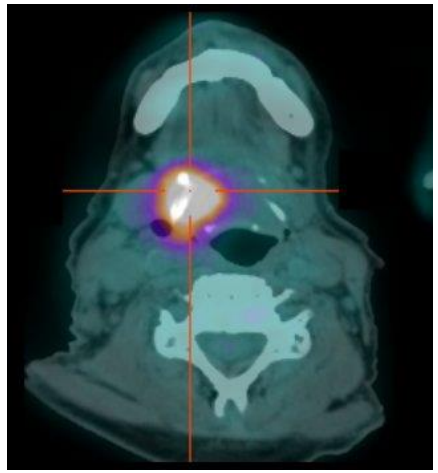
Physiologic

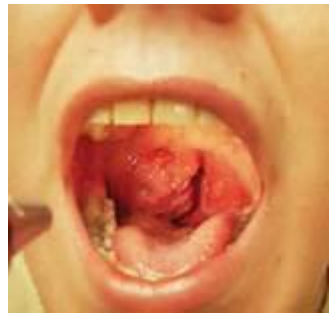
- Bilateral
- Symmetrical



Asymmetric

- Size
- Uptake



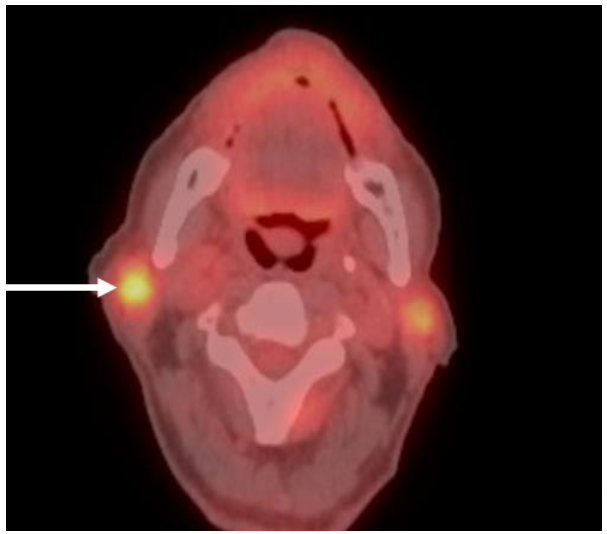


Physiologic uptake - Parotid:

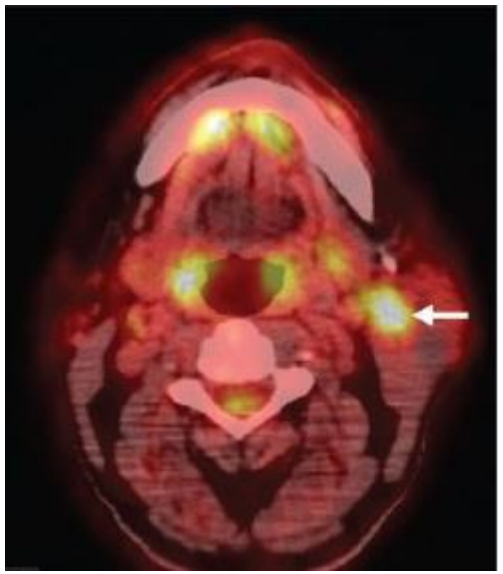
Intra & Pre parotid LNs are involved with lymphoma

DD:

- Pleomorphic adenoma
- Warthin's tumour



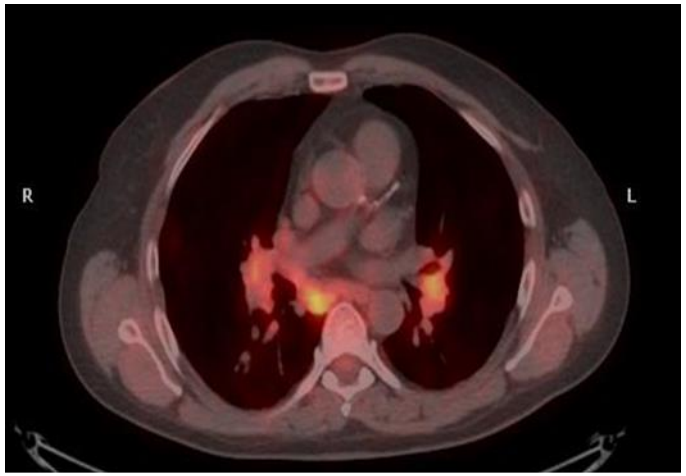
Pleomorphic adenoma



Warthin's Tumour

Dua et al 2012

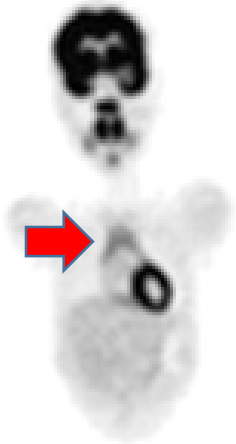
Conditions mimicking Lymphoma



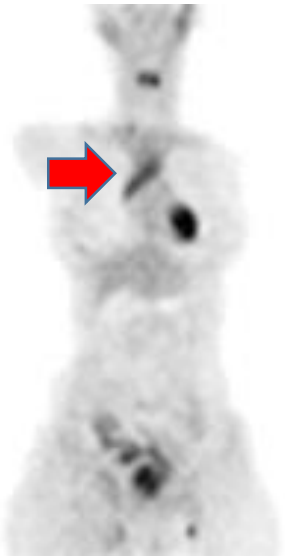
Sarcoidosis

Uptake
- Bilat
- Symmetrical
- Low-grade

Confirmation:
- EBUS
- Serum ACE



Inverted V



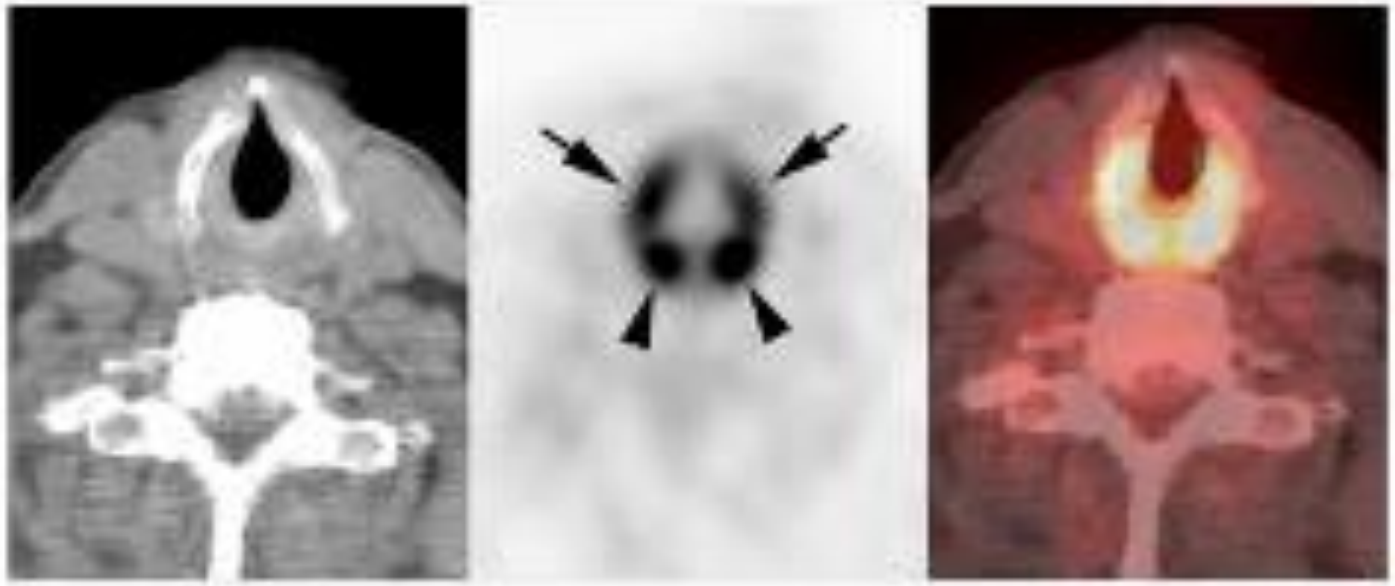
Unilateral

Focal

Thymic Hyperplasia

Post treatment
Children & young adults

Jerushalmi 2017



Arrows: vocal cord
Arrowheads: cricoarytenoid muscles

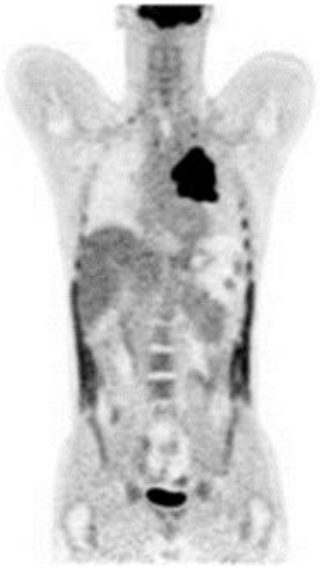
Interpretation of response for RT decisions

- Definition of CMR / PET -ve:
  - Lugano 2014: DS 1-3
  - Studies omitting RT (e.g. RAPID / H10): DS 1-2 only, DS 3 considered PET+

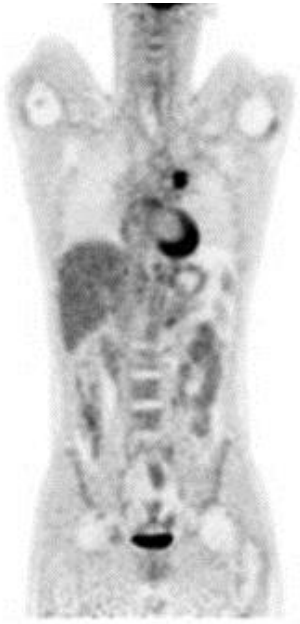
- PET +ve (DS 4-5):
  - Better (PMR)
  - Stable (NMR)
  - Worse or new areas (PMD)

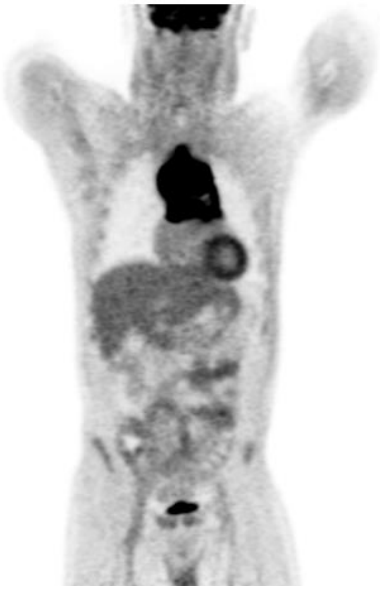
Which patient may be suitable for RT?

Baseline

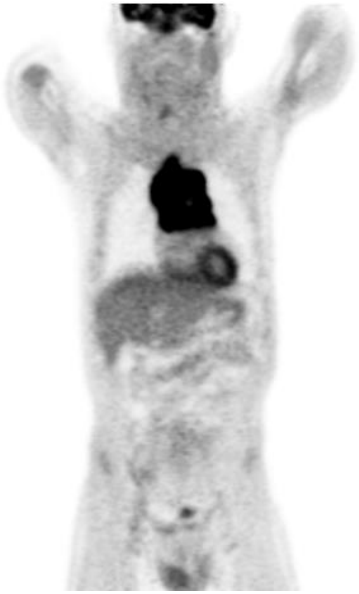


Post chemo





Baseline



Post chemo

- PET CMR does not = absence of microscopic disease (although strongly predictive of good prognosis)
  - Residual disease detection depends on:
    - Volume, intensity, background activity
    - Scanner detection limit
  - Microscopic disease presence depends on:
    - Histology, prognosis
    - Chemotherapy given
    - Initial bulk, residual soft tissue, local infiltration

- Can RT be omitted in PET-ve patients?
- Should we ignore residual masses if PET-ve?

Can RT be omitted after CMR on PET?

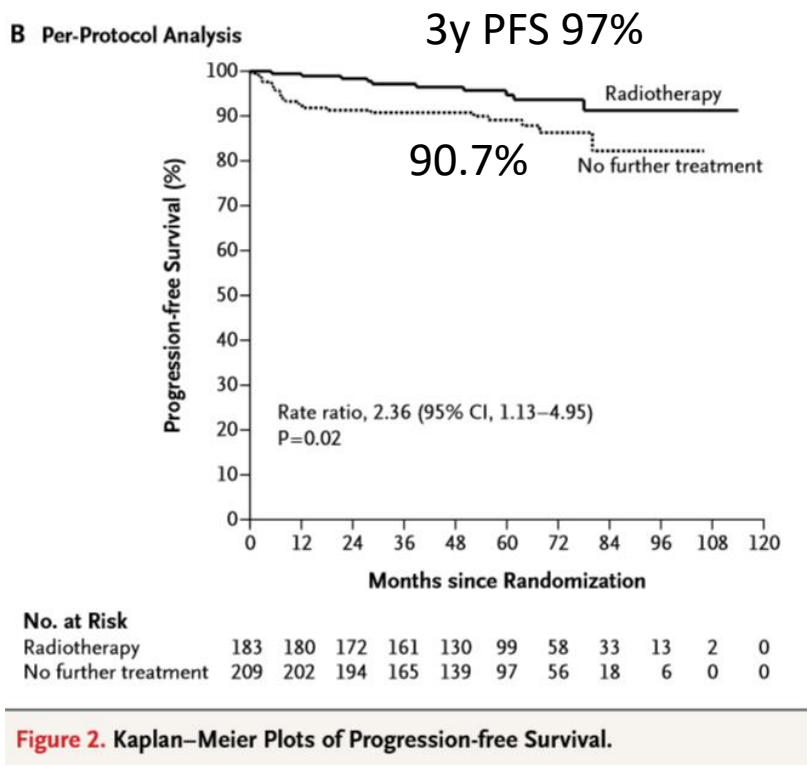


Figure 2. Kaplan–Meier Plots of Progression-free Survival.

RAPID

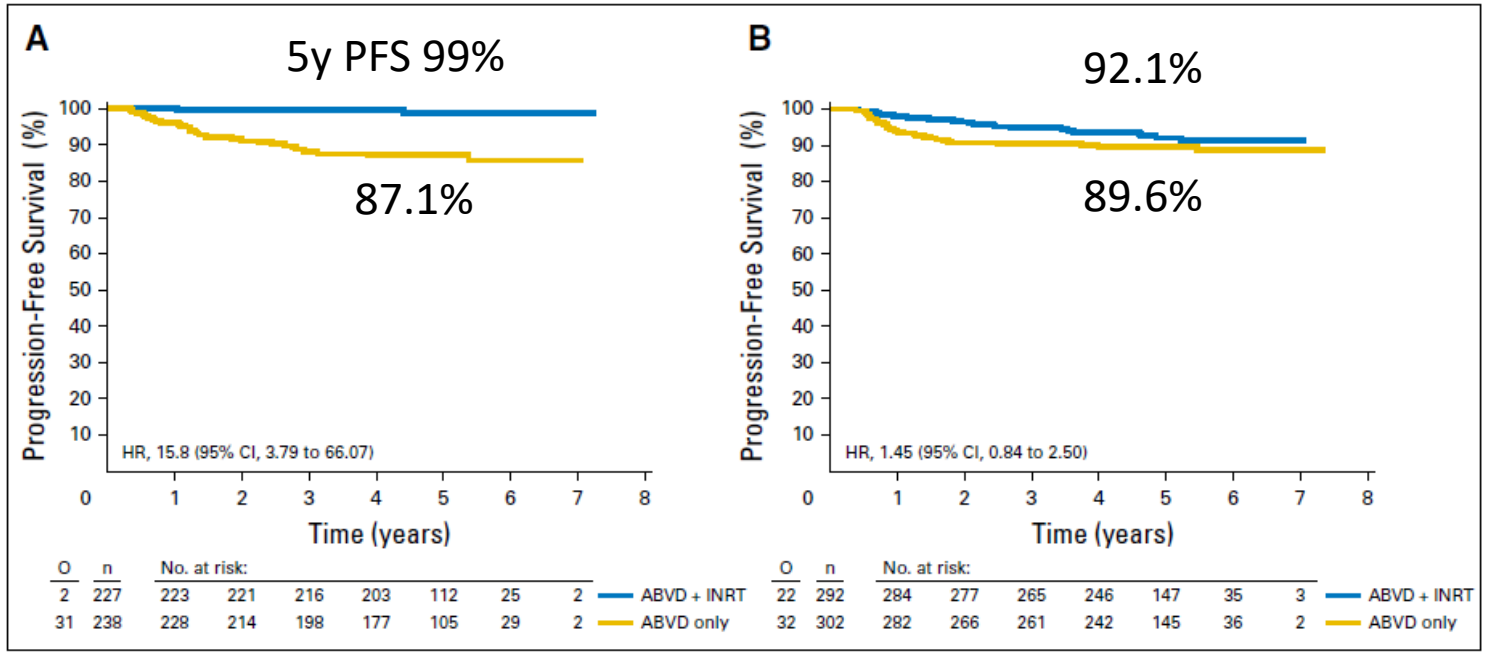


Fig 4. Progression-free survival of 1,059 early positron emission tomography–negative patients who were treated per the initial protocol. Shown are the rates of progression-free survival of the (A) favorable (F) groups of patients randomly assigned to doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) + involved-node radiotherapy (INRT; n = 227) or ABVD only (n = 238) and of the (B) unfavorable (U) groups randomly assigned to ABVD + INRT (n = 292) or ABVD only (n = 302). HR, hazard ratio, O observed; n, number of patients.

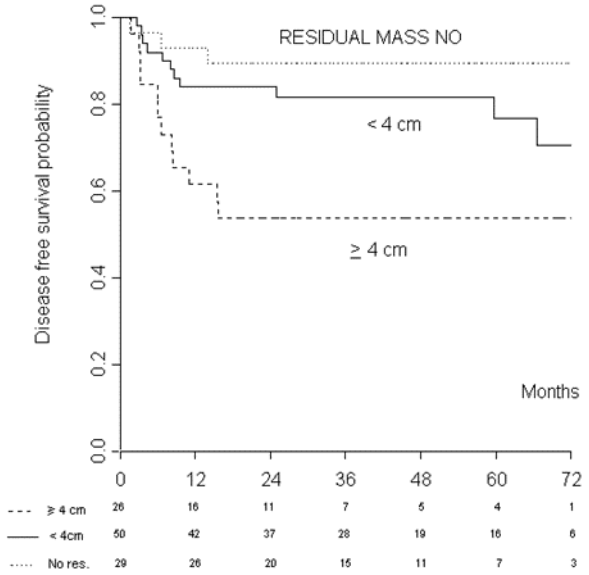
H10

Early stage HL – CMR defined as DS 1-2.

CMR does not = no microscopic disease

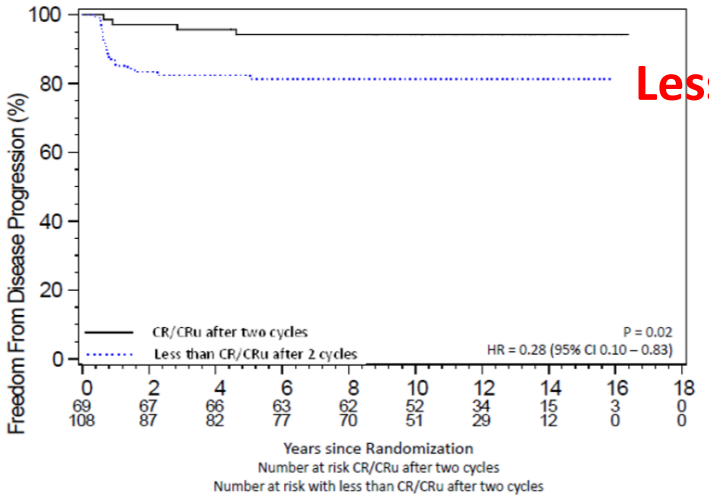
Should we ignore residual masses if PET –ve?

HL
Magagnoli 2011



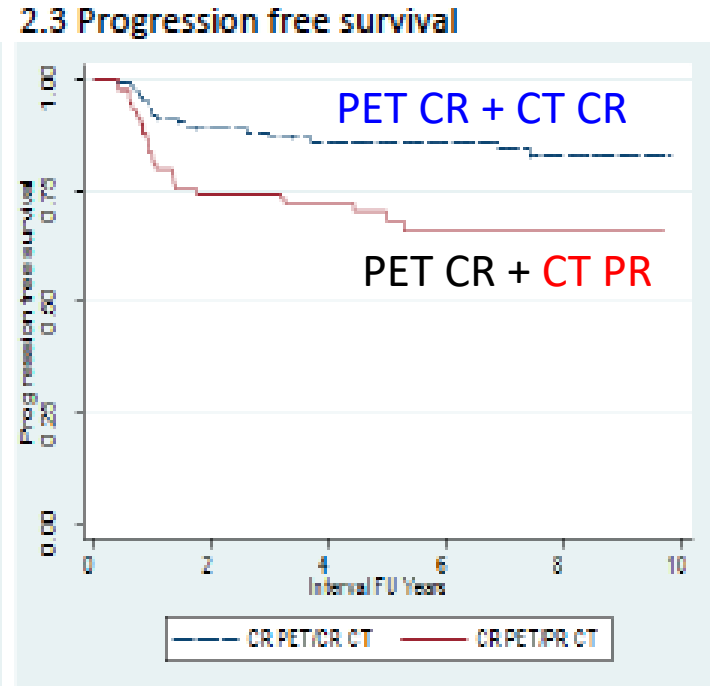
Supplementary Appendix Figure 5B:
FFDP: ABVD Alone by CR/CRu

NCIC HD6
Meyer 2011

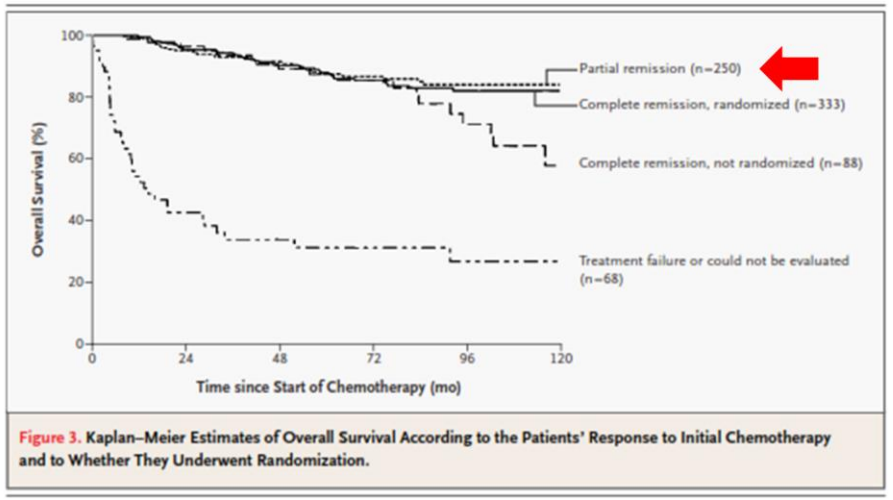


Less < CR

DLBCL
Dabaja 2013



EORTC
Aleman




Thank you for listening

Supplementary slides

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**

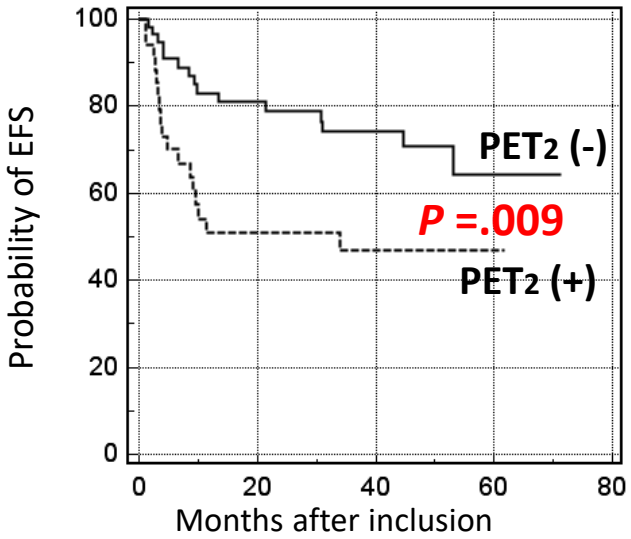
- can be used to direct biopsy
  (especially if suspected transformation)

- A baseline PET-CT scan is also desirable for subsequent response assessment

Visual vs. quantitative analysis
DLBCL 2 cycles

n = 92 PET 2

Visual analysis

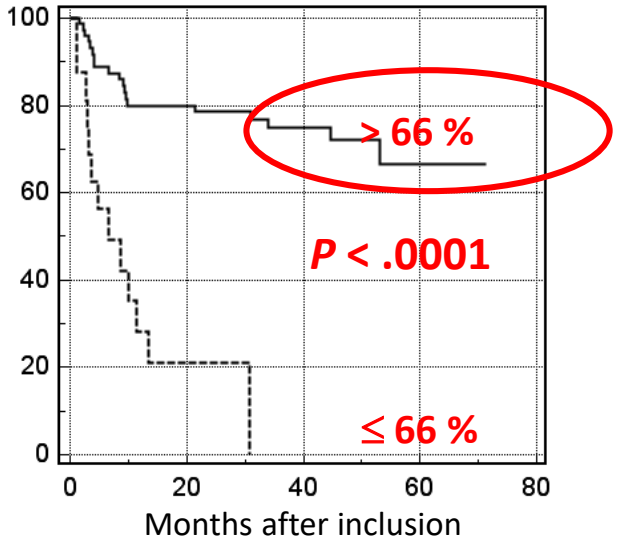


NPV=74%, PPV=50%

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

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

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

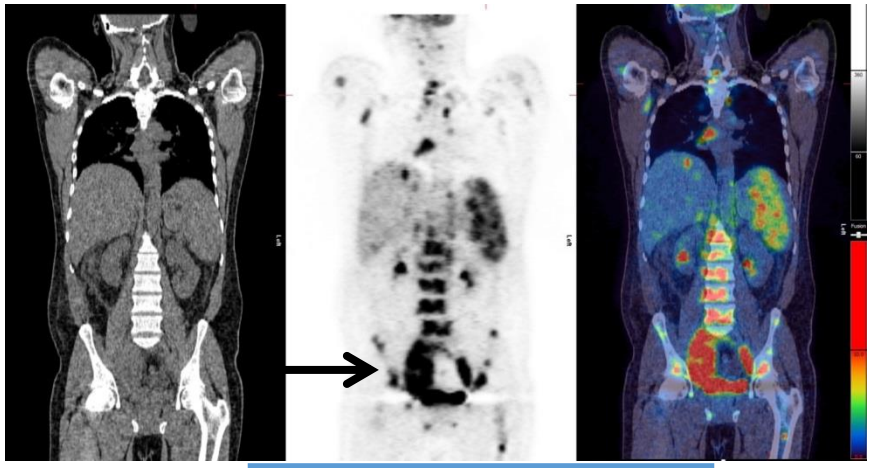
- Cons:
  - Additional **radiation**
  - **Resource** implications
  - Small **errors** in FDG measurement in tumours (unlikely to be significant) and 10-15% increase in liver/MBP uptake

Delta SUV (Δ SUV)

DLBCL interim scans

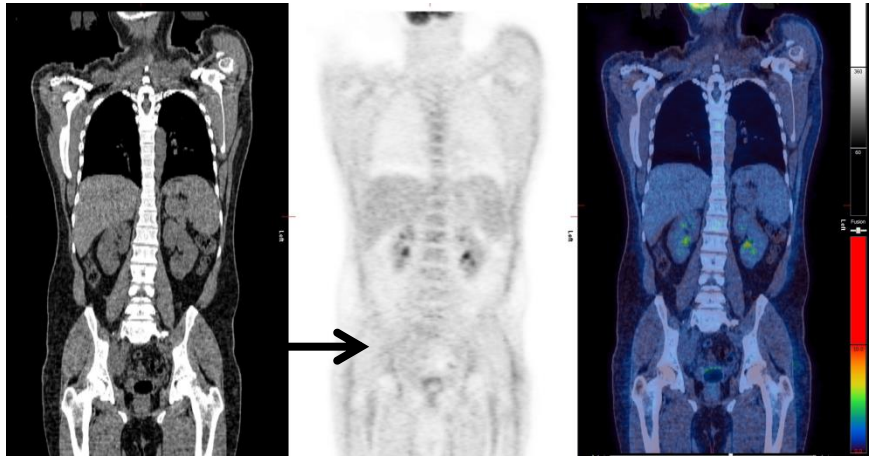
Cut-off 66% at 2 cycles ; 70% at 4 cycles

Staging



SUV = 25.0

Interim



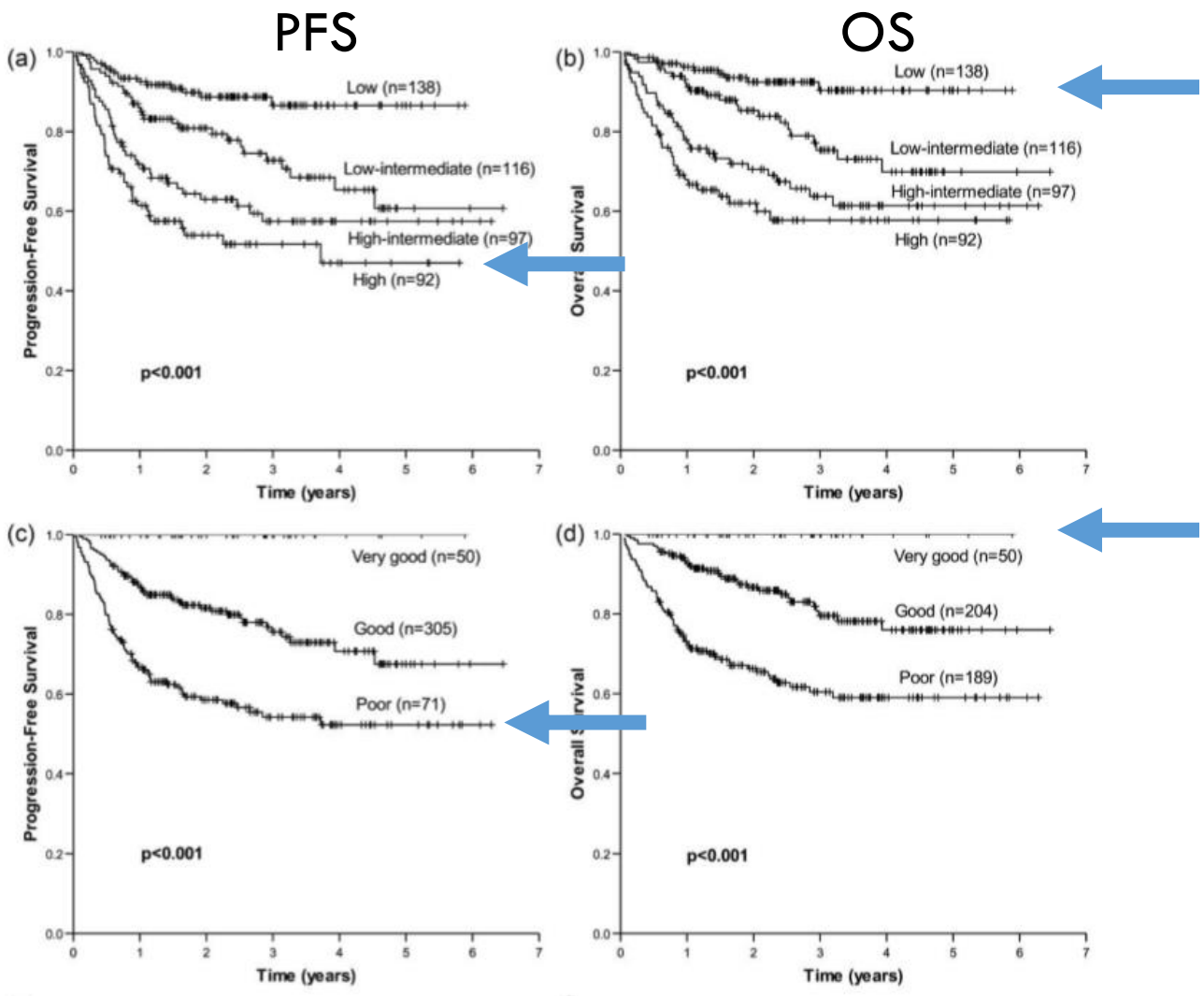
SUV = 2.6

ΔSUV 90%

Does PET improve IPI?

IPI

R-IPI

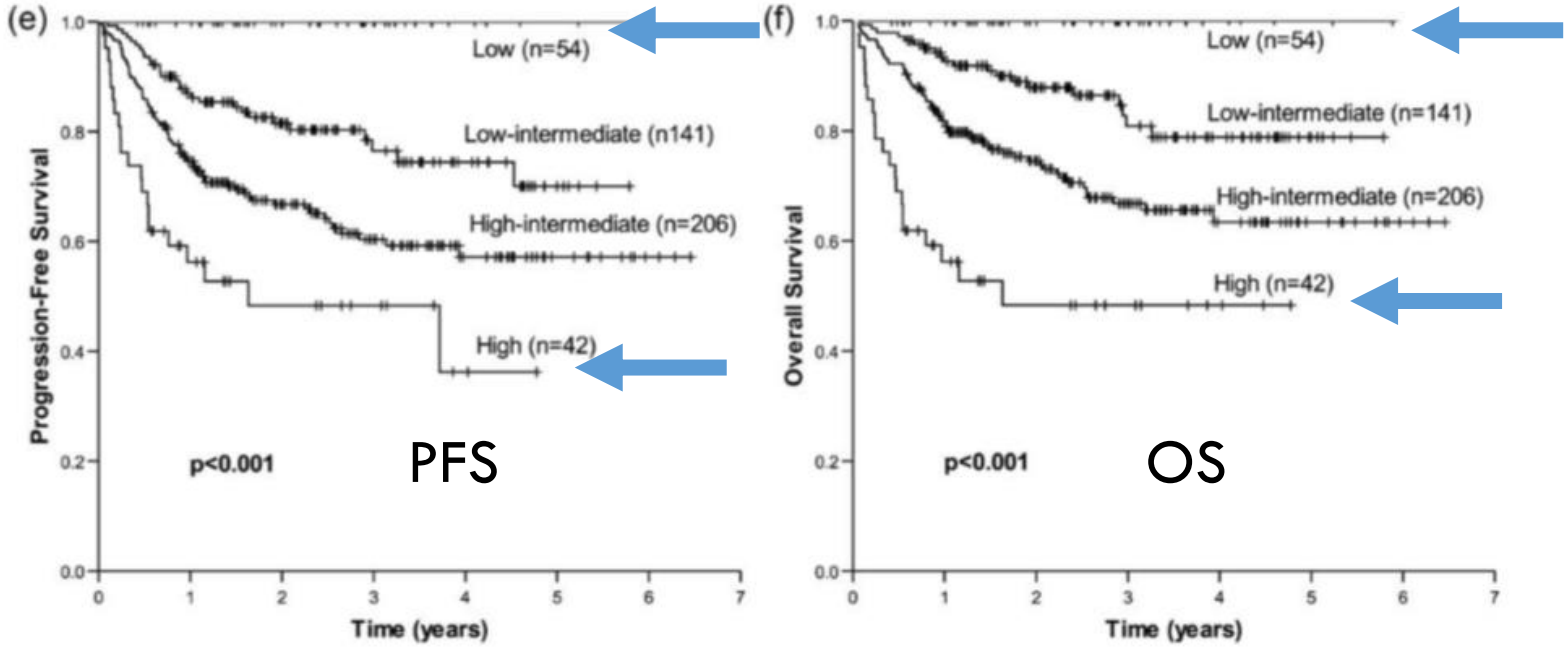


n = 443

El-Galaly, Am J Hem 2015

Prognostic scores using pet in dlbcl

NCCN-IPI



Each scores 1 point	Each scores 2	Scores 3
Age >40	Age > 60	Age > 75
Stage III/IV	LDH > 3 ULN	
ECOG PS ≥ 2		
GI/lung/liver/CNS/BM sites		
LDH 1-3 ULN		

0-1	low
2-3	low-intermediate
4-5	high-intermediate
6-8	high

ESTRO School

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
- 2011 Lugano imaging

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

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

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

The Copenhagen Model

ILROG
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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

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IV-Contrast

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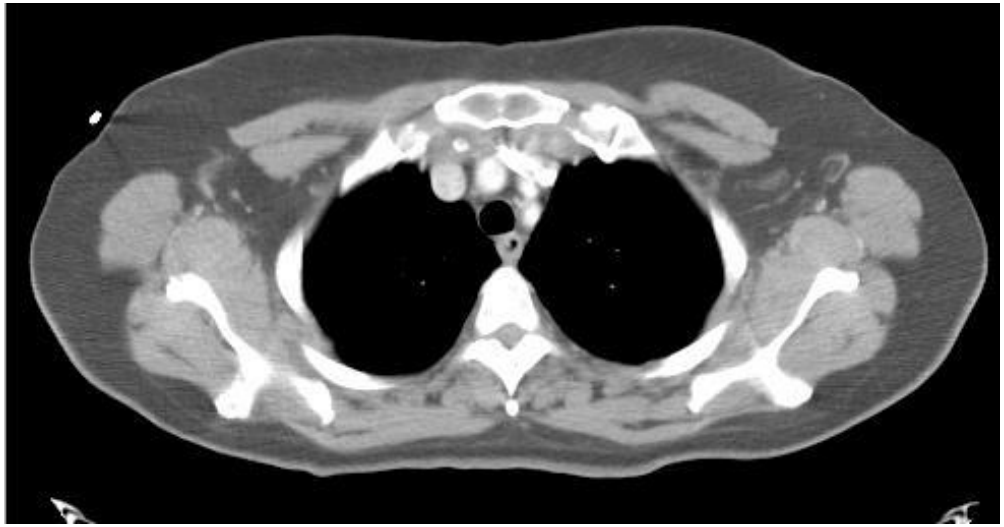
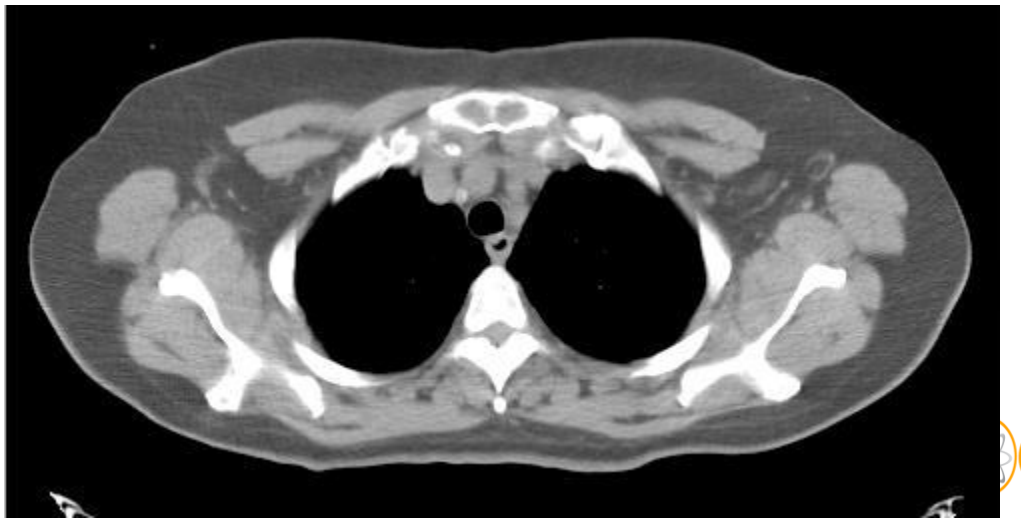
with and without IV contrast





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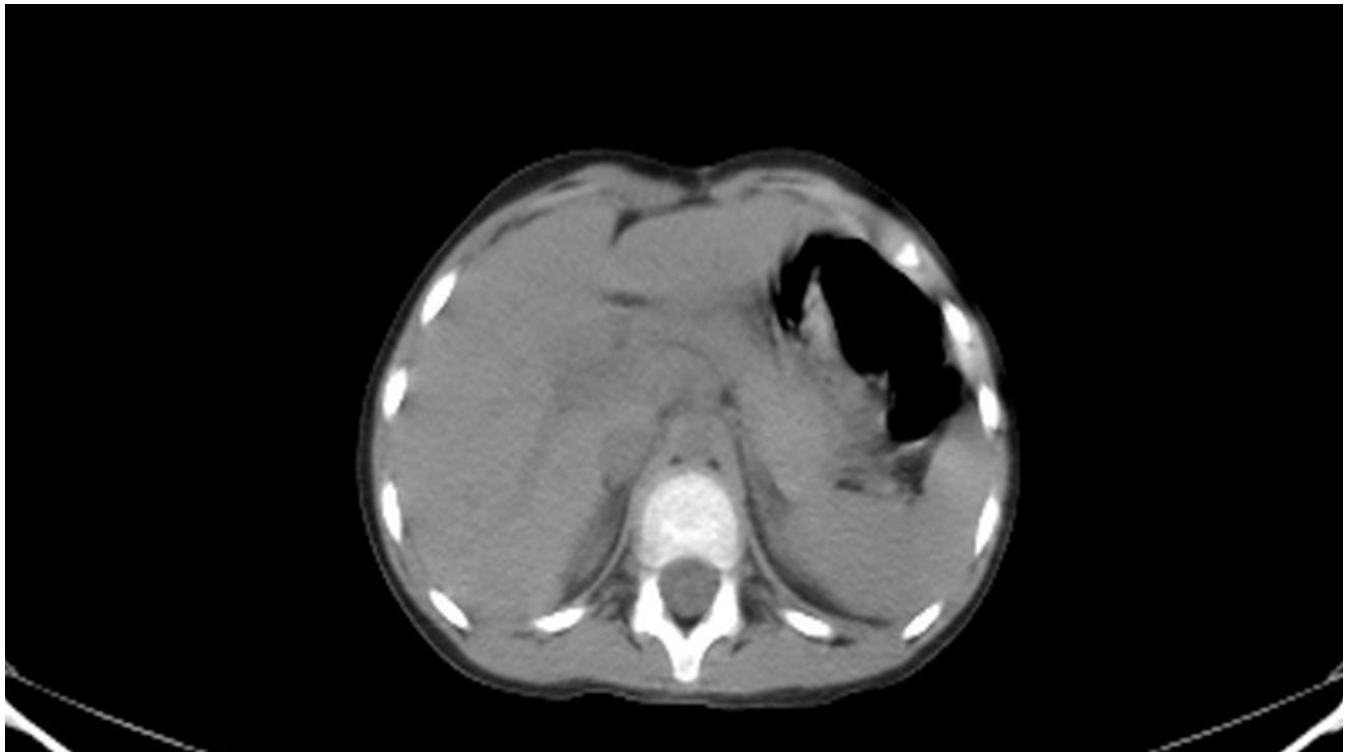
CT scan without IV contrast



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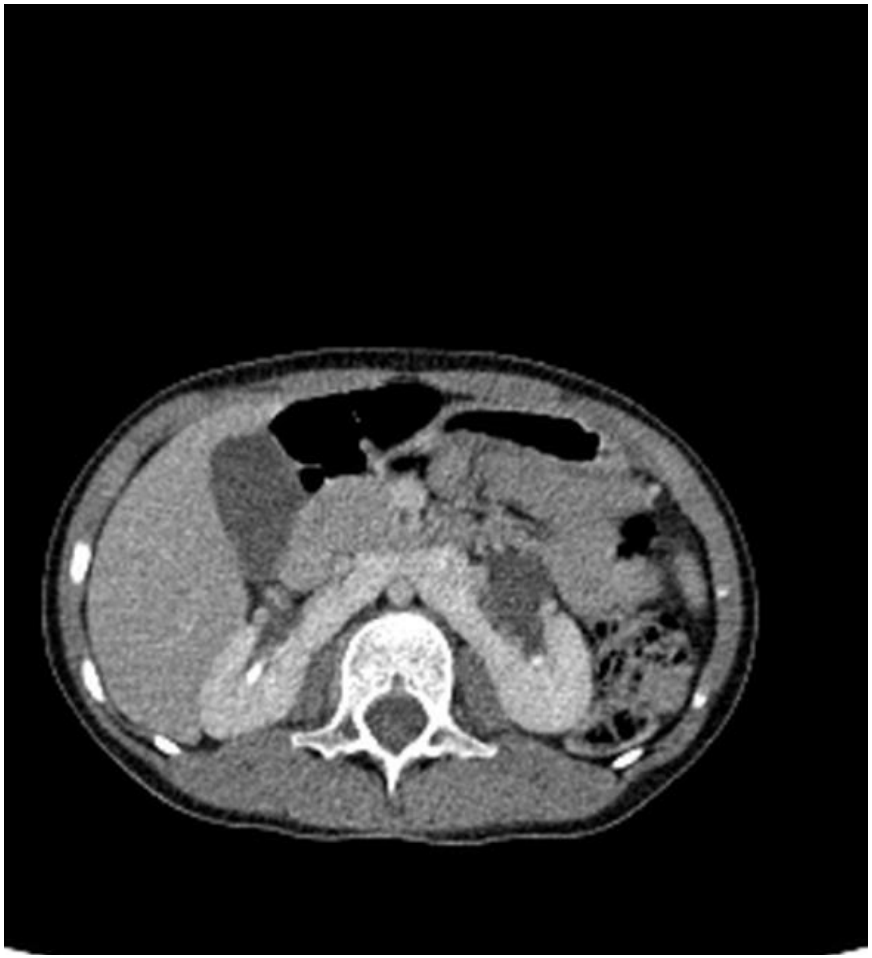
CT scan with IV contrast



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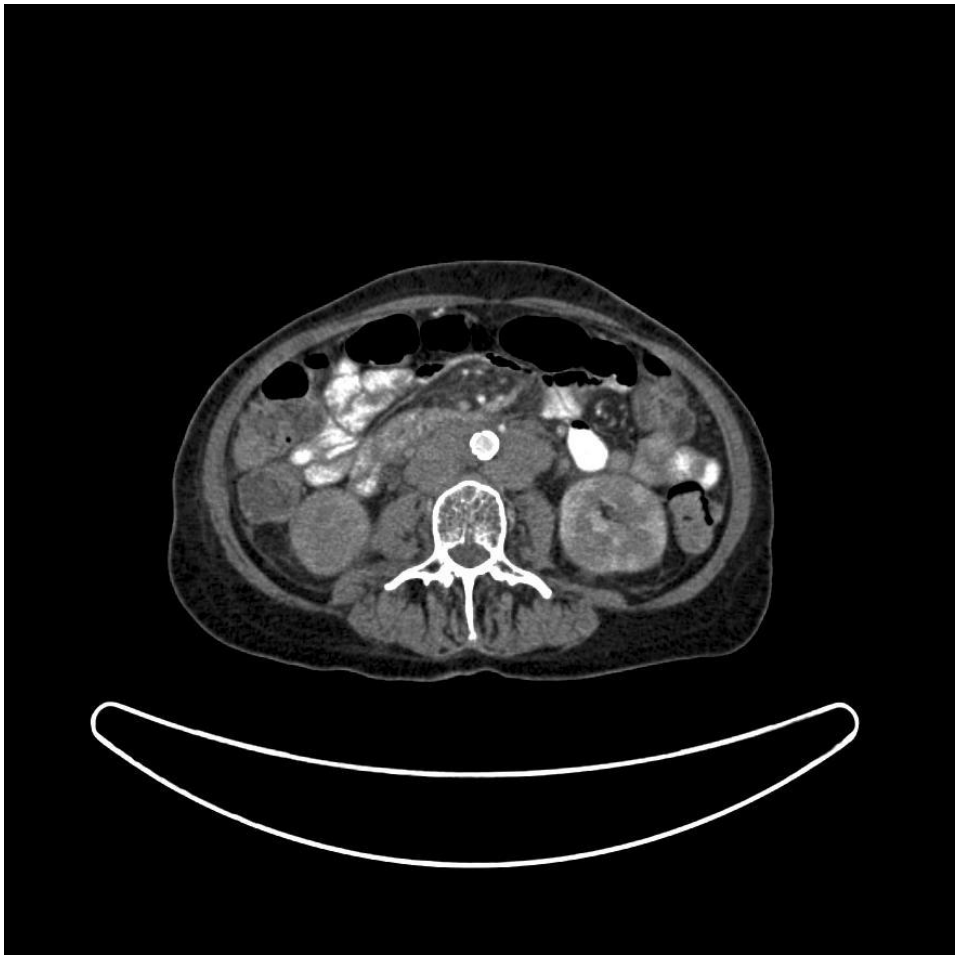
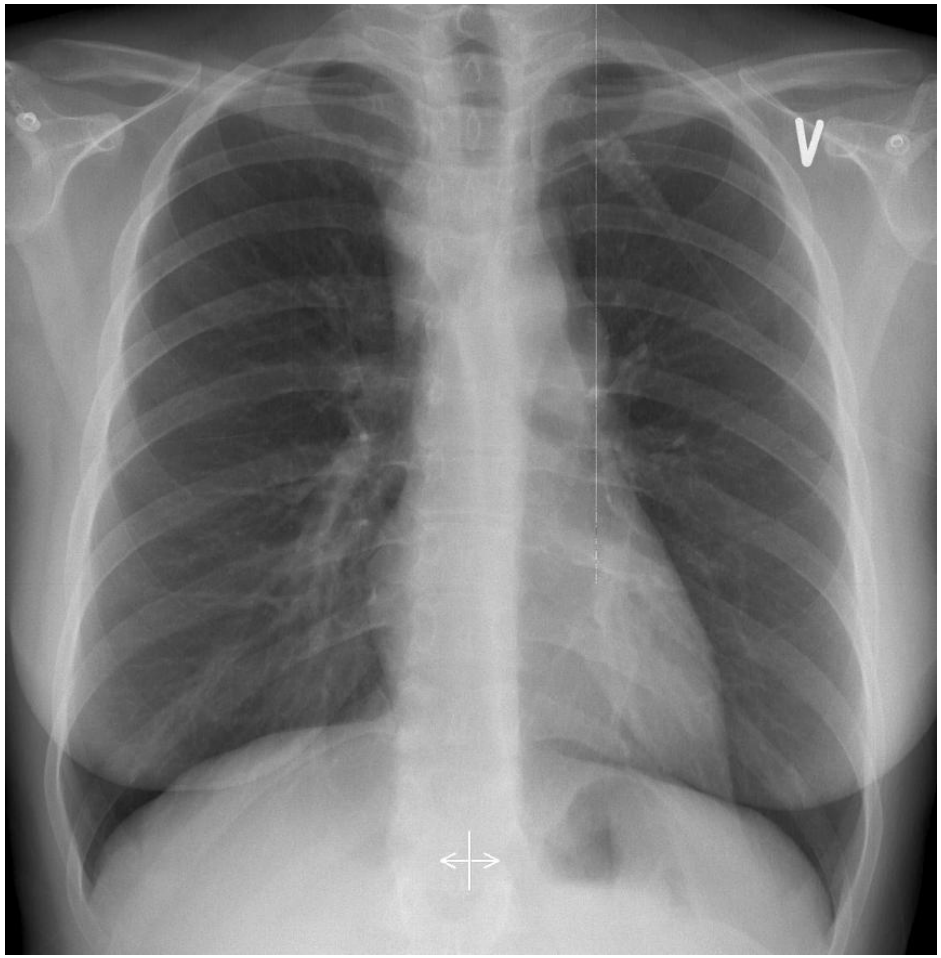
Oral contrast



Chest X-ray is not required



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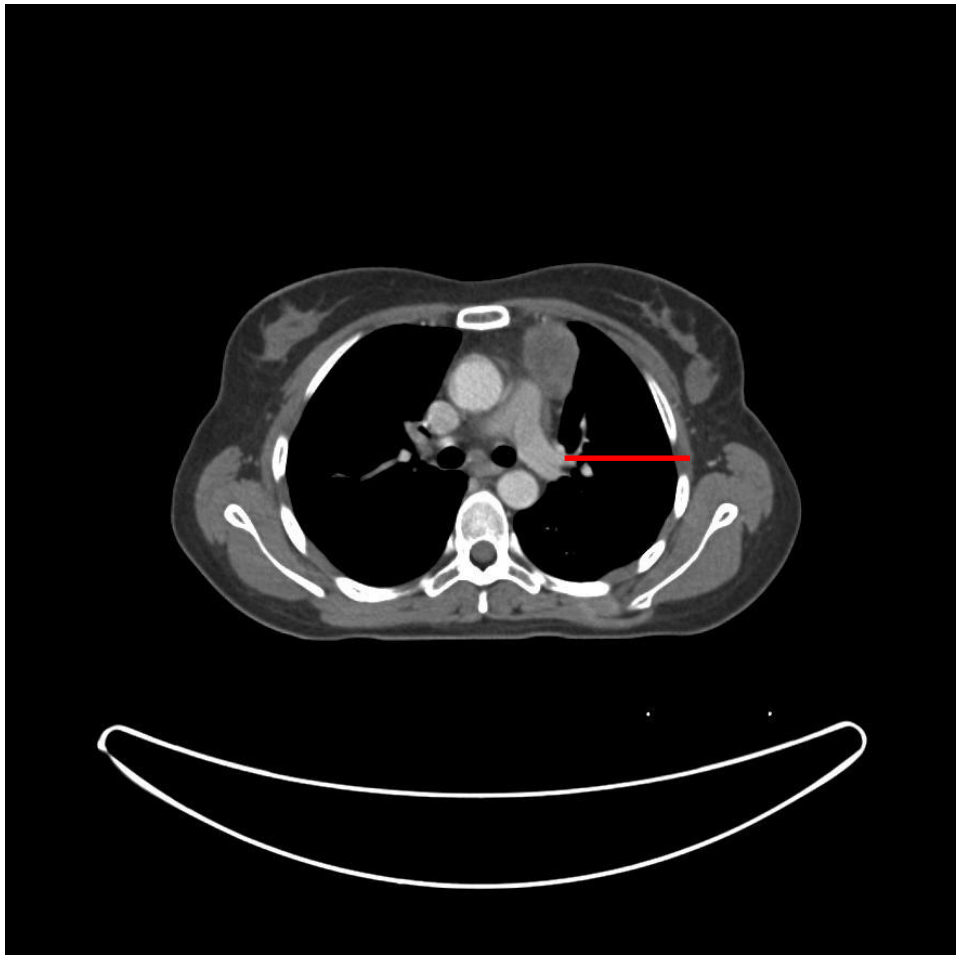
10 % have a normal chest x-ray



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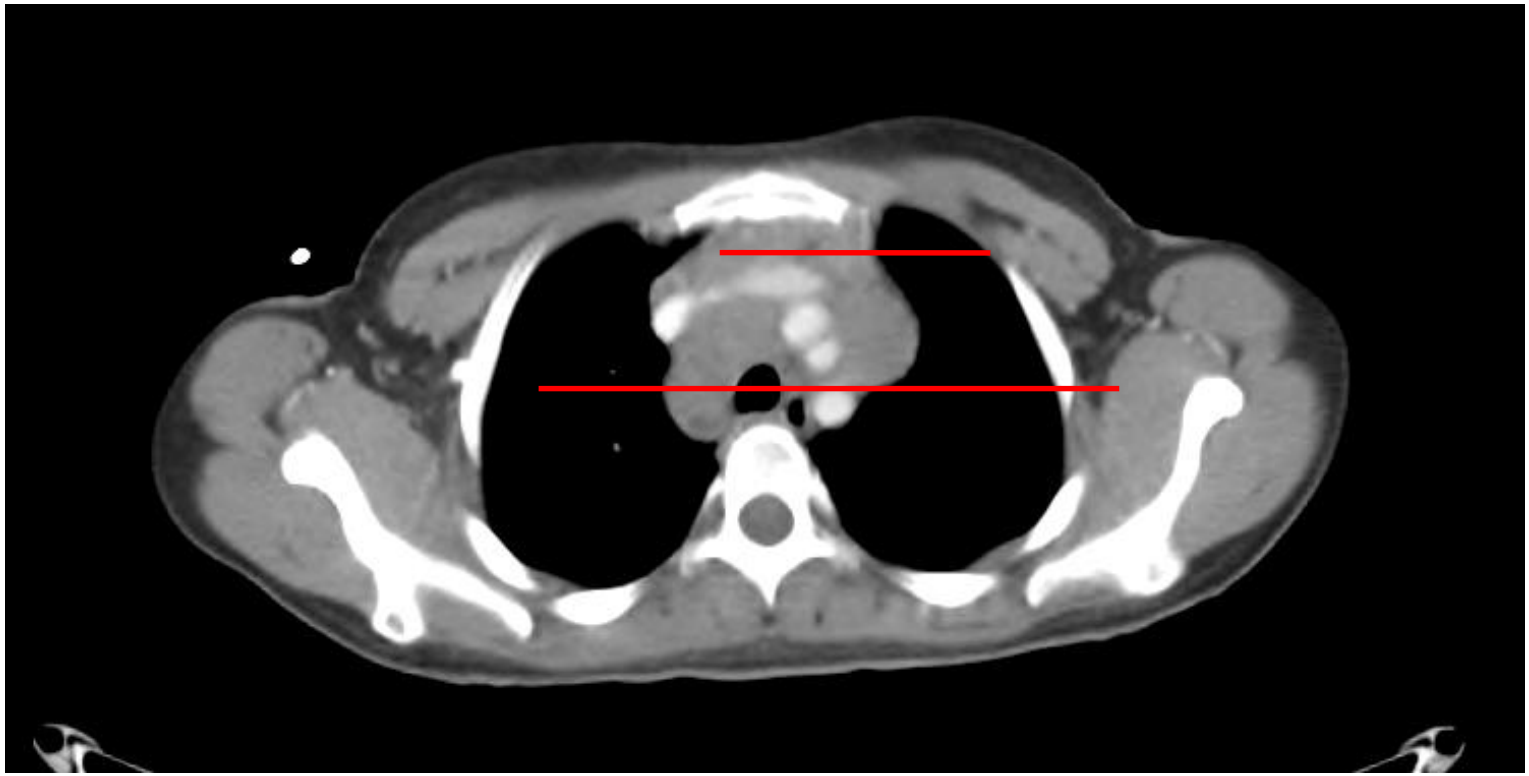
Enlarged mediastinum



10 cm or greater than 1/3 of the trans-thoracic diameter at any level of thoracic vertebrae

CT identifies more hilar nodes

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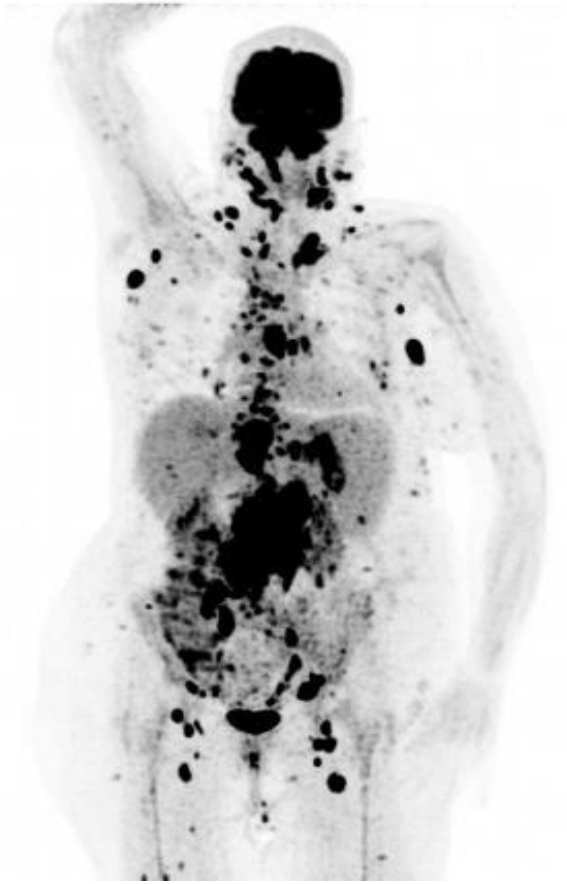
Lymphomas can be found anywhere



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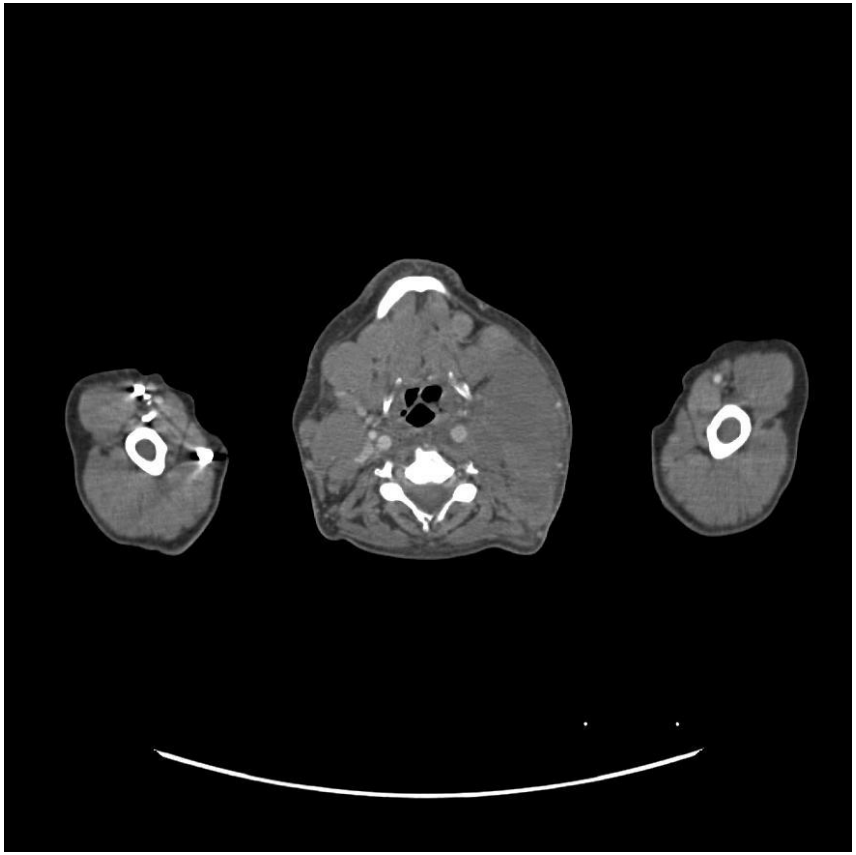
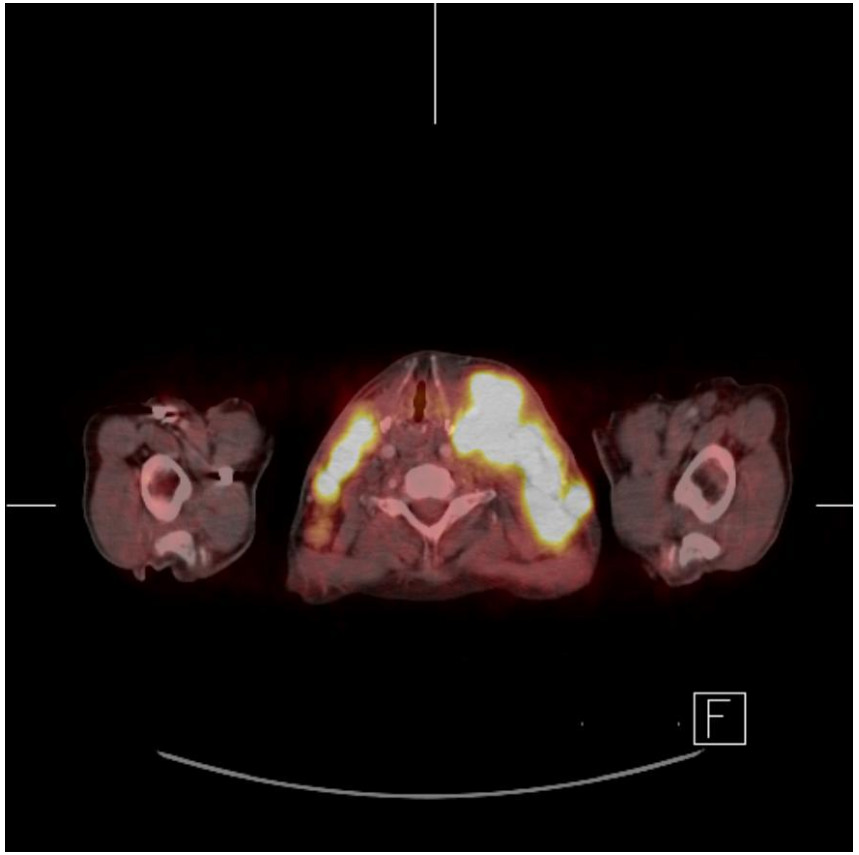
Lymph node > 1.5 cm





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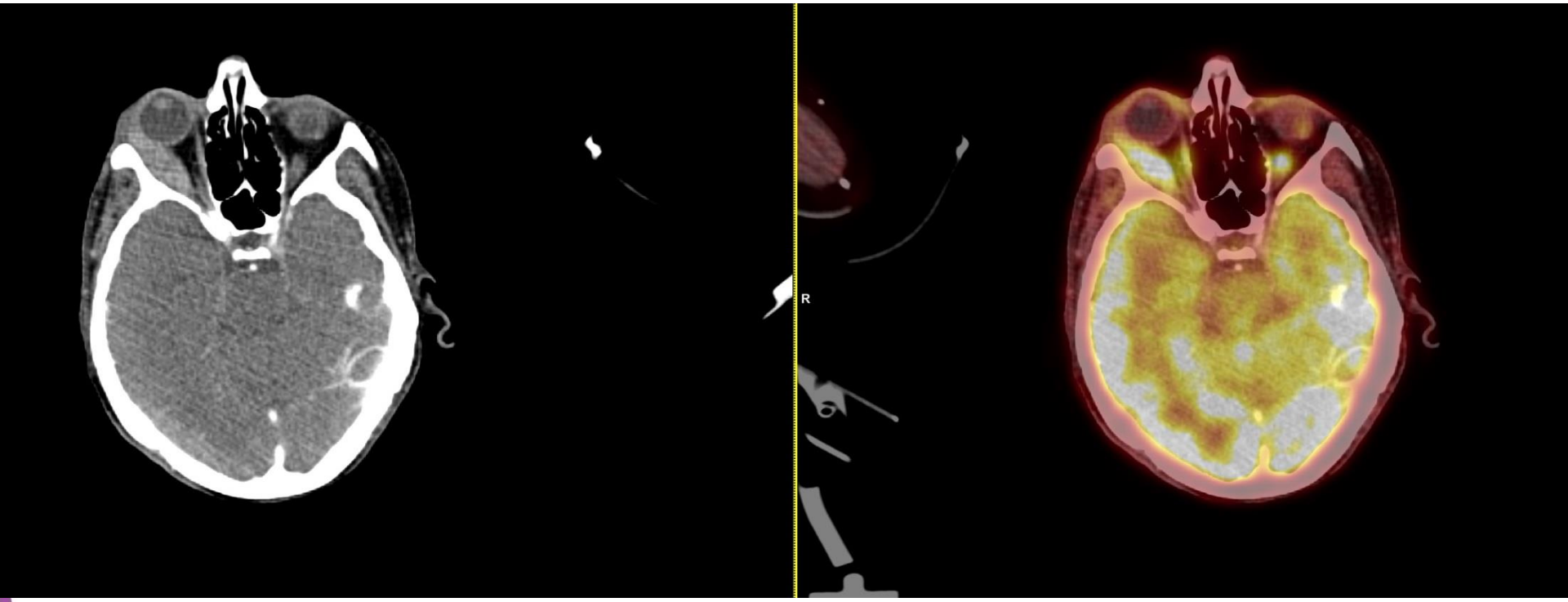
Lymphoma in the rigth orbita



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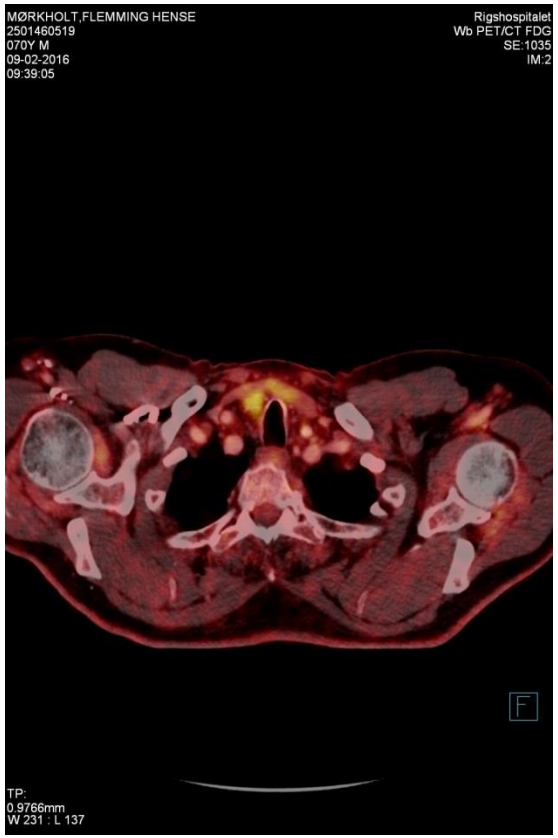
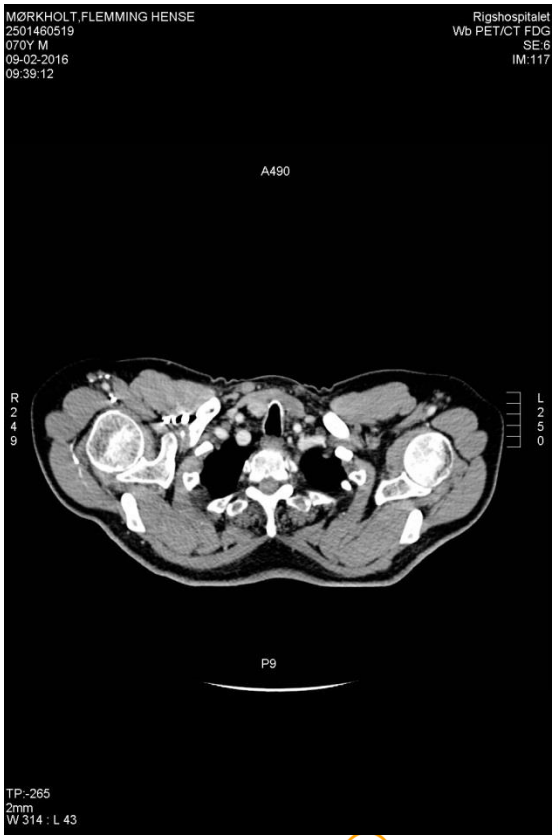
Lymphoma infiltration of the thyroid gland





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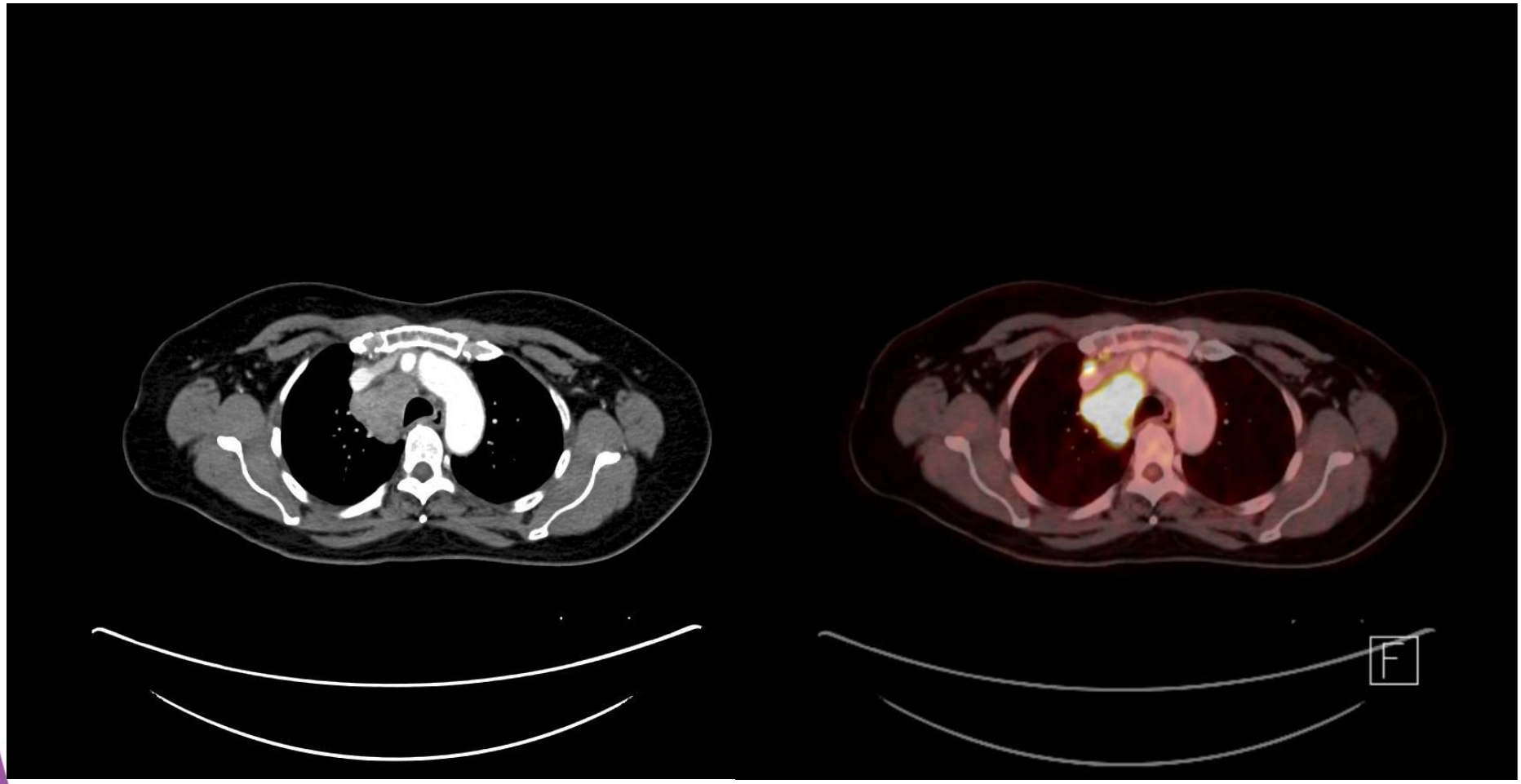
Lymphoma in mediastinum



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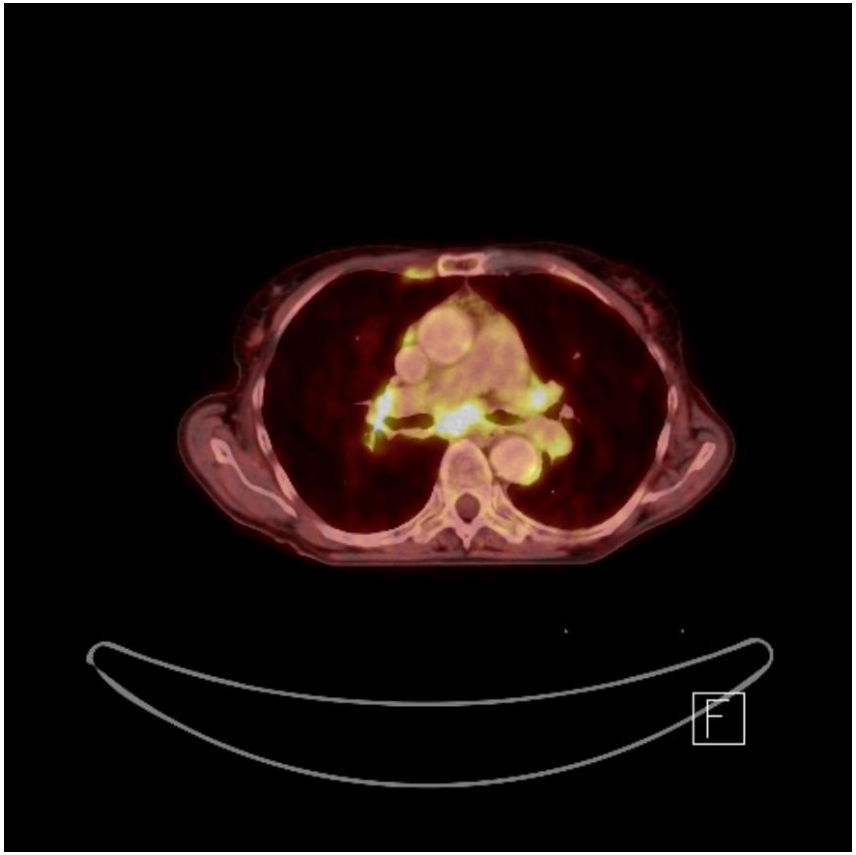
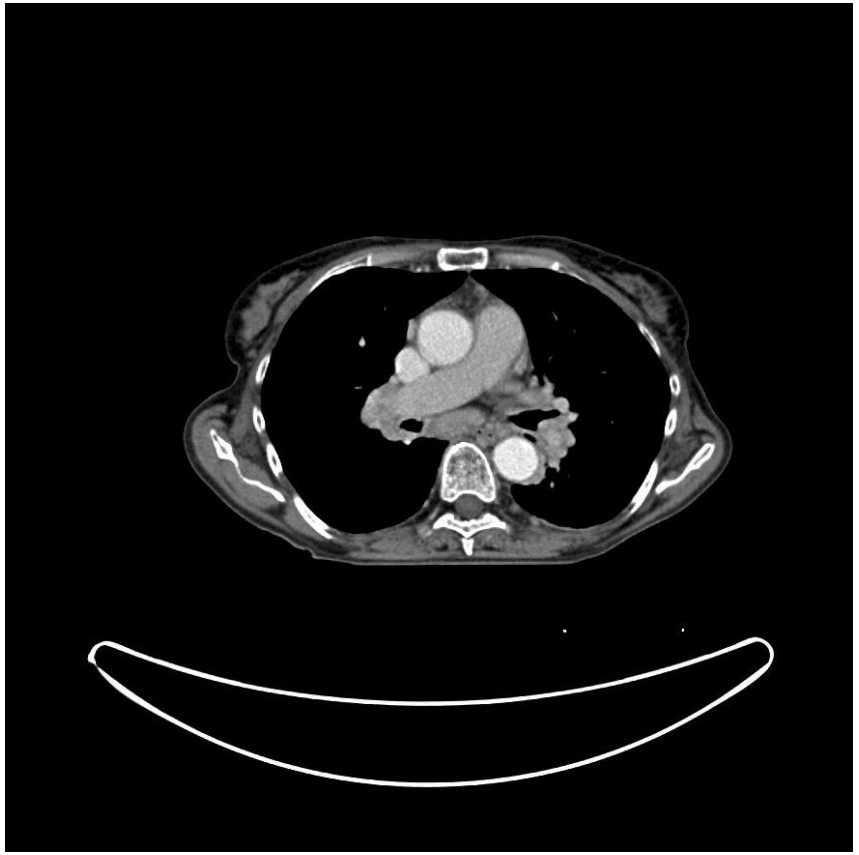
Lungs, involvement of lymph nodes





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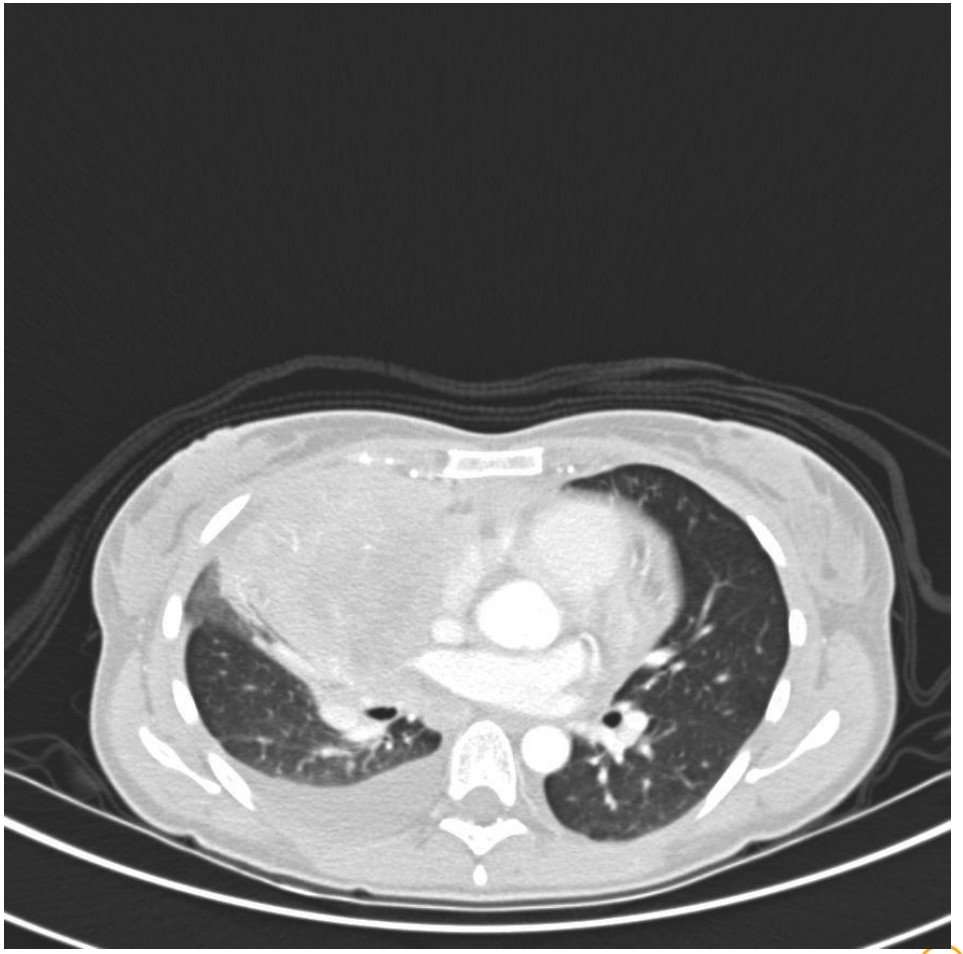
Lungs



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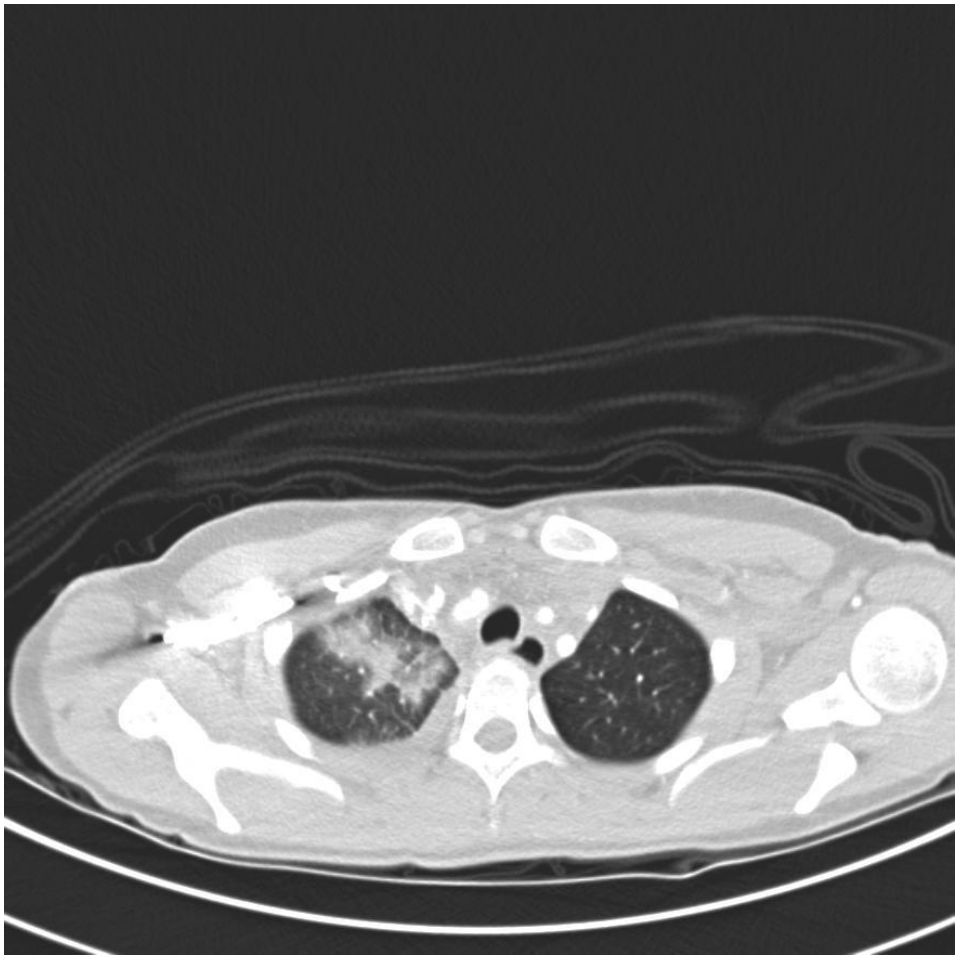
More diffuse infiltration, snow balls



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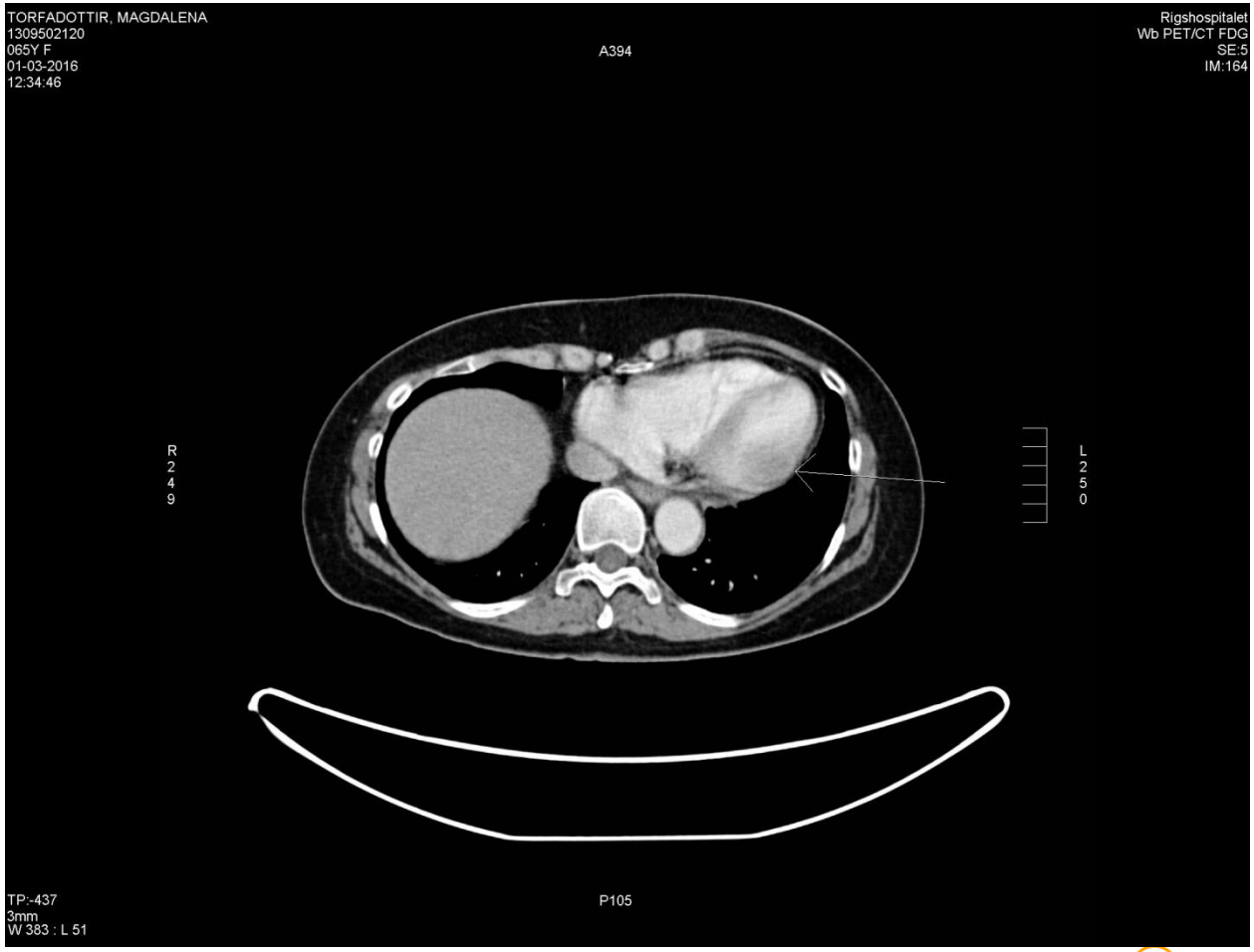
Lymphoma infiltration of the left ventricle



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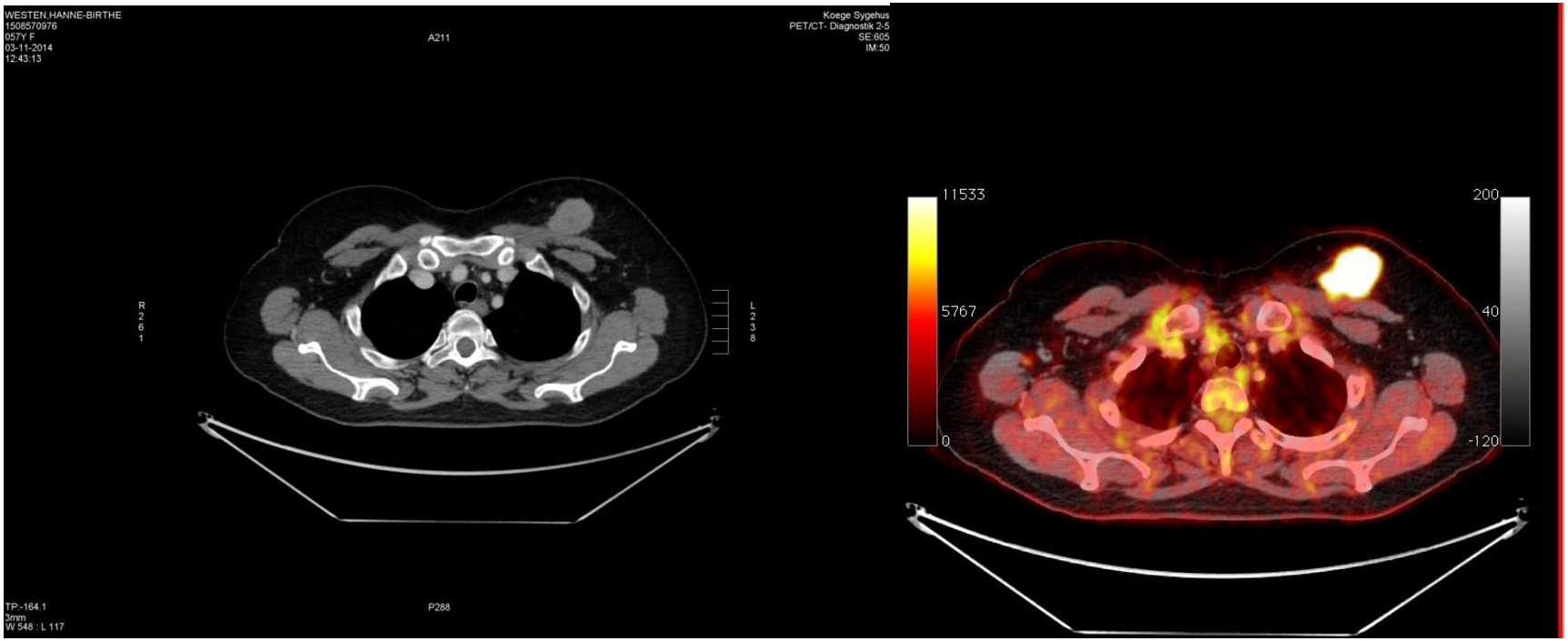
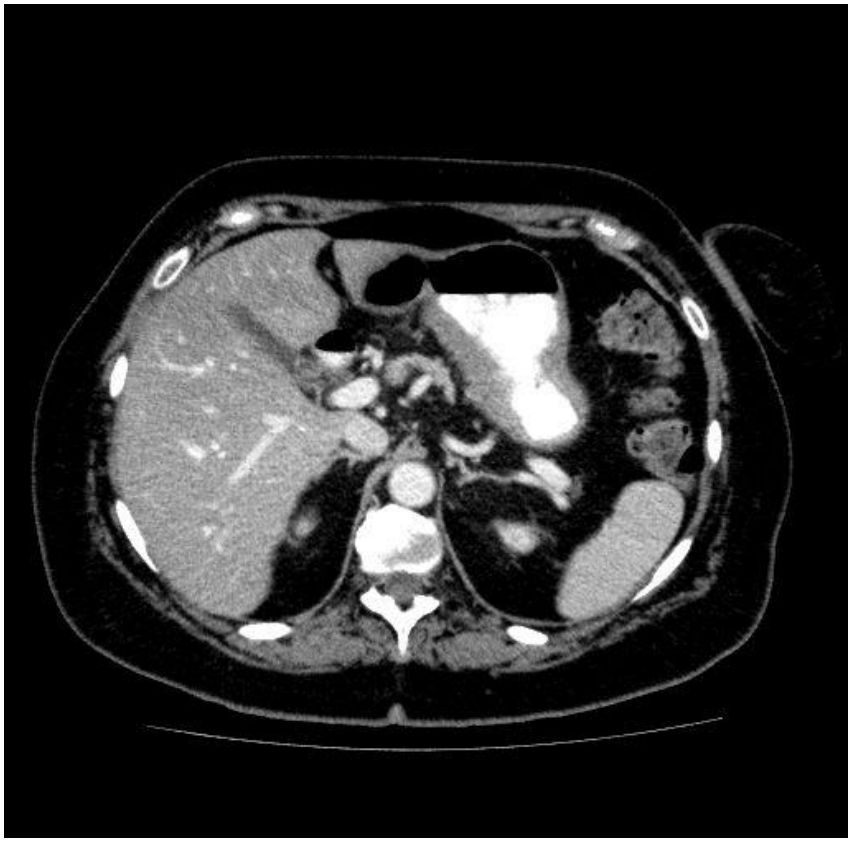
Lymphoma infiltration of the breast



Lymphoma in the stomach



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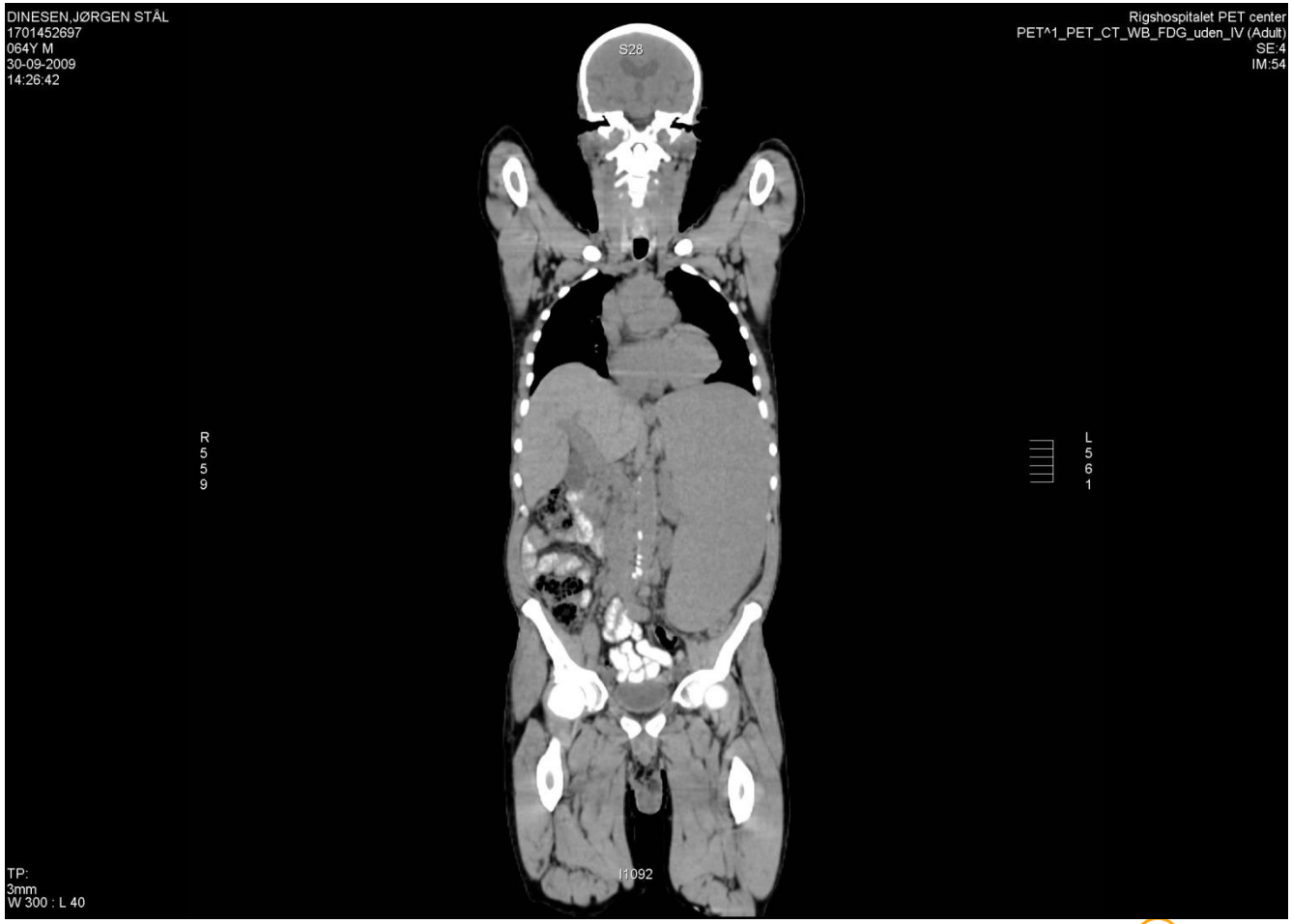
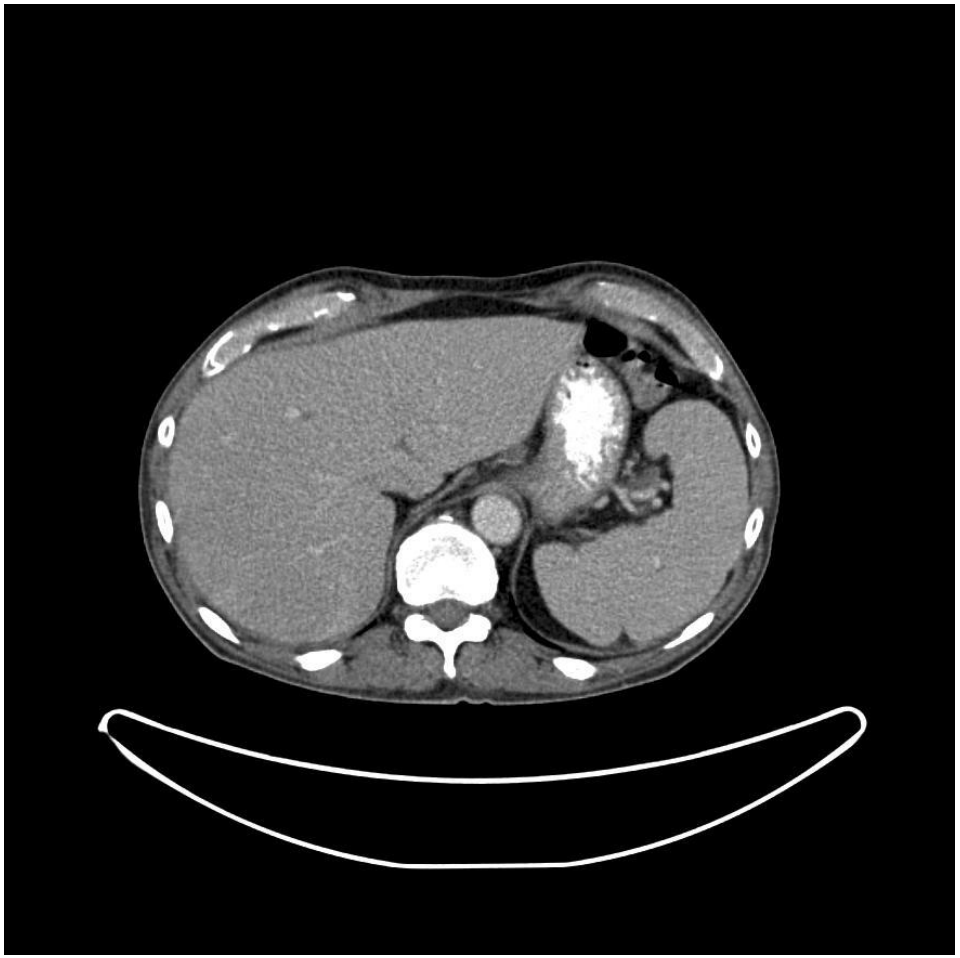
Spleen involvement

- Normal size and still contain lymphoma or enlarged and not involved.
- 10 -13 cm in vertical length.
- Best determined by PET/CT
- Diffuse infiltration
- Focal nodular lesion
- Large solitary mass

Spleen – large solitary mass



Spleen diffuse infiltration



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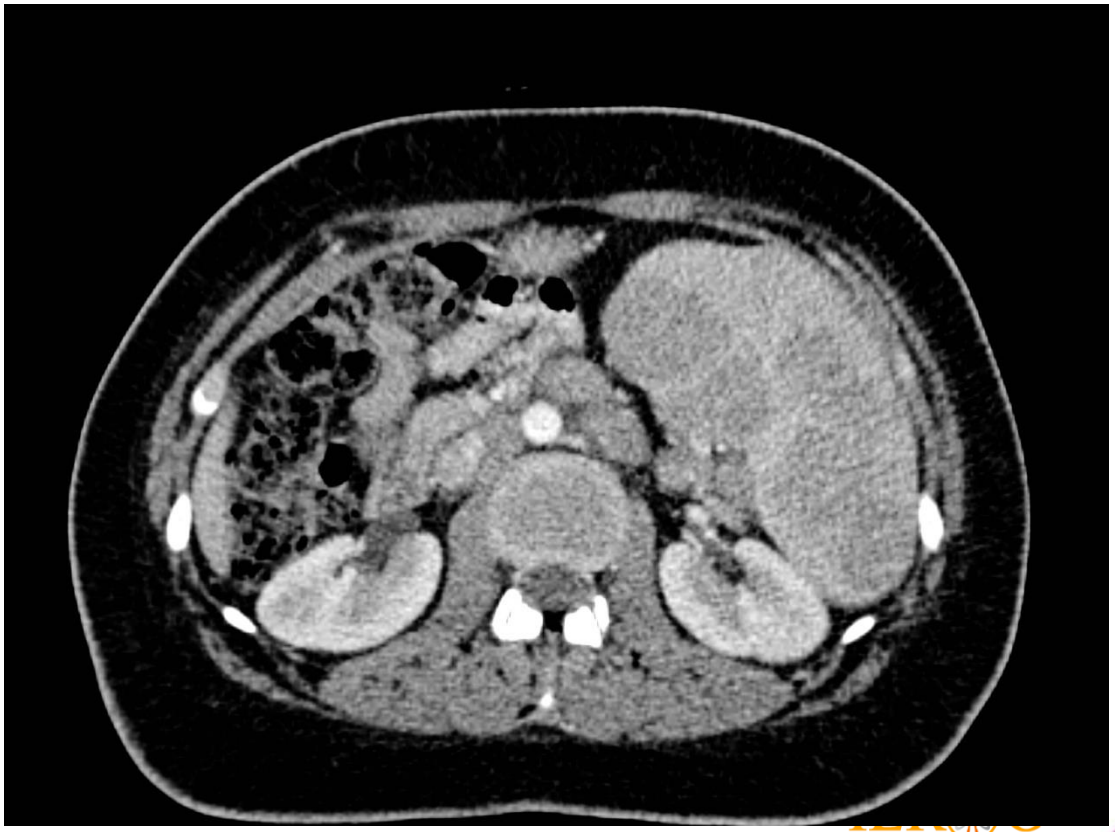
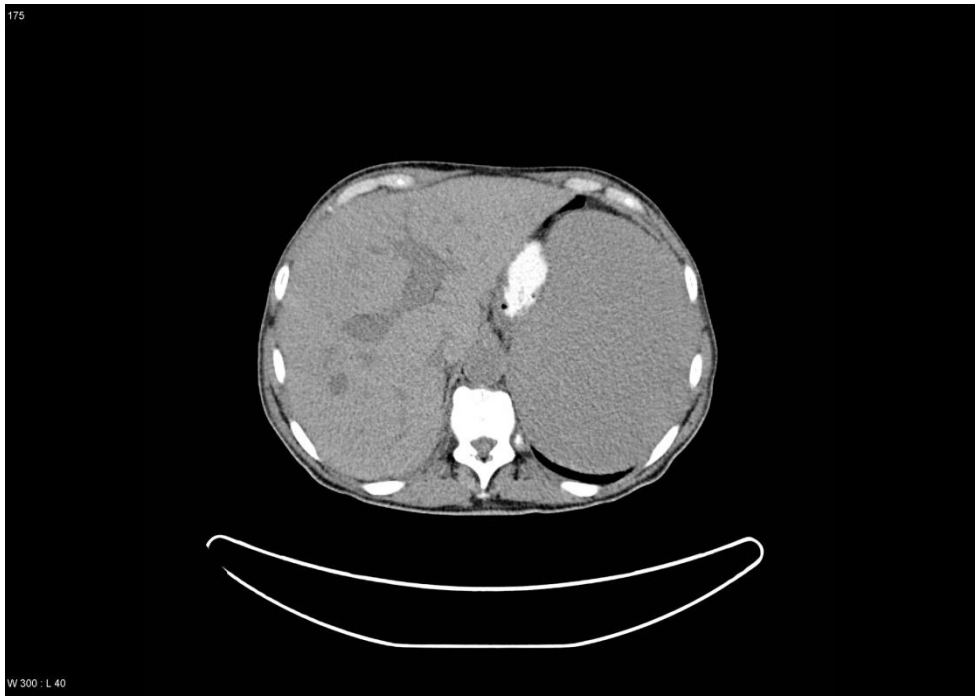
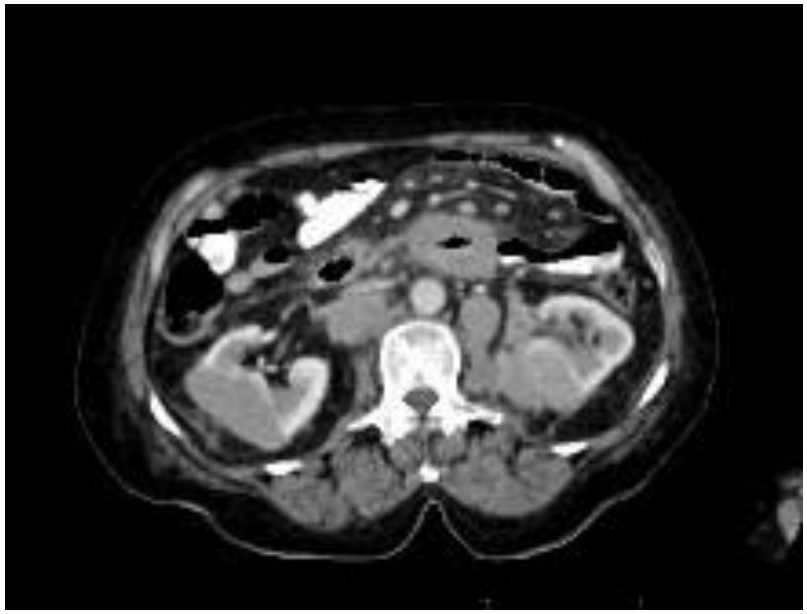
Spleen Focal nodula lesion

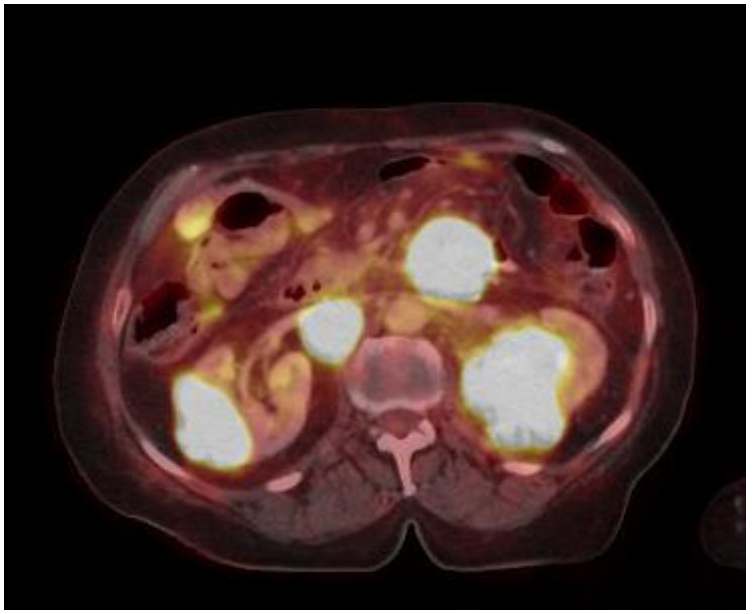


Liver involvement also best detected with PET/CT

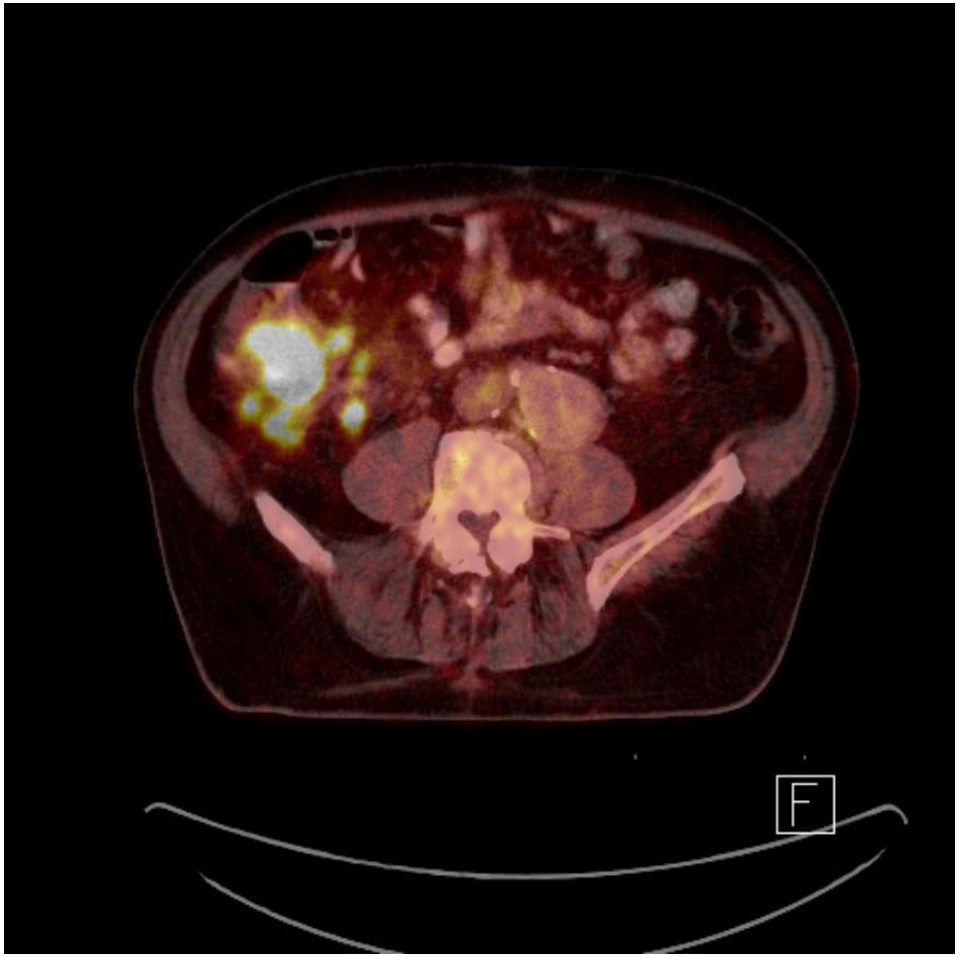


Lymphoma infiltration of the kidneys





Colon



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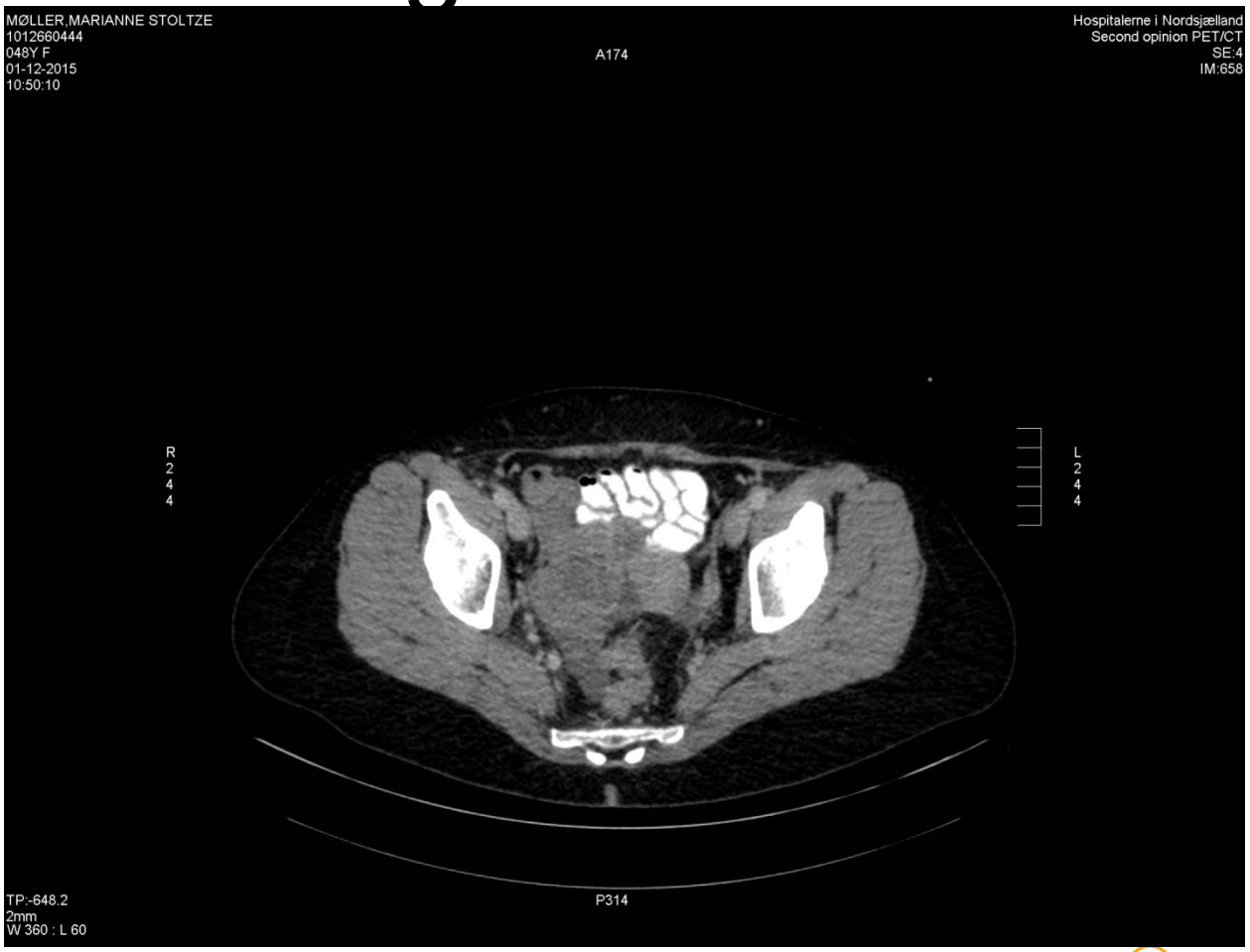
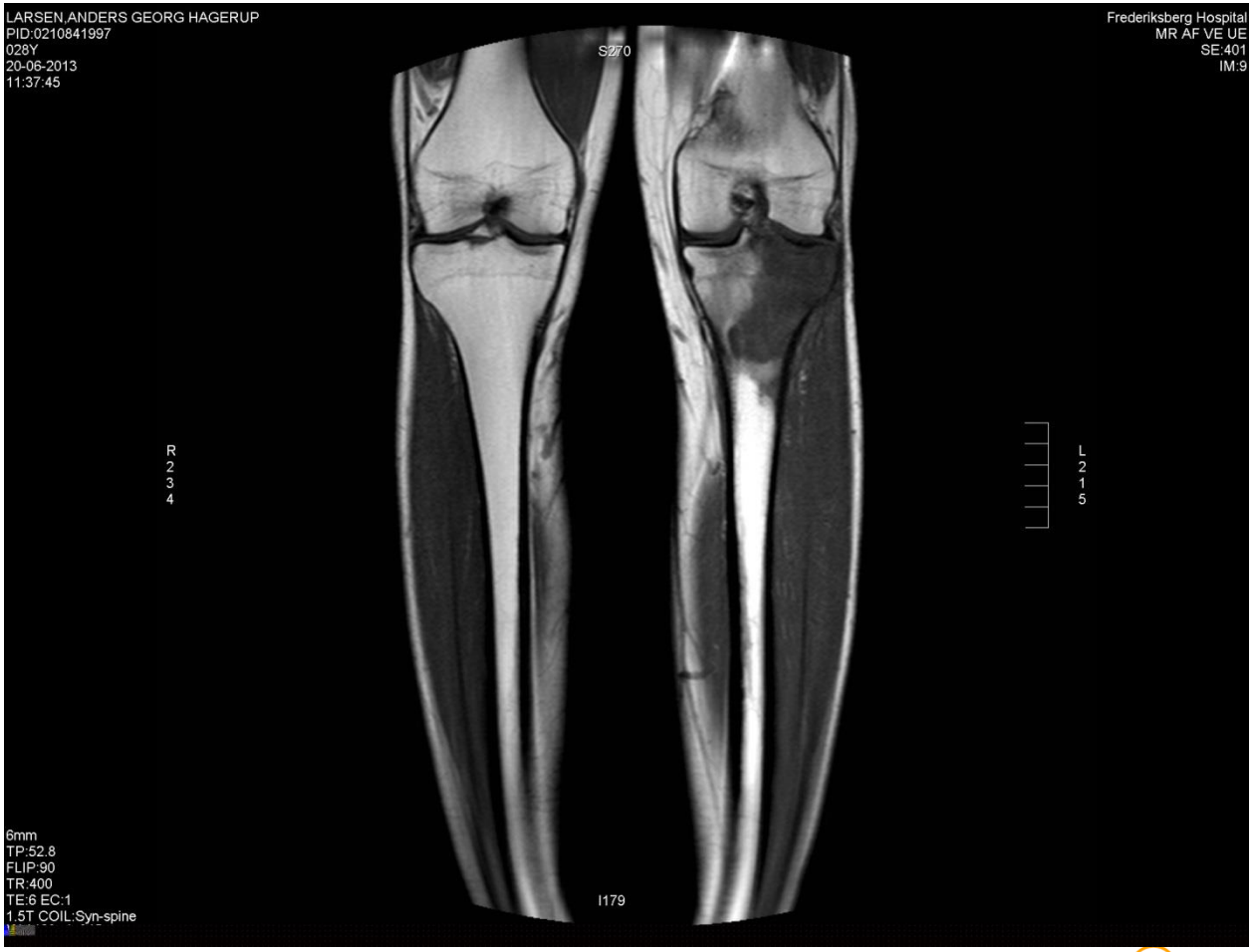
Lymphoma infiltration of the right ovarie



Lymphoma infiltration of the bone



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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Extranodal lymphomas: Characteristics, the role of radiotherapy, volumes doses and techniques:

Primary breast lymphoma

Berthe Aleman

Radiation oncologist

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

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Breast lymphoma

General

- 0.5% of breast malignancies, ~1% of all NHL, <3% of extranodal lymphomas
- Clinical presentation: usually unilateral painless breast mass
- Average age at diagnosis: 55 to 60 years

Pathology

- B-cell lymphoma
  - Mostly DLBCL
  - Also: indolent lymphomas such as marginal zone lymphoma and follicular lymphoma
- T-cell lymphoma
  - Breast Implant–Associated Anaplastic Large-Cell Lymphoma

Literature

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	%
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RT + CT	59	29
S + RT + CT	42	21
Any surgery	100	49
Any RT	130	64
Any CT	164	80

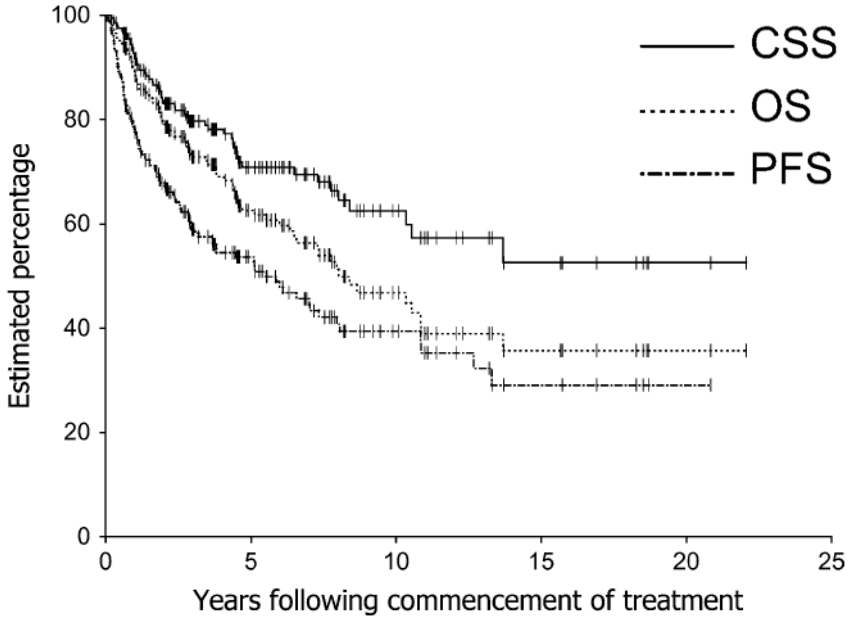
Initially involved breast only: 50%
Initially involved breast + regional lymph nodes: 35%

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 IPI score, anthracycline-containing CT , and 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

Role of radiation therapy in primary breast DLBCL in the Rituximab era: a SEER database analysis

Aim:

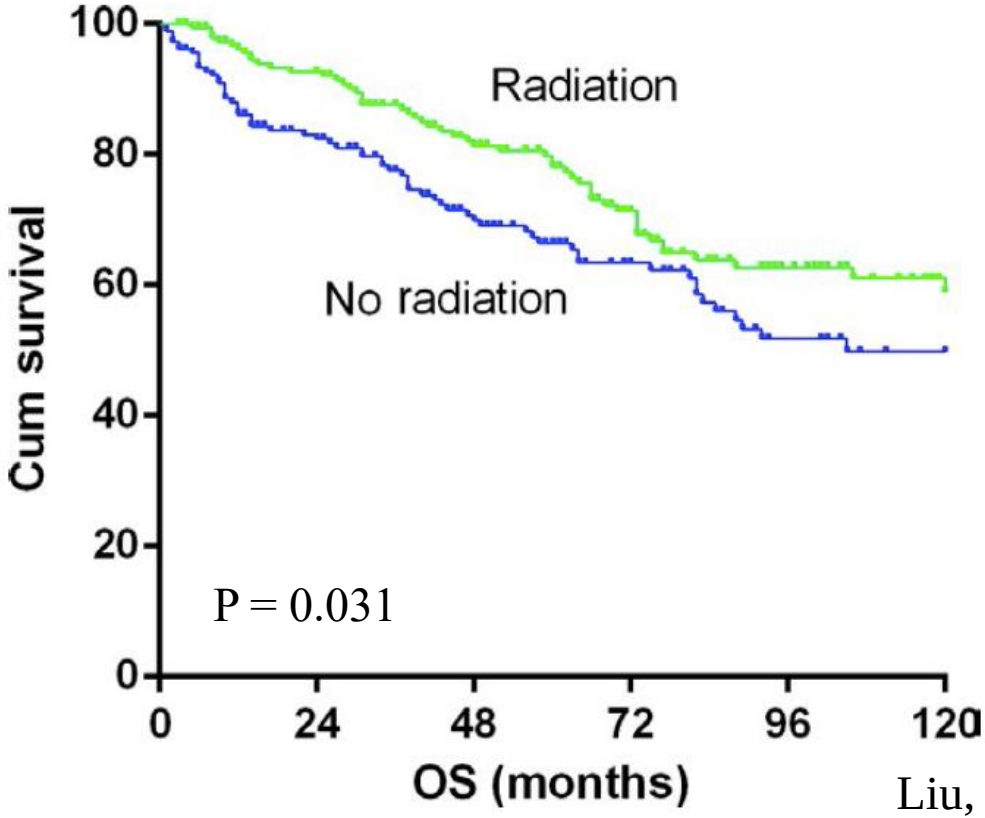
- Evaluate role of consolidation RT in PB-DLBCL patients treated with rituximab

Patients:

- PB-DLBCL diagnosed 2001- 2014
- N=386
- 52% received RT
- Median age: 64 years (range, 19–93 years)
- Median fup time: 45 months (range, 0–167 months)

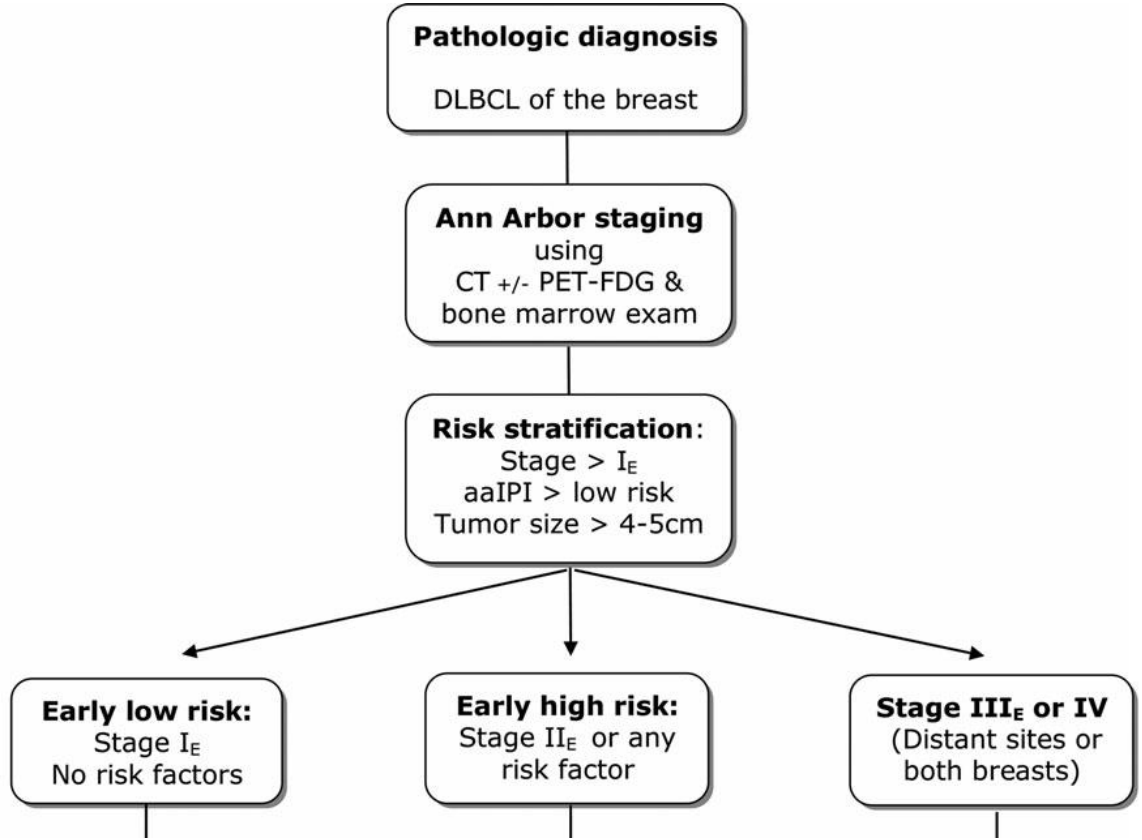
Liu, Cancer Medicine 2018

Role of radiation therapy in primary breast DLBCL in the Rituximab era: a SEER database analysis



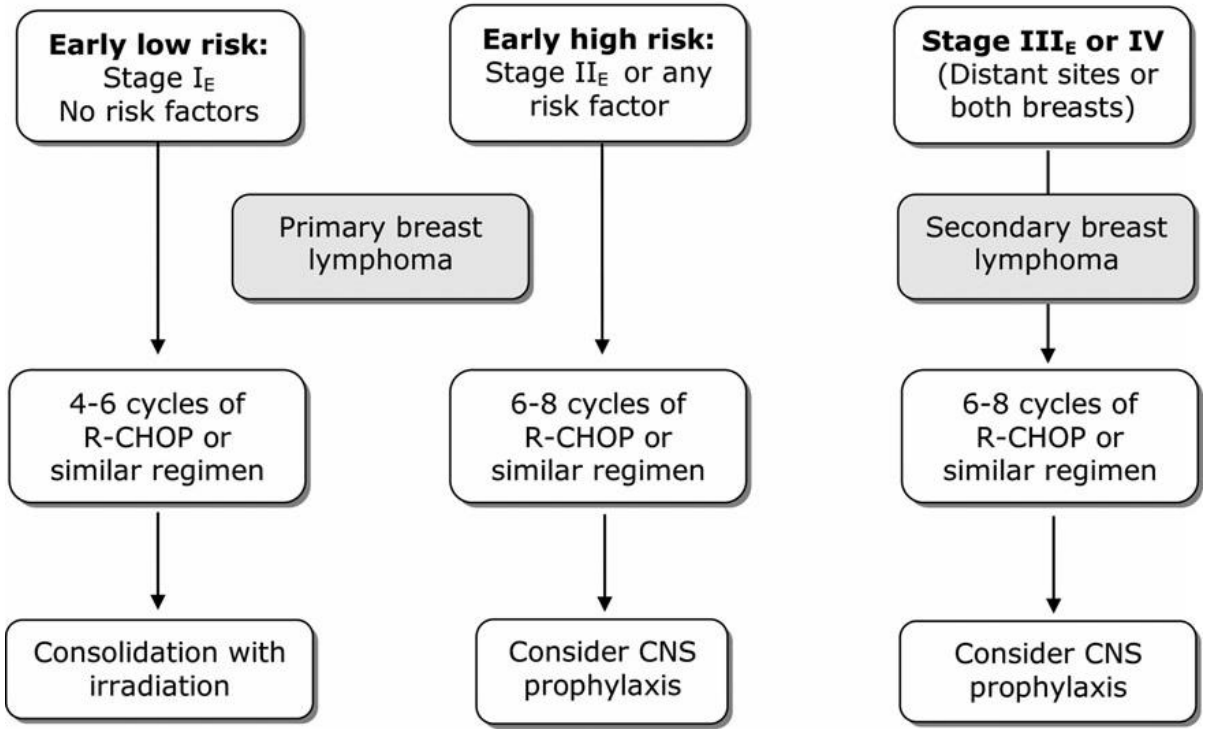
Liu, Cancer Medicine 2018

Suggested algorithm for newly diagnosed PB-DLBCL



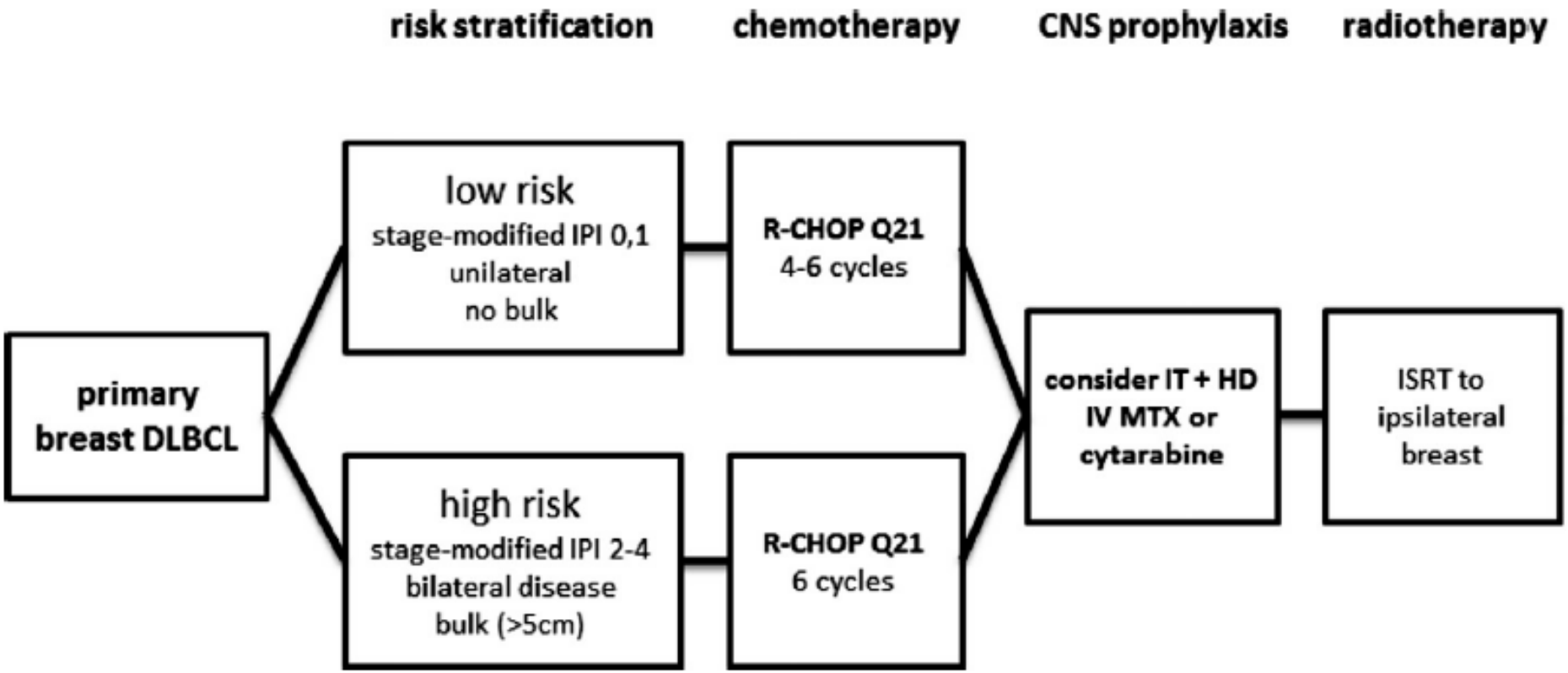
Aviv et al, Ann Oncol 2013

Suggested algorithm for newly diagnosed PB-DLBCL



No recommendation on RT dose/fields

Aviv et al, Ann Oncol 2013



Cheah et al., Cancer Treatment Reviews, 2014

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

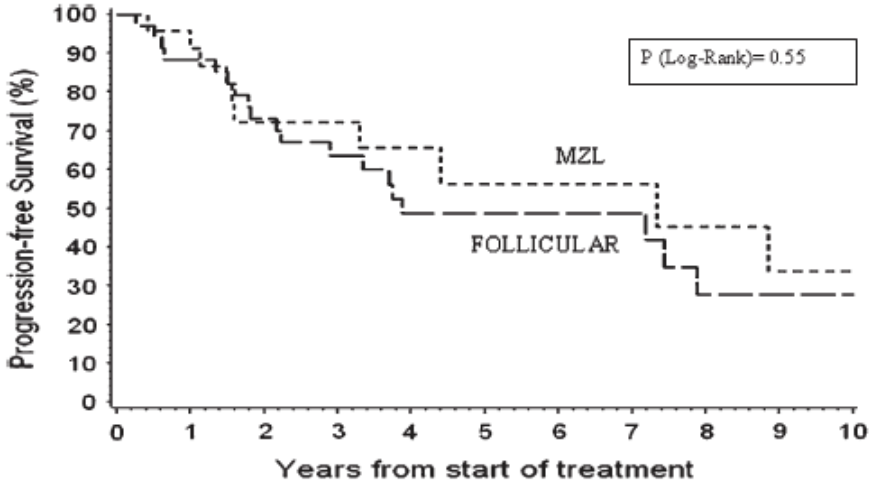
Follicular and marginal zone primary breast lymphoma (PBL): results from International Extranodal Lymphoma Study Group

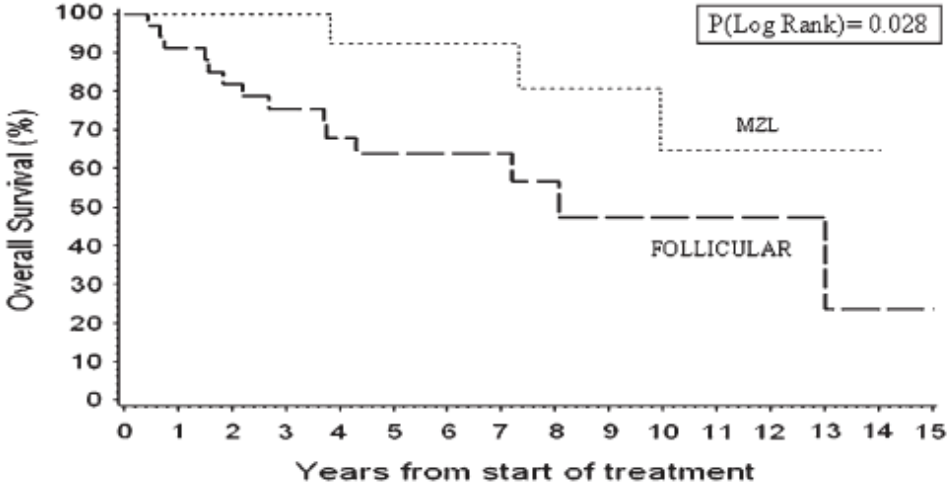
Results:

- 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

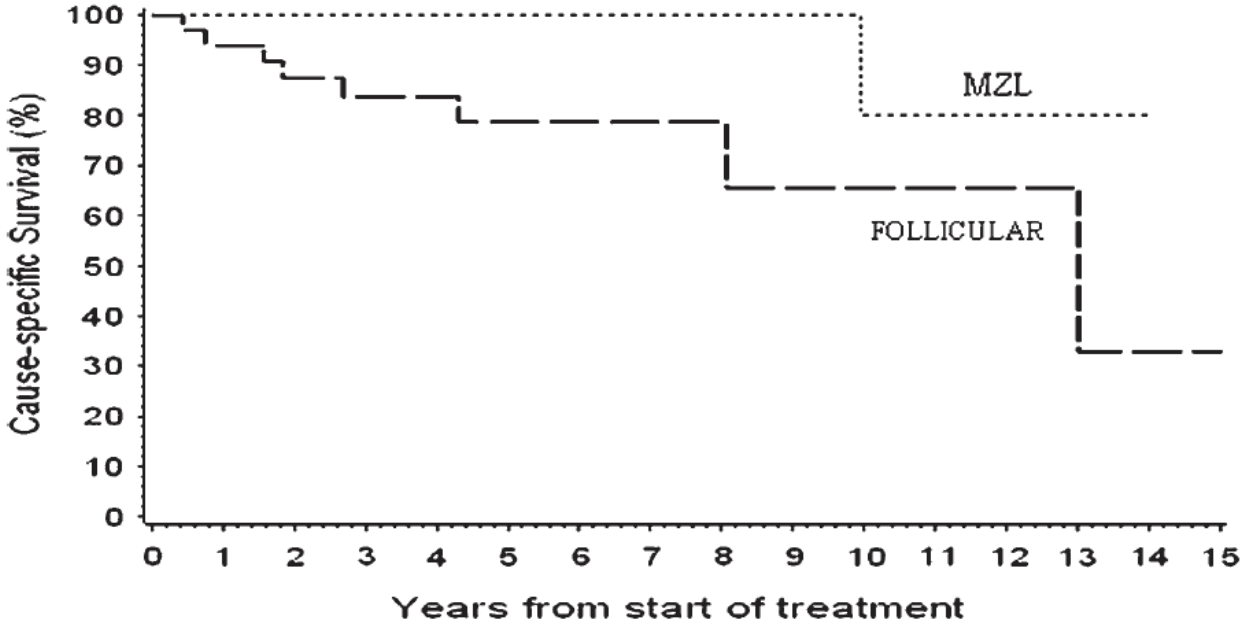




Overall response rate: 98% (93% complete response)
Relapses were mostly in distant sites (18 of 23 cases)
No patients relapsed within RT fields.

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

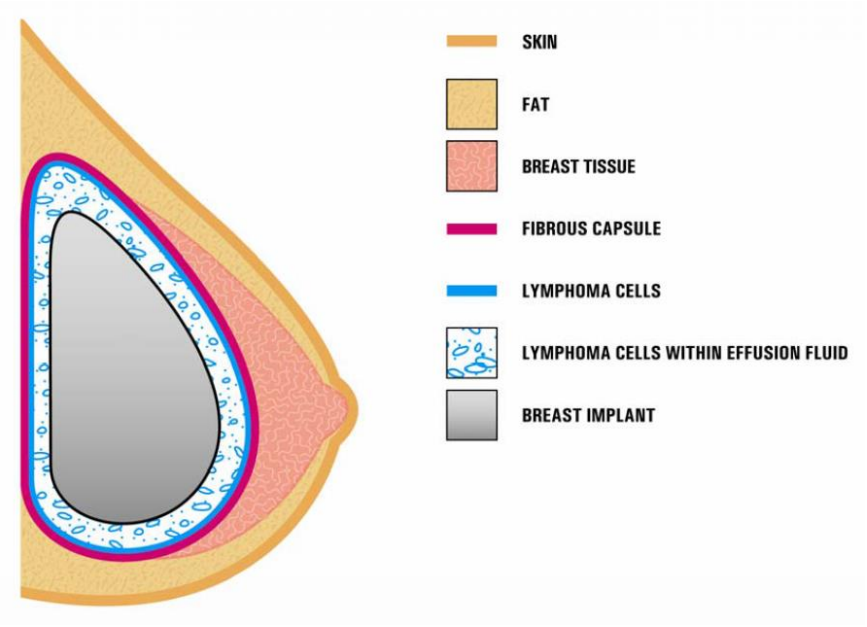
Conclusions:

- 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

Breast Implant–Associated Anaplastic Large-Cell Lymphoma

- T-cell lymphoma arising around breast implant
- 1st case reported in 1997



Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast

- Population-based, case-control study in NL
- 32 patients with primary breast-ALCL with ipsilateral breast implants
- Estimated prevalence of breast implants in ♀♀ aged 20-70 years: 3.3%
- Cumulative risks of breast-ALCL in ♀♀ with implants were 29 per million at 50 years and 82 per million at 70 years.

De Boer et al., JAMA Oncol. 2018

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Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma

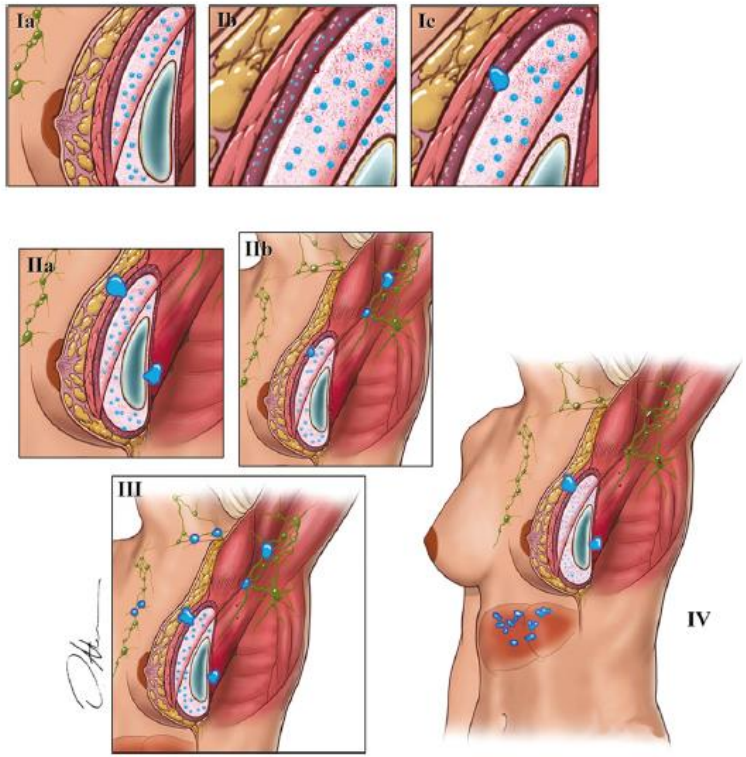

Table 1. Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma

TNM or Stage Designation	Description
T: tumor extent	
T1	Confined to effusion or a layer on luminal side of capsule
T2	Early capsule infiltration
T3	Cell aggregates or sheets infiltrating the capsule
T4	Lymphoma infiltrates beyond the capsule
N: lymph node	
N0	No lymph node involvement
N1	One regional lymph node (+)
N2	Multiple regional lymph nodes (+)
M: metastasis	
M0	No distant spread
M1	Spread to other organs/distant sites
Stage	
IA	T1N0M0
IB	T2N0M0
IC	T3N0M0
IIA	T4N0M0
IIB	T1-3N1M0
III	T4N1-2M0
IV	TanyNanyM1

Breast Implant–Associated Anaplastic Large-Cell Lymphoma

(retrospective analysis 87 patients)

Purpose

- To evaluate the efficacy of different therapies used in patients with BI-ALCL to determine an optimal treatment approach.

Patients and Methods

- A clinical follow-up of 87 patients with BI-ALCL, including 50 previously reported in the literature and 37 unreported.

Clemens et al., JCO 2016

Breast Implant–Associated Anaplastic Large-Cell Lymphoma

(retrospective analysis 87 patients)

Results

- Median follow-up time: 45 months (range, 3 to 217 months).
- Median OS time after diagnosis of BI-ALCL:13 years
- OS rate: 93% and 89% at 3 and 5 years, respectively
- Significantly EFS and OS in patients with:
  - lymphoma confined by the fibrous capsule surrounding the implant (vs lymphoma that had spread beyond the capsule)
  - a complete surgical excision that consisted of total capsulectomy with breast implant removal compared (vs partial capsulectomy, systemic chemotherapy, or radiation therapy)

Clemens et al., JCO 2016

Breast Implant–Associated Anaplastic Large-Cell Lymphoma
(retrospective analysis 87 patients)

Conclusion

- Surgical management with complete surgical excision is essential to achieve optimal EFS in patients with BI-ALCL

Clemens et al., JCO 2016

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

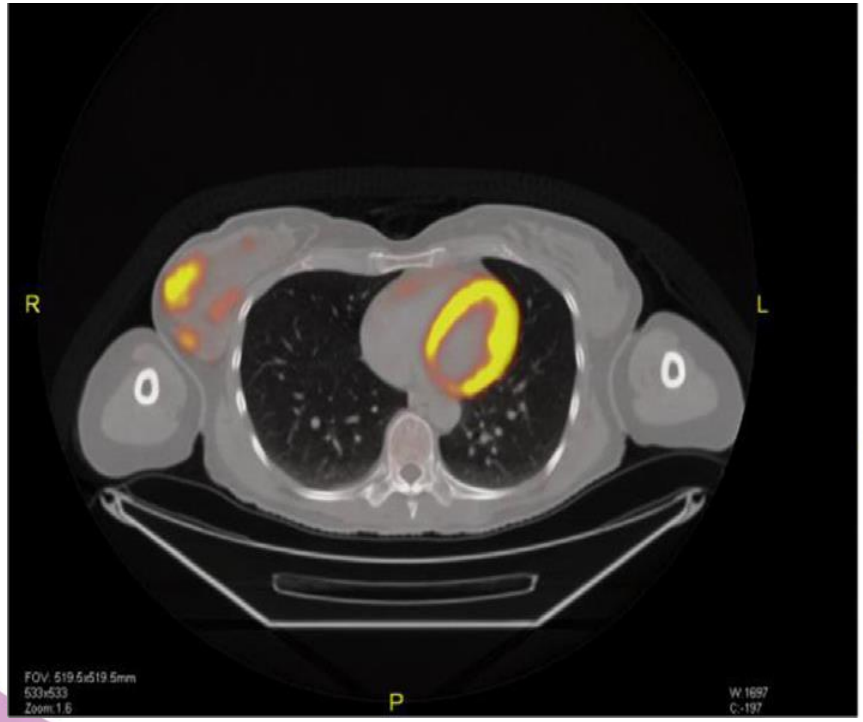
Breast lymphoma

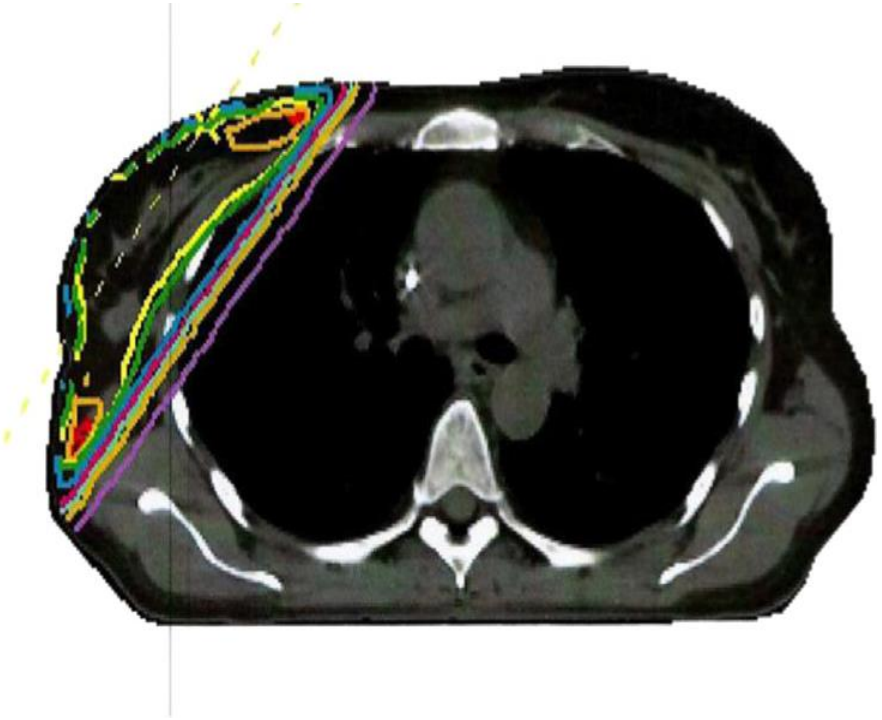
Technique

- 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 (24 Gy/12 fx??)
- DLBCL:
  - CR after chemo: 30 Gy/15 fx
  - PR after chemo: 40 Gy/20 fx

Yahalom et al. ILROG guideline, IJROBP 2015

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Questions?

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Extranodal lymphomas: Skin

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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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Guidelines

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

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

IJROBP 2015; 92: 32-39

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Willemze[1], E. Hodak[2], P. L. Zinzani[3], L. Specht[4] & M. Ladetto[5], on behalf of the ESMO Guidelines Committee*

Ann Oncol 2018; 29 (Suppl 4): iv30-iv40

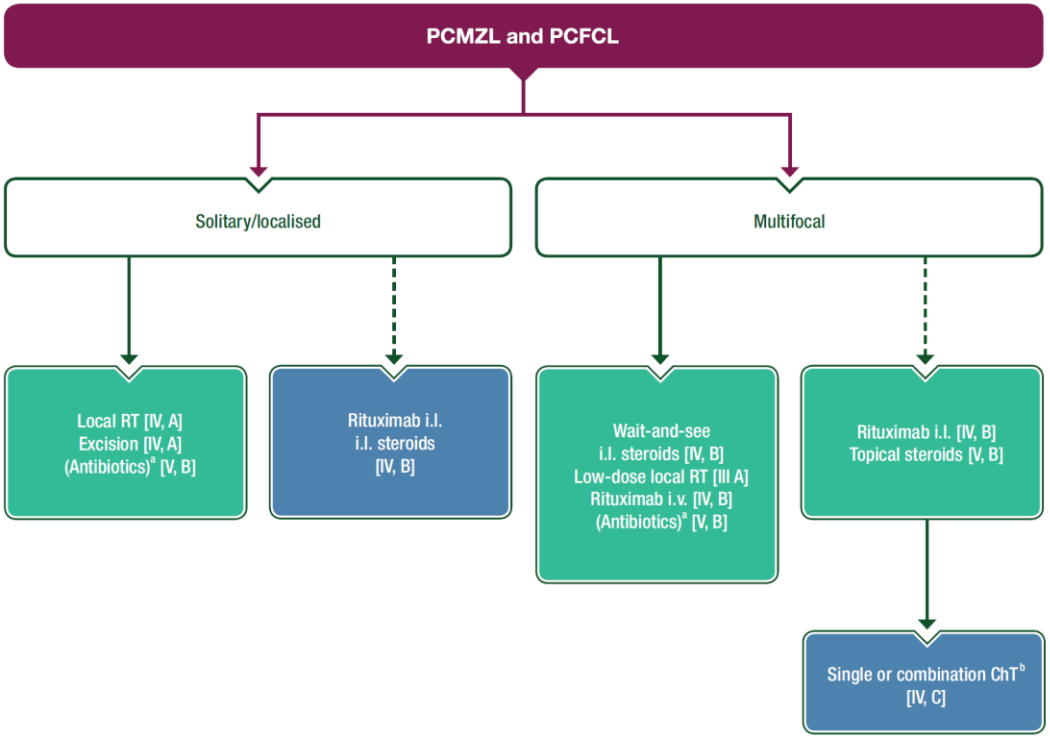

Figure 3. Recommendations for the initial management of PCMZL and PCFCL.
[a]In the case of evidence for *Borrelia burgdorferi* infection.
[b]Single or combination chemotherapy appropriate for low-grade malignant B cell lymphomas.
ChT, chemotherapy; i.l., intralesional; i.v., intravenous; PCFCL, primary cutaneous follicle centre lymphoma; PCMZL, primary cutaneous marginal zone lymphoma; RT, radiotherapy.

ESMO Guidelines

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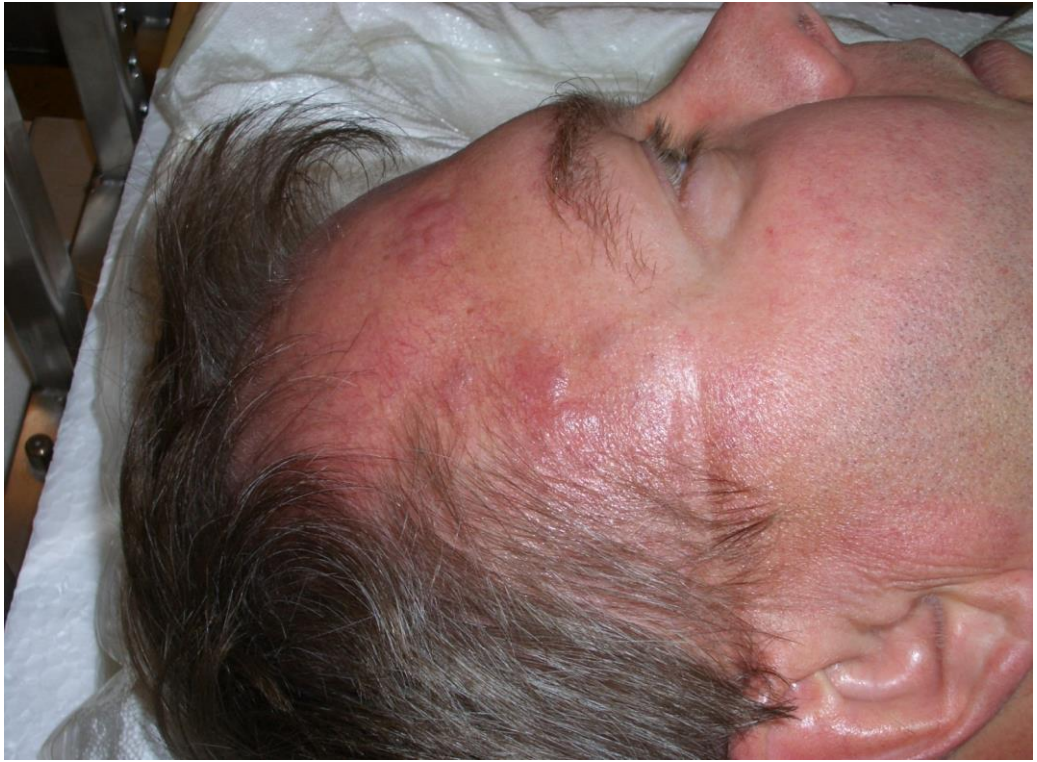
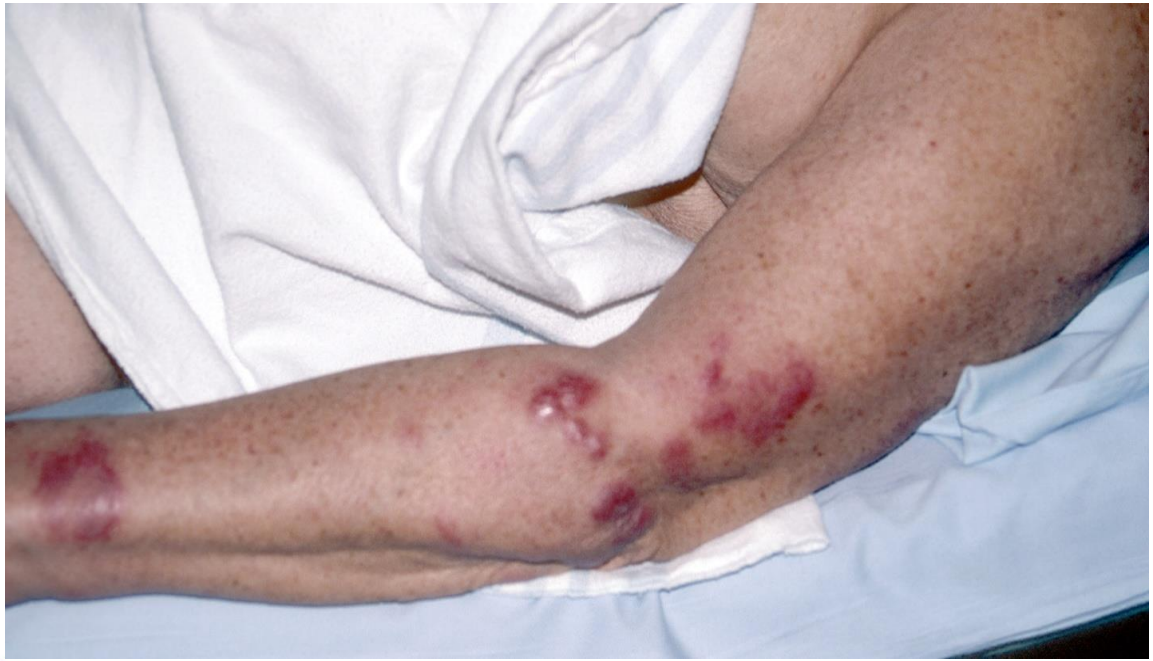
Marginal zone lymfom



Dose for localized disease:
24-30 Gy

Primary cutaneous follicle center lymphoma PCFCL



Dose for localized disease:
24-30 Gy

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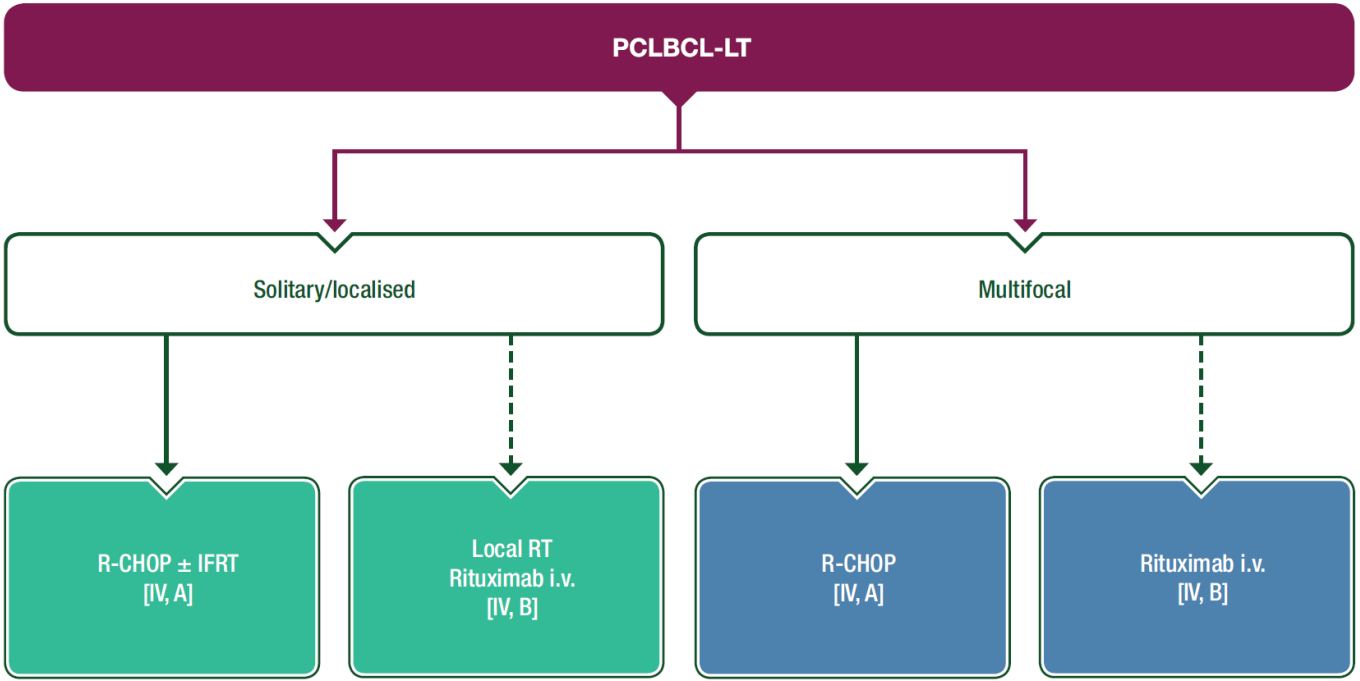

ESMO Guidelines

Figure 4. Recommendations for the initial management of PCLBCL-LT.
IFRT, involved-field radiotherapy; i.v., intravenous; PCLBCL-LT, primary cutaneous large B cell lymphoma, leg type; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RT, radiotherapy.

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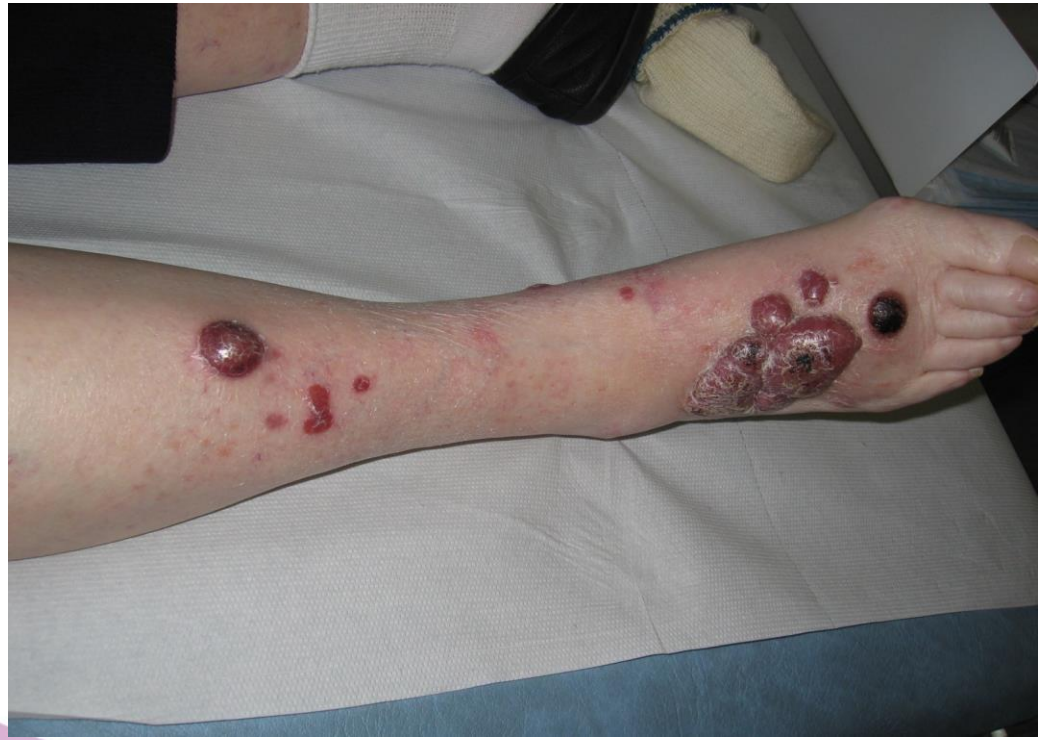
Primary cutaneous diffuse large B-cell lymphoma, leg type



Dose for localized disease: 36-40 Gy

If no systemic treatment is given, 40 Gy is recommended

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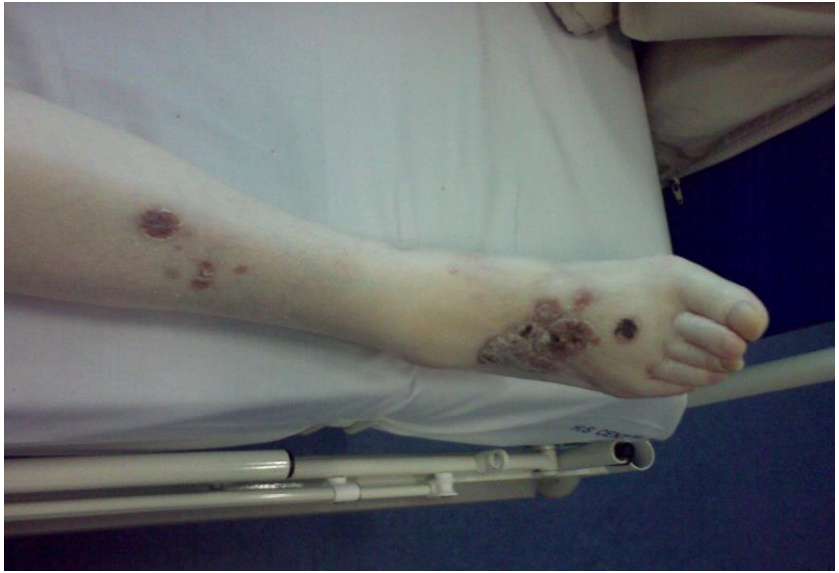
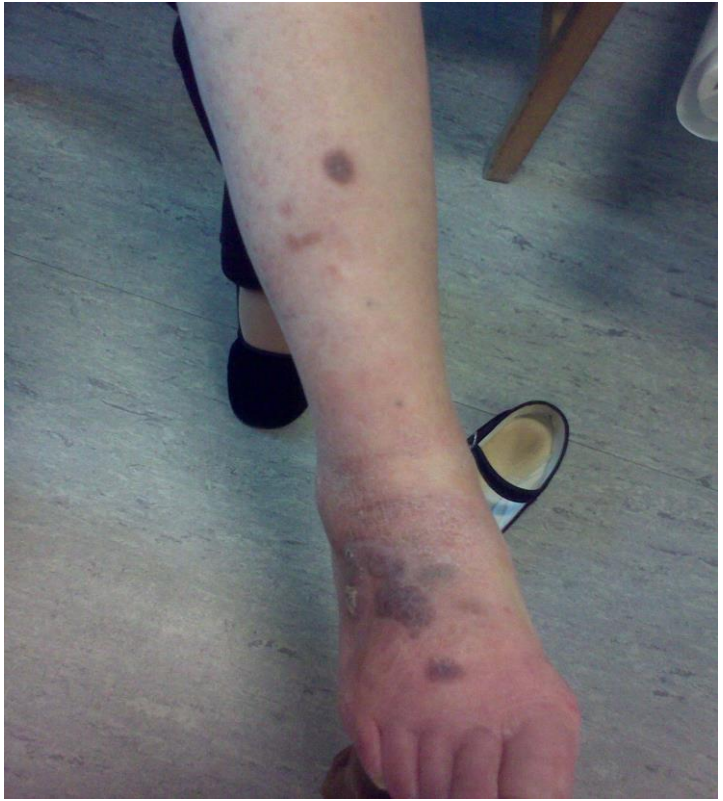


After 2 cycles R-CHOP21



After radiotherapy

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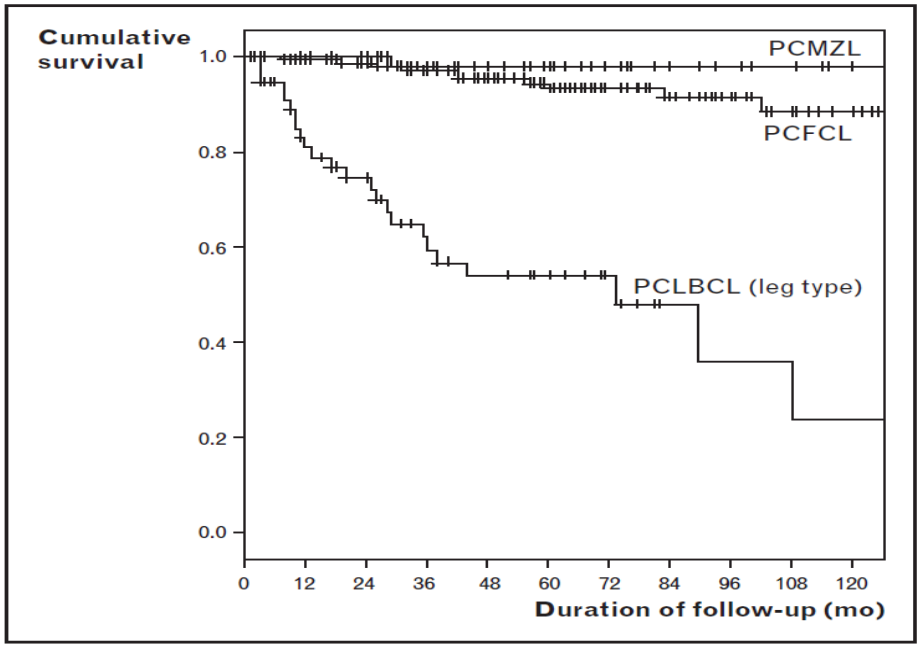
Figure 1 Disease-related 5-year-survivals of 280 Dutch patients with cutaneous B-cell lymphoma reclassified according to the World Health Organization–European Organization for the Research and Treatment of Cancer classification (N.J. Senff, unpublished data)



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).

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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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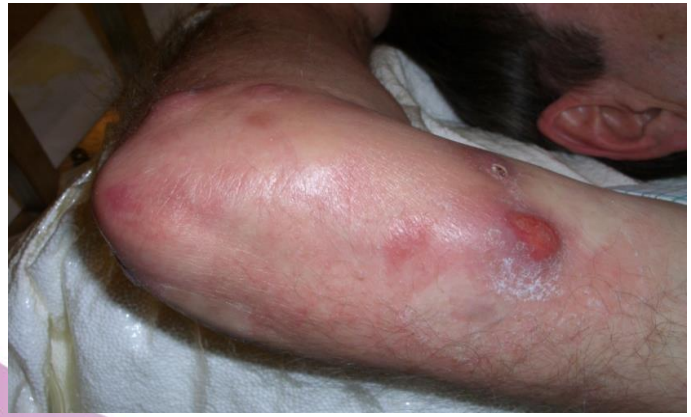
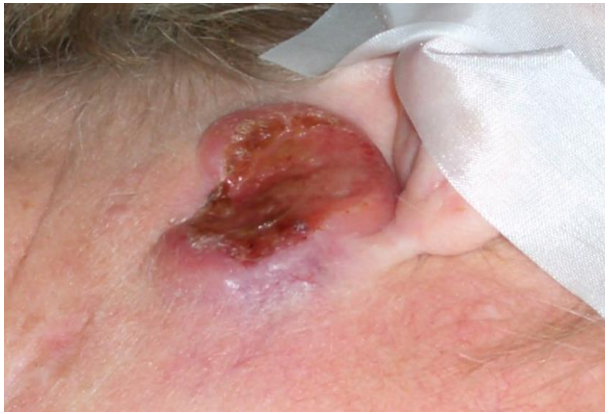
Primary Cutaneous CD30+ neoplasms (lymphomatoid papulosis, ALCL)

- 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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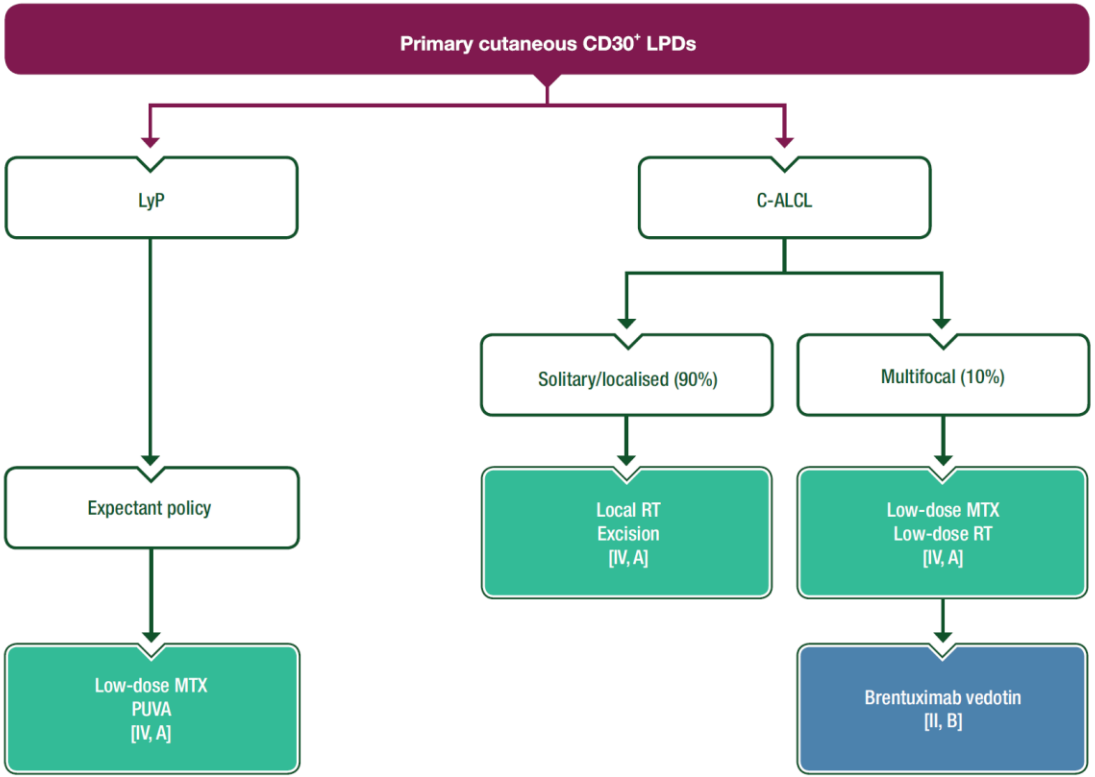

Figure 2. Recommendations for the initial management of primary cutaneous $CD30^+$ LPDs.
C-ALCL, cutaneous anaplastic large cell lymphoma; LPD, lymphoproliferative disorder; LyP, lymphomatoid papulosis; MTX, methotrexate; PUVA, psoralens plus ultraviolet A; RT, radiotherapy.

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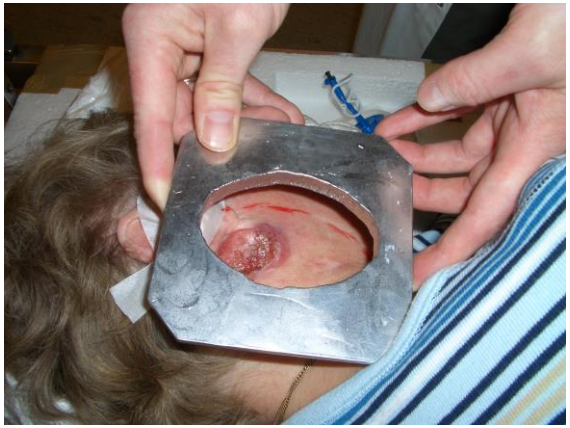
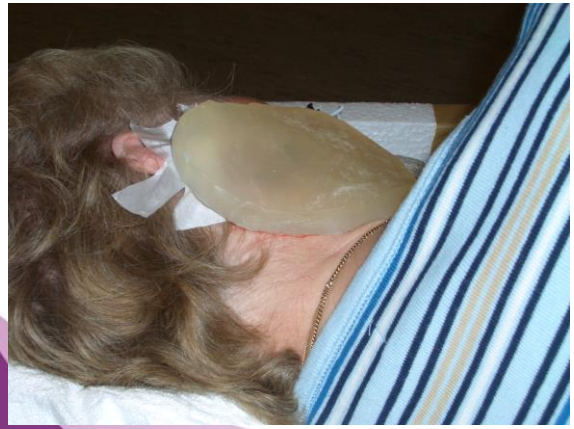
Localized skin lymphomas: ISRT





- 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

Staging of Mycosis fungoides and Sézary syndrome

Table 3. Revised TNMB classification of MF/SS [6]

T (skin)

T1	Limited patch/plaque (involving < 10% of total skin surface)
T2	Generalised patch/plaque (involving ≥ 10% of total skin surface)
T3	Tumour(s)
T4	Erythroderma

N (lymph node)

N0	No clinically abnormal peripheral lymph nodes
N1	Clinically abnormal peripheral lymph nodes; histologically uninvolved
N2	Clinically abnormal peripheral lymph nodes; histologically involved (nodal architecture uneffaced)
N3	Clinically abnormal peripheral lymph nodes; histologically involved [nodal architecture (partially) effaced]
Nx	Clinically abnormal peripheral lymph nodes; no histological confirmation

M (viscera)

M0	No visceral involvement
M1	Visceral involvement

B (blood)

B0	No circulating atypical (Sézary) cells (or < 5% of lymphocytes)
B1	Low blood tumour burden (≥ 5% of lymphocytes are Sézary cells, but not B2)
B2	High blood tumour burden (≥ 1000/μl Sézary cells and positive clone)

MF, mycosis fungoides; SS, Sézary syndrome; TNMB, tumour, node, metastasis, blood.

Table 4. Revised clinical staging system for MF/SS [6]

Clinical stage				
IA	T1	N0	M0	B0-1
IB	T2	N0	M0	B0-1
IIA	T1–2	N1-2	M0	B0-1
IIB	T3	N0–2	M0	B0-1
III	T4	N0–2	M0	B0-1
IVA1	T1–4	N0-2	M0	B2
IVA2	T1–4	N3	M0	B0-2
IVB	T1–4	N0–3	M1	B0-2

MF, mycosis fungoides; SS, Sézary syndrome.

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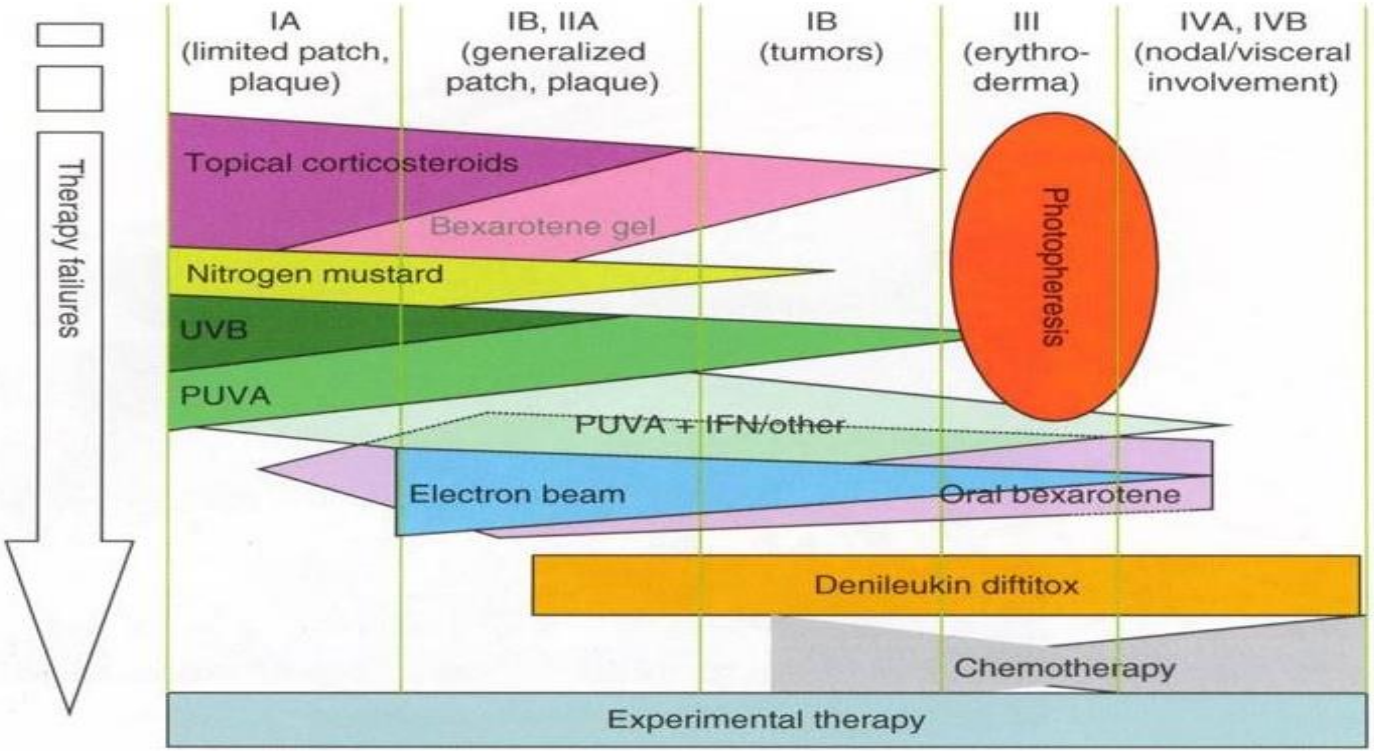

Fig. 19.3 Treatment of MF by stage. Stage is across the *top* of the diagram from T1 (*left*) to T4 (*right*)

+ HDAC inhibitors, low-dose Alemtuzumab, Adcetris,

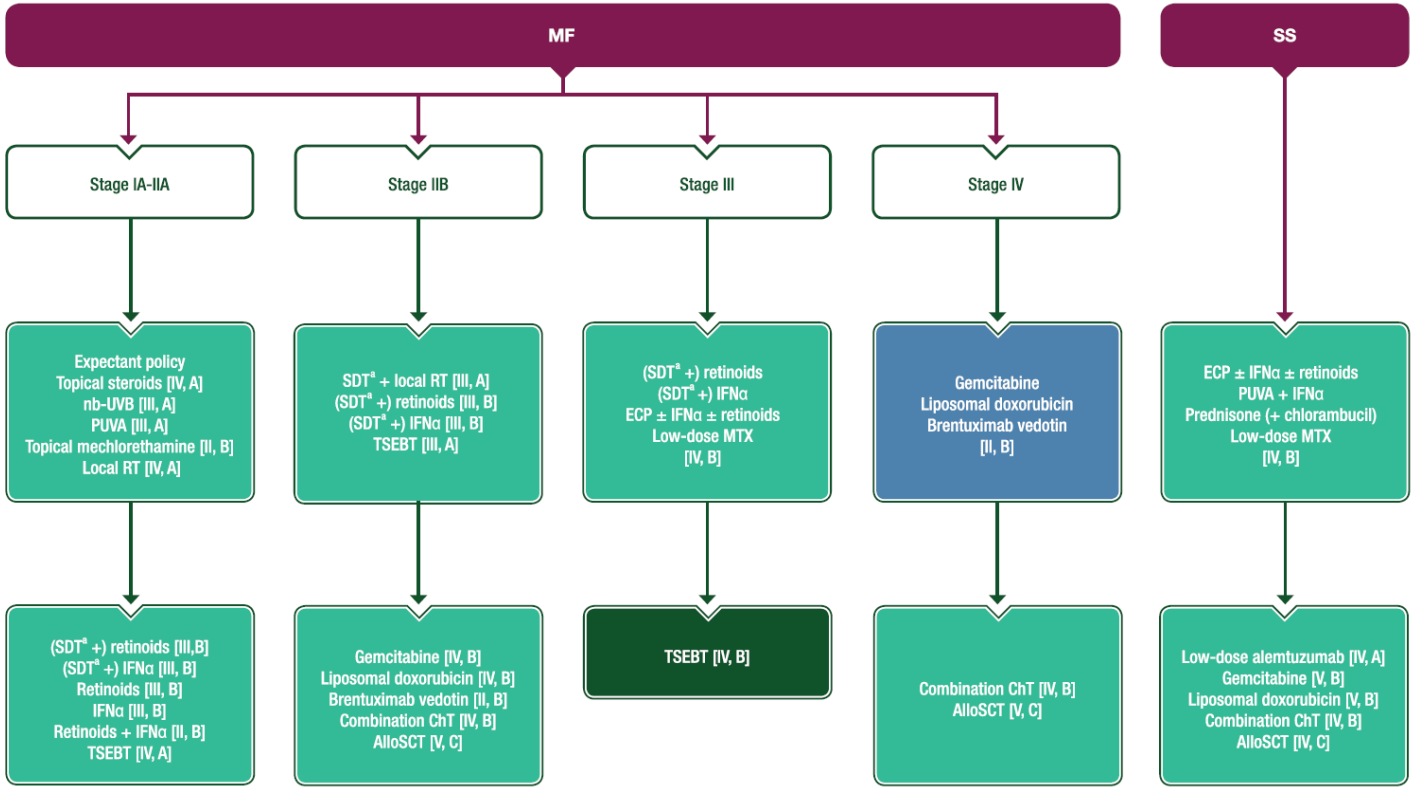

Figure 1. Recommendations for the treatment of MF/SS.

[a]Most commonly PUVA.

AlloSCT, allogeneic stem cell transplantation; ChT, chemotherapy; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; PUVA, psoralens plus ultraviolet A; RT, radiotherapy; SS, Sézary syndrome; SDT, skin-directed therapy; TSEBT, total skin electron beam therapy.

ESMO Guidelines

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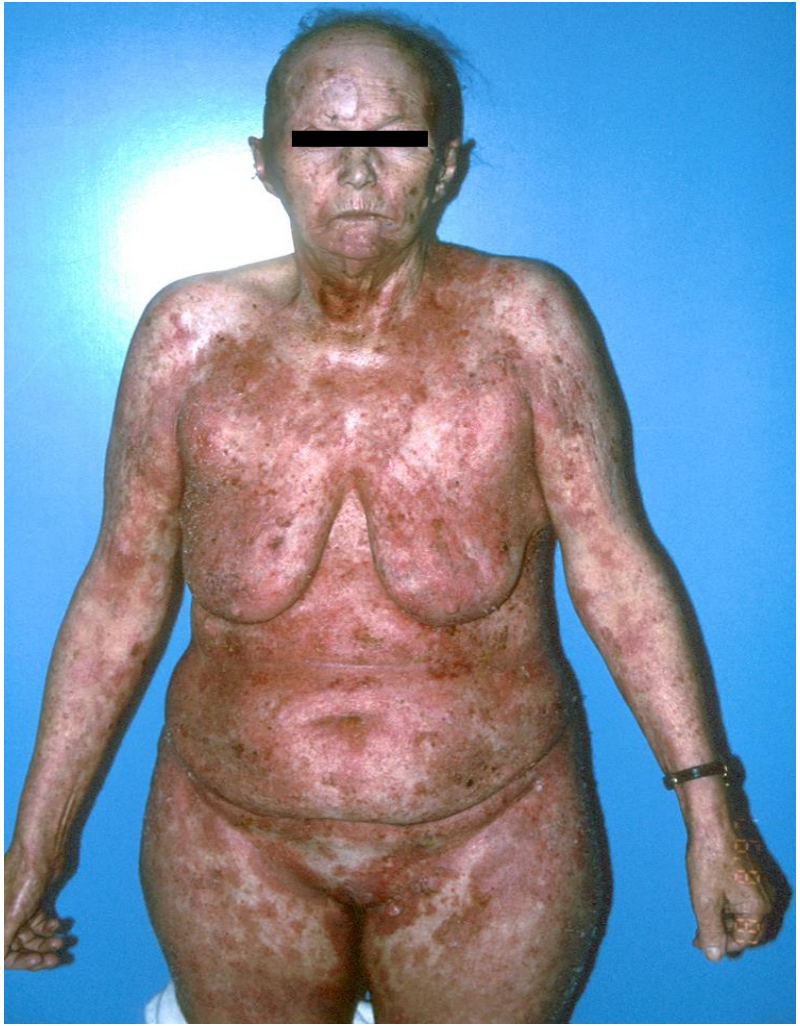

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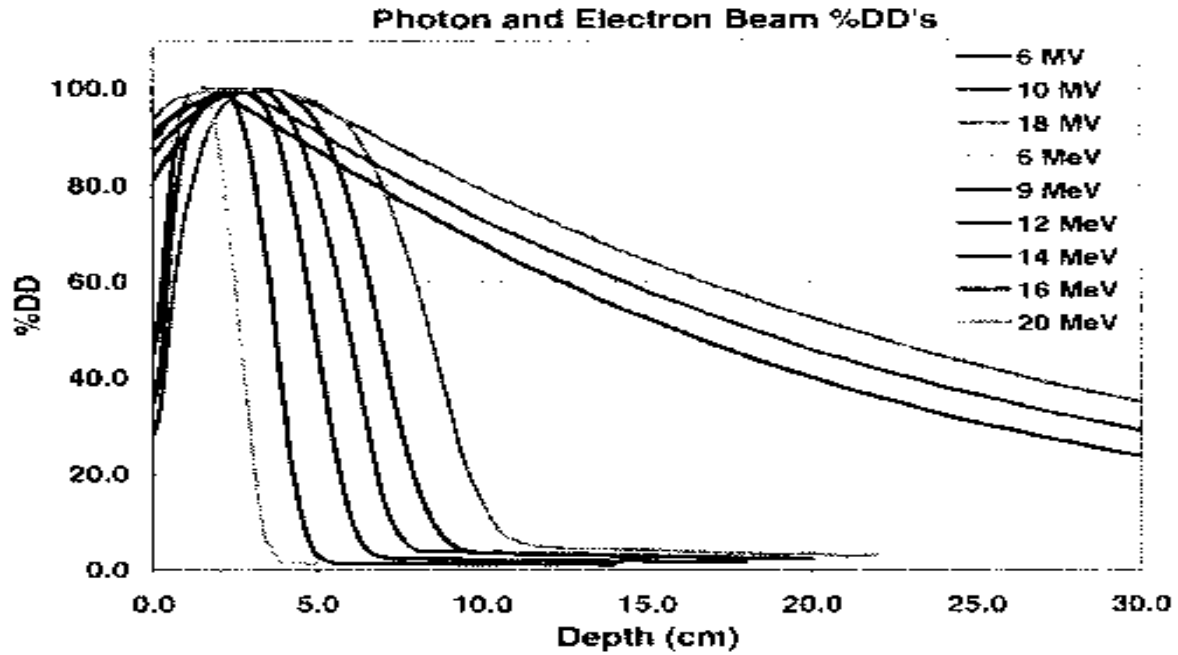
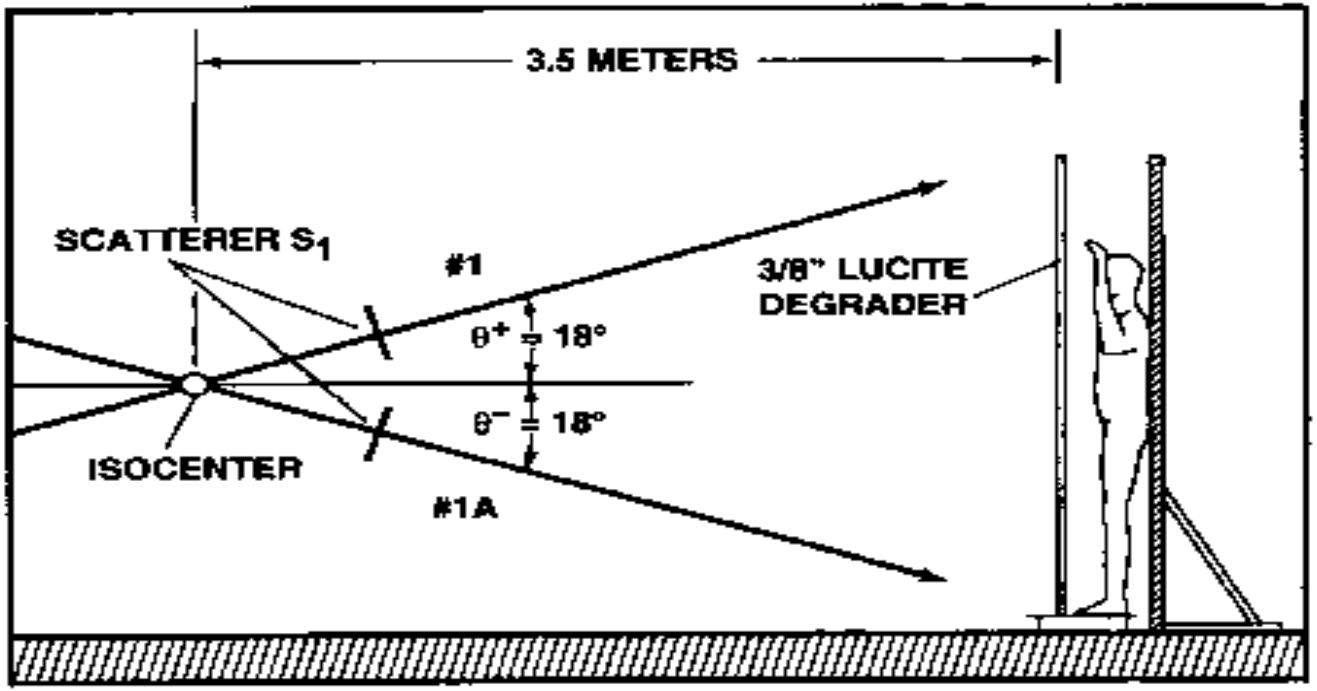
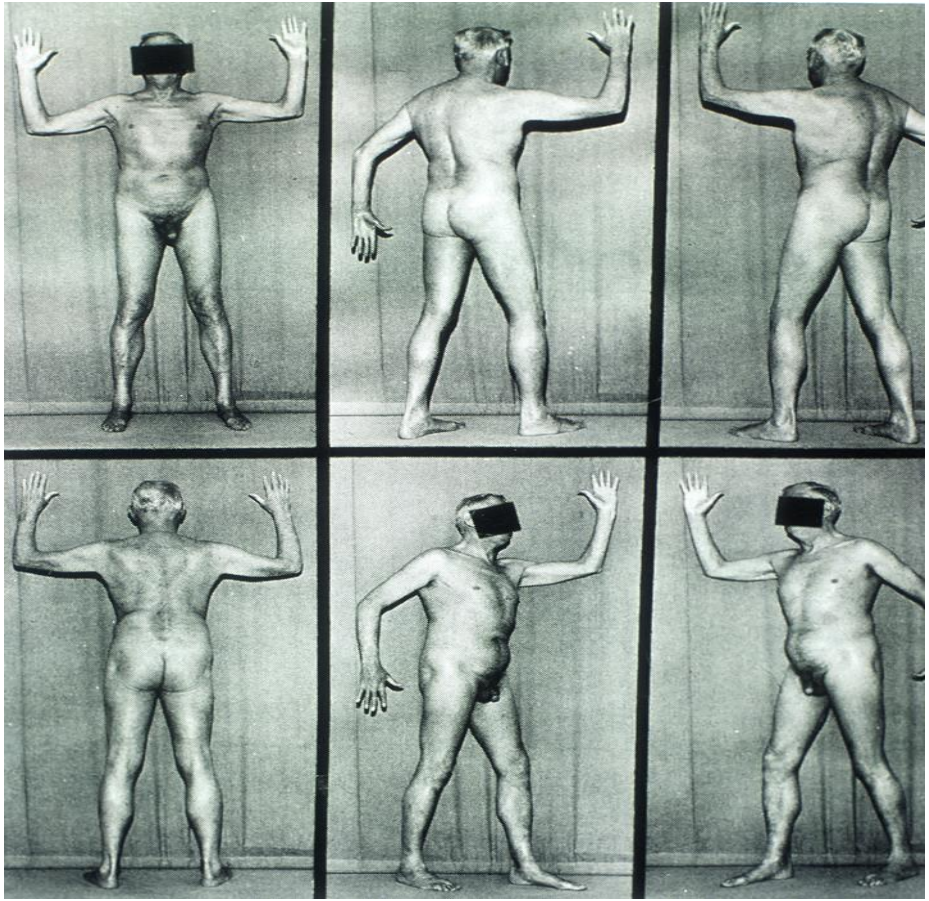
X-ray vs. electron depth-dose-curves



Total skin electron beam therapy (TSEBT)





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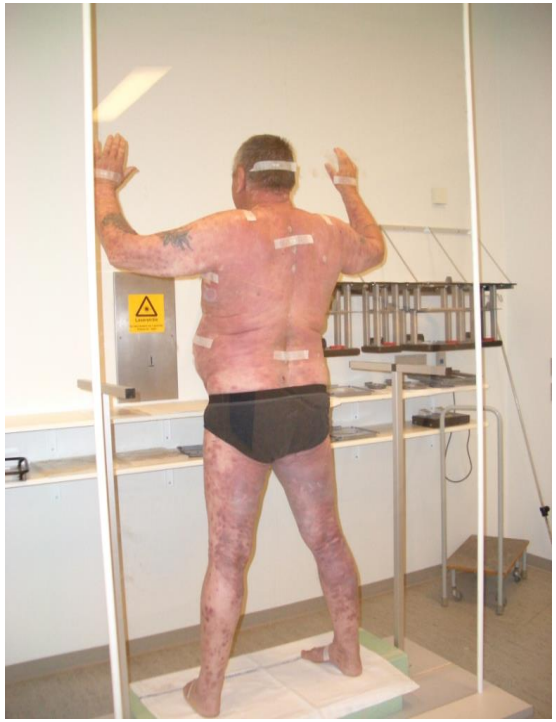
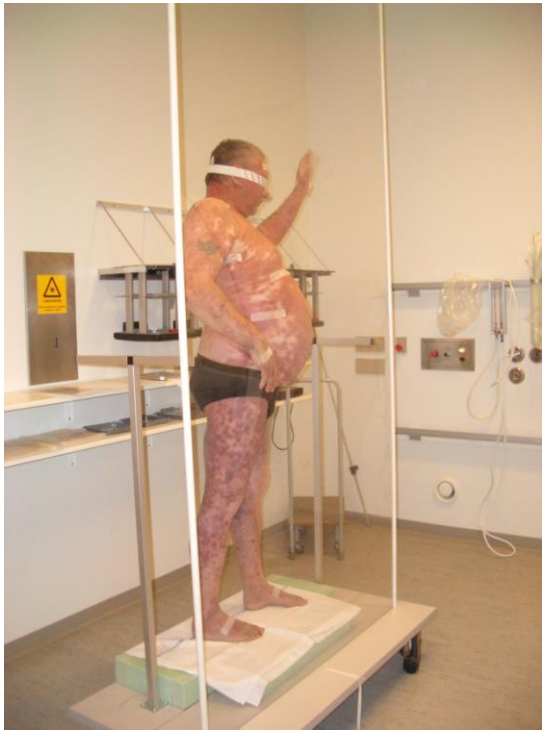
TSEBT





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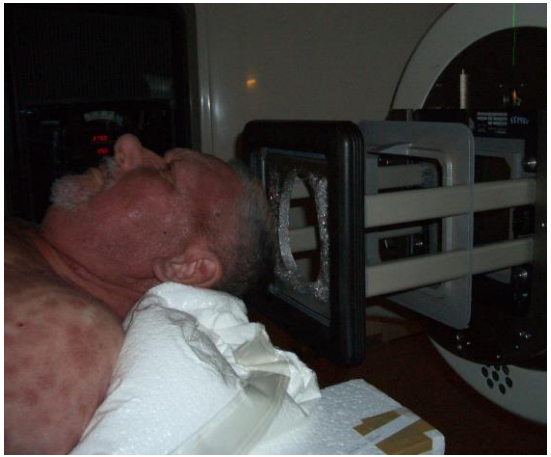
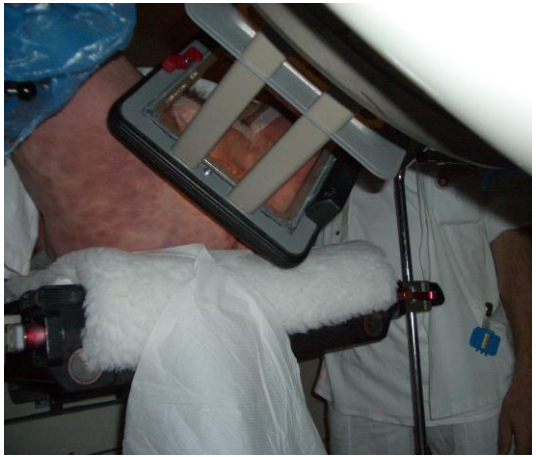
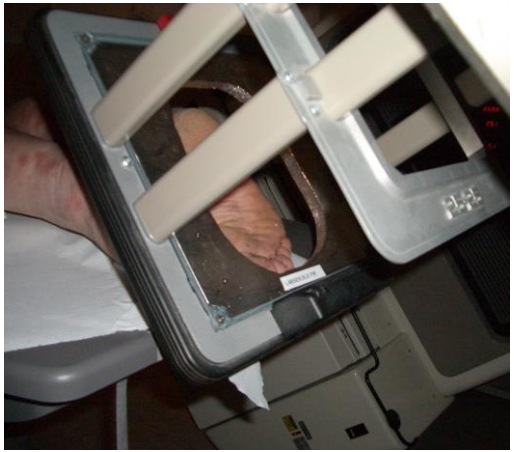
Additional treatment of ”shadowed areas”



Scalp

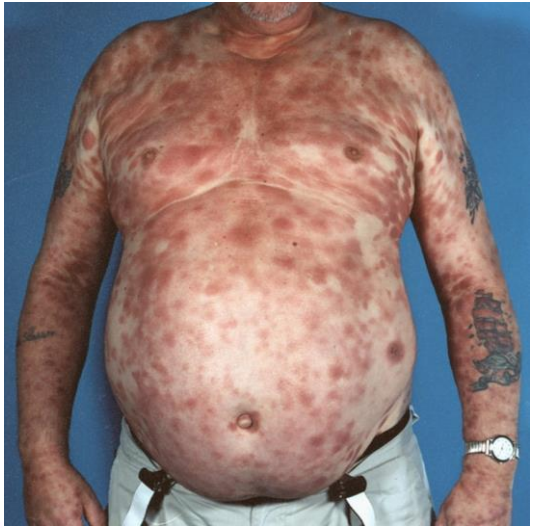


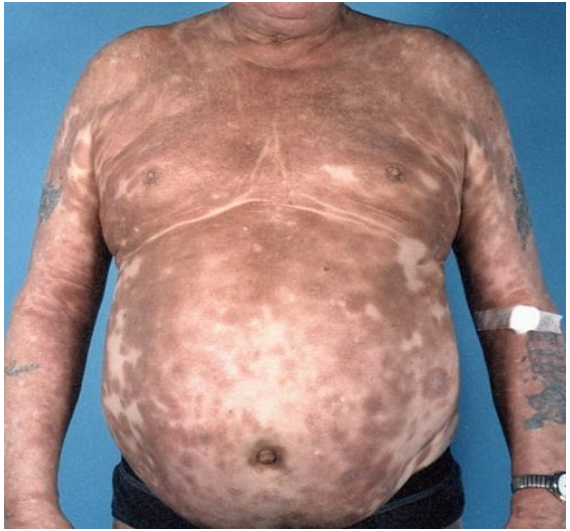
Perineum

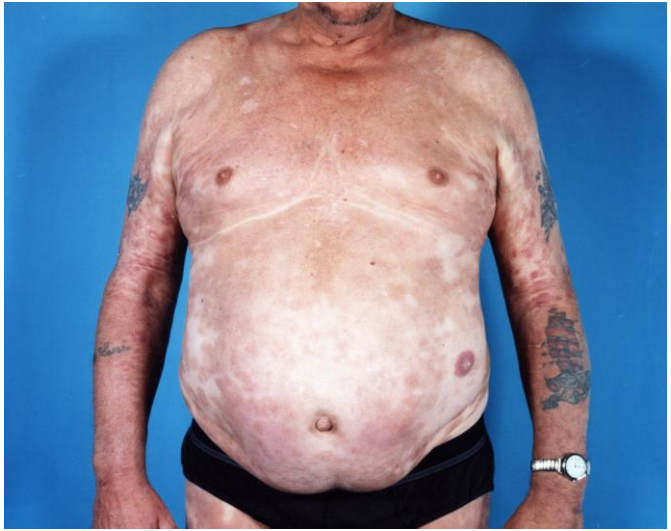


Soles

TSEBT, pt. with generalized plaques, before and 1 month after and 1 year after







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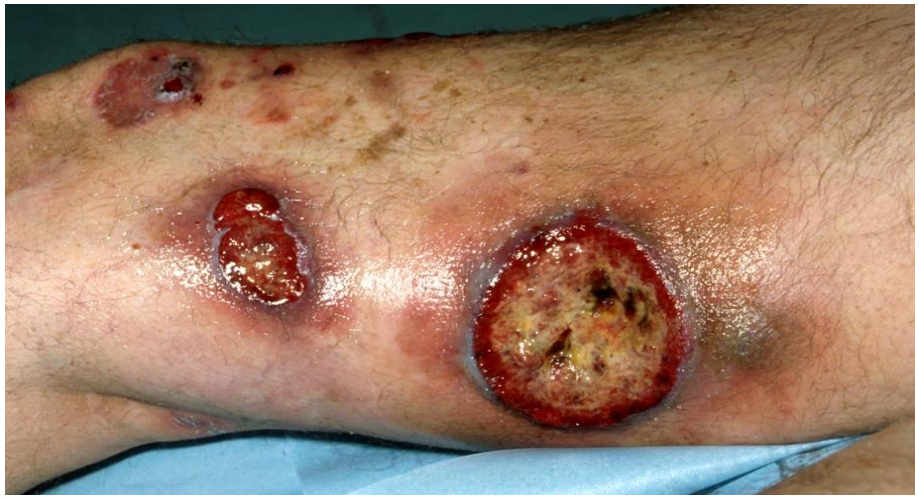
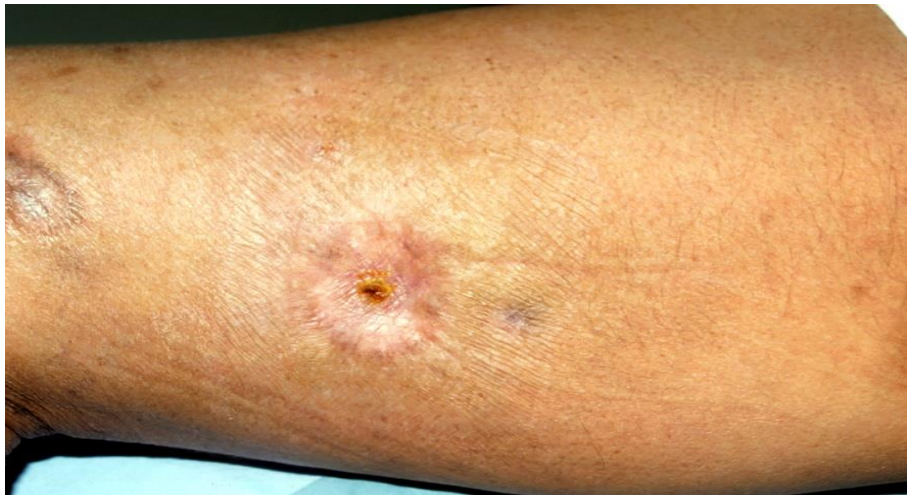
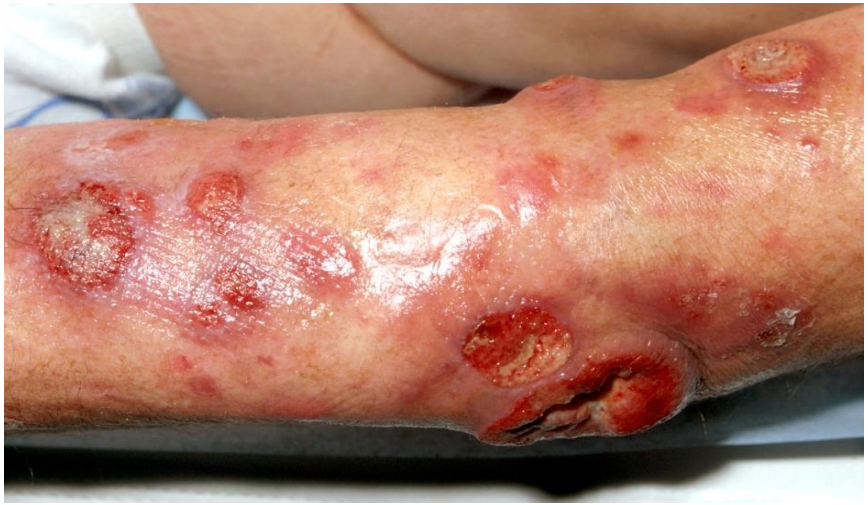
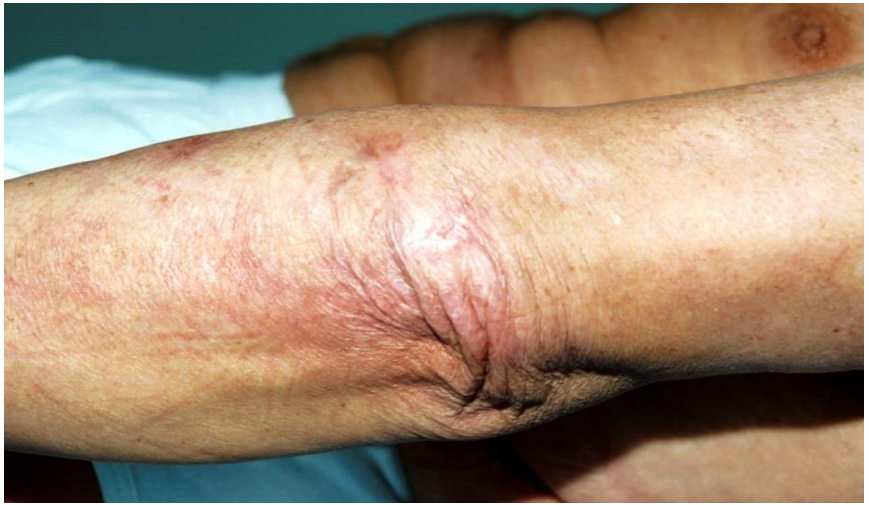
TSEBT, pt. with tumors, before and 6 months after





TSEBT, pt. with tumors, before and 6 months after





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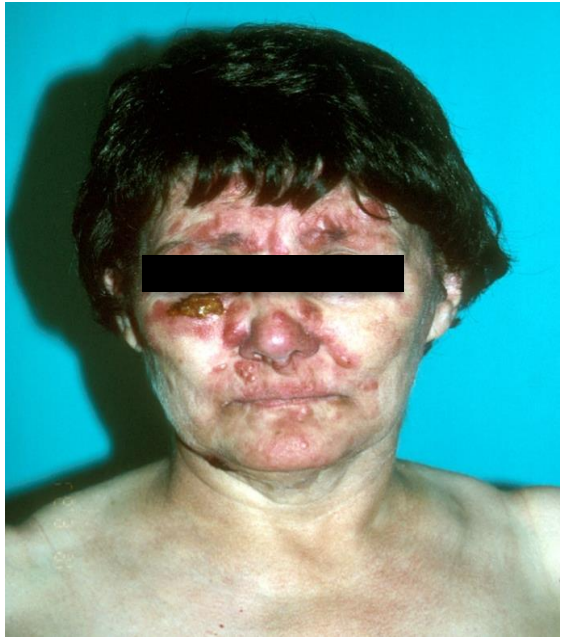
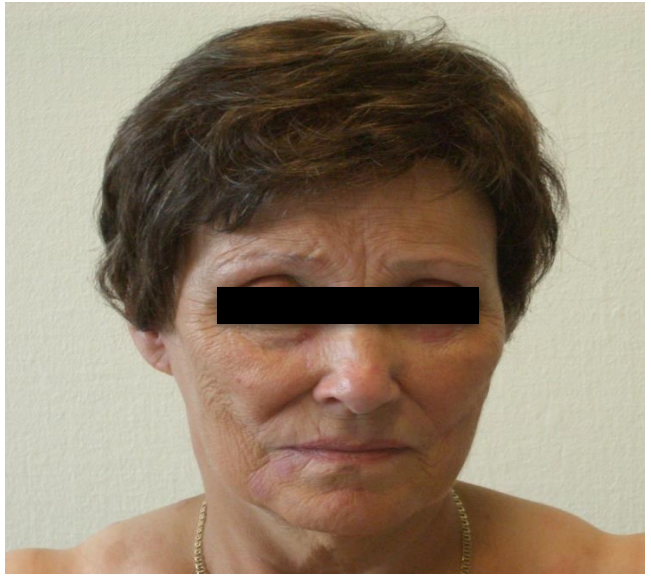
TSEBT, pt. with plaques and small tumors, before and 7 years after





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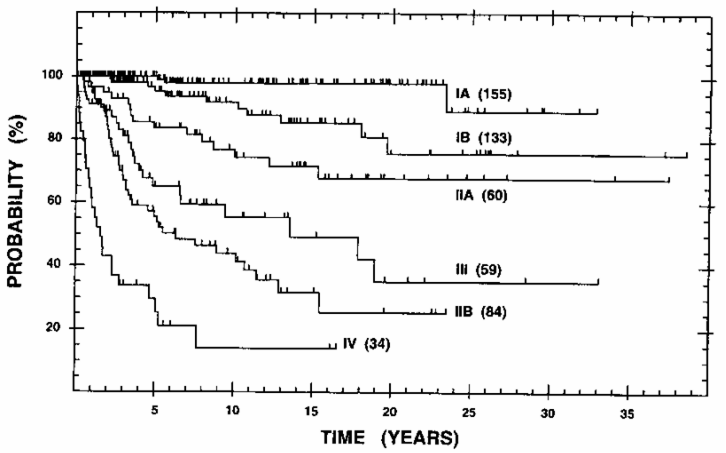
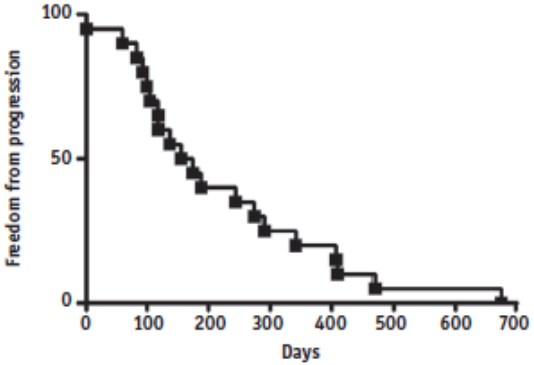
TSEBT outcome



Cause-specific survival after 30 Gy (Stanford data)



PFS with low dose 10-12 Gy (Kamstrup, IJROBP 2015; 92: 138-43

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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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Extranodal lymphomas: Characteristics, the role of radiotherapy, volumes doses and techniques:

Testicular lymphoma

Berthe Aleman

Radiation oncologist

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

ILROG
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Testicular lymphoma

General

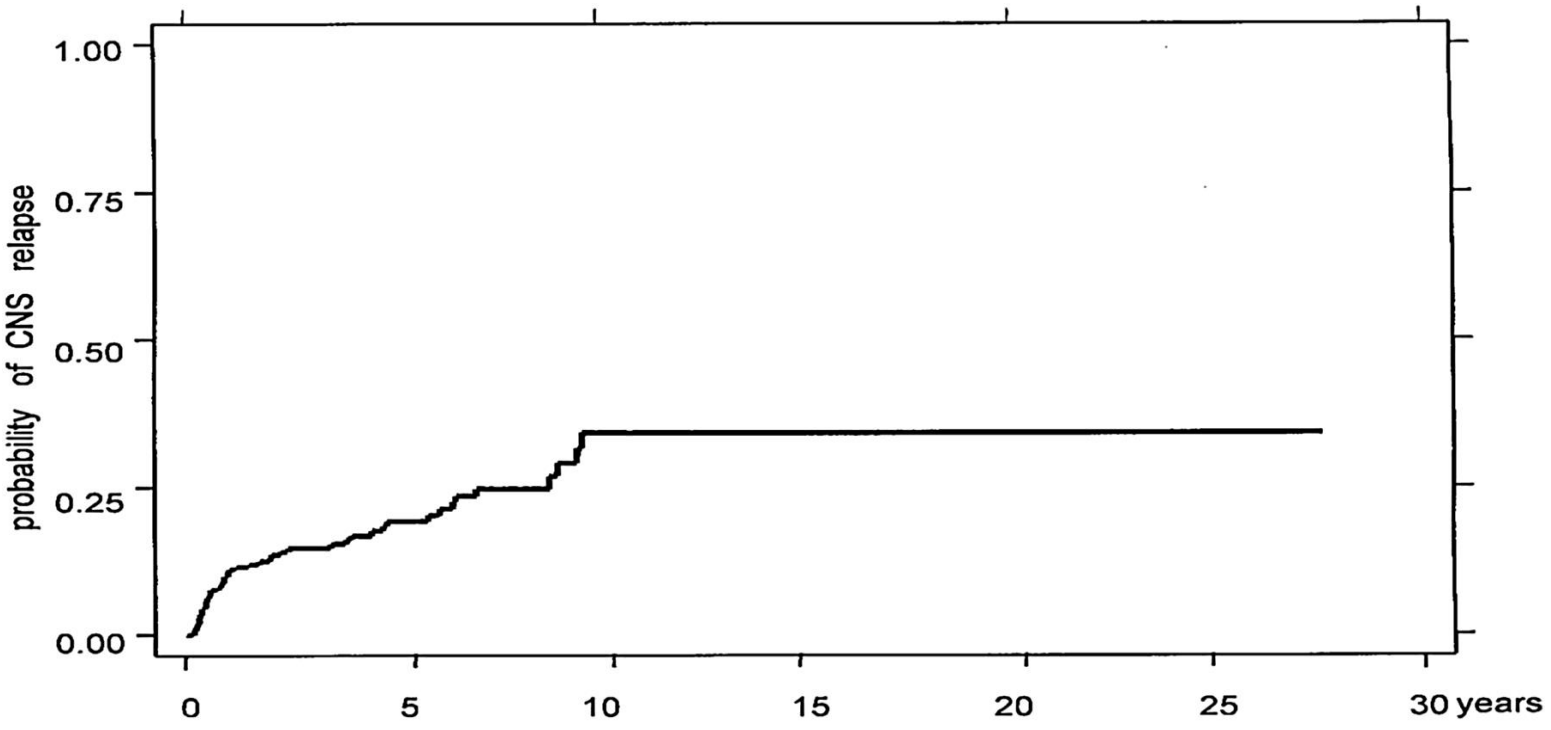
- Primary testicular lymphoma (PTL) is an uncommon and aggressive form of extranodal non-Hodgkin lymphoma (NHL)
- Annual incidence at 0.09 to 0.26 per 100 000 population
- 0,5% of testicular malignancies and 1-2% of all NHL cases
- Median age at diagnosis: 66 - 68 years

Testicular lymphoma

General (continued)

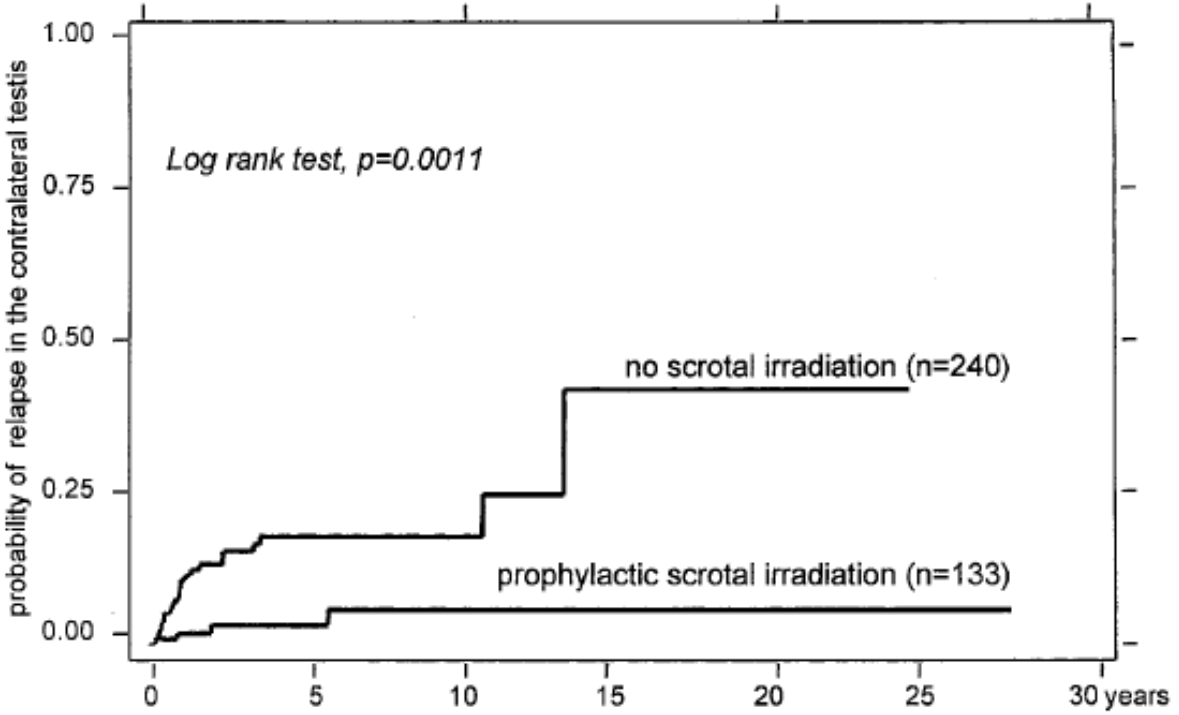
- PTL is both the most common testicular malignancy in men age >60 years and the most common bilateral testicular neoplasm.
- The common histology is DLBCL
- Sanctuary sites: CNS and contralateral testicle

Time to CNS recurrence; IELSG retrospective study (n=381; 1968-1998)



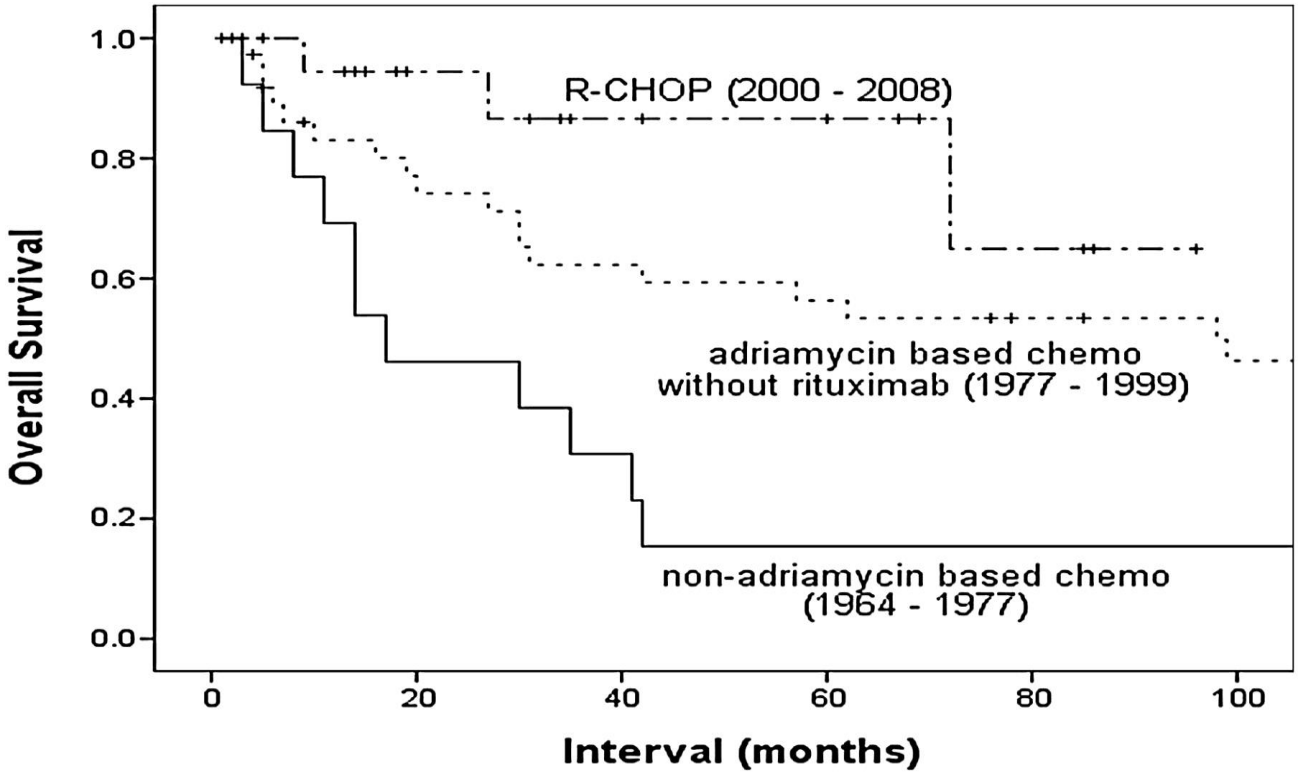
Zucca et al, J Clin Oncol 2003:20-27

Continuous risk of recurrence in the contralateral testis by prophylactic scrotal radiotherapy; IELSG retrospective study (n=381; 1968-1998)



Zucca et al, J Clin Oncol 2003:20-27

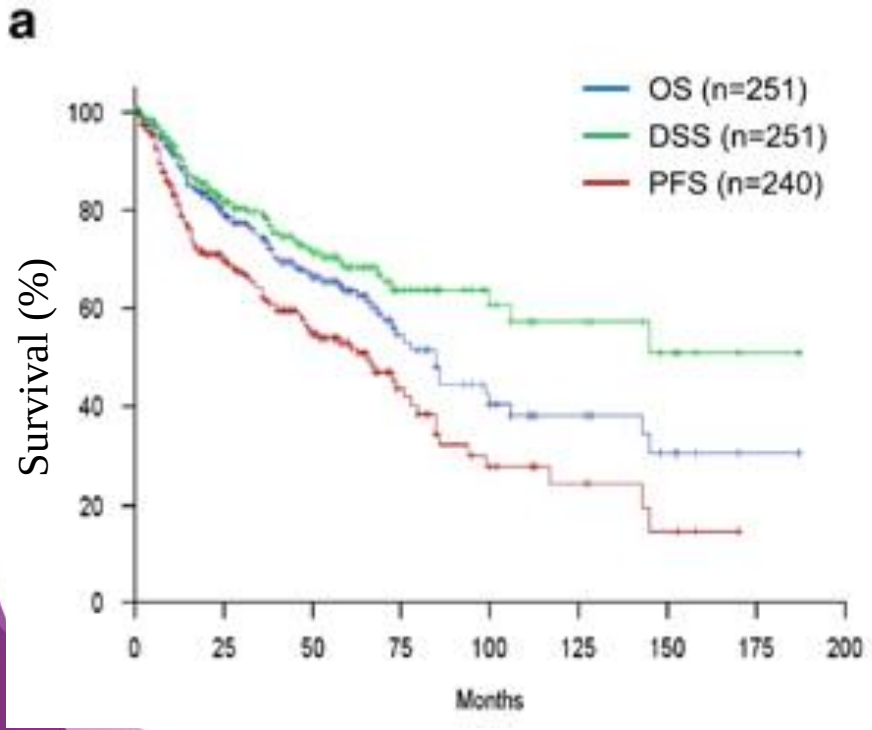
OS of patients with PTL treated at MDACC, by chemotherapy strategy

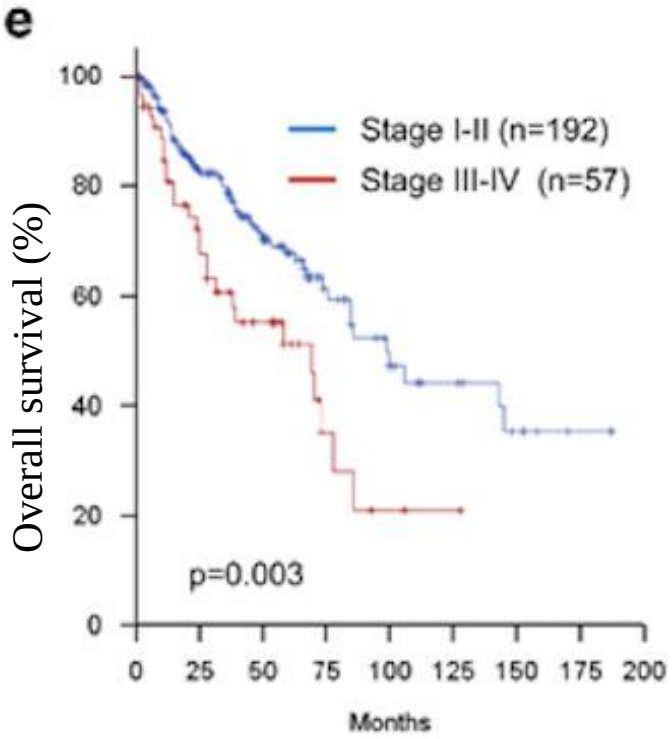


Mazloom et al. Leuk Lymphoma 2010: 1217-1224

Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure **in rituximab era**:

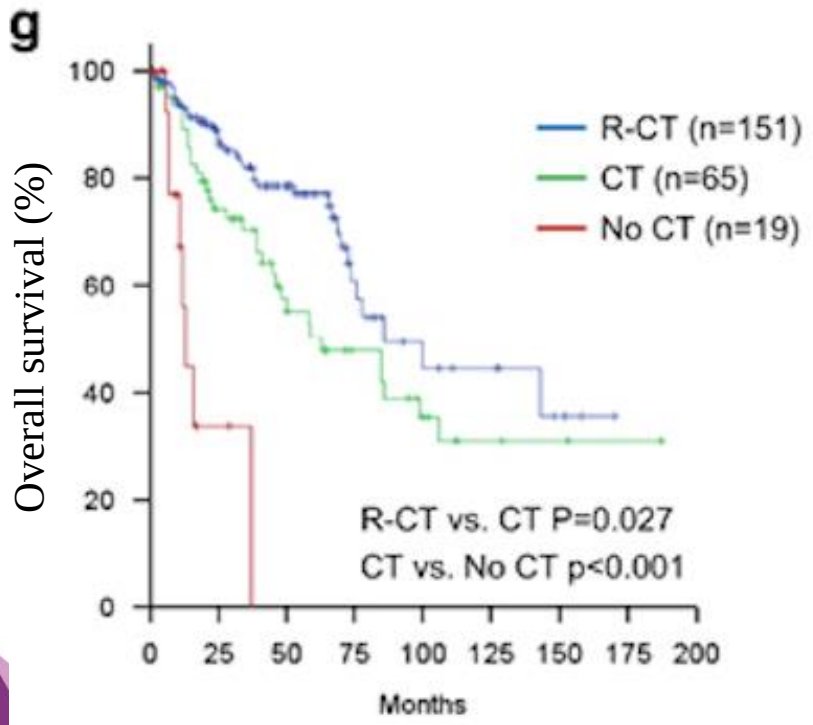
a report from the International PTL Consortium (n=280; 1993-2014)

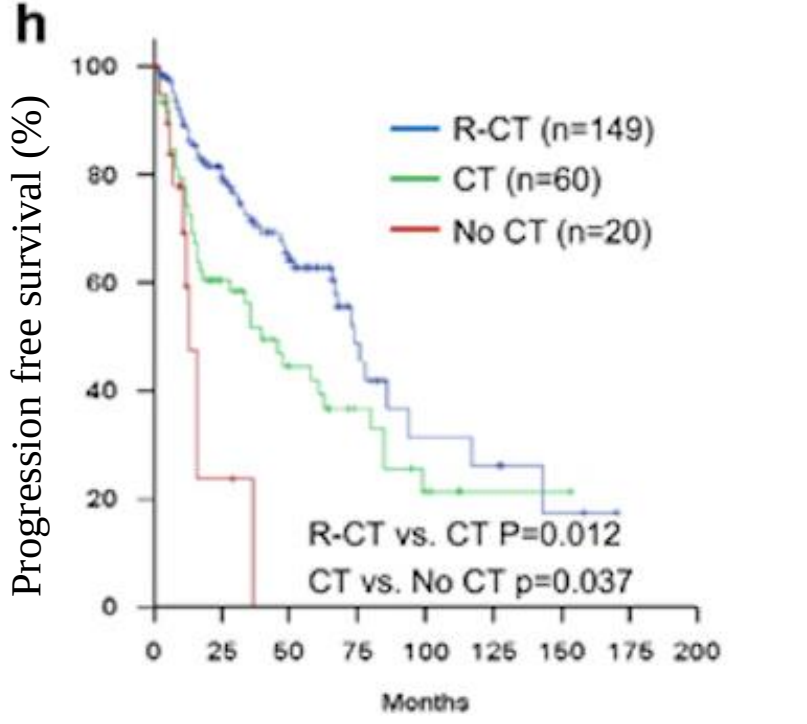




Deng et al, Leukemia 2016: 361-372

Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure in rituximab era:
a report from the International PTL Consortium (n=280; 1993-2014)

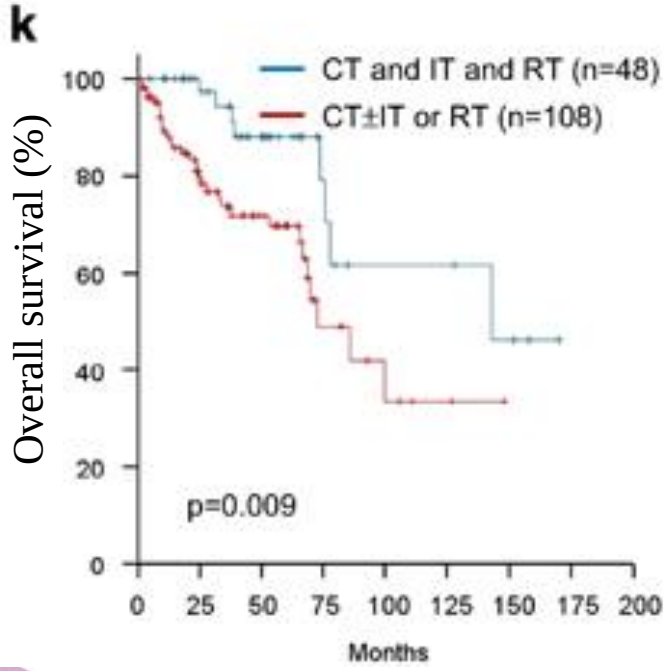




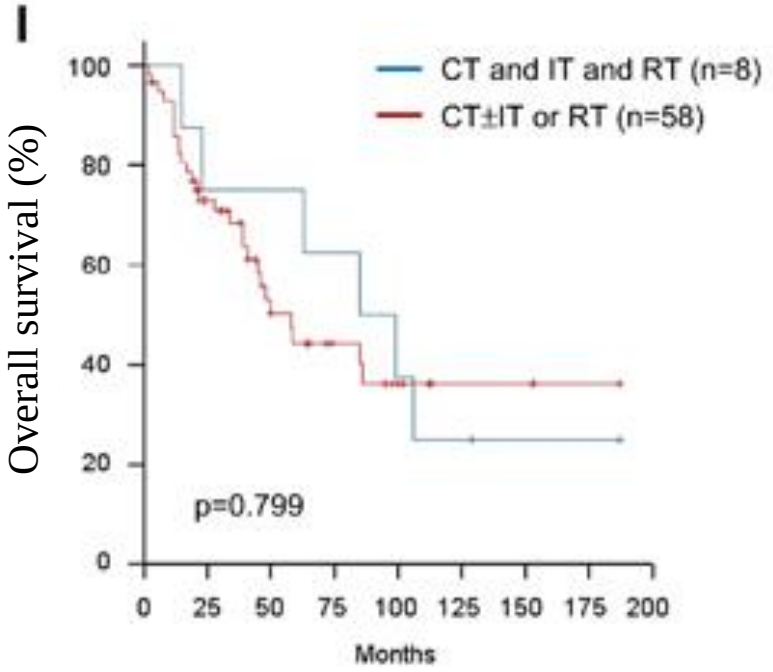
Deng et al, Leukemia 2016: 361-372

Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure in rituximab era:
a report from the International PTL Consortium (n=280; 1993-2014)

Treatment with rituximab



Treatment without rituximab



Deng et al, Leukemia 2016: 361-372

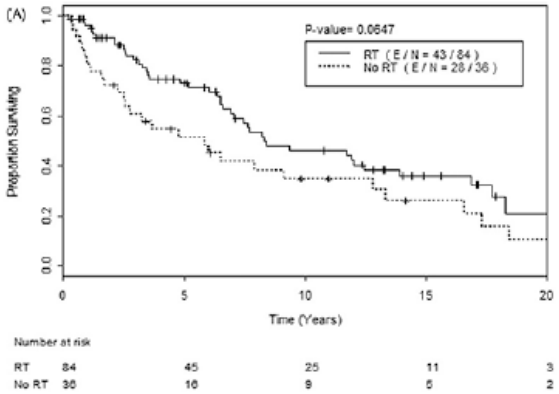
RT improves survival in patients with testicular DLBCL

- Retrospective analysis of 120 Stage I–IV testicular DLBCL patients treated 1964- 2015 at MDACC
- Aim: assess benefits of prophylactic contralateral testicular RT and prophylactic CNS therapy
- Testicular RT: 70%; median dose 30.6 Gy (range, 24–40 Gy), at a median 1.8 Gy per fraction
- CNS profylaxis: 61% (intrathecal or high dose MTX)

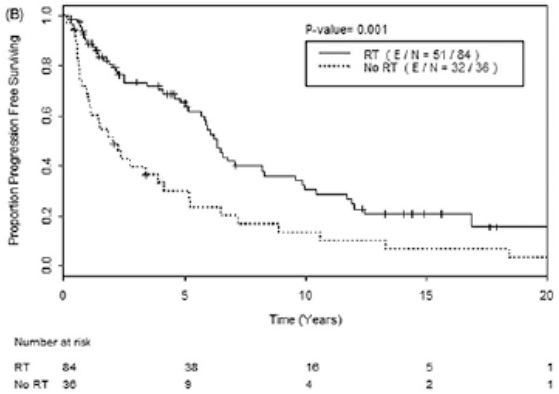
Ho et al, Leuk Lymphoma 2017

RT improves survival in patients with testicular DLBCL;
evaluation **testicular RT**

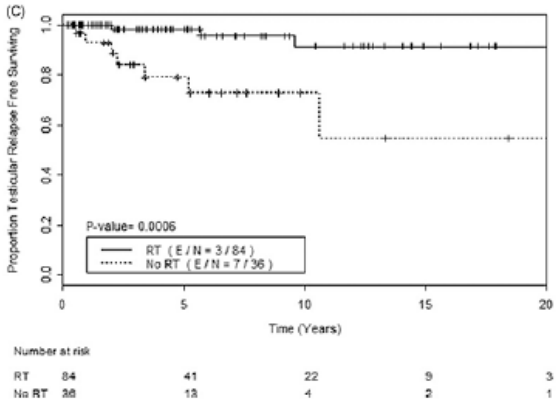
Overall survival



Progression Free Survival



Testicular Relapse Free Survival

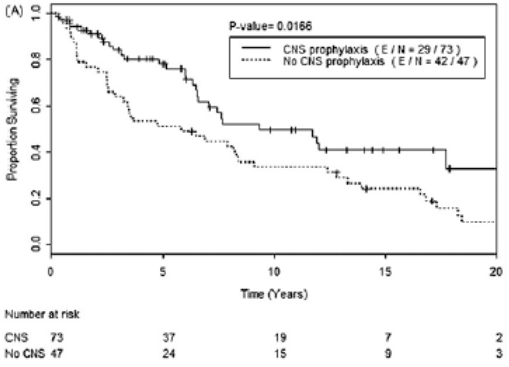


- On multivariate analysis RT was significantly associated with improved OS and PFS
- PFS benefit persisted among patients receiving modern therapy

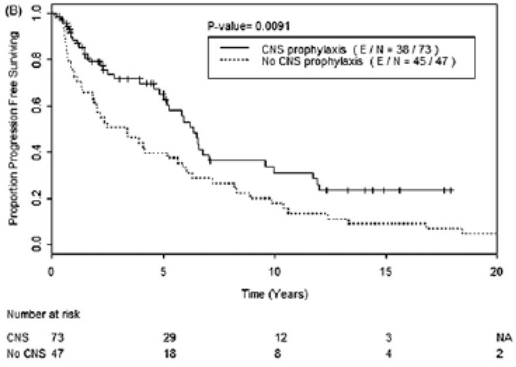
Ho et al, Leuk Lymphoma 2017

RT improves survival in patients with testicular DLBCL:
evaluation of **CNS profylaxis**

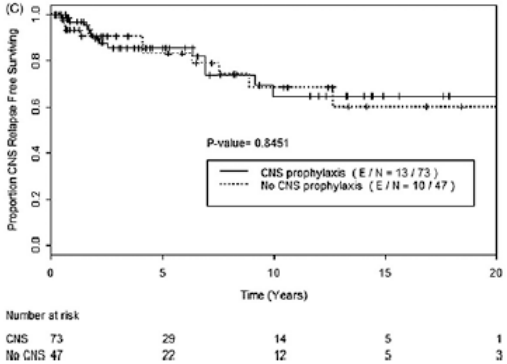
Overall survival



Progression Free Survival



CNS Relapse Free Survival



- No factors were significantly associated with CRFS in MVA, including CNS prophylaxis.

Ho et al, Leuk Lymphoma 2017

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

Cheah et al. Blood 2014;123:486-493

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.

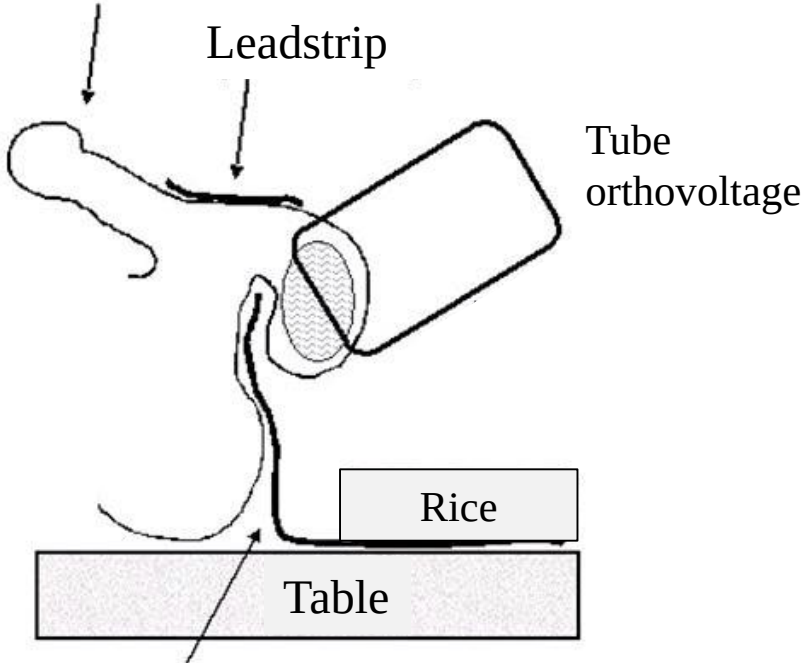
Yahalom et al. ILROG guideline, IJROBP 2015

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

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

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?
  - Regular measurement testosterone

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KING'S College LONDON
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NHS Foundation Trust

Extra-nodal Lymphoma
Rare sites

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Rare sites

- Kidneys
- Bladder
- Prostate
- Small intestine / Duodenum
- Large intestine
- Liver
- Uterus
- Ovaries
- Endocrine organs
- Heart

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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

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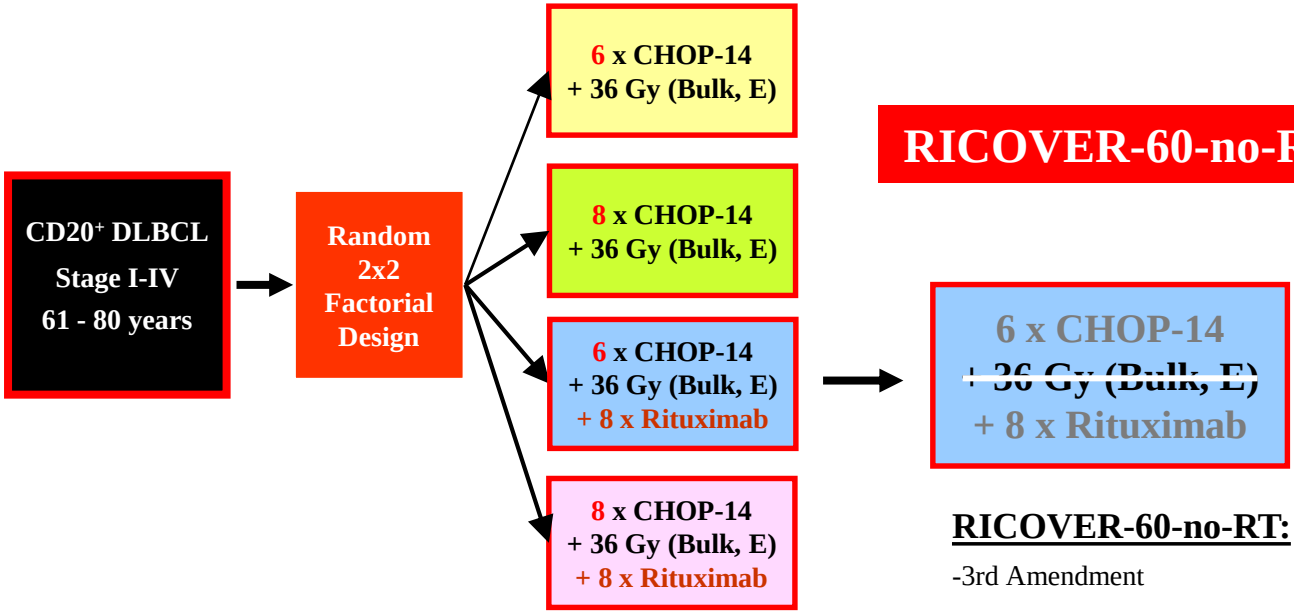
RICOVER-60



Held, JCO 2014l

RICOVER-60-no-RT:

-3rd Amendment

-Recruitment 08/2005 – 10/2007

-Number of Patients 166

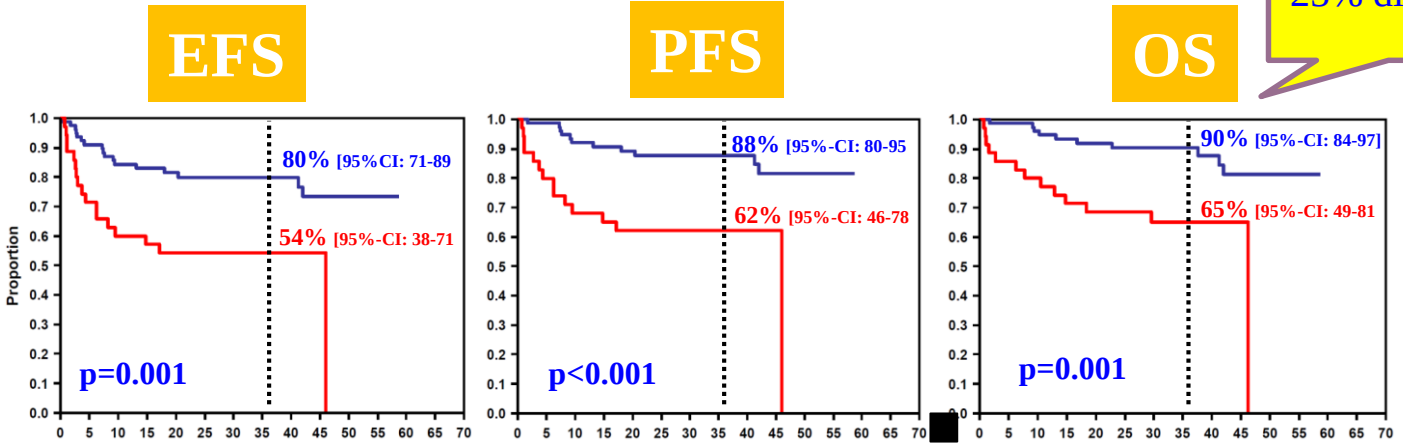
-Median Observation 39 Months

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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Follicular lymphoma (FL)	
In situ follicular neoplasia	• New name for in situ follicular lymphoma reflects low risk of progression to lymphoma.
Pediatric-type FL	• A localized clonal proliferation with excellent prognosis; conservative therapeutic approach may be sufficient.
	• Occurs in children and young adults, rarely in older individuals.
Large B-cell lymphoma with IRF4 rearrangement	• New provisional entity to distinguish from pediatric-type FL and other DLBCL.
	• Localized disease, often involves cervical lymph nodes or Waldeyer ring.
Duodenal-type FL	• Localized process with low risk for dissemination.
Predominantly diffuse FL with 1p36 deletion	• Accounts for some cases of diffuse FL, lacks BCL2 rearrangement; presents as localized mass, often inguinal.

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

- Liver

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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:

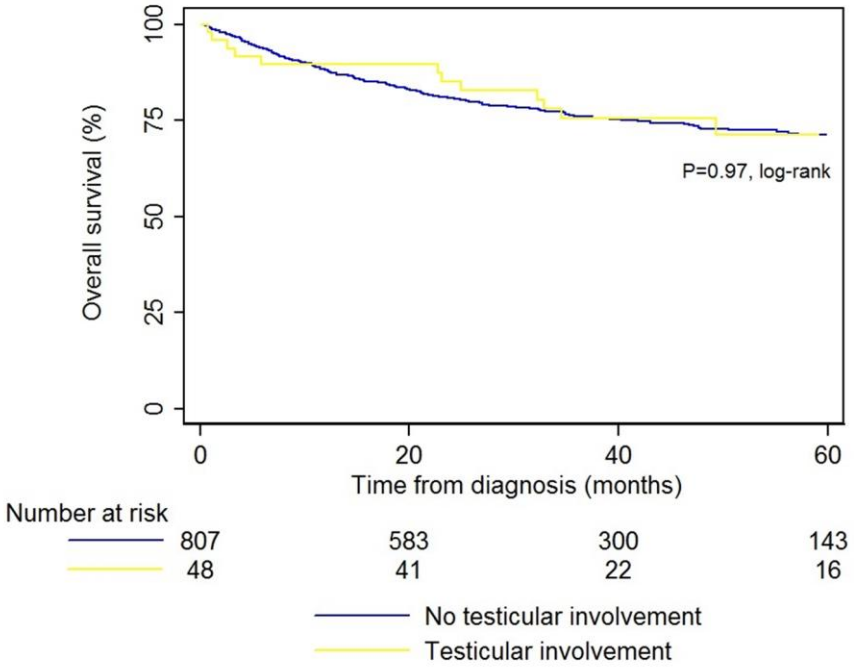
- Bladder: FDG excretion is urine (PET for staging nodes / others sites)
- Planning: bladder full v empty. Rectal volume. IV contrast
- CTV: whole organ
- Fertility issues

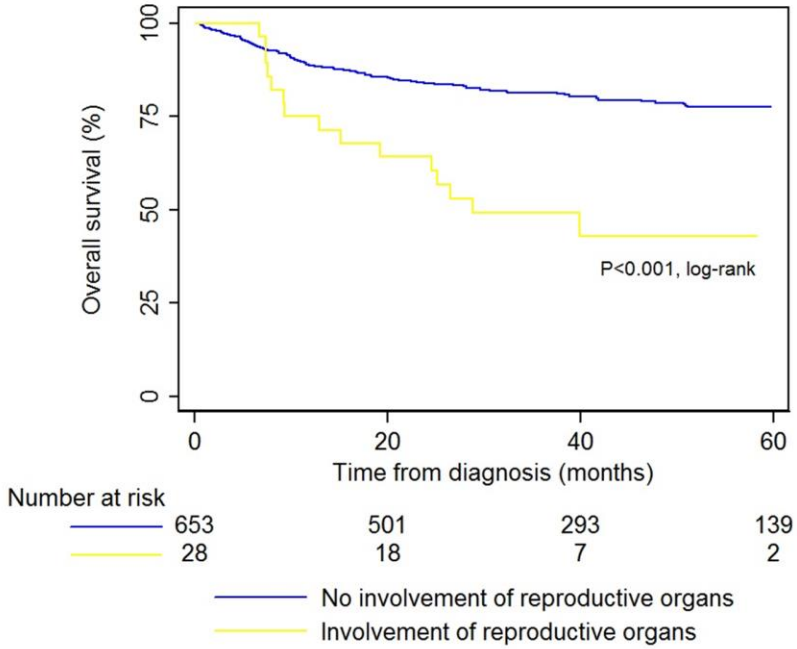
Female patients with DLBCL and involvement of the reproductive organs have poor outcomes and markedly increased risk of CNS relapse with R-CHOP(-like) therapy

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]

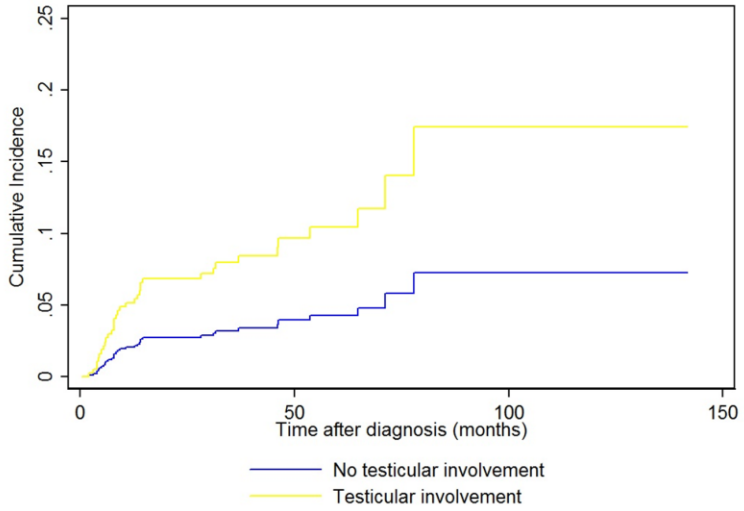
- 1,536 patients, 76 (5%): reproductive organ involvement.
- Testicular involvement = 48 (6%) of men
- Female reproductive organ involvement = 28 (4%) of women
  (uterus n=15, ovaries n=11, both n=2).

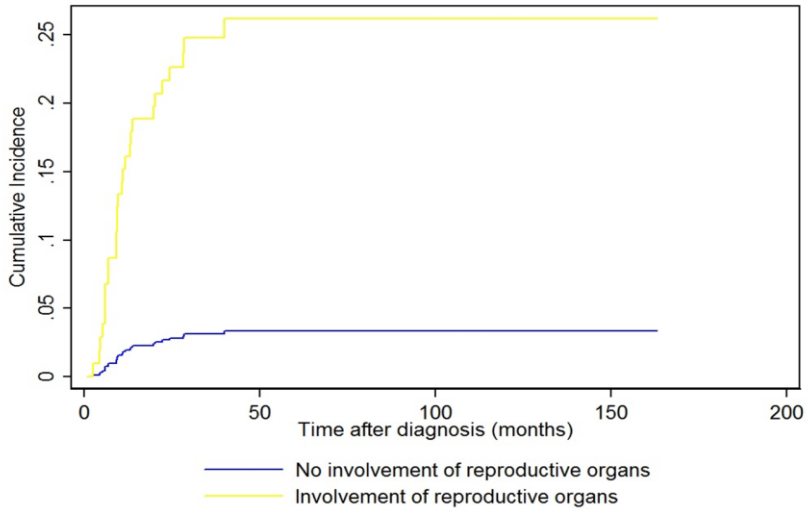
OS


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



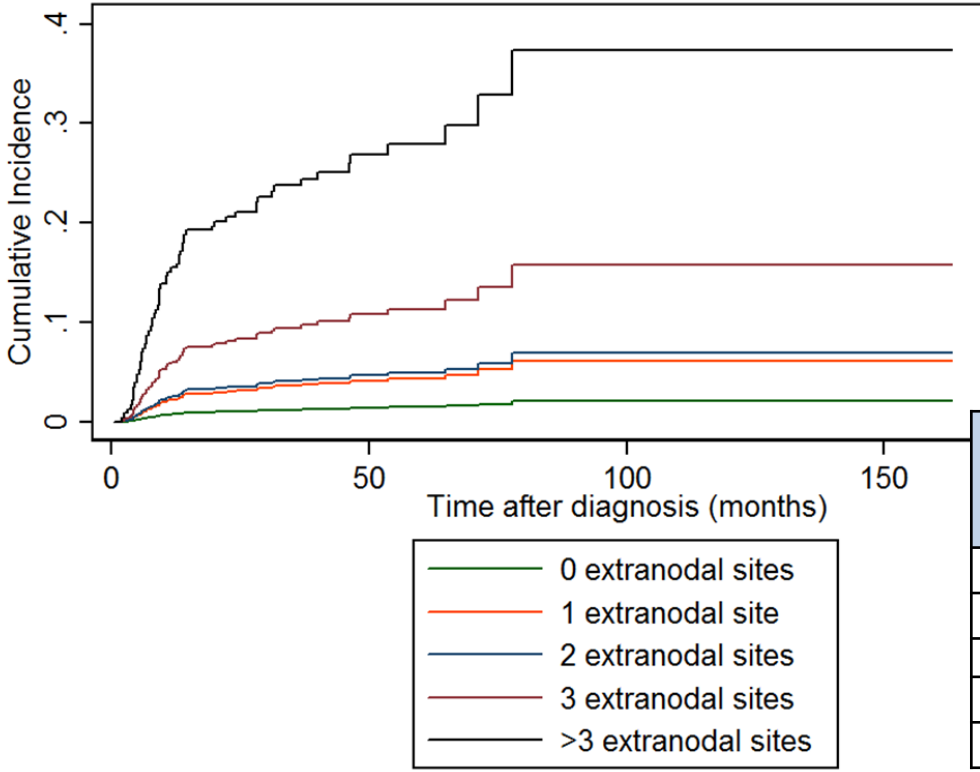


CNS relapse

Uterine: 7/16 (44%) HR=17

Ovarian: 0/11

CNS progression rate with deaths before CNS relapse as competing events



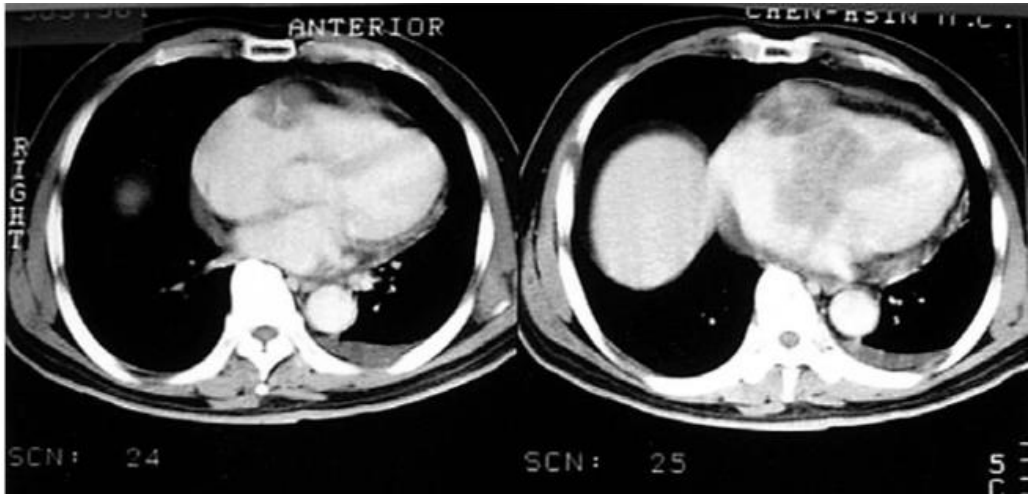
3-year incidence of CNS relapse % (95%CI)	Unadjusted hazard ratio HR (95% CI)
1.7 (0.9-3.5)	**1.0 (ref)**
4.0 (2.5-6.4)	**3.0 (1.3-6.7)**
4.8 (2.4-9.4)	**3.4 (1.3-8.5)**
12.8 (6.6-24.0)	**8.1 (3.1-20.9)**
32.1 (20.1-48.8)	**22.0 (9.0-53.6)**

Cardiac

Table 1. Summary of selected cases of primary cardiac lymphoma reported in the recent literature

Reference	Sex	Age (yr)	Presentation	Location of tumor	Tumor type	Treatment response and survival time
Saotome et al[6]	M	69	Pericardial effusion	Right atrium extending to other chambers	Lymphoma, large cell	C/T with CHOP; survived for 18 days; died of low-output syndrome and multiple organ failure
Rolla et al[5]	M	72	Moderate AS, pericardial effusion, heart failure, syncope	Right atrium and right ventricle wall	Lymphoma, large B cell	Died after 1st course of C/T; died of fatal ventricular arrhythmia
Tai et al[4]	M	70	Complete AV block, peritonitis	Pericardium, right atrium	Diffuse large B cell	3 C/T with COP + 3 CHOP; survived > 2 years
Cordel et al[7]	M	83	Hepatosplenomegaly, acute body weight loss	Right ventricle	Diffuse large B cell, lymphoma	Complete recovery after C/T with cyclophosphamide, prednimustine etoposide; survived > 1 year
Canellos et al[8]	F	Adult	Heart failure, chest pain, complete AV block	Right atrium, right ventricle	Diffuse large B cell, lymphoma	C/T with complete regression
Nakayama et al[9]	F	61	Complete AV block, pericardial effusion	Right atrium	Lymphoma	C/T with recovery
Chim et al[2]	M	32	Palpitation, heart failure	Right atrium, right ventricle	NHL, diffuse large B cell	C/T with CHOP+R/T; survived > 18 months
Cartagna et al[10]	F	78	Pleural effusion, heart failure, pericardial effusion	Right atrium	High-grade B cell lymphoma, Burkitt's type	Exploratory thoracotomy, but inoperable; died 2 days later
Nakchbandi and Day[11]	F	77	GI symptoms, heart failure, pericardial effusion, CHF, AF	RV, epicardium	Diffuse large B cell, lymphoma	C/T with CHOP; survived > 18 months
Anghel et al[12]	M	52	Dyspnea, pericardial effusion, obstruction of IVC	Right atrium, interatrial septum	Large B cell, lymphoma	High-dose C/T + autologous PBS transplantation + Rutuximab ; CR > 24 months
Anghel et al[12]	F	70	Pericardial tamponade, low-output cardiac failure	Right atrium	Large B cell, lymphoma	Pericardiocentesis; C/T with COP; died 2 weeks later
Beckwith et al[13]	M	61	Dyspnea, hepatomegaly, heart failure	Right atrium	Diffuse large B cell, lymphoma	Partially resected with bovine pericardial patch over LA wall; C/T with CHOP x 3 courses; died of CNS involvement; survived 2 months
Mejhert et al[14]	M	59	Heart failure, AF	Right atrium, inferior vena cava	B-cell lymphoma	CHOP (cisplatin + hydroxyurea + oncovin + prednisolone) x 8 cycles; survived 10 months; died of septic shock
Hsueh et al, this report	M	58	SOB, chest distress, second-degree AV block	Right atrium	Diffuse large lymphoma	C/T with COP + CHOPBE; survived 11 months; died of sepsis

CR = complete remission; C/T = chemotherapy; COP = cyclophosphamide + vincristine + prednisolone; CHOPBE = cyclophosphamide + doxorubicin + vincristine + prednisolone + bleomycin + etoposide; CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone; AS = aortic stenosis; AV = atrioventricle; GI = gastrointestinal; CHF = congestive heart failure; AF = atrial fibrillation; IVC = inferior vena cava; PBS = peripheral stem cell; LA = left atrium; CNS = central nervous system; RT = radiotherapy; RV = right ventricle; SOB = shortness of breath; NHL = non-Hodgkin's lymphoma.



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Questions / Comments?

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Hypersplenism, splenomegaly

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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

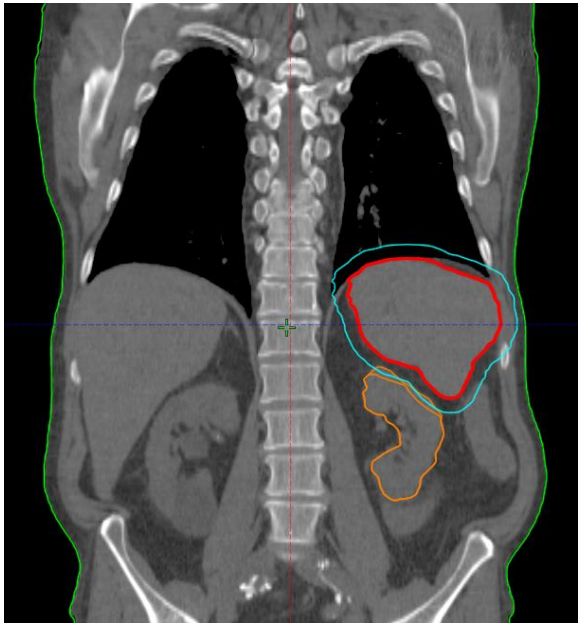
Splenic irradiation

- 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

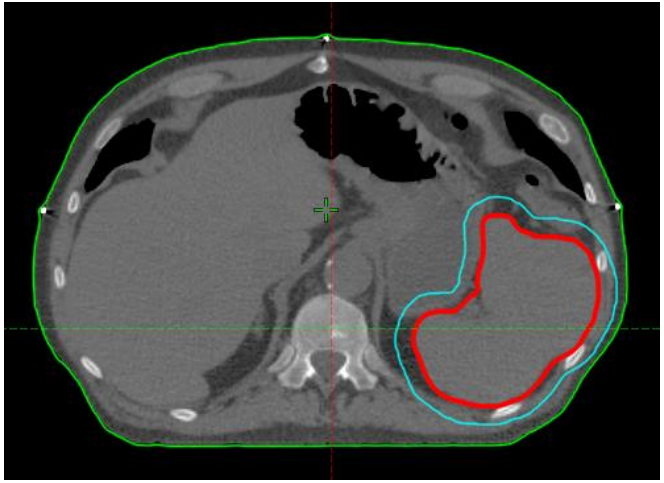
Splenic irradiation

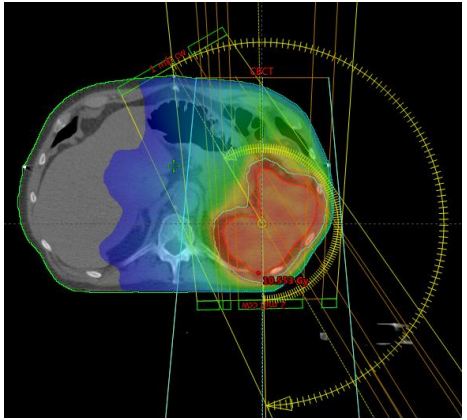
- Often significant extramedullary hematopoiesis in enlarged spleen
- Irradiation must be done with caution, risk of severe long-lasting pancytopenia
- E.g., 0.5 Gy x 20, 5 F/W
- Close monitoring of blood counts

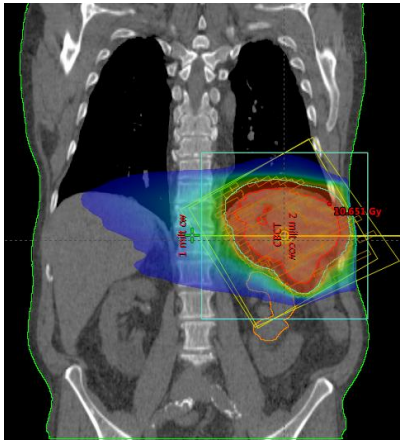
Splenic irradiation



70 year old male,
CMMOL, pain







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Leukemia treatment: TBI, Chloroma, CNS leukemia, Lymphoblastic lymphoma

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Vice-chairman, International Lymphoma Radiation Oncology Group

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Total Body Irradiation (TBI)

- High dose (typically 12 Gy) for convenitonal myeloablative conditioning for:
  - Allogeneic transplantation:
    - Tumour cell kill
    - Immunosuppression
    - Eradication of cell populations with genetic defects
  - Autologous transplantation:
    - Tumour cell kill
- Low dose (typically 2-4 Gy) for reduced intenstity conditioning (RIC) for:
  - Allogeneic transplantation:
    - Immunosuppression

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Indications for allogeneic or autologous transplant

- Leukemias
  - ALL, AML CML
- Lymphomas or other myeloproliferatvive diseases
  - Non Hodgkin lymphoma, Hodgkin lymphoma, myelodysplasia
- Immunologic diseases
  - Aplastic anemia
- Genetic diseases
  - Wiscott-Aldrich syndrome, Fanconi anemia

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Advantages for TBI as conditioning

- No ”sanctuary” (testes, CNS)
- Homogeneous dose distribution, independent of blood supply
- No cross-resistance
- No dosage change if organ dysfunction (as opposed to breakdown and elimination of drugs via liver or kidneys)
- Dose distribution in the body may be modified by blocking or boosting

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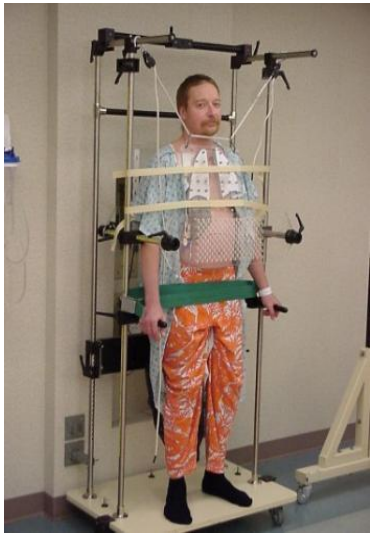
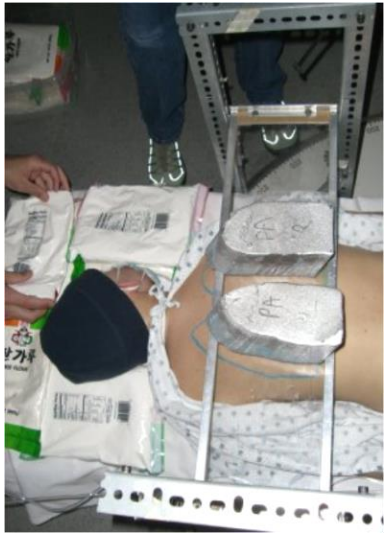
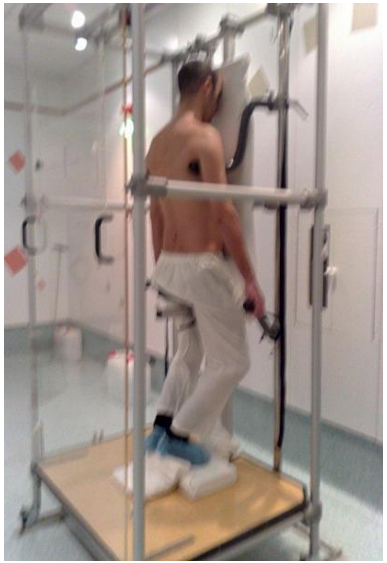
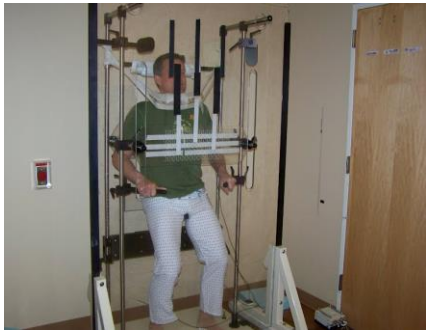
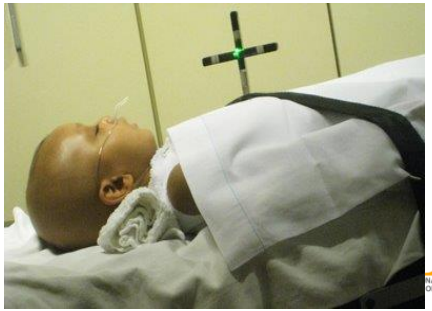
Many different treatment techniques



Most prevalent methods of delivering TBI

- Patient standing or lying down at extended SSD
- Reduced dose rate (about 10% of normal)
- One field using the diagonal dimension
- Plexiglas barrier close to patient to defeat the skin-sparing
- Blocking of critical organs (usually lungs, sometimes kidneys, liver, and previously irradiated sites)
- Point measurements for planning and dose verification
- Large dose heterogeneity

New methods

- CT-based 3D planning in treatment position
- Helical tomographic IMRT or VMAT at standard SSD
- Allows conformal avoidance of normal organs
- Allows treatment in supine position
- Multiple abutting fields are required

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Royal Marsden-Copenhagen technique

- Step-and-shoot IMRT technique
- No high dose rates or field junctioning
- Traditional extended SSD
- Whole-body CT-scans used for planning
- Several multileaf collimator fields used to optimize
- Testicular boost 4 Gy for male ALL pts.

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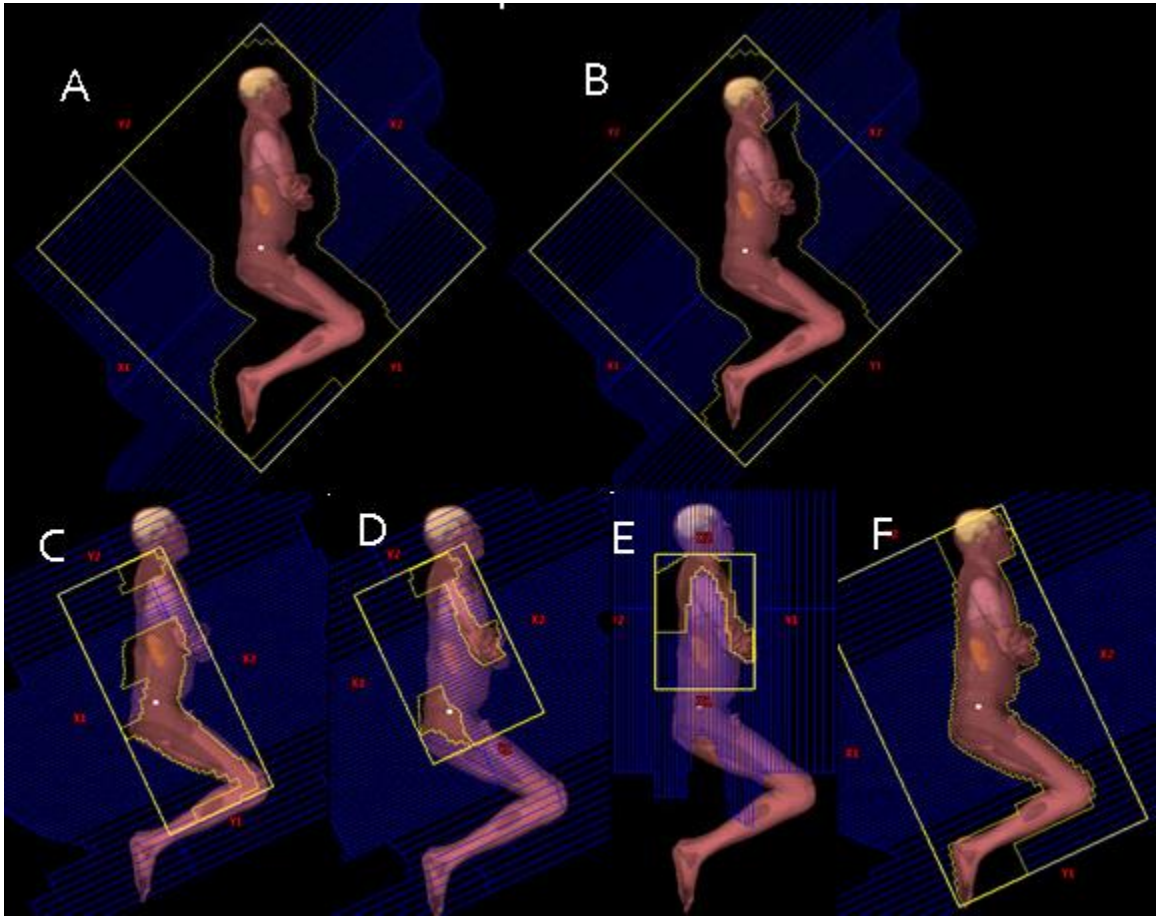

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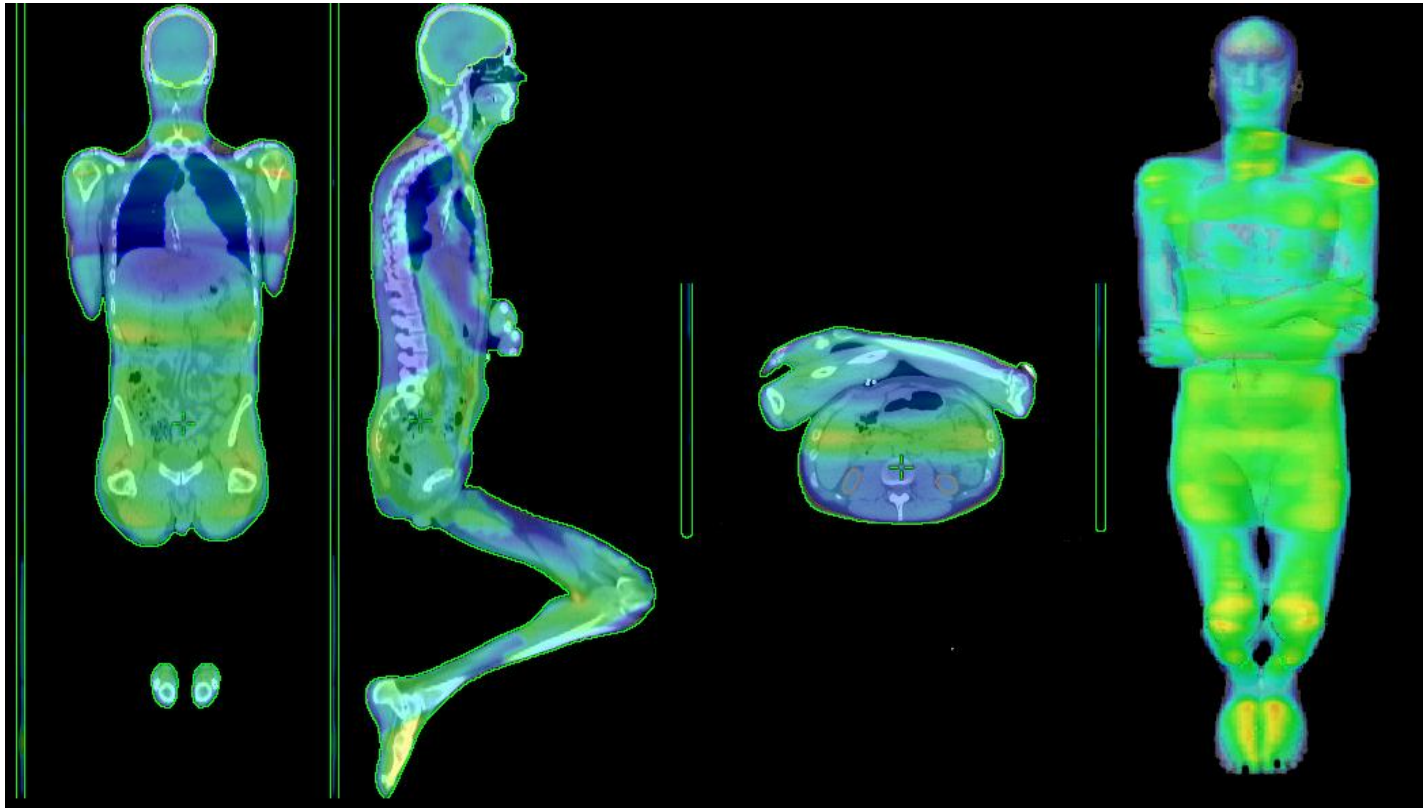

Clinical plan, dose colour wash 90-115 % of prescription dose

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Acute toxicity

- Interstitial pneumonitis
- Nausea and vomiting
- Parotitis
- Dry mouth and mucositis
- Diarrhea
- Fatigue
- Decreased appetite
- Erythema
- Esophagitis
- Alopecia

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Long-term toxicity

- Cataract (30-40 %)
- Gonadal failure
- Thyroid and kidney dysfunction
- Decreased bone mineral density
- Veno-occlusive disease
- Metabolic syndrome
- Second cancer
- Cardiovaxcular disease
- In children multiple endocrine disorders

Total marrow irradiation

- Target is skeletal bone
- Potential of
  - greater dose homogeneity
  - lower organ doses
  - reduced toxicity
  - Dose excalation
- Remains investigational

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Total Body Irradiation: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG)

Jeffrey Y.C. Wong, MD,* Andrea Riccardo Filippi, MD,† Bouthaina Shbib Dabaja, MD,‡ Joachim Yahalom, MD,§ and Lena Specht, MD, DMSc‖

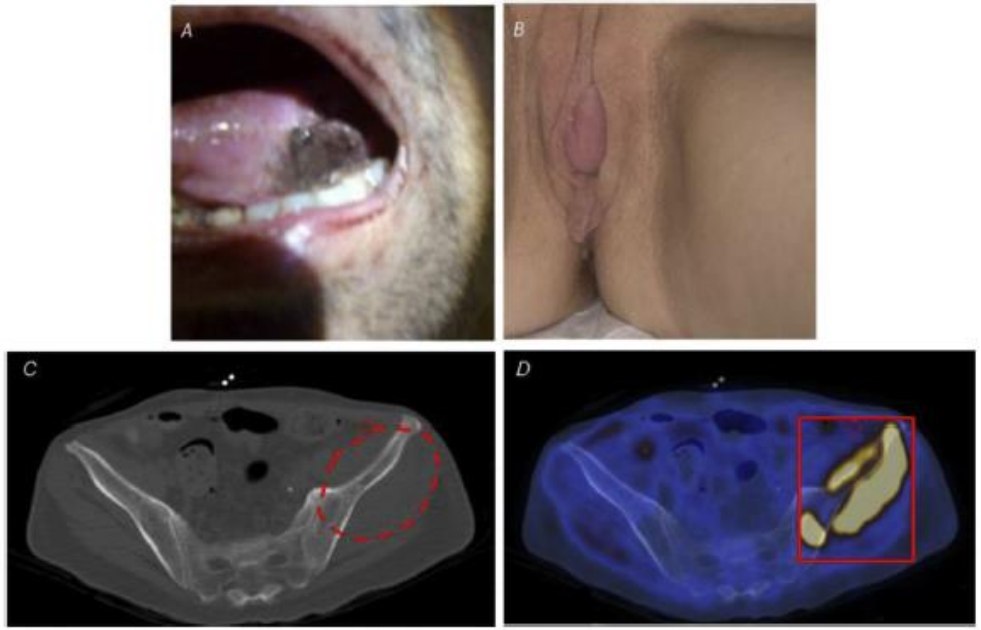
IJROBP 2018; 101: 521-9

Extramedullary mainfestations of acute leukemia: chloroma and leukemia cutis

- Occur in 10-15 % of patients with AML
- Can occur in:
  - CML in accelerated phase
  - MDS
  - without marrow involvement (rare)

Chloroma

- Soft tissue masses
- Can occur everywhere, often in
  - Soft tissues
  - Bone
  - Periosteum
  - Lymph nodes



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RT of chloroma and leukemia cutis

- Provides rapid and durable local control for patients with
  - Isolated chloroma
  - Isolated recurrence after transplant
  - Palliation
- In persistent diffuse leukemia cutis: TSEBT
- 24 Gy in 12 fractions (does not preclude TBI conditioning)

Use of Radiation in Extramedullary Leukemia/ Chloroma: Guidelines From the International Lymphoma Radiation Oncology Group

Richard L. Bakst, MD,* Bouthaina Shbib Dabaja, MD,†
Lena K. Specht, MD, DMSc,‡ and Joachim Yahalom, MD§

IJROBP 2018; 102: 314-9

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RT in CNS leukemia

- Rarely used as prophylaxis in ALL
- Considered for overt CNS leukemia at diagnosis or relapse, especially when other CNS directed therapy has failed
- Considered for ALL or AML pts. undergoing allogeneic transplant and have a history of CNS involvement

RT in CNS leukemia (cont)

- Interval of 2 weeks between i.t. MTX or Ara-C and CNS-directed RT recommended
- Choice of cranio-spinal vs. cranial RT depends on expected long-term outcome
- High suspicion of therapy-related neurotoxicity in heavily pre-treated pts. presenting with CNS-related symptoms

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RT in CNS leukemia (cont)

- Recommended RT dose 18-24 Gy
- Reduced dose of 18 Gy to the spine can be considered
- In pts. who are to receive a myeloablative regimen with TBI, the cranial/CSI dose should be factored into the TBI and the total dose should not exceed 24 Gy

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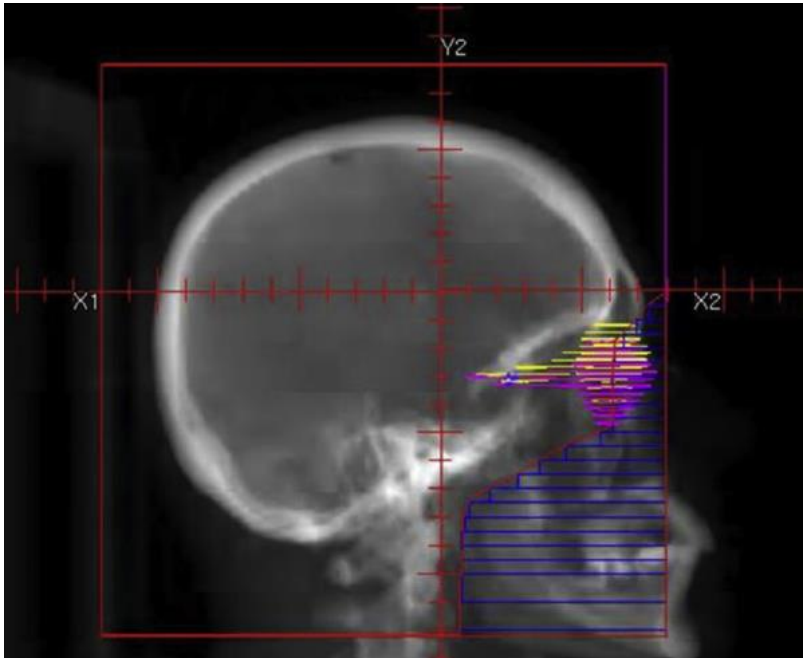
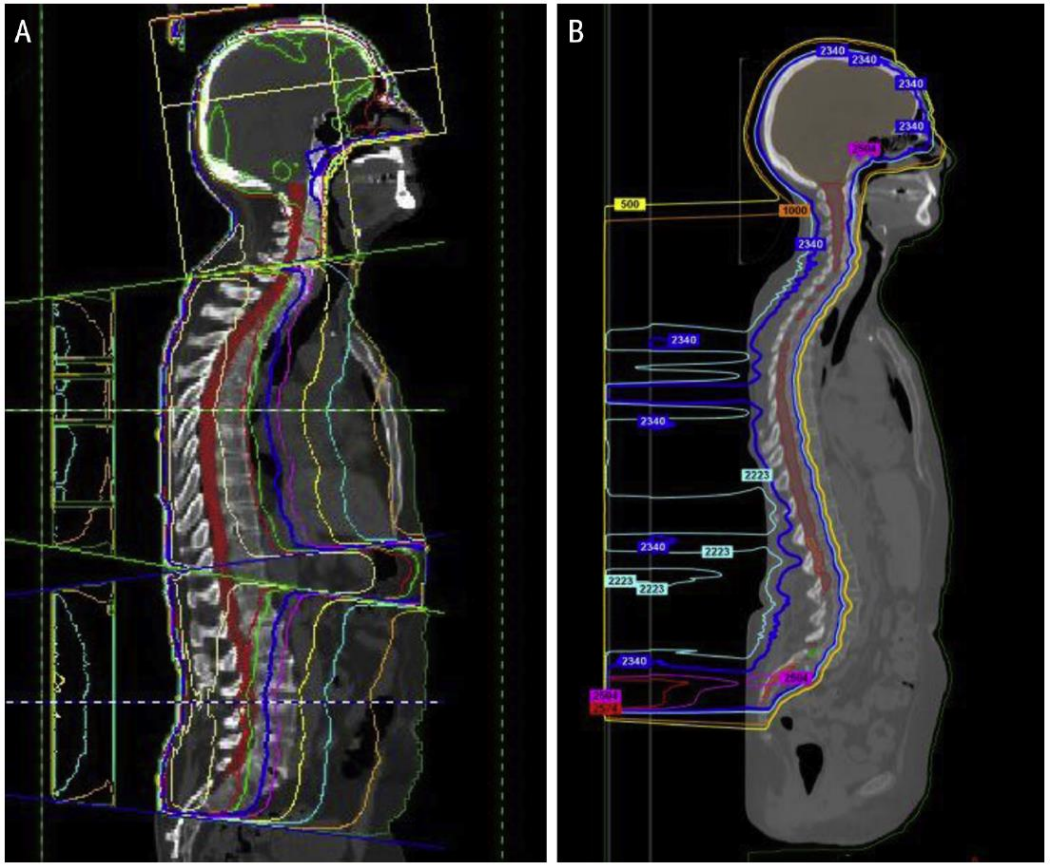
Whole brain irradiation

- Opposed lateral beams
- Include leptomeninges and spaces harboring CSF
- Include:
  - Posterior 2/3 of globe
  - Cribriform plate
  - Middle temporal fossa
  - Medulla oblongata (lower border at bottom of C2)



Craniospinal irradiation: photons vs. protons



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Radiation in Central Nervous System Leukemia: Guidelines From the International Lymphoma Radiation Oncology Group

Chelsea C. Pinnix, MD, PhD,* Joachim Yahalom, MD,†
Lena Specht, MD, DMSc,‡ and Bouthaina Shbib Dabaja, MD*

IJROBP 2018; 102: 53-8

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Lymphoblastic lymphoma

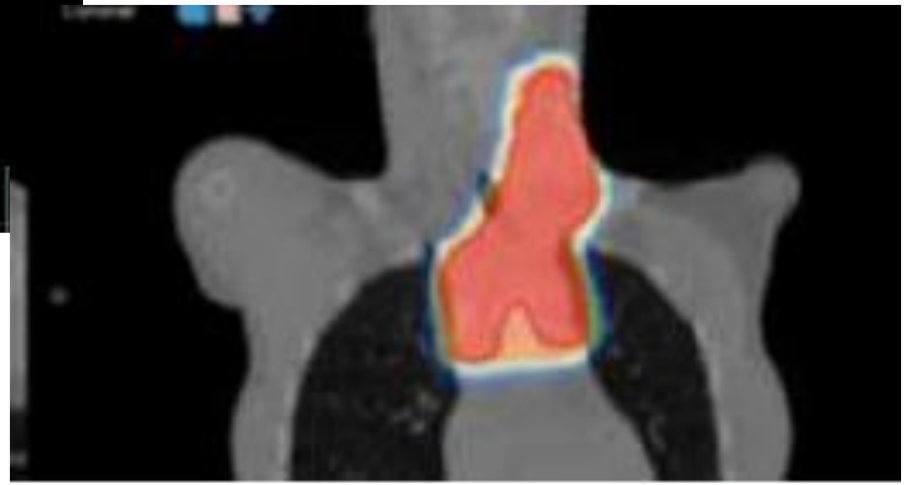
- Highly aggressive, usually T-cell lymphoma resembling ALL
- 90 % have bulky mediastinal disease originating in the thymus
- Treated with leukemia-like regimens, most commonly Hyper-CVAD

Lymphoblastic lymphoma (cont)

- Relapse occurs most often in the mediastinum
- RT provides significant improvements in local control
- Hitherto not widely used because of fear of RT-induced short- and long-term toxicities

Lymphoblastic lymphoma (cont.)

- ISRT should follow ILROG guidelines, and only include the mediastinal disease
- Advanced techniques, incl. motion management, special optimized planning solutions, and on-board imaging should be used
- Recommended dose 30-36 Gy



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Lymphoblastic Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG)

Bouthaina Shbib Dabaja, MD, Lena Specht, MD, DMSc, Joachim Yahalom, MD

IJROBP (in press)

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RADIATION ONCOLOGY GROUP

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February 16-17, 2019 • University of California, San Diego

CALL FOR ABSTRACTS OPENS LATE JUNE 2018.

REGISTRATION AND HOUSING OPEN LATE MID-AUGUST 2018.

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ILROG Educational Symposium

Radiotherapy in Modern Lymphoma Management

April 6-7 2019, Cancer Institute Hospital, Tokyo, JAPAN




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PALAZZO DEI CONGRESSI
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Two satellite workshops, organized in collaboration with **ILROG (International Lymphoma Radiation Oncology Group)**, will be devoted to radiotherapy and open to all 15-ICML attendees.

Furthermore, during the session chaired by Dr. L. Specht (Copenhagen, Denmark), Dr. T. Illidge (London, UK) and Dr. B. Dabaja (Houston, TX, USA) will address and discuss clinical cases of **“RADIOTHERAPY IN LYMPHOMA”**.

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Join as Member! (Free)

Go to ilrog.com (membership tab) and register

Or write to shuttleworth@ilrog.com

Apply for ILROG Council Membership?

Special Interest in more involvement – Check the site or write to us

Thank you

Farewell

Safe trip home

Hope to see you at other lymphoma events in the future