Associazione Italiana Radioterapia Oncologica

XXIV Congresso Nazionale AIRO 2014
Padova, 8-11 Novembre

Indicazioni, dosi e volumi clinici in radioterapia onco-ematologica: stato dell'arte.

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DICHIARAZIONE

Relatore ANDREA RICCARDO FILIPPI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Altro

Role of radiation, volumes and techniques for:

- Early Stage Hodgkin's Lymphoma
- Early Stage Diffuse Large B-Cell Lymphomas
- Early Stage Follicular Lymphomas

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Early Stage HL

- Is Chemotherapy alone an option?
- Radiation Volumes and Technique
- Could FDG-PET result after chemotherapy guide the treatment strategy?

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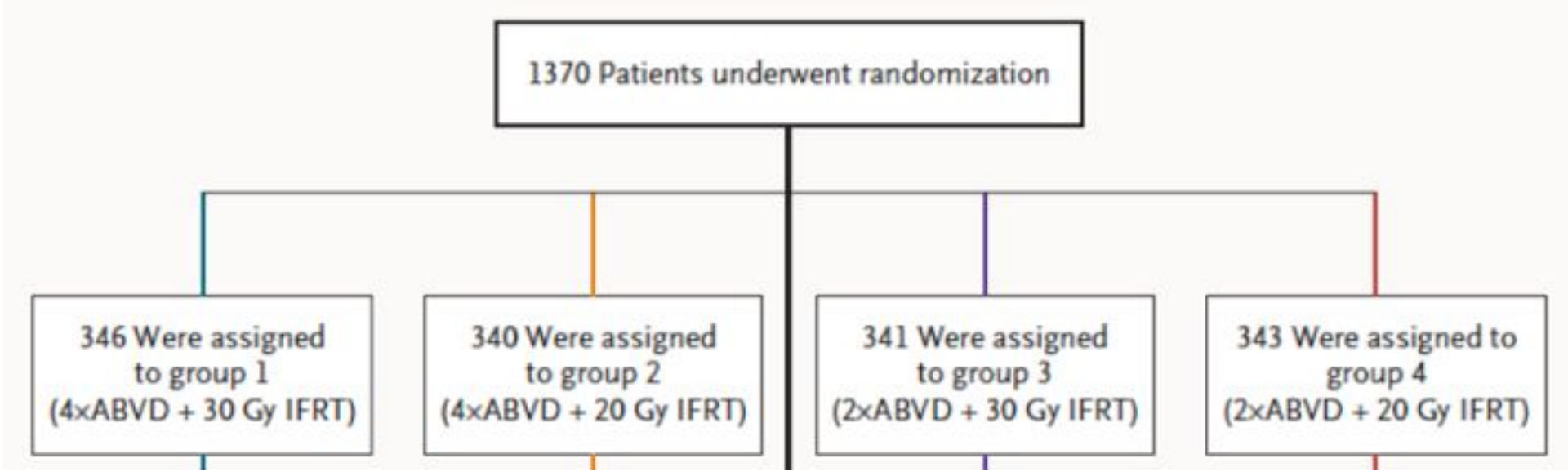
Early stage Hodgkin lymphoma: risk factors

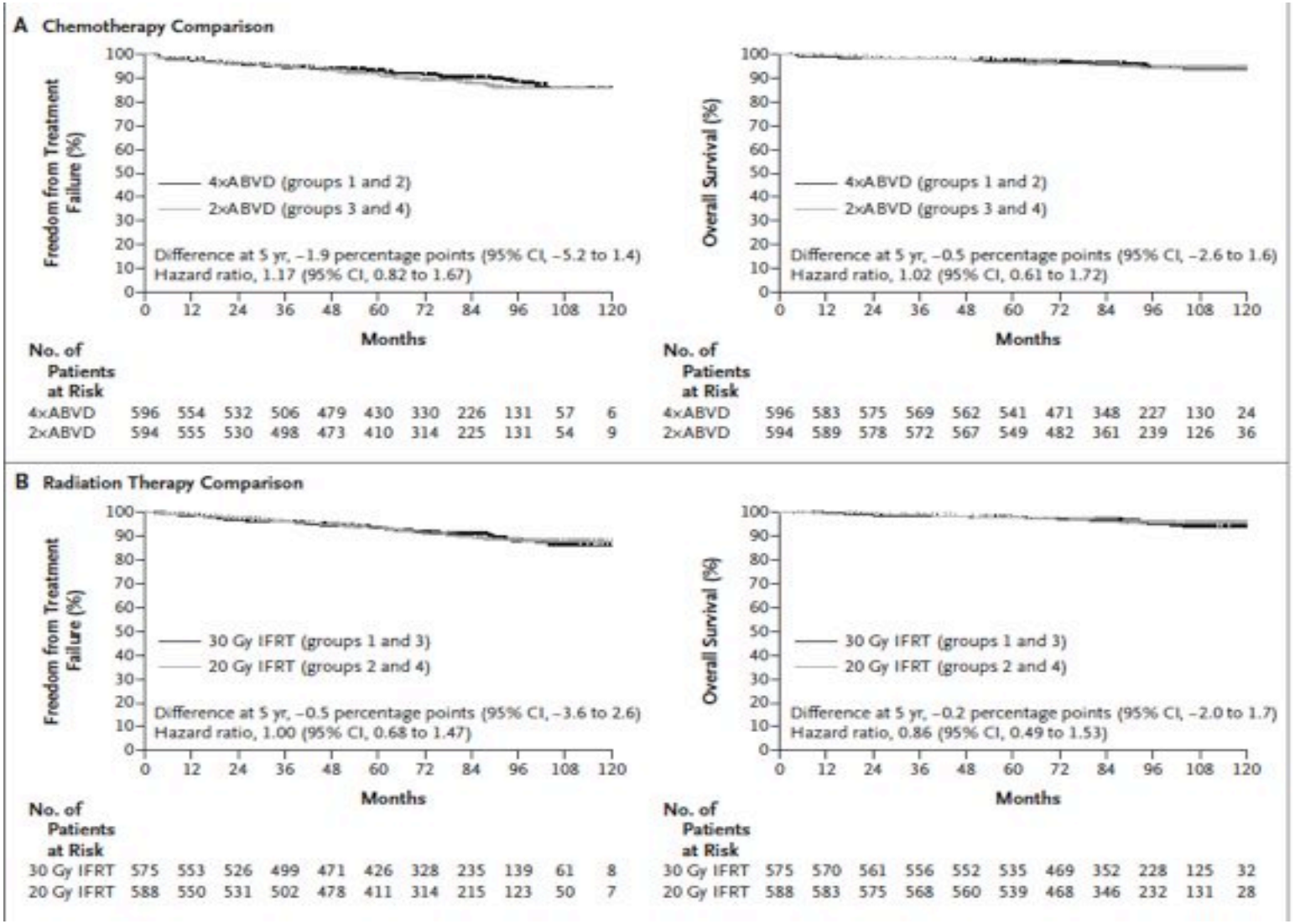
	GHSG	EORTC	NCIC and ECOG	Stanford
Risk factors	a) Large mediastinal mass b) Extranodal disease c) ESR ≥ 50 without B-symptoms or ≥30 with B-symptoms d) ≥ 3 nodal areas	a) Large mediastinal mass b) Age ≥50 years c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms d) ≥ 4 nodal areas	a) Histology other than LP/NS b) Age ≥ 40 years c) ESR ≥ 50 d) ≥ 4 nodal areas	a) B-symptoms b) Large mediastinal mass
Favourable	CS I-II without risk factors	CS I-II without risk factors	CS I-II without risk factors	CS I-II without risk factors
Unfavourable	CS I or CS IIA with ≥ 1 risk factors CS IIB with c) or d) but without a) and b)	CS I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors

HD10 Trial Design

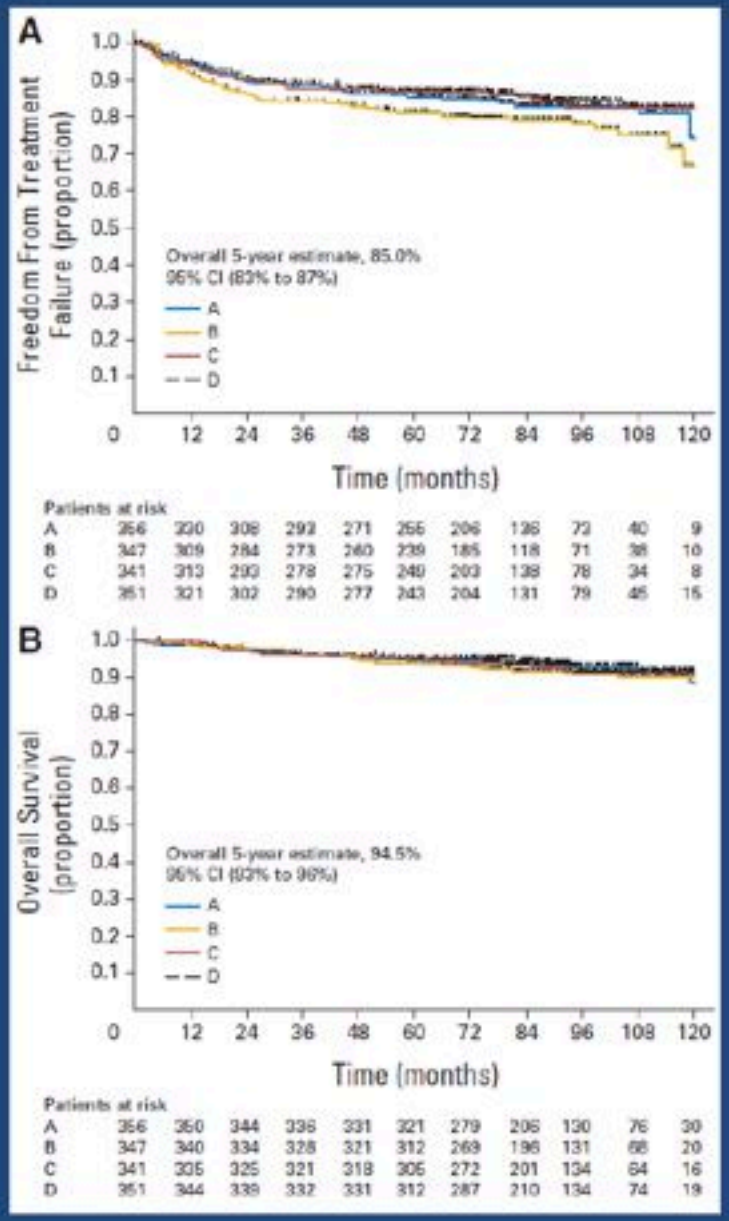


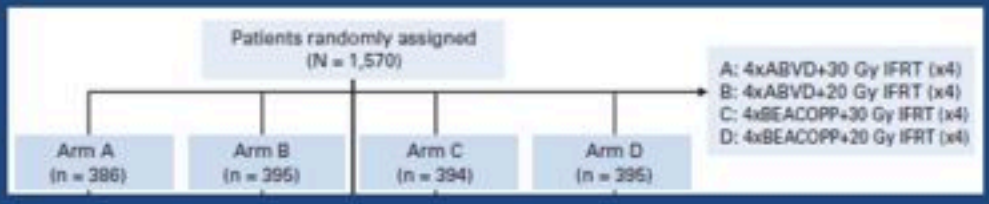
Engert A et al, N Engl J Med 2010

ABVD x 2 plus IFRT 20 Gy is the golden standard for favorable HL



Early stage unfavorable, GHSG HD 11, final results





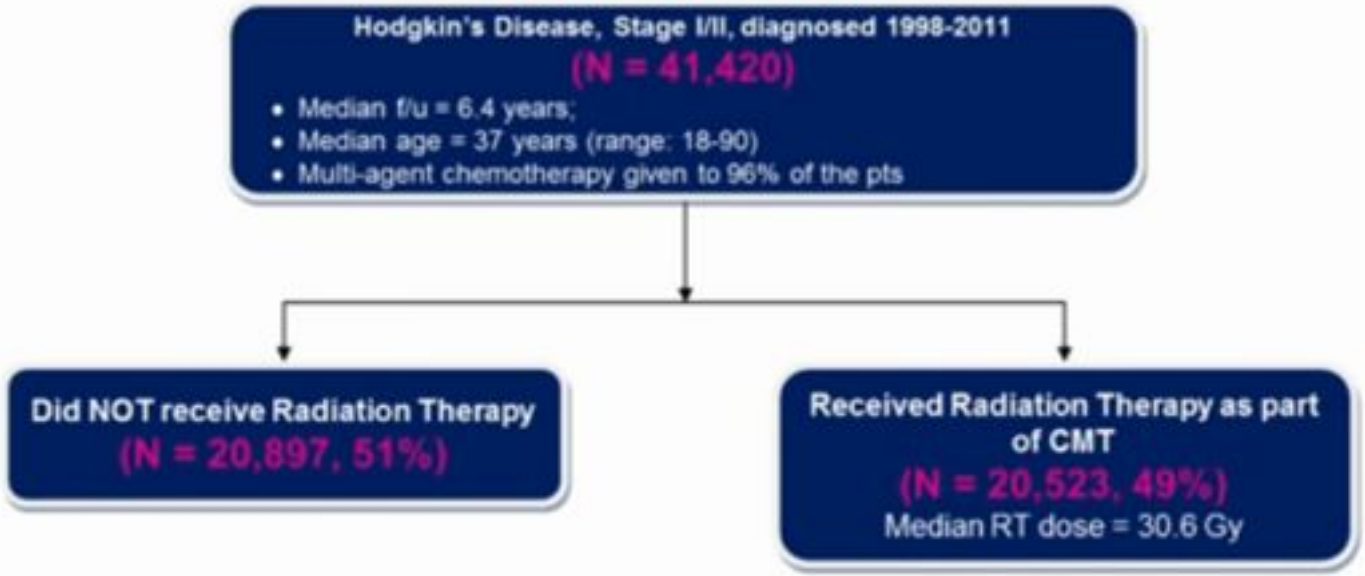
Conclusion:

- 4 cycles of ABVD + IFRT 30 Gy is superior to 4 cycles of ABVD + IFRT 20 Gy
- 4 cycles of ABVD + IFRT 30 Gy is standard treatment

With 4 cycles of BEACOPP, IFRT 30 Gy and IFRT 20 Gy are equivalent

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

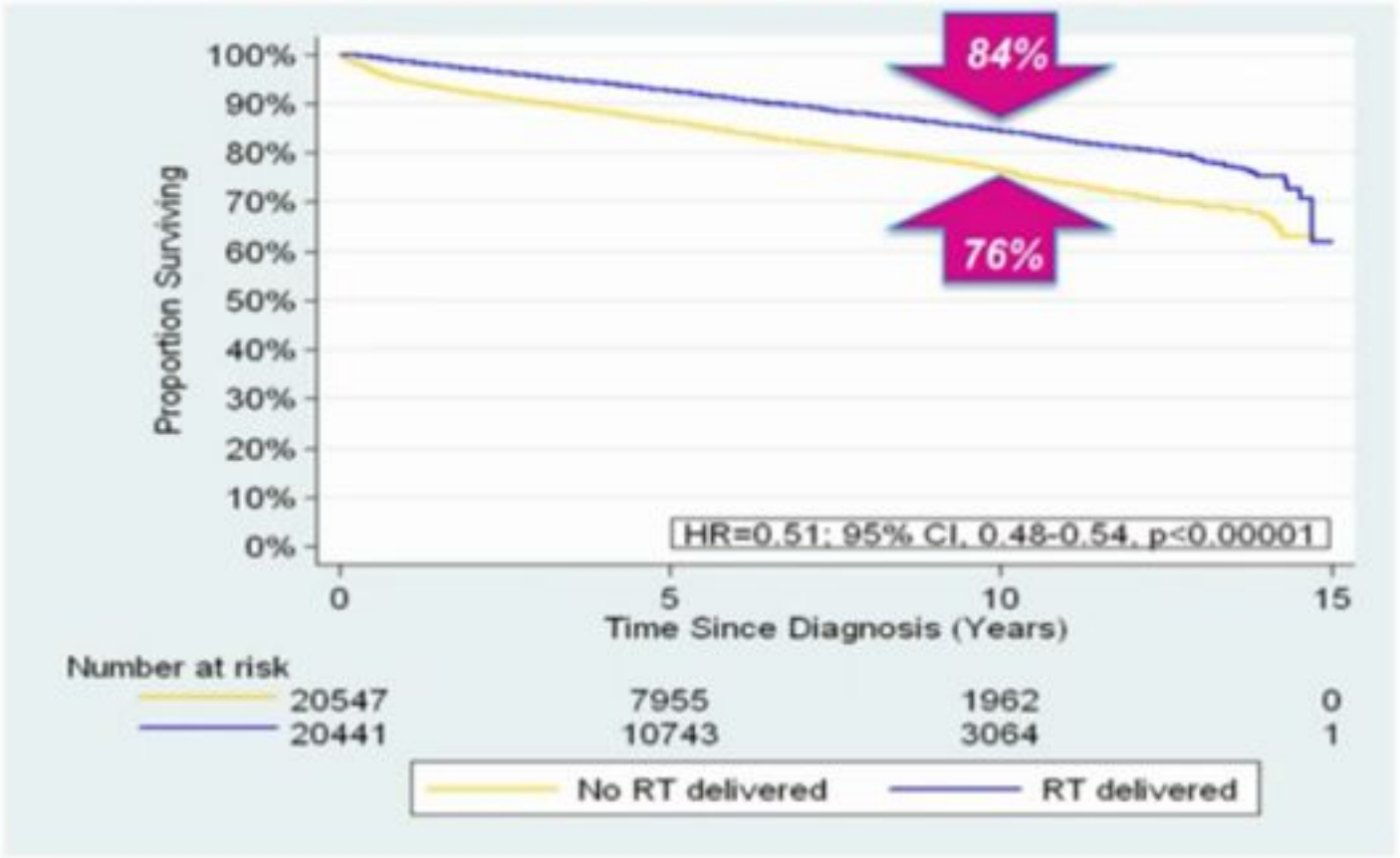
Methods



- Evaluated clinical features & survival outcomes
- The association between RT use, co-variables, and outcome was assessed in a multivariate Cox proportional hazards model.
- Survival was estimated using the Kaplan-Meier method.

Pahrik et al, Oral Presentation, ASTRO 2014

Overall Survival by RT use



Pahrik et al, Oral Presentation, ASTRO 2014

Conclusions

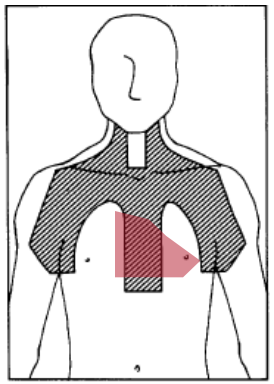
- Largest contemporary dataset of patients with early-stage HD (n=41,420)
- The use of RT is associated with improved 10-yr OS (84% vs. 76%, HR=0.51, p<0.00001)
- Utilization of RT has decreased by 15% from 1998 to 2011 (56→41%; *not part of initial treatment strategy*)
- As a surrogate for treatment failure, the omission of RT was associated with higher rates of salvage transplant.

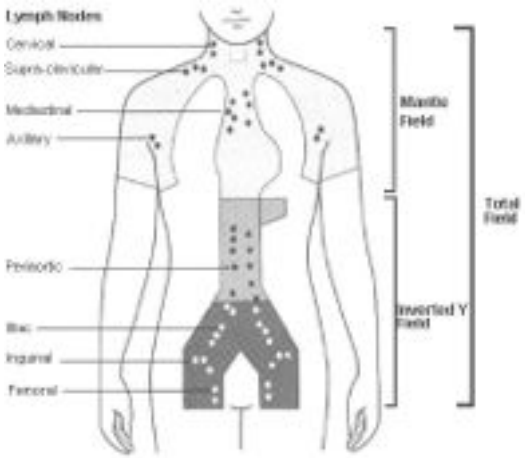
Pahrik et al, Oral Presentation, ASTRO 2014

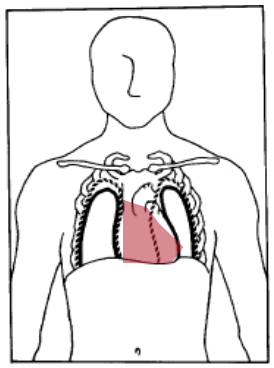
Chemotherapy alone for early stage HL

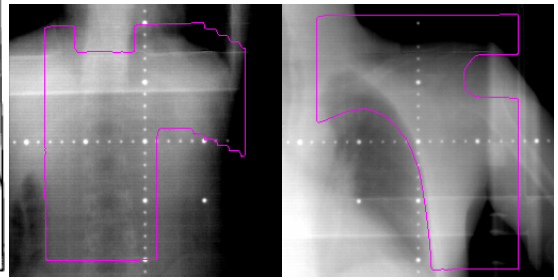
- No randomized data comparing CT alone with modern CMT
- Could the benefit for CMT be offset by long-term mortality even with modern RT?

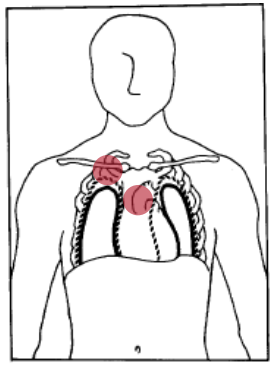
Timeline of major changes in RT in early stage HL

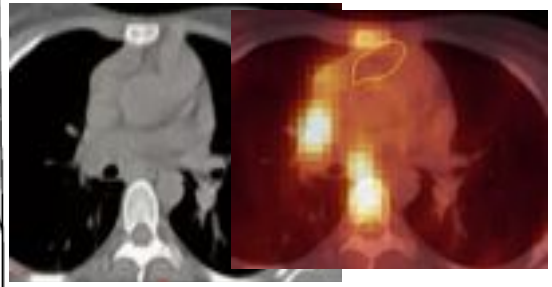












1960

Extended fields

DFT≈40 Gy

MOPP

Involved fields

DFT≈30 Gy

ABVD

INRT/ISRT

DFT≈20 Gy

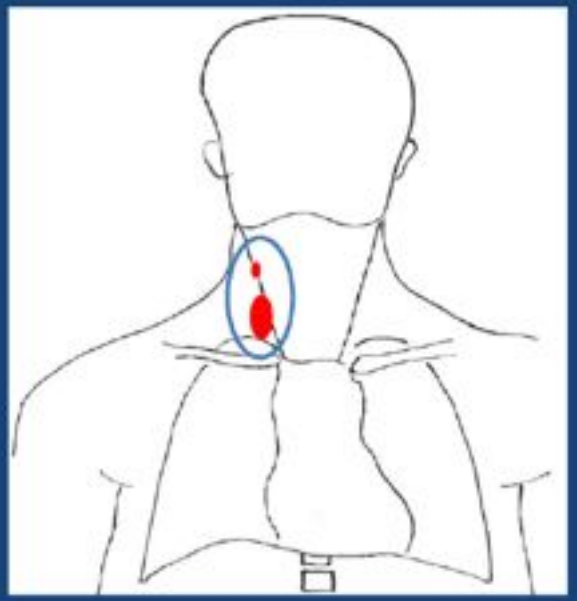
now

The concepts of INRT and ISRT

EORTC-GELA Lymphoma Group Guidelines

"Involved node radiotherapy"

INRT



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

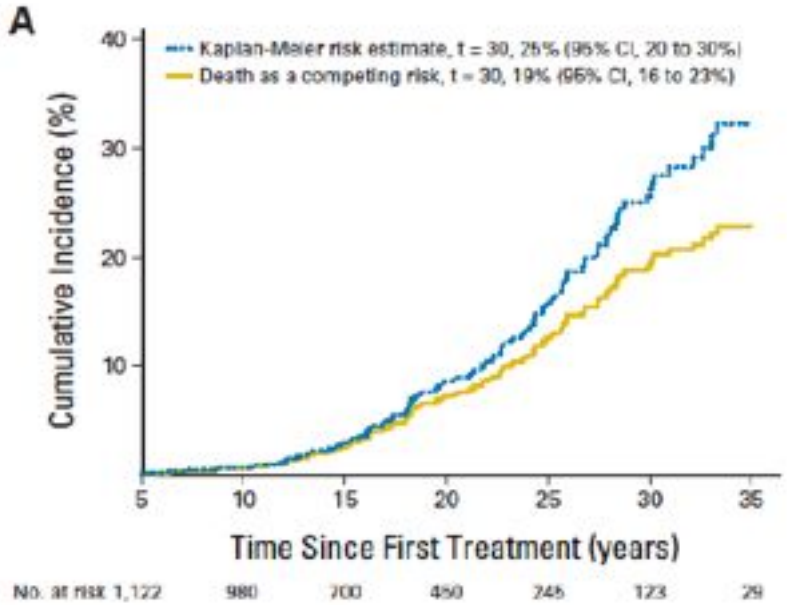
VOLUME 27 · NUMBER 26 · SEPTEMBER 10 2009

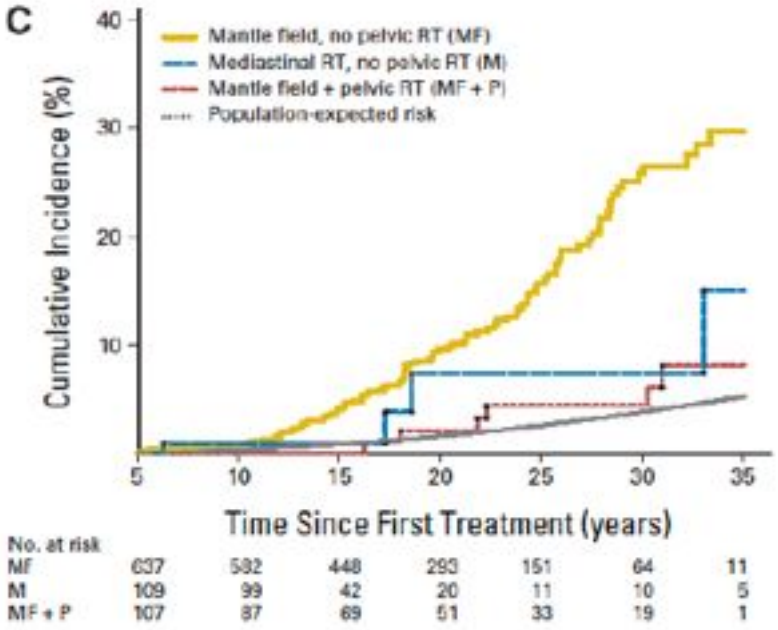
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast Cancer Risk in Female Survivors of Hodgkin's Lymphoma: Lower Risk After Smaller Radiation Volumes

Marie L. De Bruin, Judith Sparidans, Mars B. van't Veer, Evert M. Noordijk, Marieke W.J. Louwman, Josée M. Zijlstra, Hendrik van den Berg, Nicola S. Russell, Annegien Broeks, Margreet H.A. Baaijens, Berthe M.P. Aleman, and Flora E. van Leeuwen

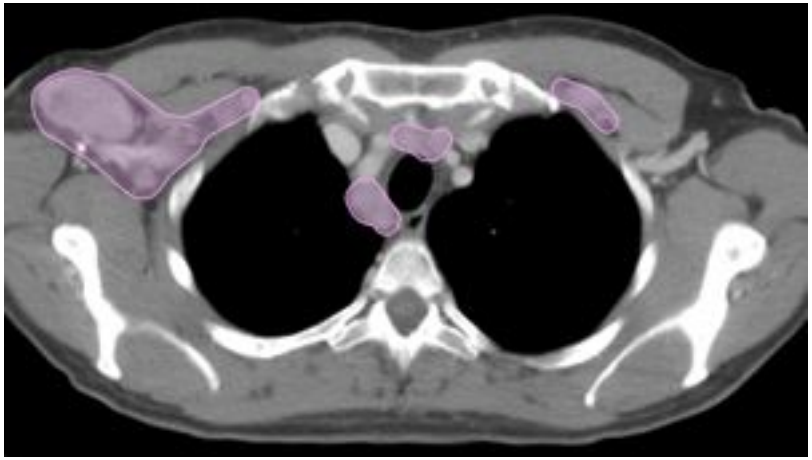


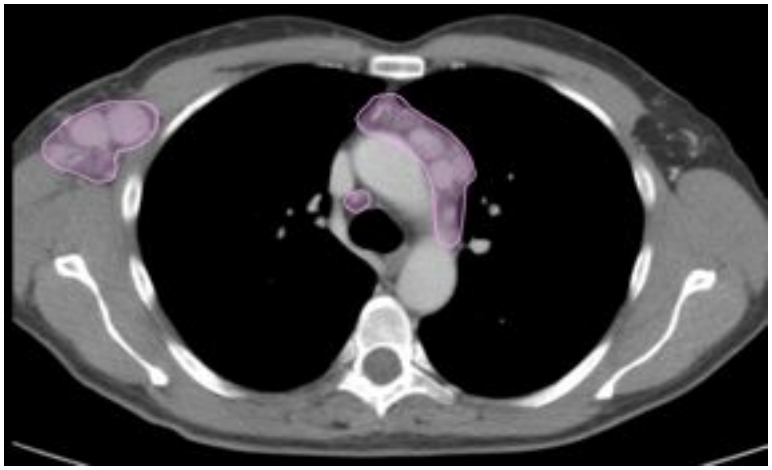


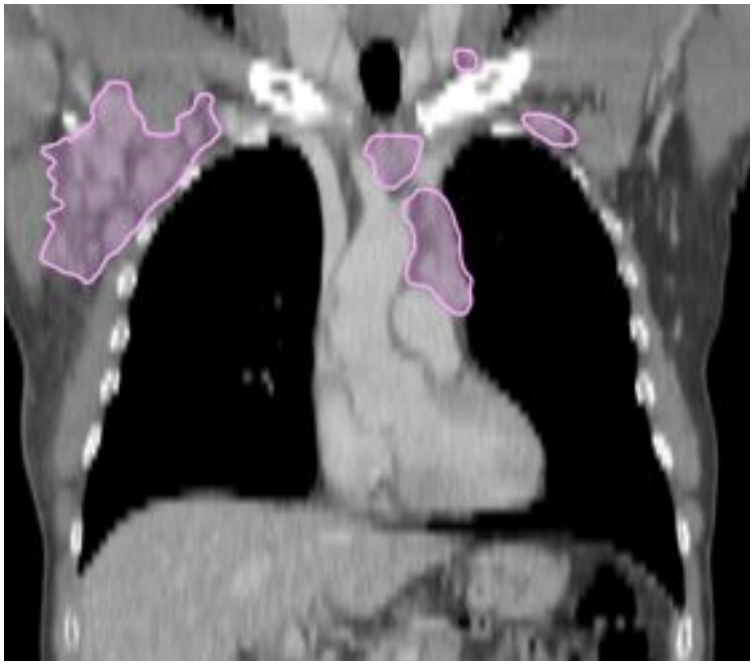
INRT Guidelines

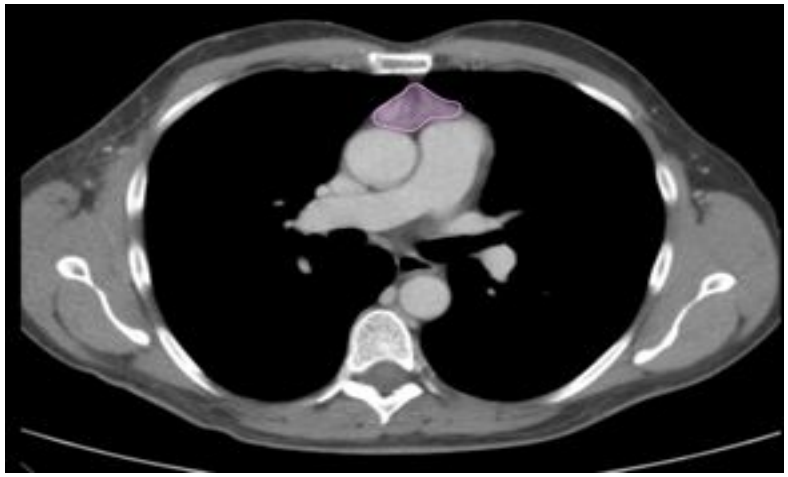
- FDG-PET scans have to be meticulously analysed to detect lymph nodes that were overlooked on CT imaging.
- Any morphological and/or functional asymmetry has to be taken into account
- A decrease in size or the disappearance of initially visible lymph nodes on the pre-CT scan as compared to the POST-CT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

GTV on pre-chemotherapy CT

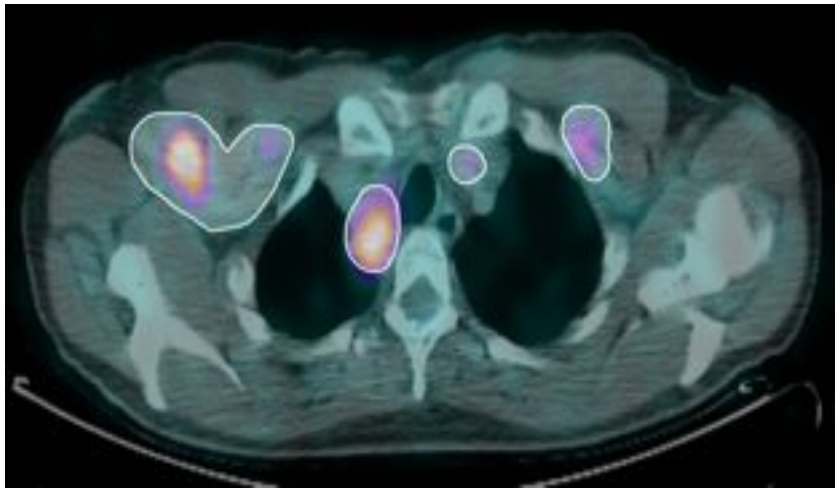


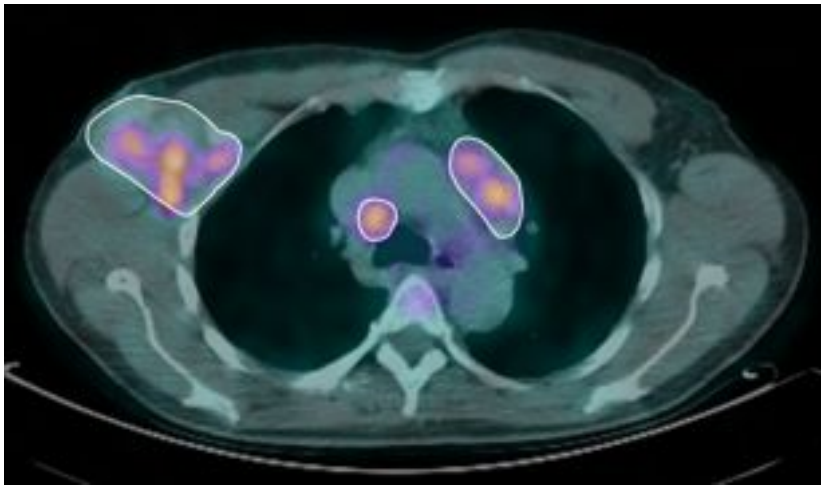


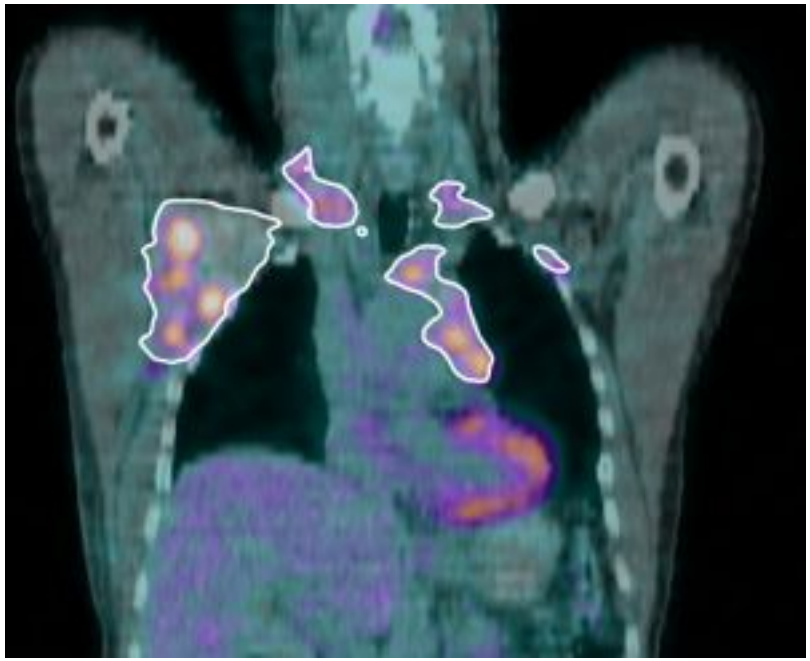


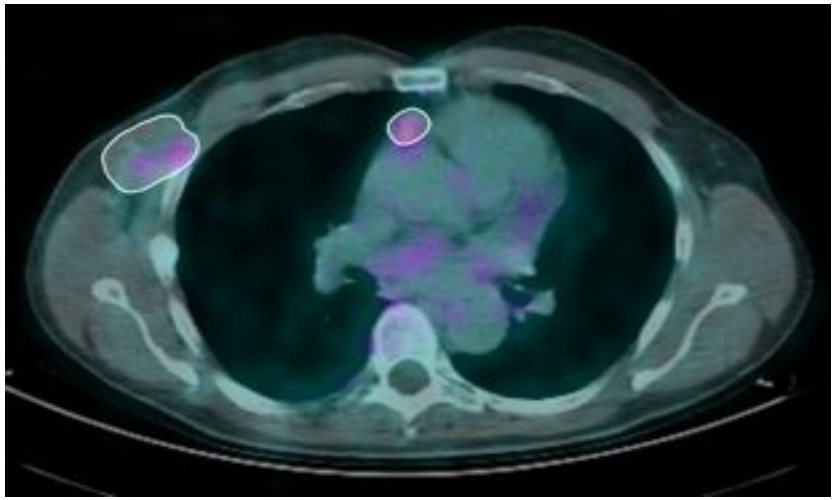


GTV on pre-chemotherapy PET









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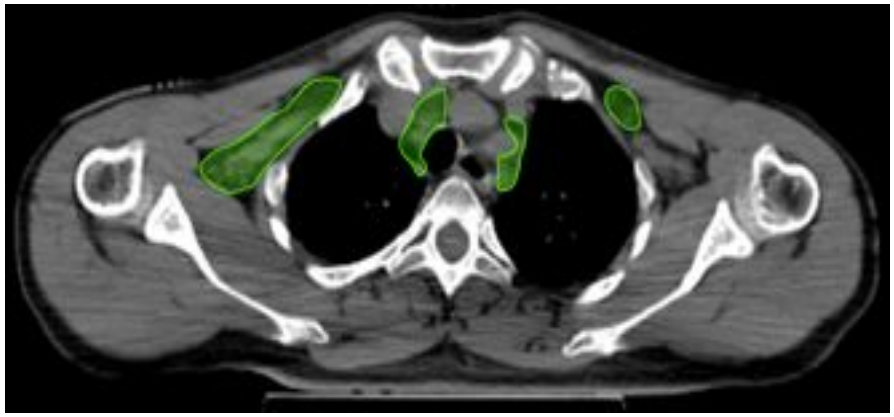
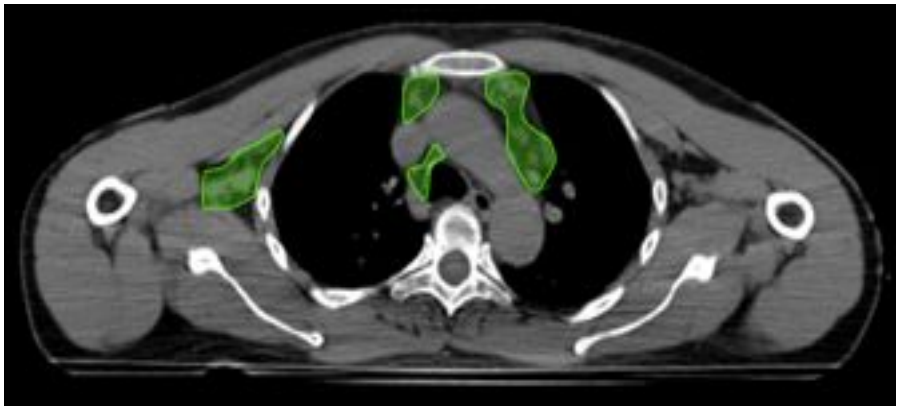
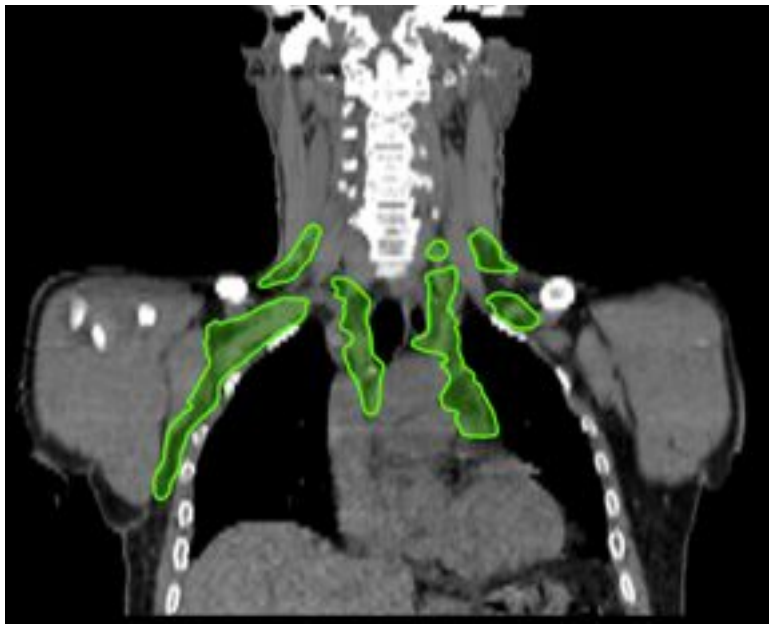
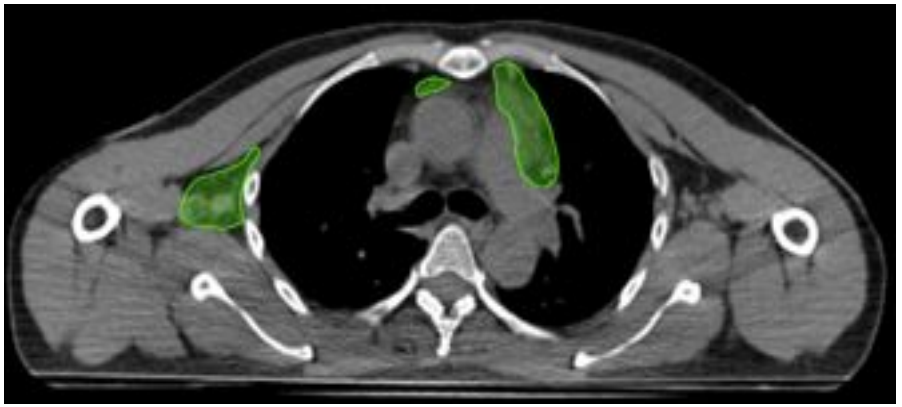
Fusion between pre-chemotherapy PET/CT and planning CT → GTVCT and GTVPET import → Modification according to response → **INRT**









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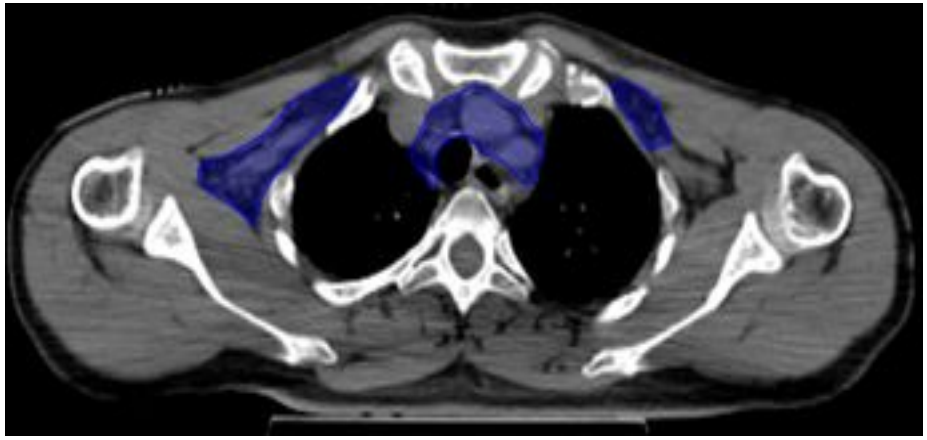
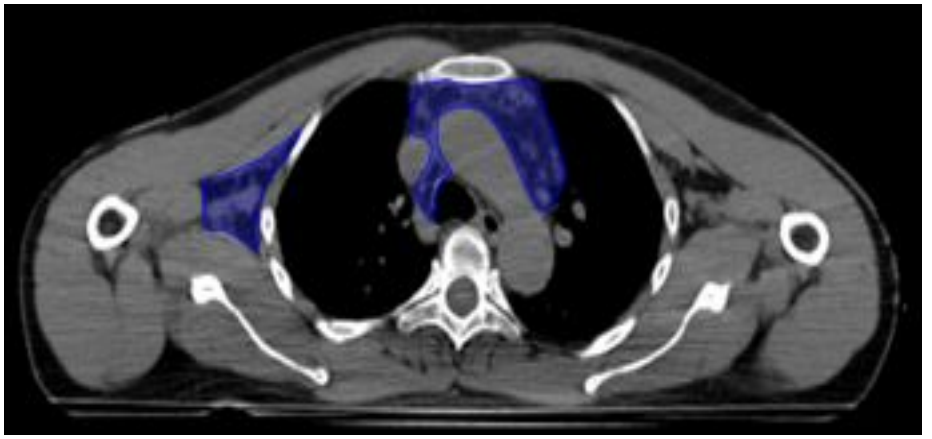
“Involved-Site” Radiotherapy

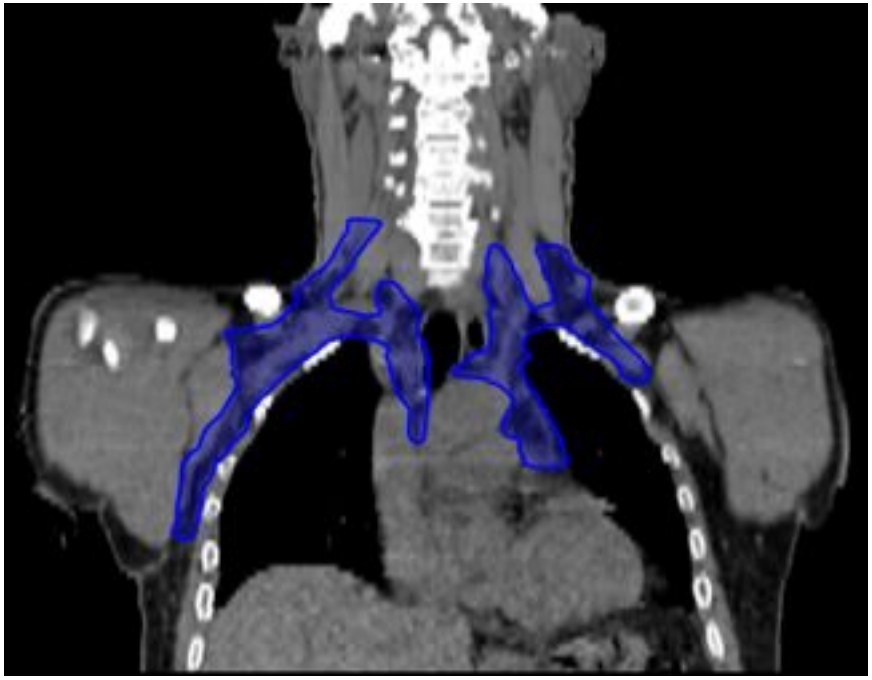
- The concept of ISRT was developed on the basis of the INRT concept
- The irradiated volume is significantly smaller than with IFRT
- If prechemotherapy imaging is available, but image fusion with the postchemotherapy planning CT scan is not possible → **ISRT**
- If no prechemotherapy imaging is available → **IFRT**

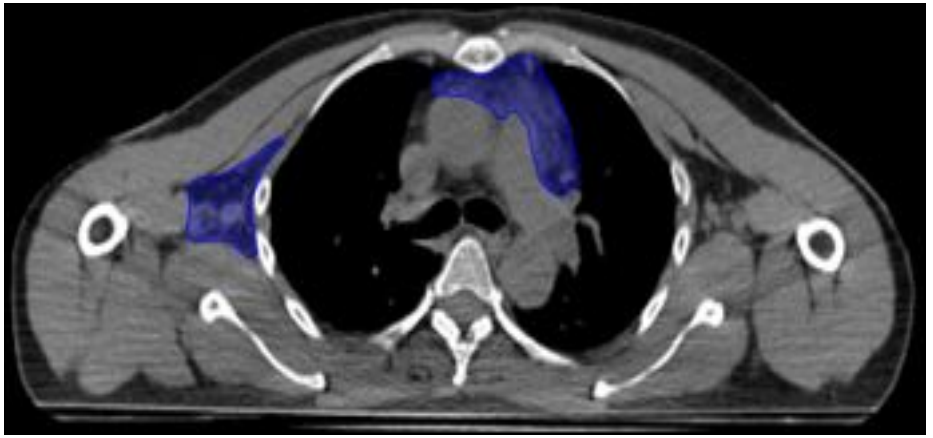
Specht et al, IJROBP 2013

“Involved-Site” Radiotherapy (ISRT)









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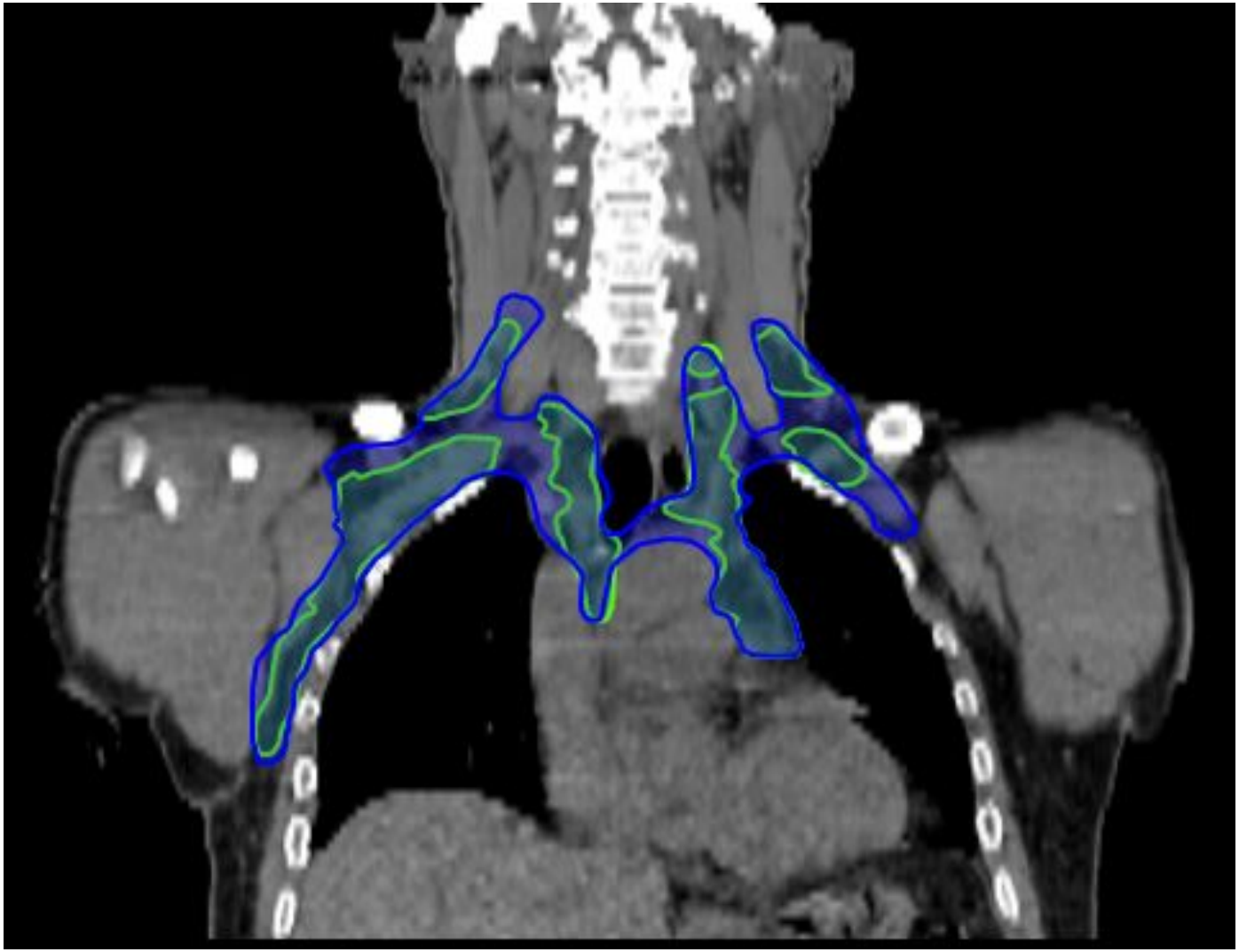
INRT *vs* ISRT



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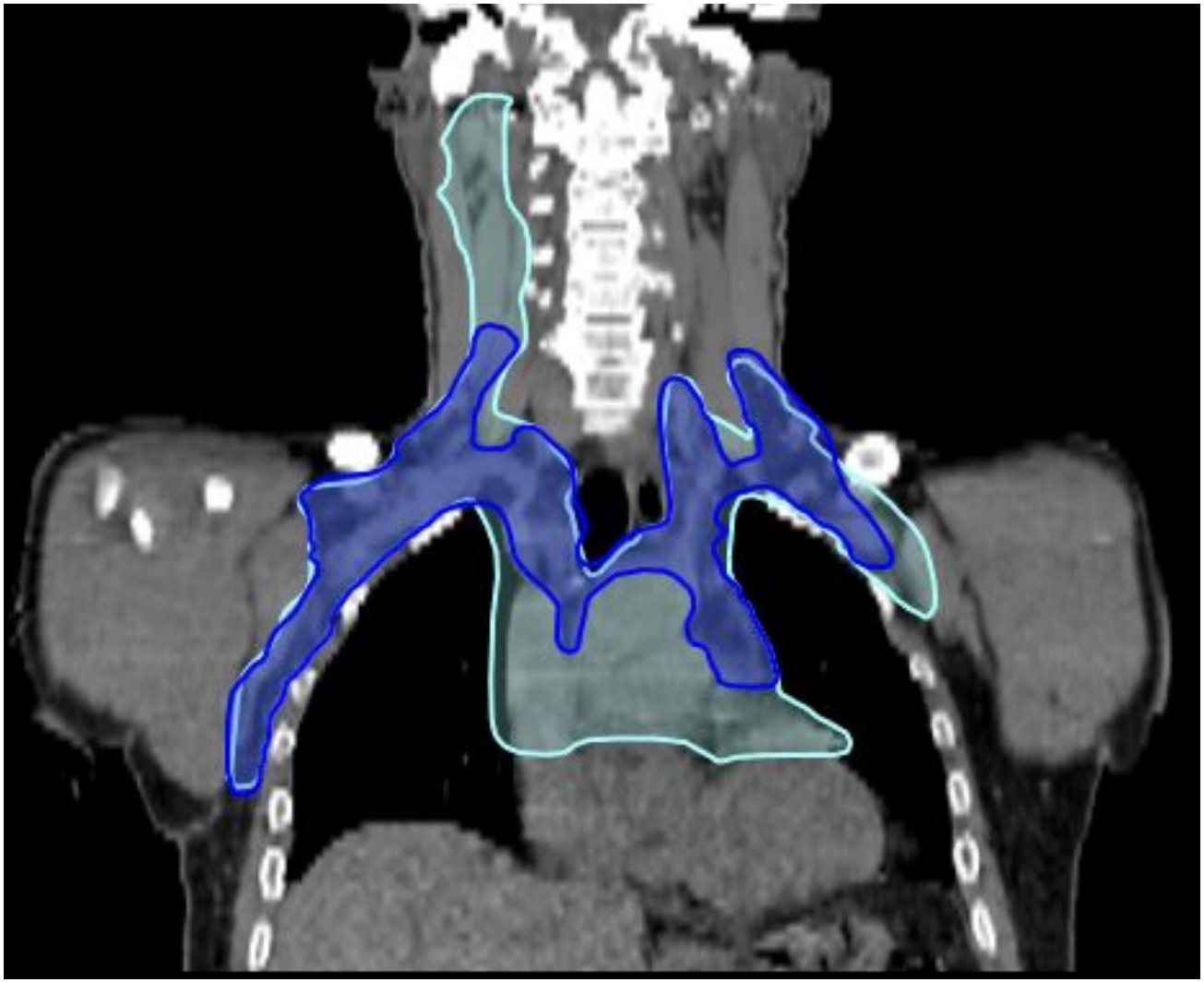
ISRT is substantially smaller than IFRT!



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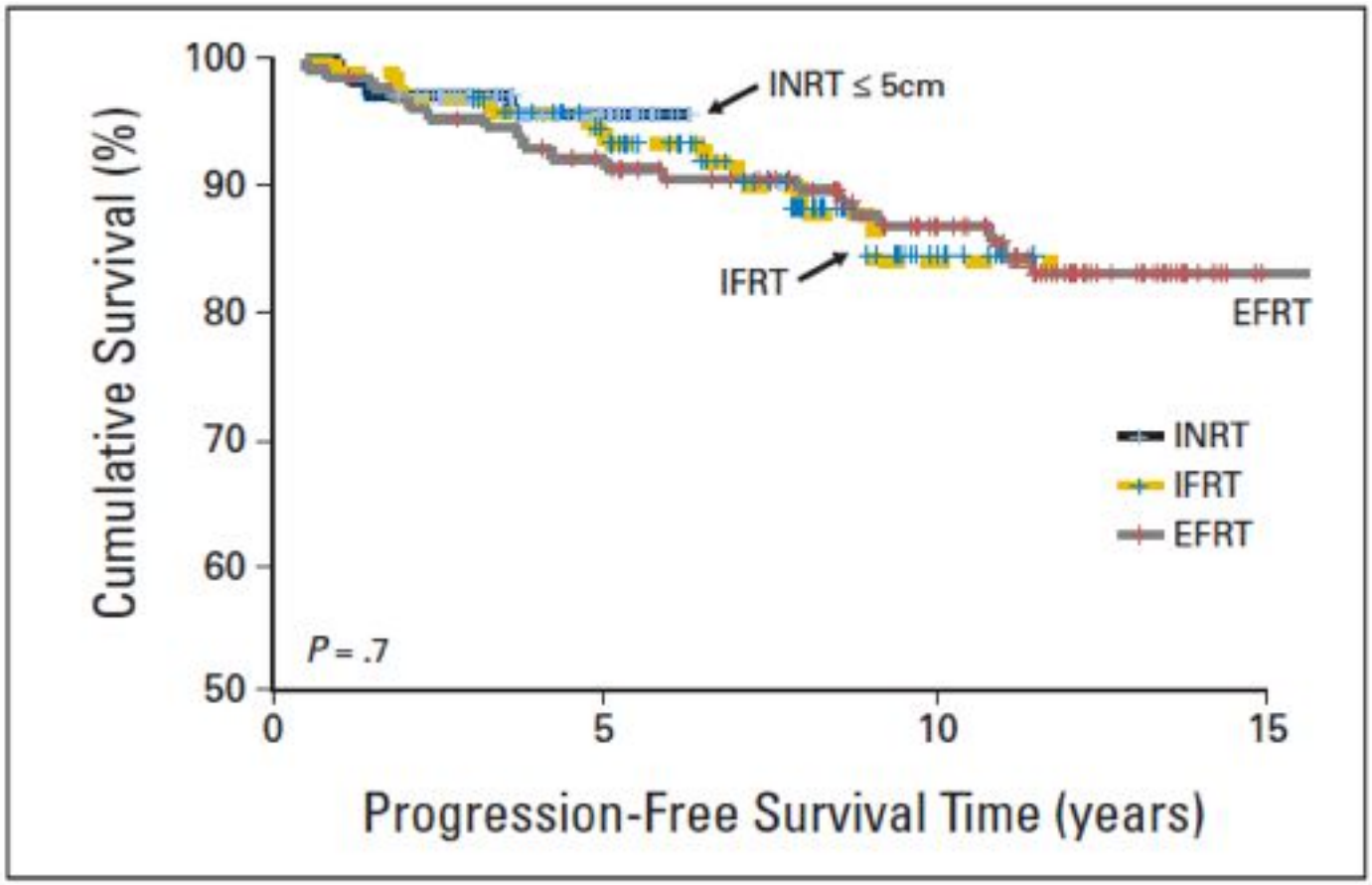
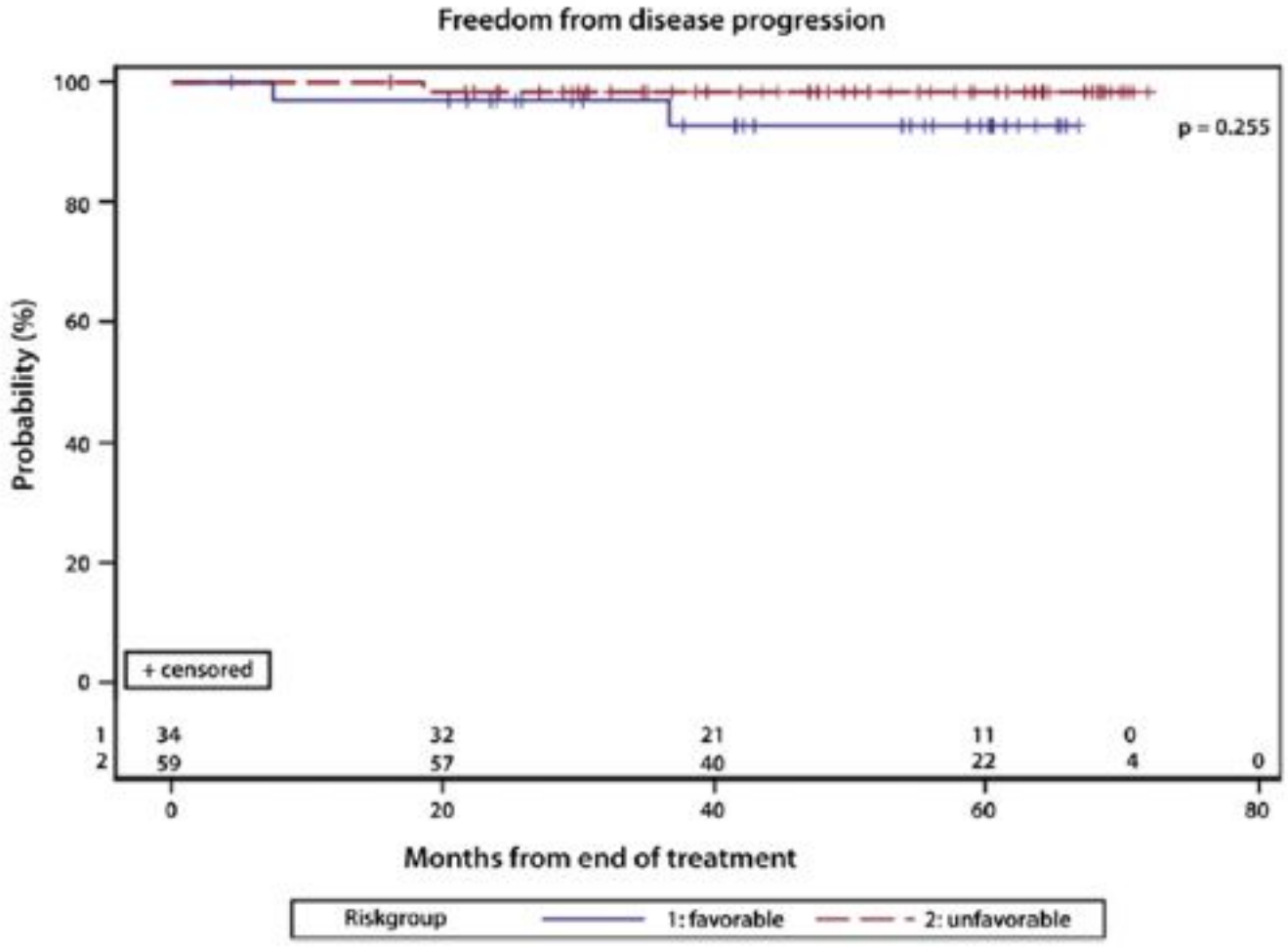
Do we have clinical data on safety and efficacy of INRT/ISRT?

INRT vs. IFRT vs. EFRT



Campbell et al, JCO 2008

Combined Modality Therapy with INRT



Maraldo et al, IJROBP 2012

Clinical data on ISRT with either 3D or IMRT

Filippi, Ciammella et al, IJROBP 2014

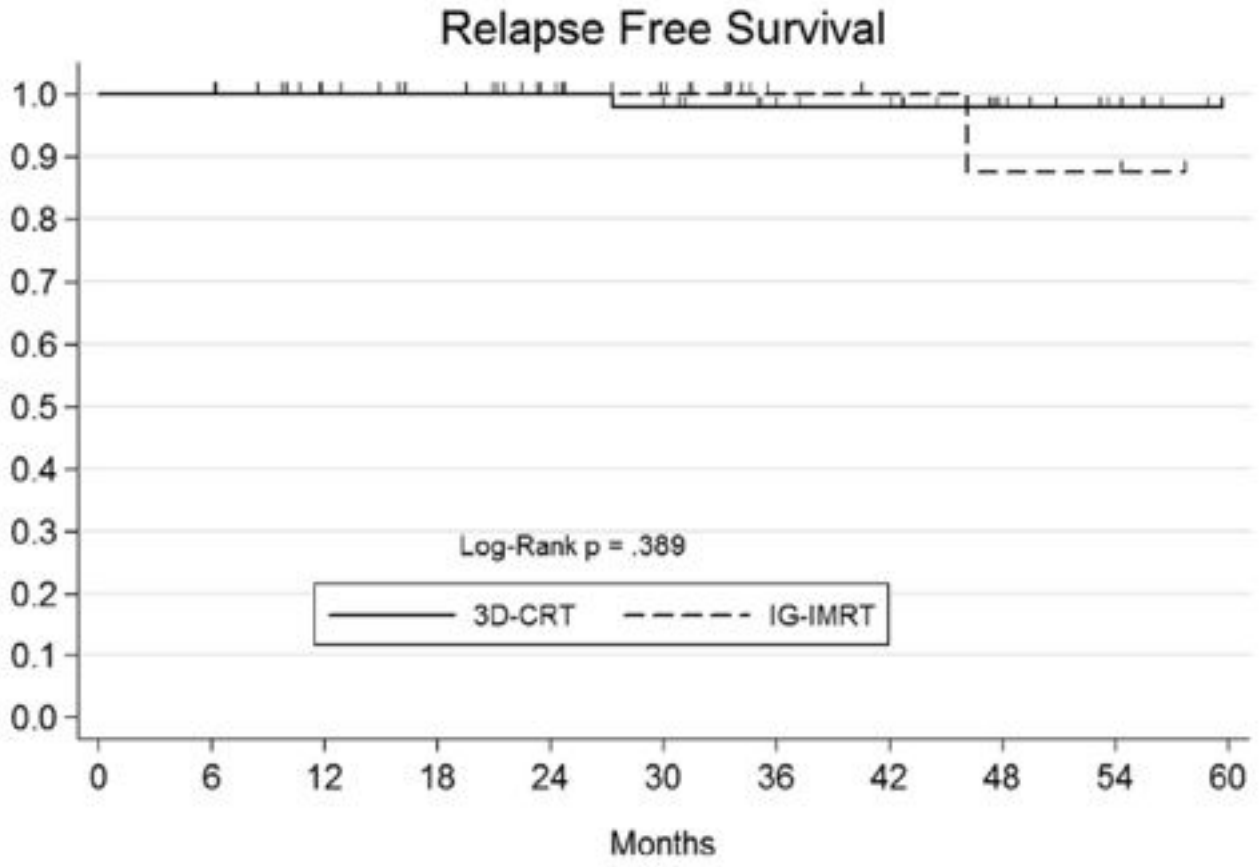
Table 2 Patient characteristics

Characteristic	All	3D-CRT*	IG-IMRT*
No. of patients	90	49 (54.4%)	41 (45.6%)
Follow-up (mo)			
Median	42	55	24
Age (y)			
Range	15-84	16-84	15-65
Mean	31	31	32
Sex			
Male	44 (48.9%)	21 (42.9%)	23 (56.1%)
Female	46 (51.1%)	28 (57.1%)	18 (43.9%)
Ann Arbor stage			
IIA	90 (100%)	49 (100%)	41 (100%)
Bulky	15 (16.7%)	7 (14.3%)	8 (19.5%)
No. of involved sites			
<4	83 (92.2%)	45 (91.8%)	38 (92.7%)
≥4	7 (7.8%)	4 (8.2 %)	3 (7.3%)
Risk factors			
Favorable	67 (74.5%)	38 (77.6%)	29 (70.7%)
Unfavorable	23 (25.5%)	11 (22.4%)	12 (29.3%)
Involved site			
Mediastinum alone	5 (5.6%)	1 (2%)	4 (9.7%)
Mediastinum and cervical area	74 (82.2%)	41 (83.7%)	33 (80.5%)
Mediastinum and cervical and axillary areas	11 (12.2%)	7 (14.3%)	4 (9.8%)

Abbreviations: 3D-CRT = 3-dimensional conformal RT; EORTC = European Organization for Research and Treatment of Cancer; IG-IMRT = image-guided intensity modulated RT.

* Values are numbers (percentages), except where noted.

ISRT with IMRT vs. ISRT with 3D-CRT



Filippi, Ciammella et al, IJROBP 2014

Early Stage HL

- Is Chemotherapy alone an option?
- May PET findings after chemotherapy guide treatment strategy?
- Future?

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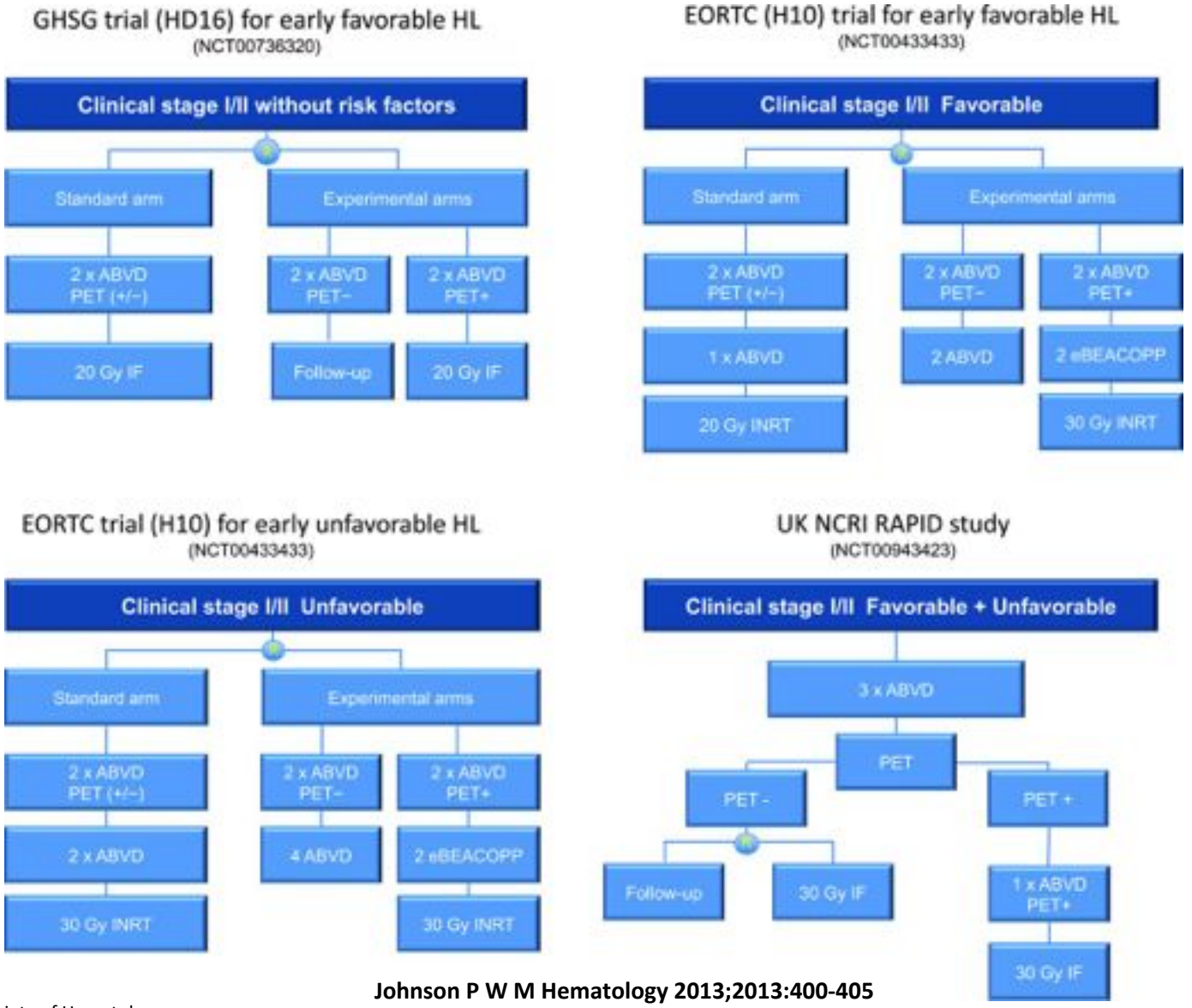
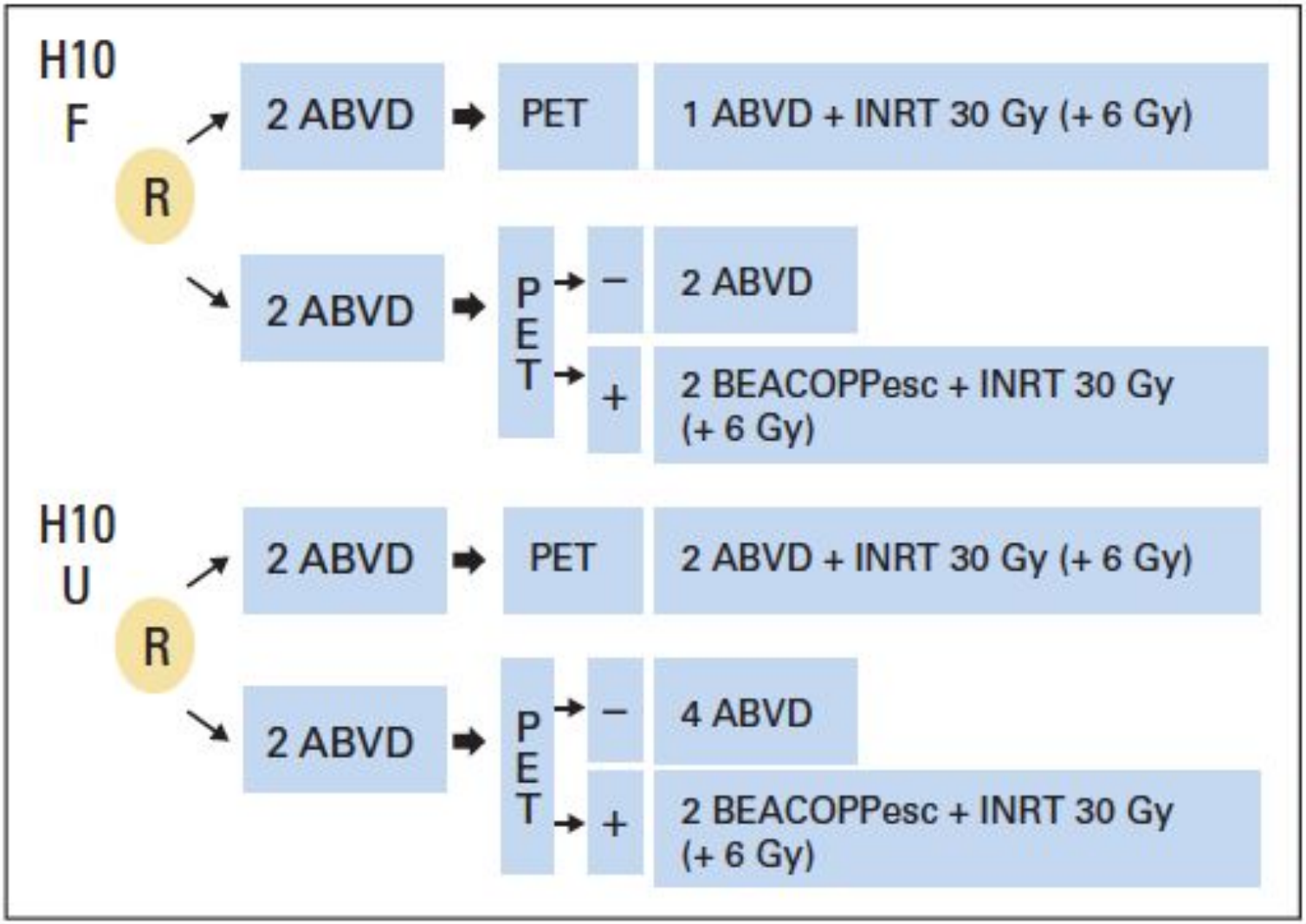
Trials testing the capacity of FDG-PET scanning to guide therapy for early-stage Hodgkin lymphoma.



Johnson P W M Hematology 2013;2013:400-405



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

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

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

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

Favorable PET-negative: 85.8%
Unfavorable PET-negative: 74.8%

Raemakers et al, JCO 2013

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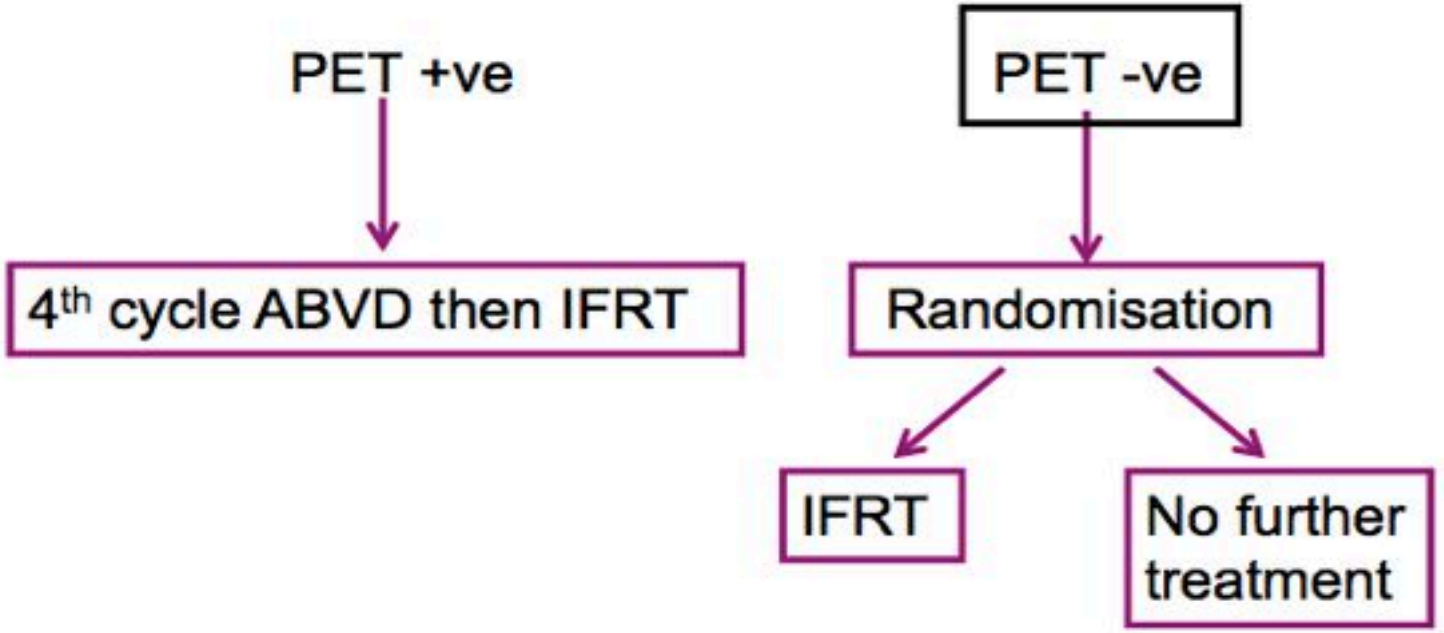
NCRI RAPID – trial design

Early stage IA or IIA, no bulky, no B symptoms

Initial treatment: **ABVD x 3**

Re-assessment: if no response, patient goes off study

if remission, PET scan performed



NCRI RAPID – results

2003 – 2010 → 602 patients (321 male, 281 female)

571 patients had a PET scan:

- Negative (Deauville's score 1 or 2): **426 patients (74.6%)** → 420 patients randomised RT *vs* observation

- Positive (Deauville's score 3 or 4 or 5): **145 patients (25.4%)**

Median follow-up time: 48 months

3-year PFS:

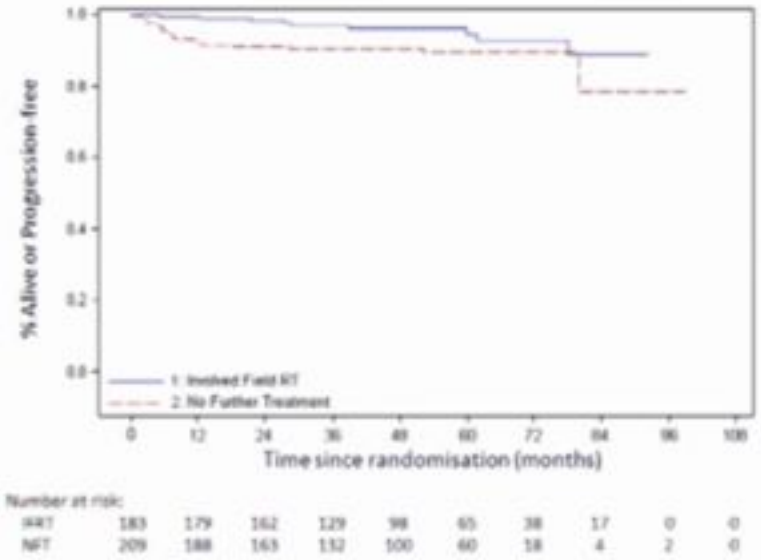
- IFRT arm **94.5%**

- No Further Treatment arm **90.8%**

- non randomised PET + patients: 86.2%

UK NCRI RAPID Trial

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



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

NCRI RAPID and EORTC-GELA-FIL H10

2 trials with similar results but different interpretations

EORTC H10

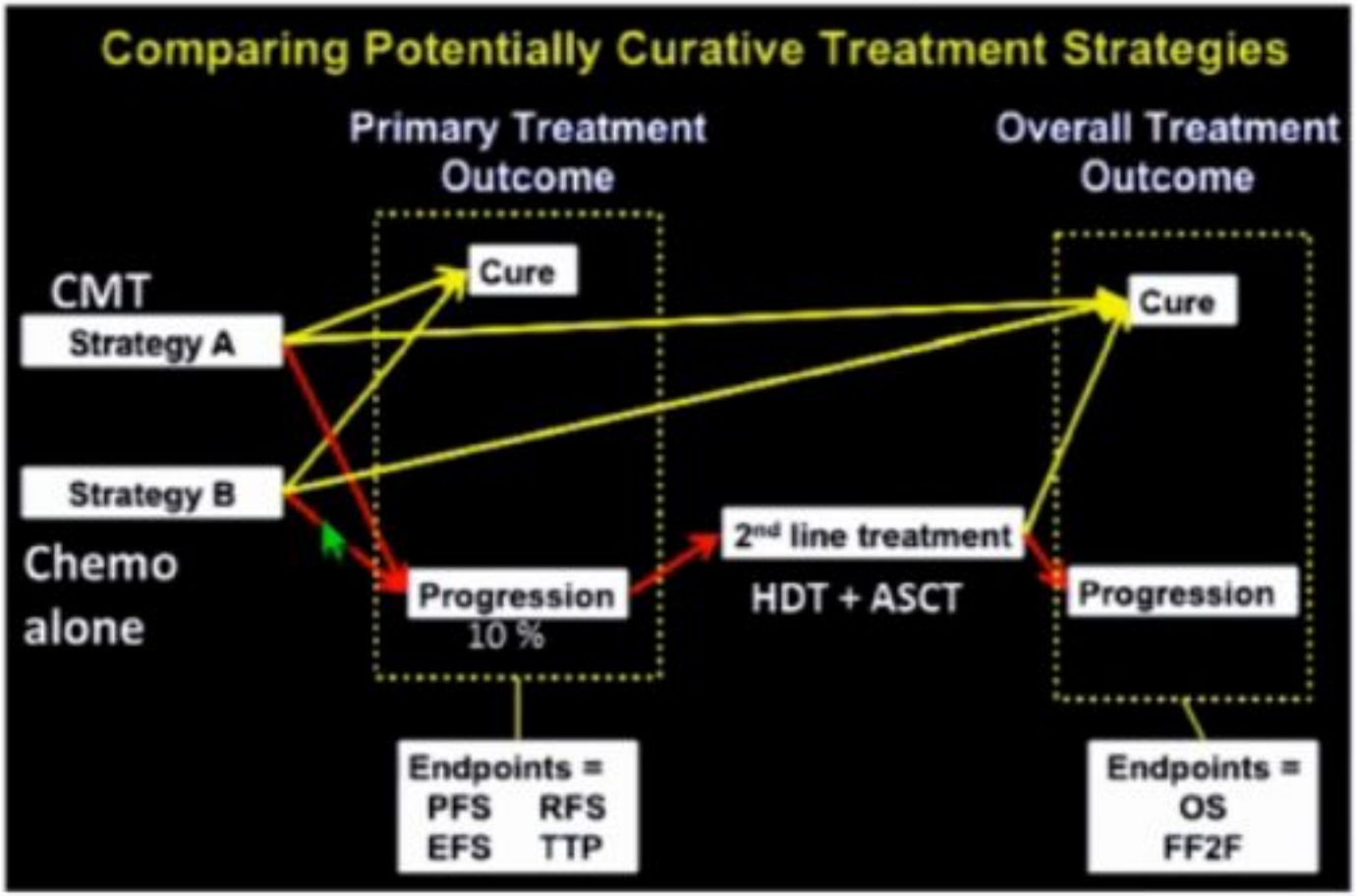
A difference in PFS of 5% was considered unacceptable (critics to the trial design?)

RAPID trial

A difference in PFS of 7% was considered acceptable

Same OS and most patients receiving standard salvage therapy (no ASCT): but more events are needed to fully confirm these data

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



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

Age-at-treatment has a strong impact on breast cancer risk in female HL survivors

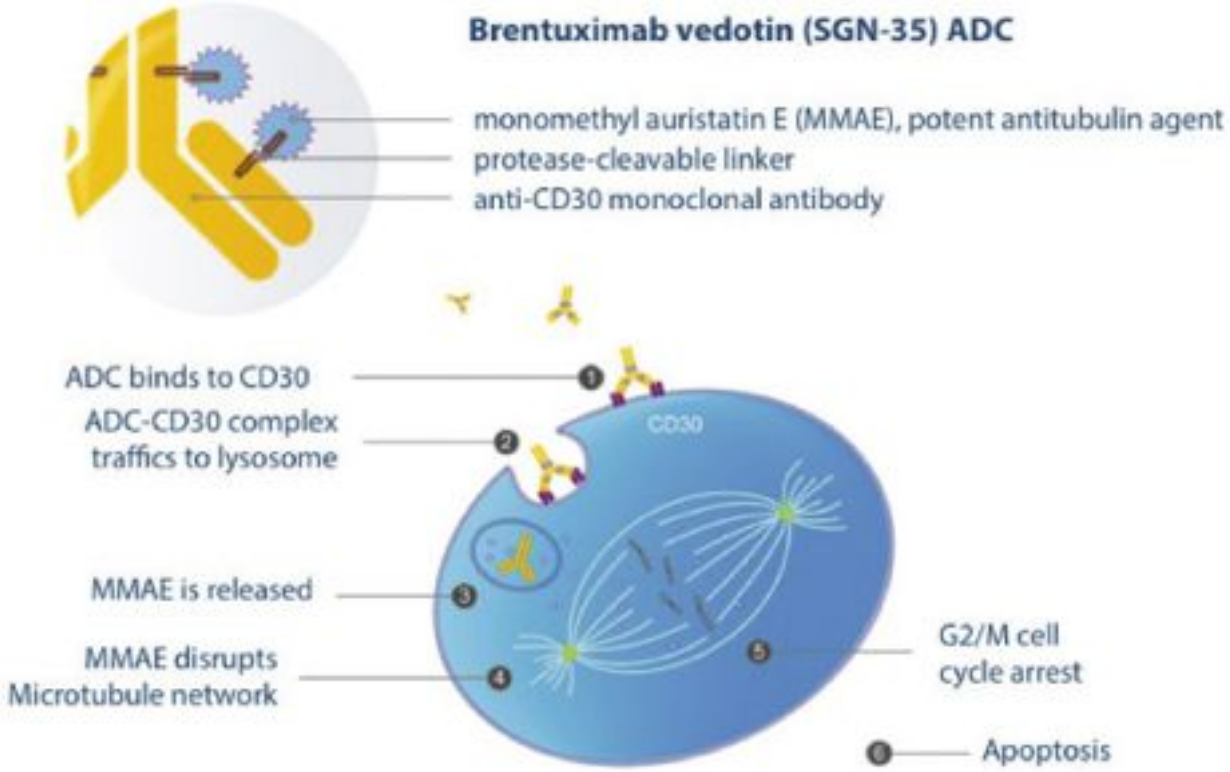
Table 3. Risk of Breast Cancer by Age and Type of Treatment

Age at First Supradiaphragmatic RT (years)	Supradiaphragmatic RT Only						Supradiaphragmatic RT Plus Alkylating CT and/or Pelvic RT					
	Observed	Expected	SIR	95% CI*	AER	95% CI*	Observed	Expected	SIR	95% CI*	AER	95% CI*
0-9	0	0.1	0.0	0.0 to 63.4	−1.3	−1.3 to 80.0	1	0.1	16.8	0.4 to 93.7	26.4	−1.0 to 155.0
10-14	11	0.5	21.2	10.6 to 38.0	77.6	36.8 to 141.9	12	0.5	24.7	12.8 to 43.2	59.5	29.5 to 105.7
15-19	45	3.1	14.5	10.6 to 19.4	60.5	42.9 to 82.5	56	3.7	15.0	11.3 to 19.4	56.8	41.9 to 74.9
20-24	48	6.8	7.0	5.2 to 9.3	43.2	30.0 to 59.6	37	8.9	4.2	2.9 to 5.8	20.8	12.7 to 31.1
25-29	30	7.8	3.9	2.6 to 5.5	29.5	16.6 to 46.6	33	10.9	3.0	2.1 to 4.3	19.2	10.3 to 30.7
30-35	28	8.6	3.3	2.2 to 4.7	33.8	17.4 to 55.5	23	12.4	1.9	1.2 to 2.8	11.5	2.3 to 23.9
P heterogeneity			< .001		.013				< .001		< .001	

Abbreviations: AER, absolute excess risk per 10,000; CT, chemotherapy; RT, radiotherapy; SIR, standardized incidence ratio.
*All SIRs and AERs with CIs not including 1.0 are significant at $P < .001$.

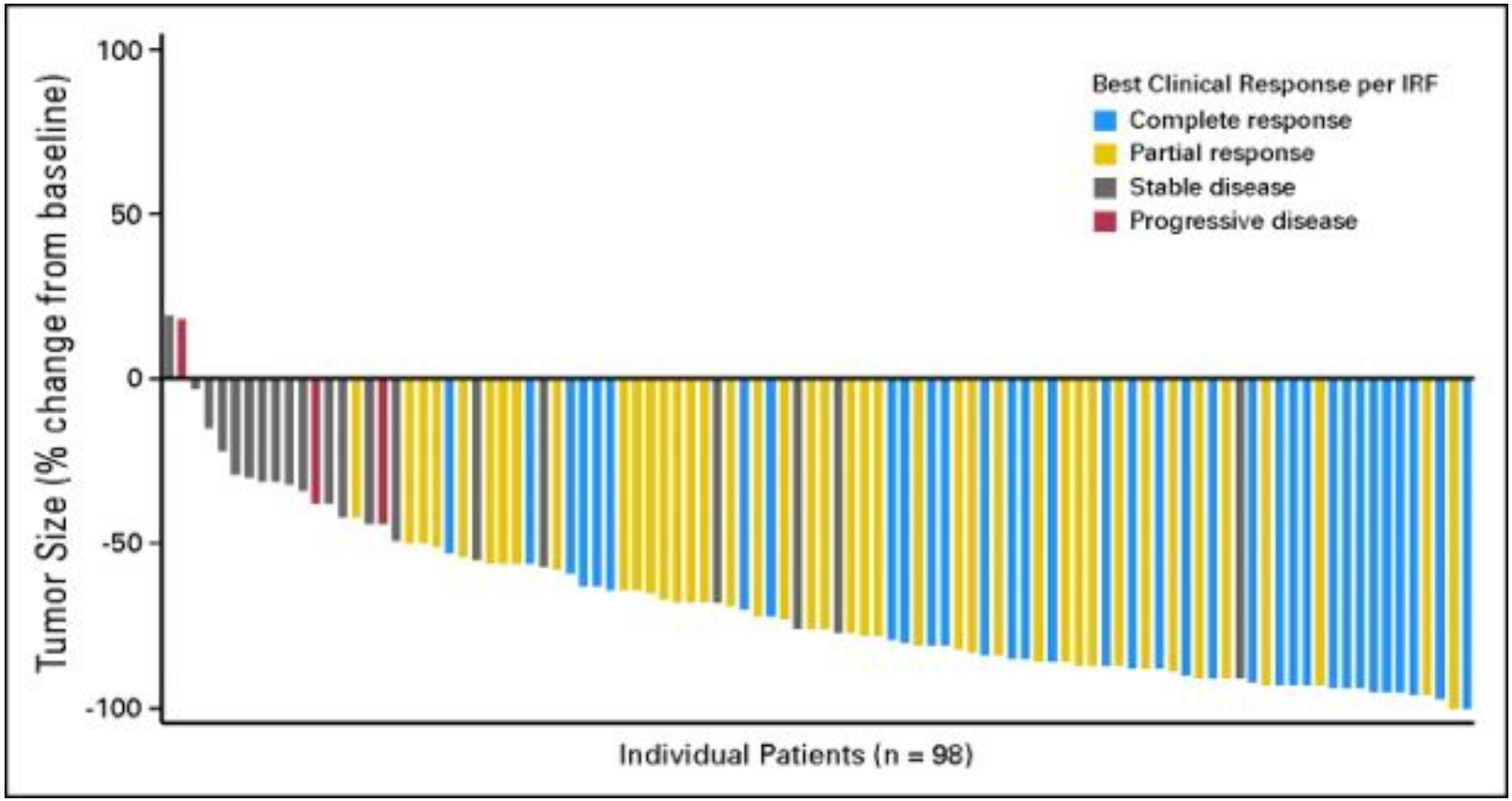
Swerdlow et al, J Clin Oncol 2012

Brentuximab Vedotin (SGN-35) Mechanism of Action



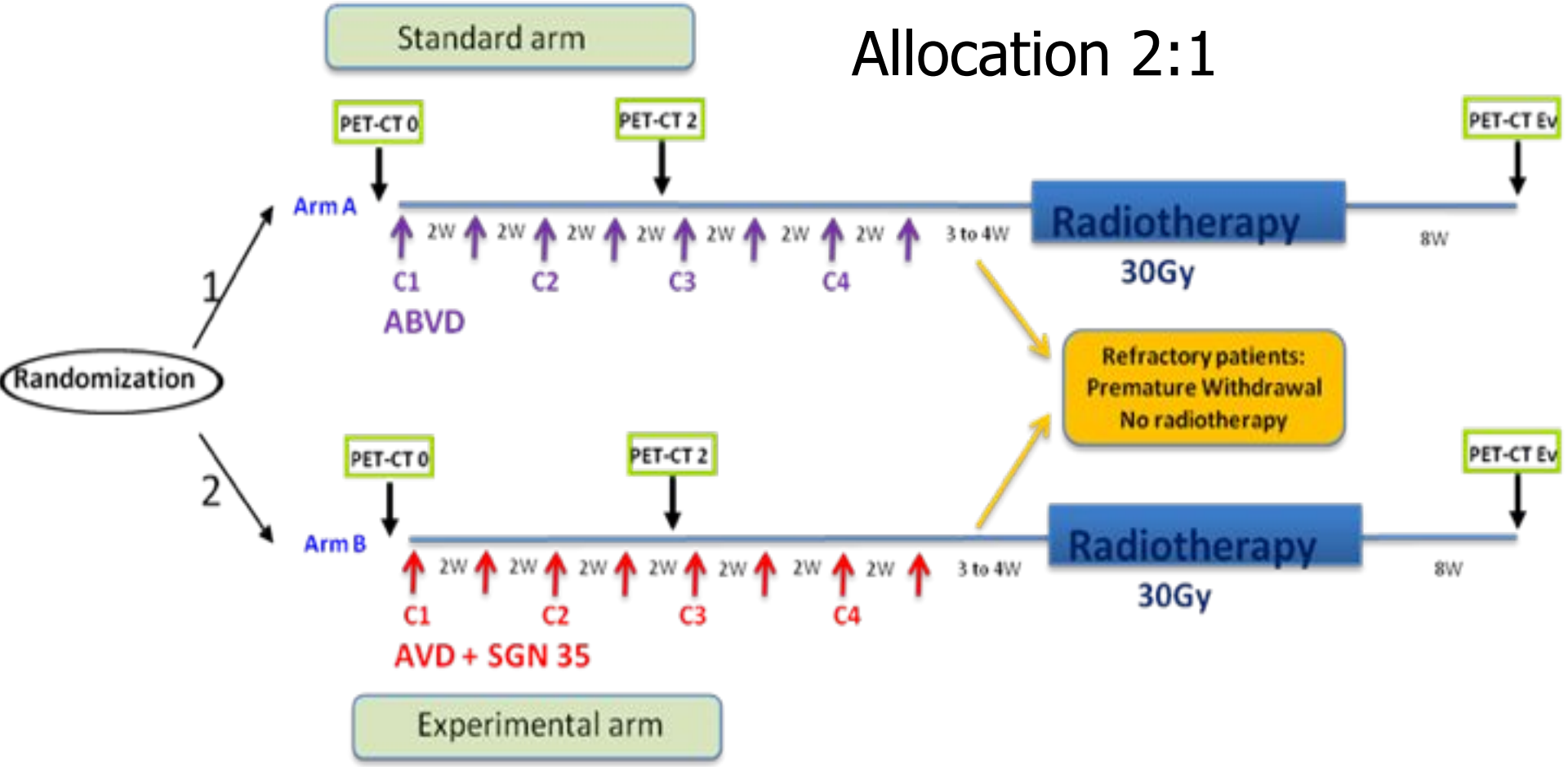
ADCETRIS, Seattle Genetics-Millenium Takeda

Maximum percent reduction in the sum of the product of diameters in individual patients (n = 98) per Cheson et al.12 Tumor size reductions were observed in 96 (94%) of 102 patients.



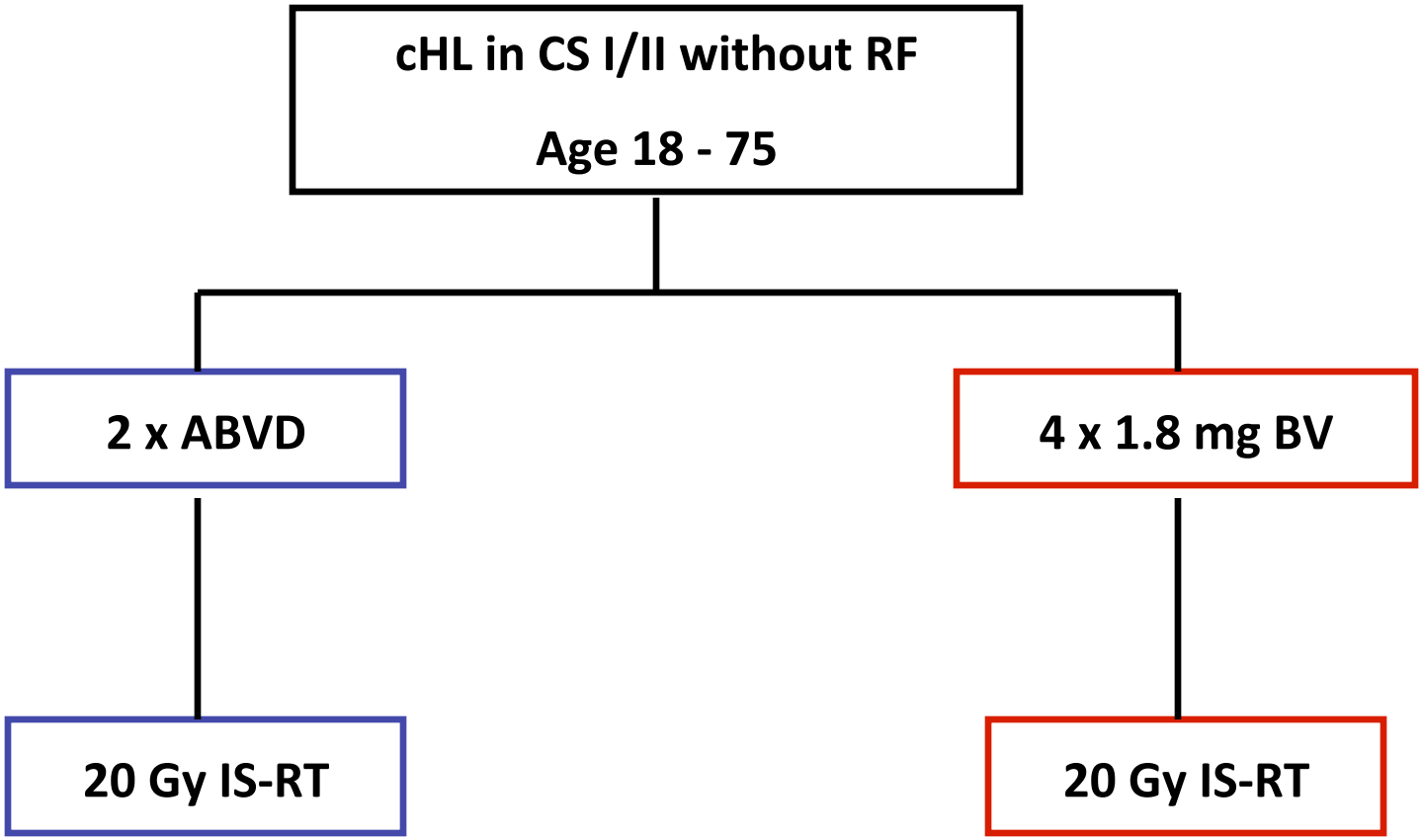
Younes A et al. JCO 2012;30:2183-2189

BREACH STUDY



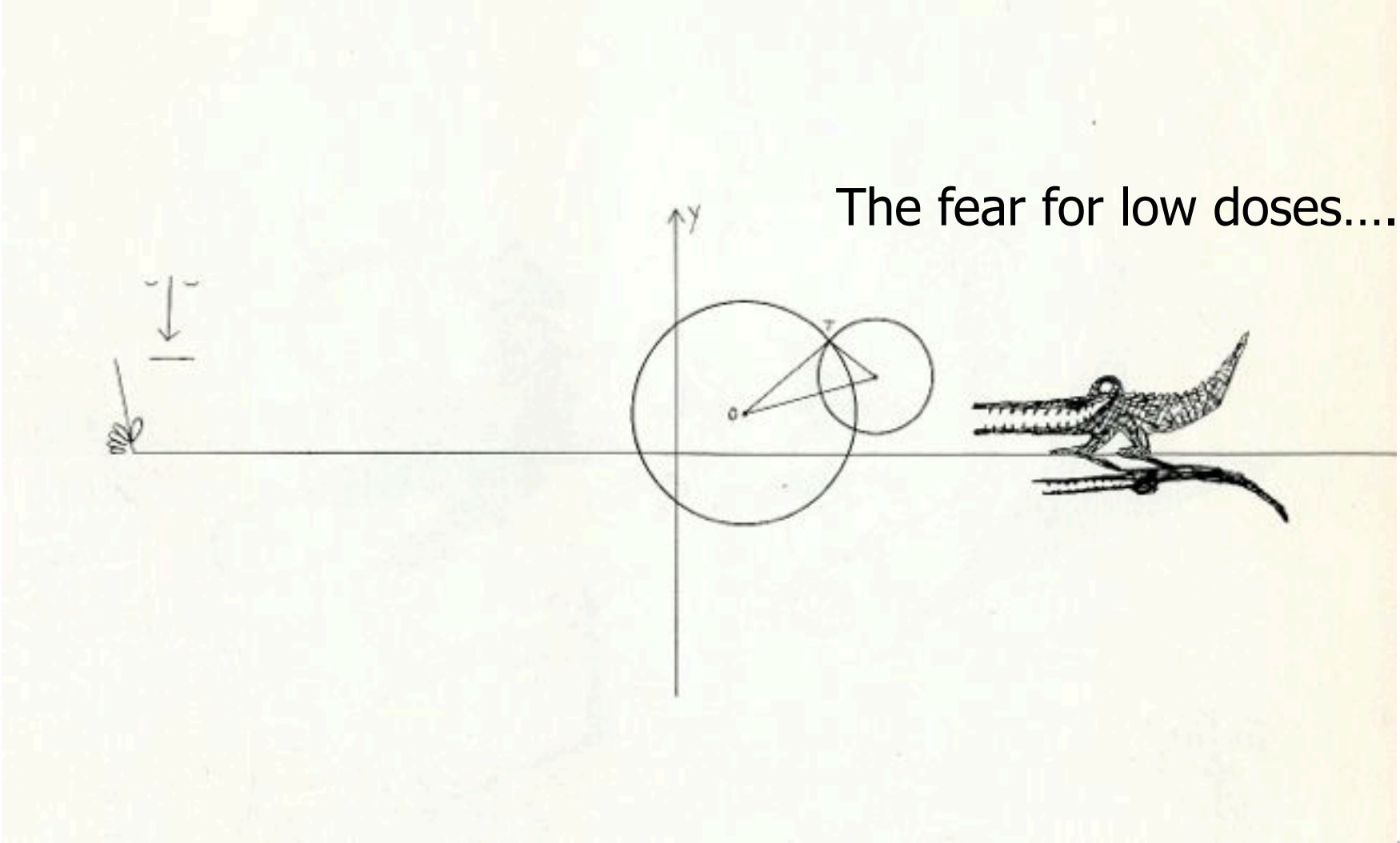
Potential Phase III trial for early-stage favorable HL

GHSG
www.ghsg.org



Department of Oncology
University of Turin

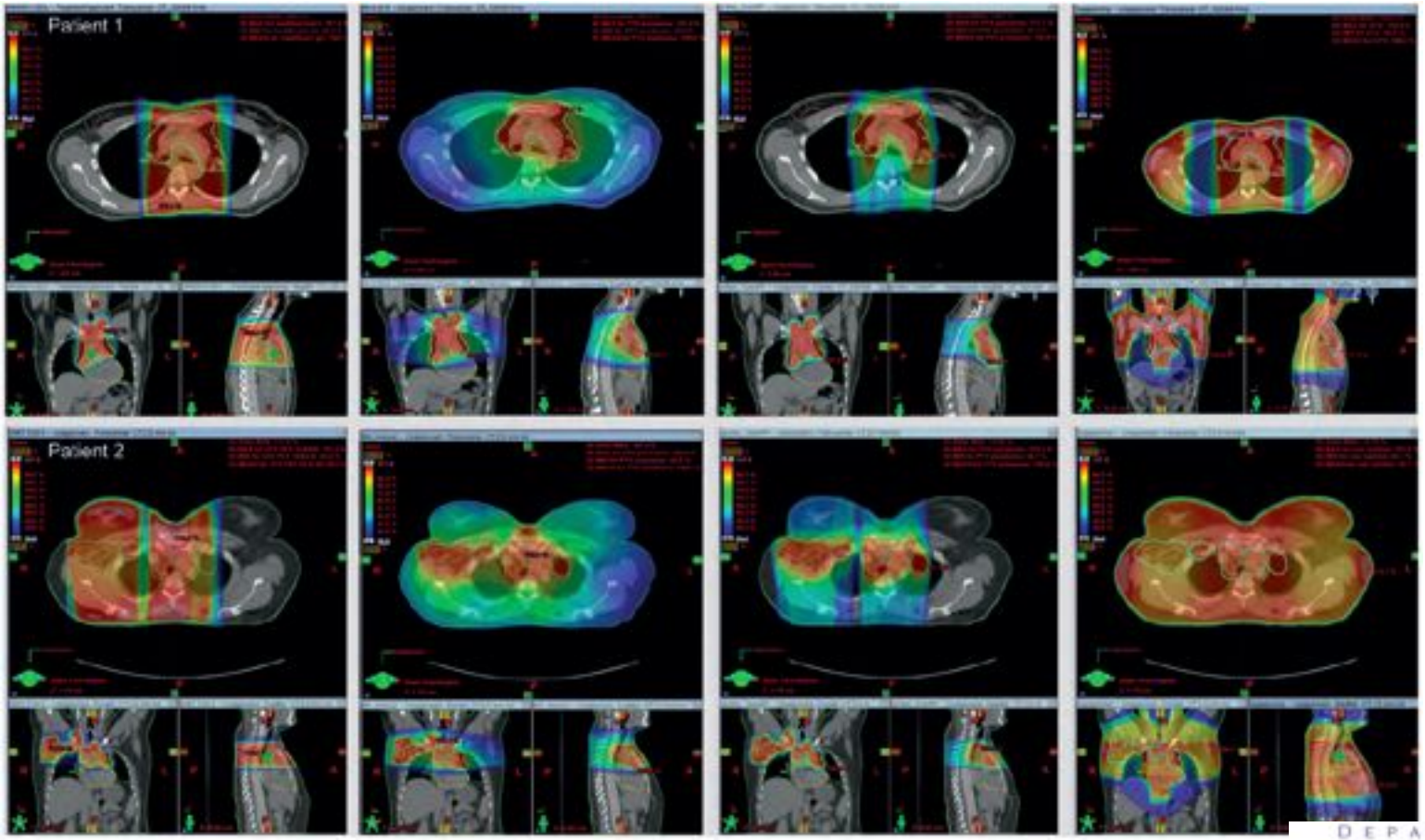
Highly-Conformal Techniques for early stage HL?



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

M. V. Maraldo[1*], N. P. Brodin[1,2], M. C. Aznar[1], I. R. Vogelius[1], P. Munck af Rosenschöld[1,2], P. M. Petersen[1,3] & L. Specht[1,3]

[1]Department of Radiation Oncology, Rigshospitalet; [2]Faculty of Sciences, Niels Bohr Institute; [3]Departments of Hematology and Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark



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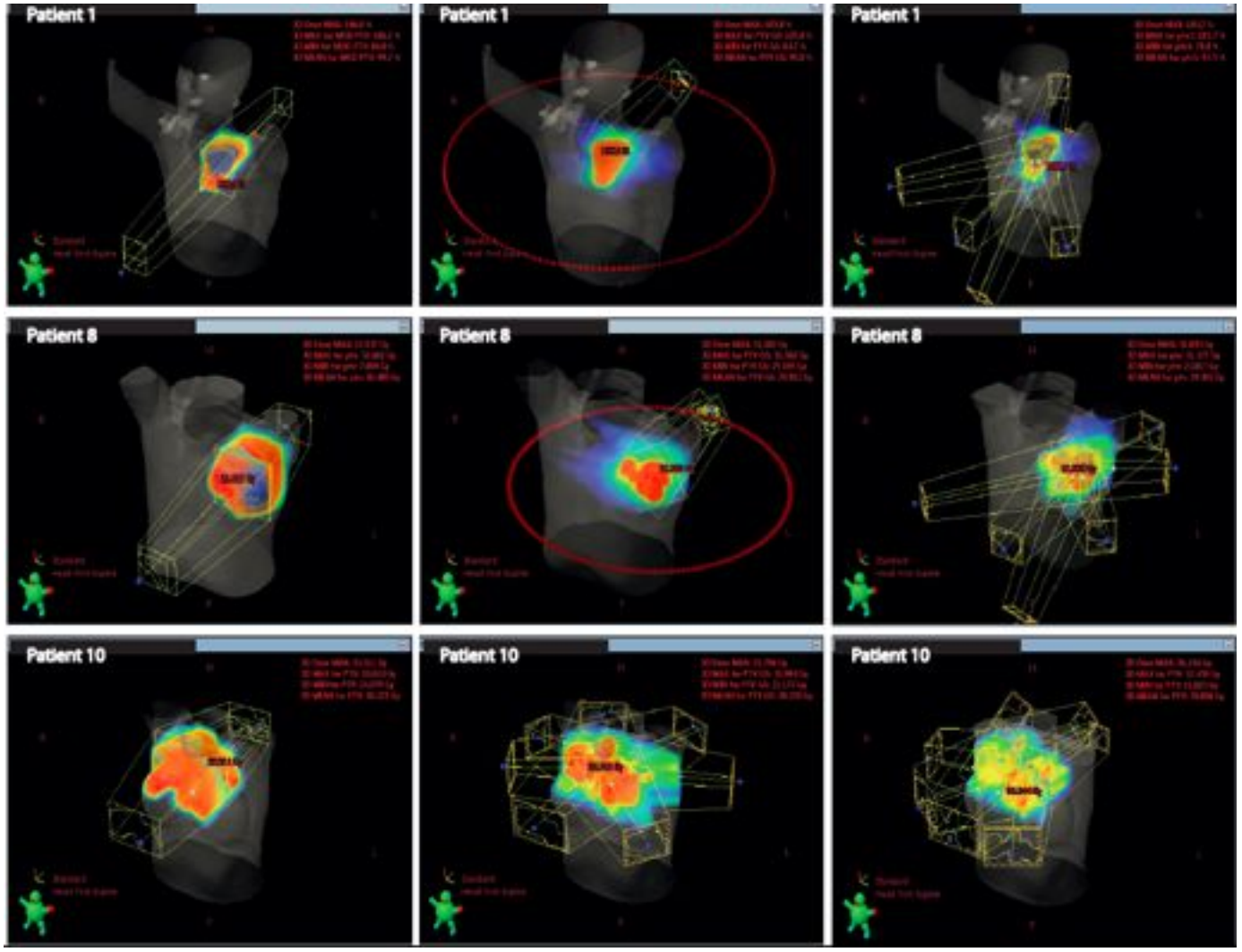
	3D CRT		VMAT		PT		MF		*P* value[a]			
										Pair-wise comparisons		
	Median	Range	Median	Range	Median	Range	Median	Range	all	3D CRT versus VMAT	3D CRT versus PT	VMAT versus PT
Risk estimates (%)												
Cardiac mortality (CMort)	1.0	(0.2–2.7)	1.1	(0.3–2.1)	0.9	(0.1–1.9)	2.9	(2.2–3.4)	<0.0001	0.528	0.0003	<0.0001
Cardiac morbidity (CMorb)	1.3	(0.5–7.1)	1.3	(0.6–4.0)	1.1	(0.5–3.3)	8.6	(4.6–14.3)	<0.0001	0.854	0.012	0.0002
Myocardial infarction (MI)	5.5	(0.7–30.1)	5.9	(1.1–23.8)	4.7	(0.4–20.4)	19.8	(6.9–37.7)	<0.0001	0.843	0.001	<0.0001
Valvular disease (VD)	0	(0–0.2)	0	(0)	0	(0)	0.4	(0–3.7)	<0.0001	0.338	0.246	0.035
Radiation-induced lung cancer (LC)	4.4	(2.4–9.7)	6.0	(3.1–11.4)	3.3	(1.4–9.7)	10.5	(6.3–15.1)	<0.0001	<0.0001	0.0002	<0.0001
Radiation-induced breast cancer (BC)	3.7	(0.2–11.8)	8.0	(0.6–13.4)	1.4	(0–8.1)	23.0	(7.5–34.5)	<0.0001	0.003	0.002	<0.0001
Life years lost (LYL)												
Total LYL	0.9	(0.2–1.6)	1.1	(0.2–2.3)	0.7	(0.1–1.6)	2.1	(0.6–3.6)	<0.0001	<0.0001	<0.0001	<0.0001

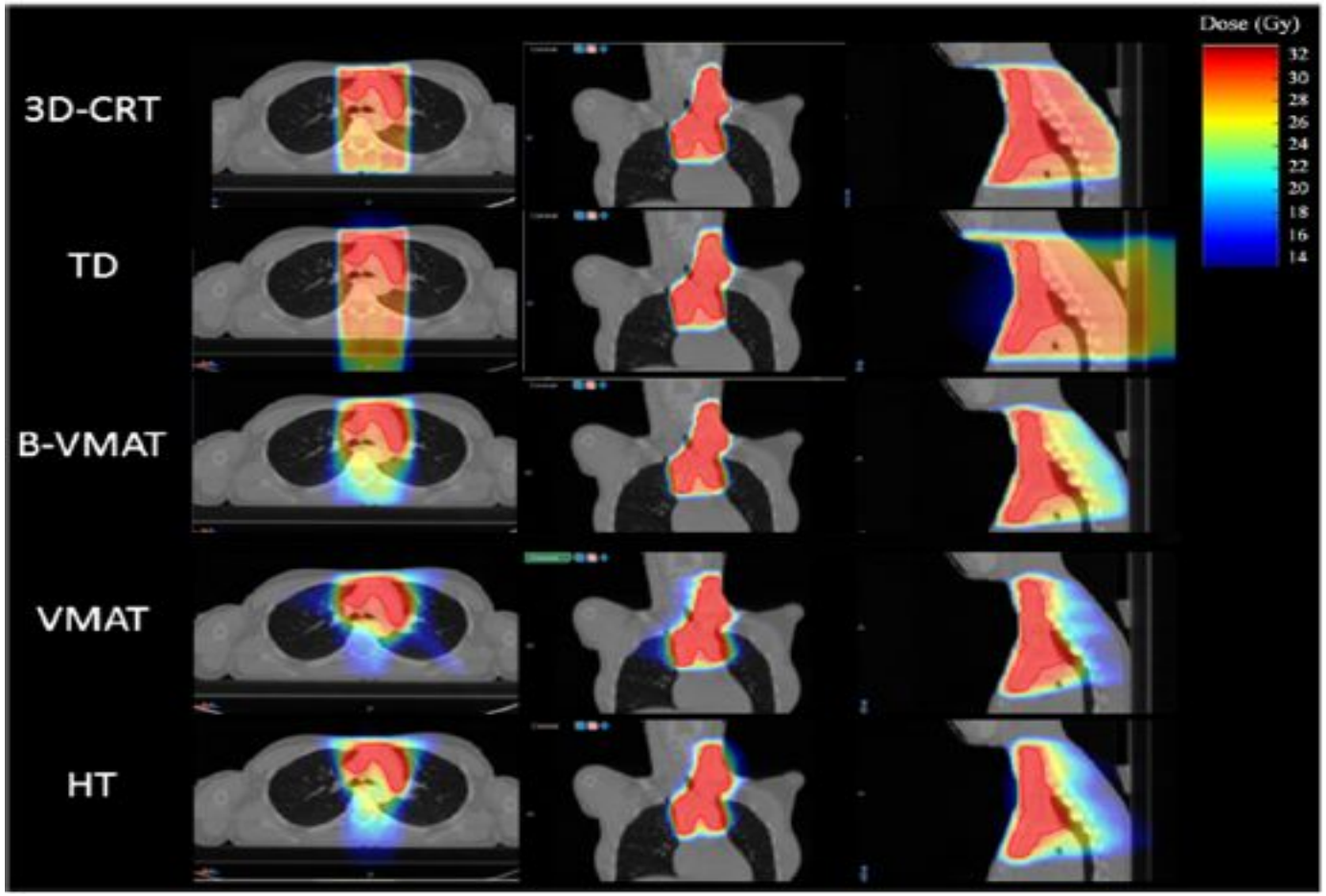
Maraldo MV et al, Ann Oncol 2013

What are we thinking about when we think IMRT in HL?



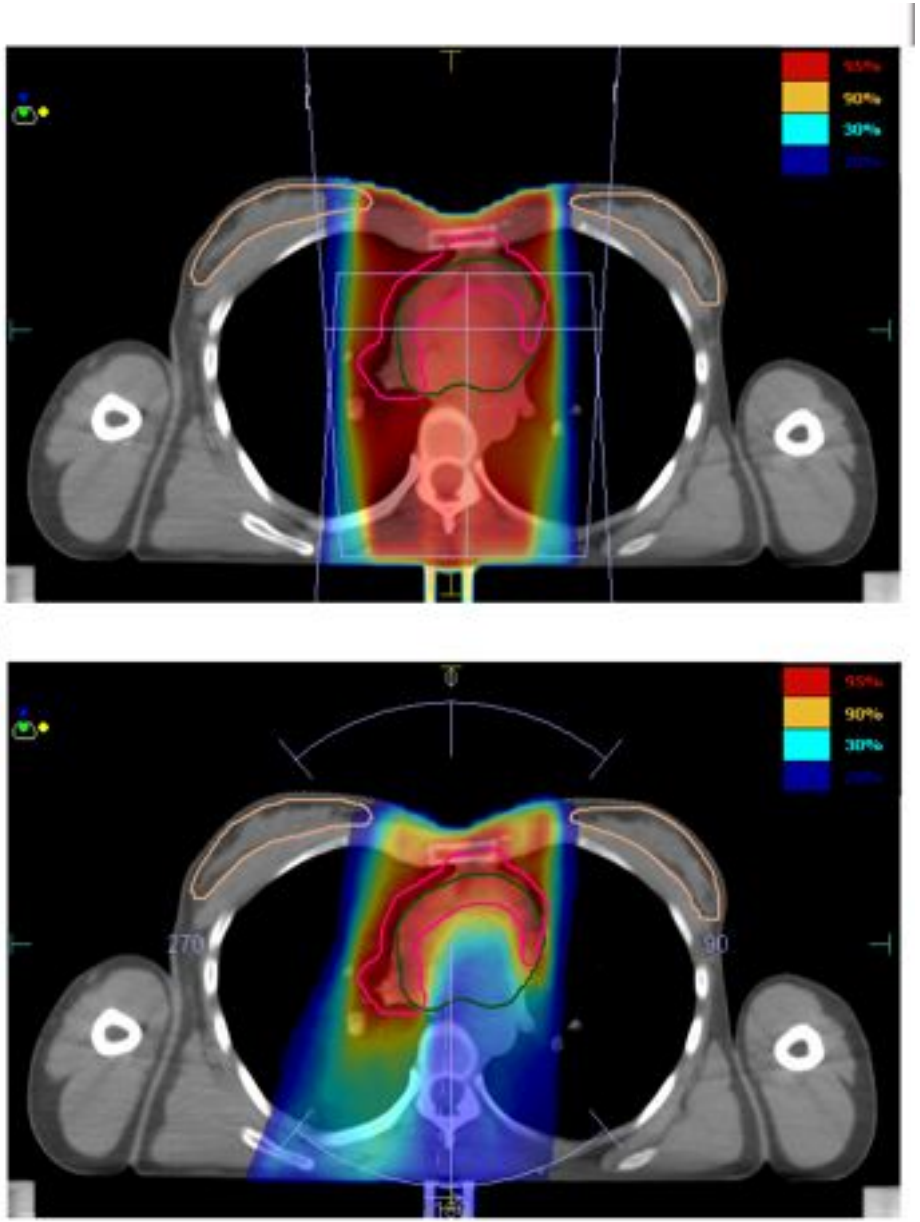
Maraldo MV et al, ILROG Centers, ASTRO 2014

Different planning solutions for mediastinal HL, including optimzed VMAT



Fiandra et al, Rad Oncol 2012

Optimized (butterfly) VMAT vs. 3D-CRT



Fillippi AR et al, submitted

Patients' characteristics

Characteristic	*n*	%
No. of patients	38	
Age (y)		
Range	15 – 43	
Mean	30	
Sex		
Male	13	34.2
Female	25	65.8
Ann Arbor Stage		
I	8	21.1
II	30	78.9
Bulky	8	21.1
EORTC prognostic groups		
Favorable	21	55.3
Unfavorable	17	44.7
Involved sites		
Mediastinum alone	8	21.1
Mediastinum and unilateral neck	19	50
Mediastinum and bilateral neck	11	28.9

Fillippi AR et al, submitted

Absolute Excess Risk of Heart Diseases

	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

Fillippi AR et al, submitted

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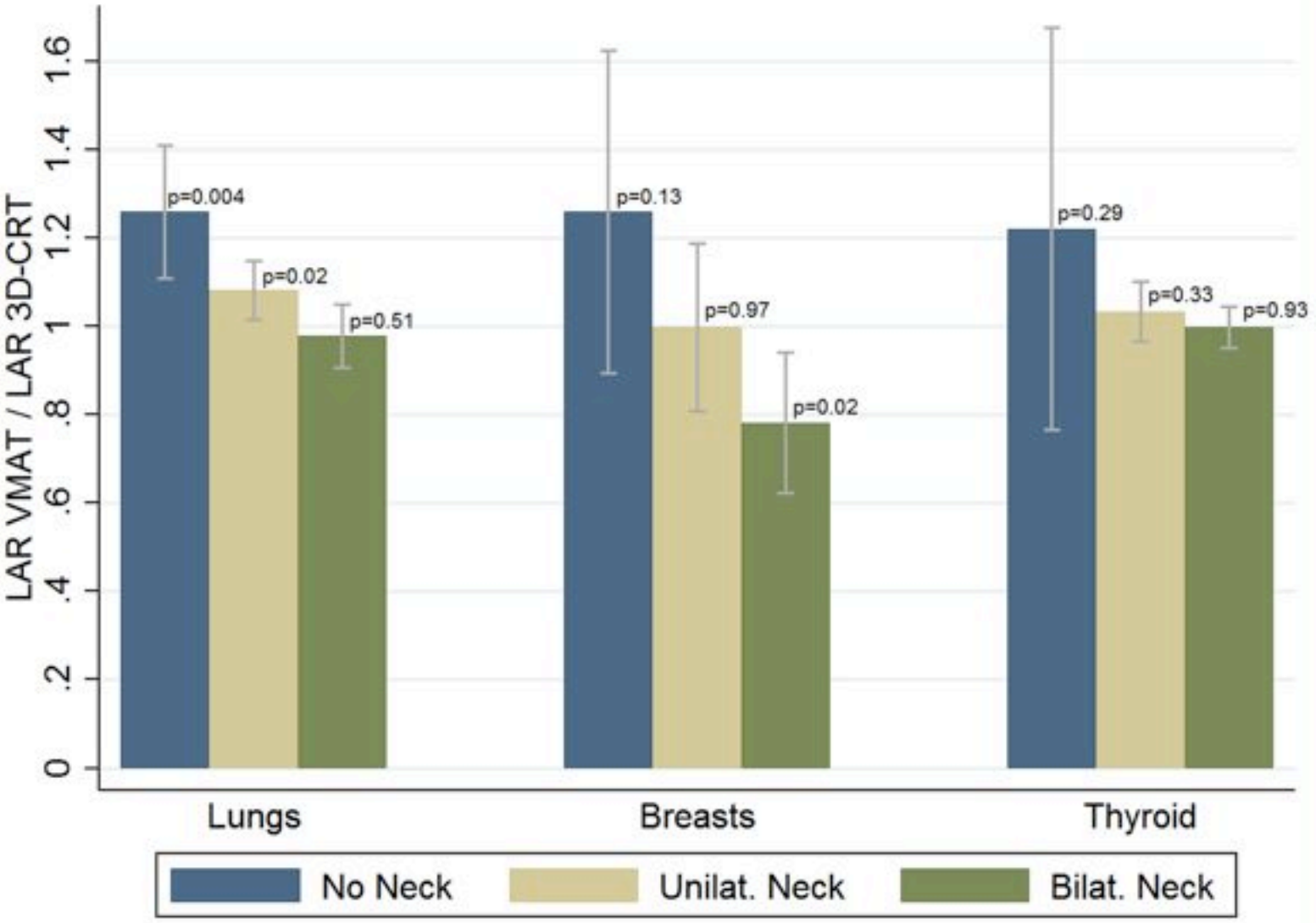

Fillippi AR et al, submitted

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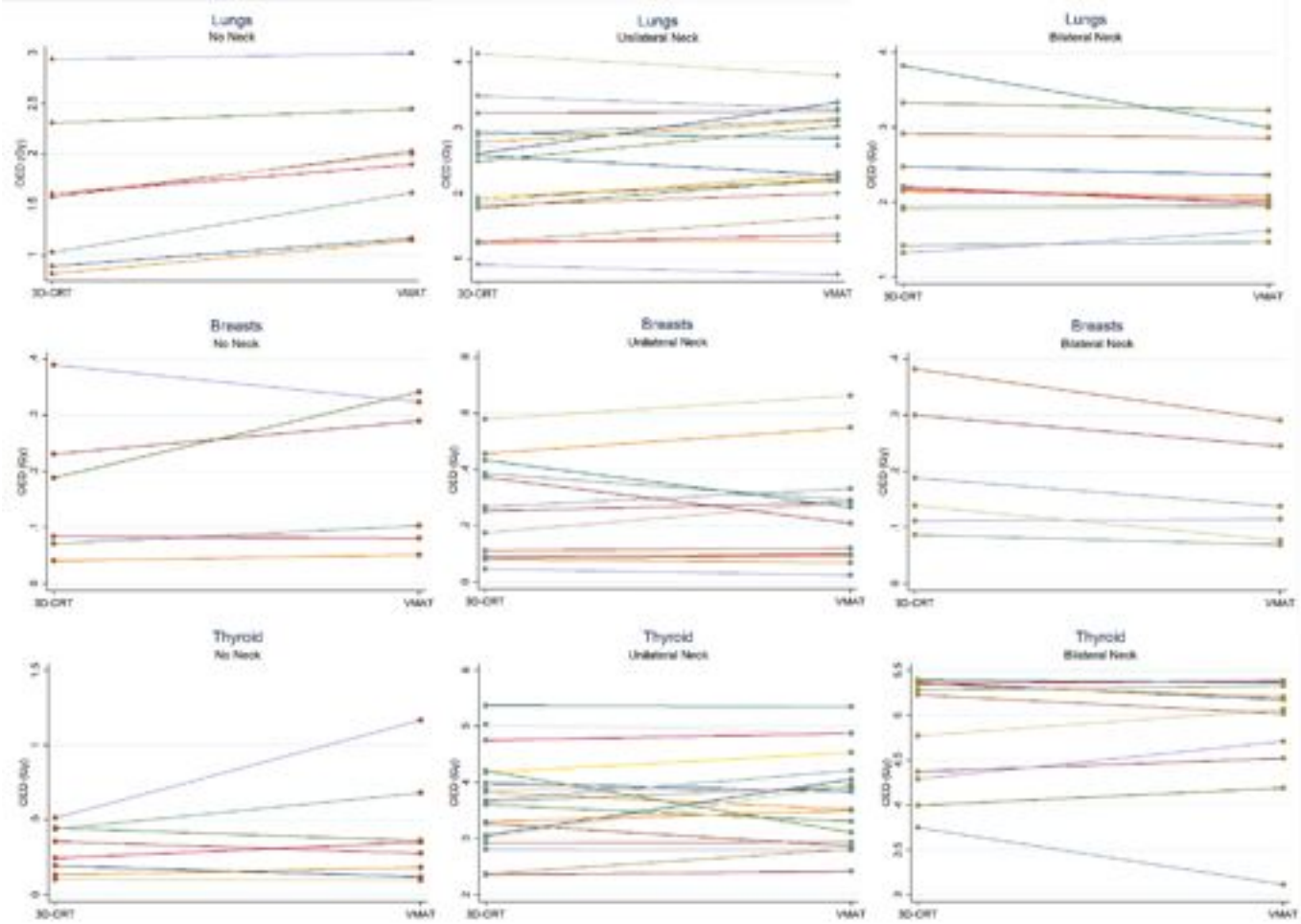
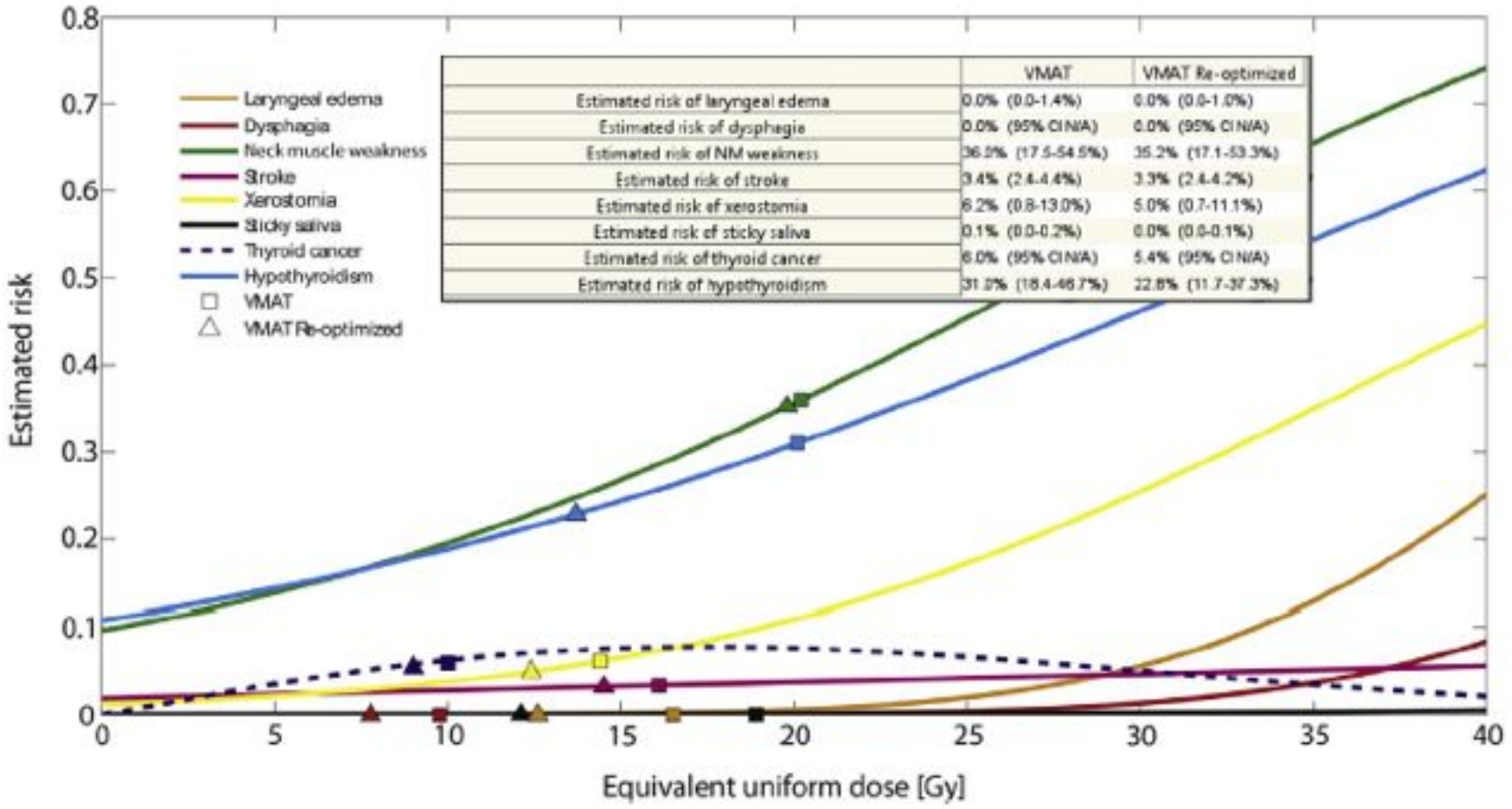


Fillippi AR et al, submitted

Interactive Decision-Support Tool for Risk-Based Radiation Therapy Plan Comparison for Hodgkin Lymphoma

N. Patrik Brodin, PhD,* Maja V. Maraldo, MD,* Marianne C. Aznar, PhD,*,§
Ivan R. Vogelius, PhD,* Peter M. Petersen, MD, PhD,*,†,‡ Søren M. Bentzen, PhD, DSc,*,‖
and Lena Specht, MD, DMSc*,†,‡



	VMAT	VMAT Re-optimized
Estimated risk of laryngeal edema	0.0% (0.0-1.4%)	0.0% (0.0-1.0%)
Estimated risk of dysphagia	0.0% (95% CI N/A)	0.0% (95% CI N/A)
Estimated risk of NM weakness	36.0% (17.5-54.5%)	35.2% (17.1-53.3%)
Estimated risk of stroke	3.4% (2.4-4.4%)	3.3% (2.4-4.2%)
Estimated risk of xerostomia	6.2% (0.8-13.0%)	5.0% (0.7-11.1%)
Estimated risk of sticky saliva	0.1% (0.0-0.2%)	0.0% (0.0-0.1%)
Estimated risk of thyroid cancer	6.0% (95% CI N/A)	5.4% (95% CI N/A)
Estimated risk of hypothyroidism	31.0% (18.4-46.7%)	22.8% (11.7-37.3%)

Brodin P et al, IJROBP 2013

Take home messages

- Modern radiotherapy for HL is a highly individualized treatment restricted to limited treatment volumes
- Modern imaging and treatment techniques should be used to limit normal tissue irradiation
- Involved Site Radiotherapy (ISRT) represents a significant reduction in the irradiated volume compared to previous techniques
- Radiation oncologists should be involved in the initial management of HL patients, and ensure optimal imaging for RT planning
- These changes will lead to significantly lower risks of long term complications while maintaining the high cure rates of HL

From Specht & ILROG Steering Committee , ASTRO 2014

Radiation Therapy in early stage DLBCL?

- "Classic" trials investigating the role of CMT in DLBCL (some of them with risk stratification)
- Trials investigating the role of CMT in DLBCL in the Rituximab era
- Data on the role of RT from systematic reviews, retrospective analysis and epidemiologic registry

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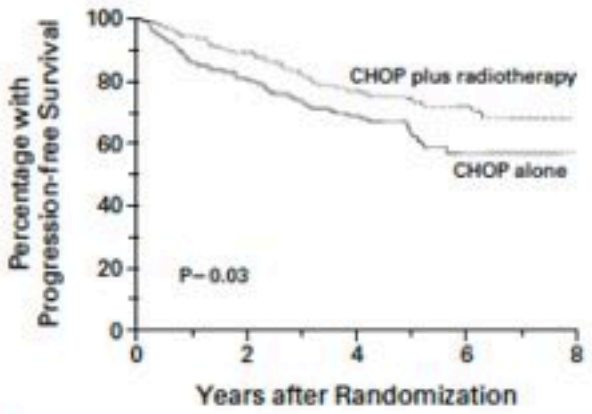
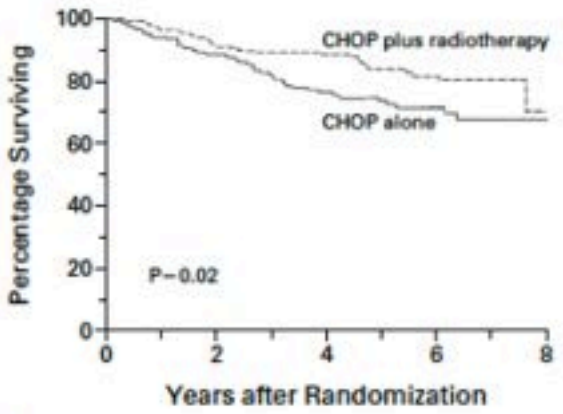
CHOP x 8 vs. CHOP x 3 + IFRT in Stage I/II DLBCL



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.



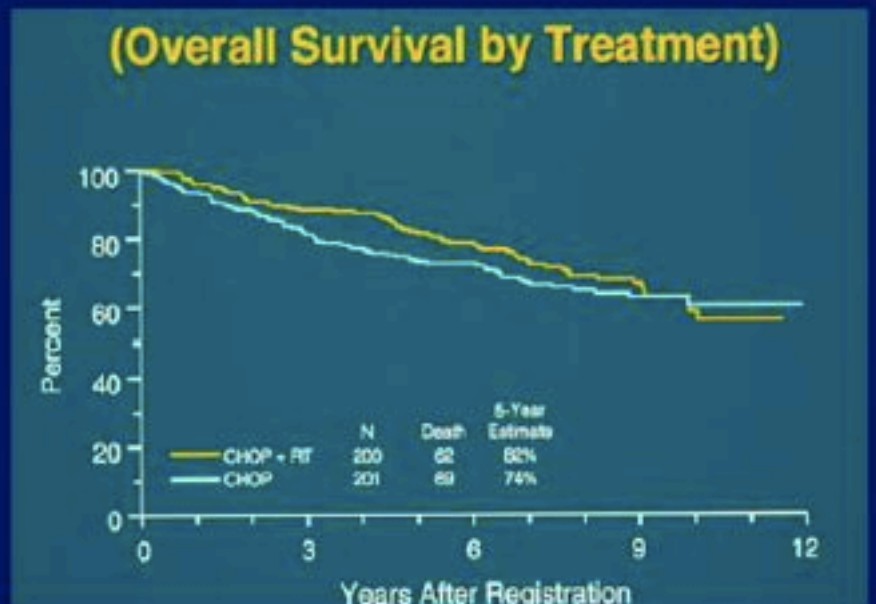
No. at Risk					
CHOP alone	201	187	120	61	14
CHOP plus radiotherapy	200	185	128	75	17

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

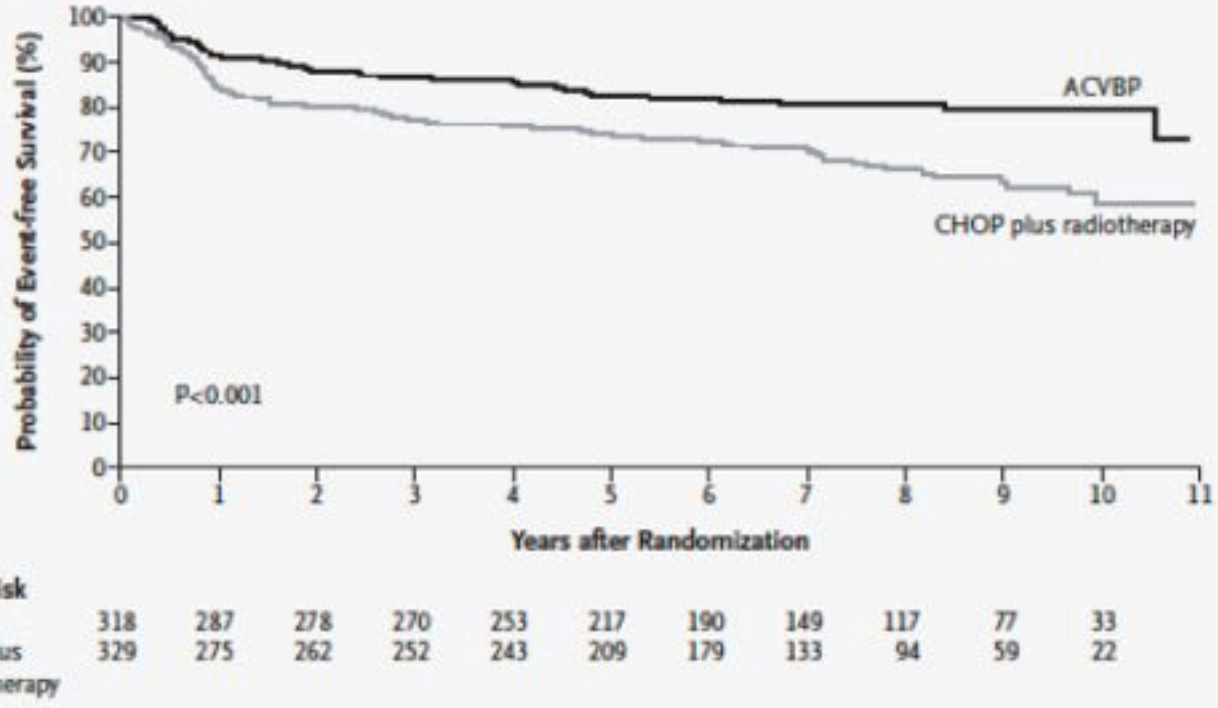
SWOG 8736: Updated Results



- Median f/u= 8.2 yrs
- FFS curves overlap at 7 years
- OS curves overlap at 9 years
- Late relapses and lymphoma deaths in CMT arm

Miller et al. ASH, 2001

ACVBP vs CHOP + RT in Stage I/II aggressive Lymphoma



No. at Risk											
ACVBP	318	287	278	270	253	217	190	149	117	77	33
CHOP plus radiotherapy	329	275	262	252	243	209	179	133	94	59	22

Figure 1. Event-free Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

Overall Survival

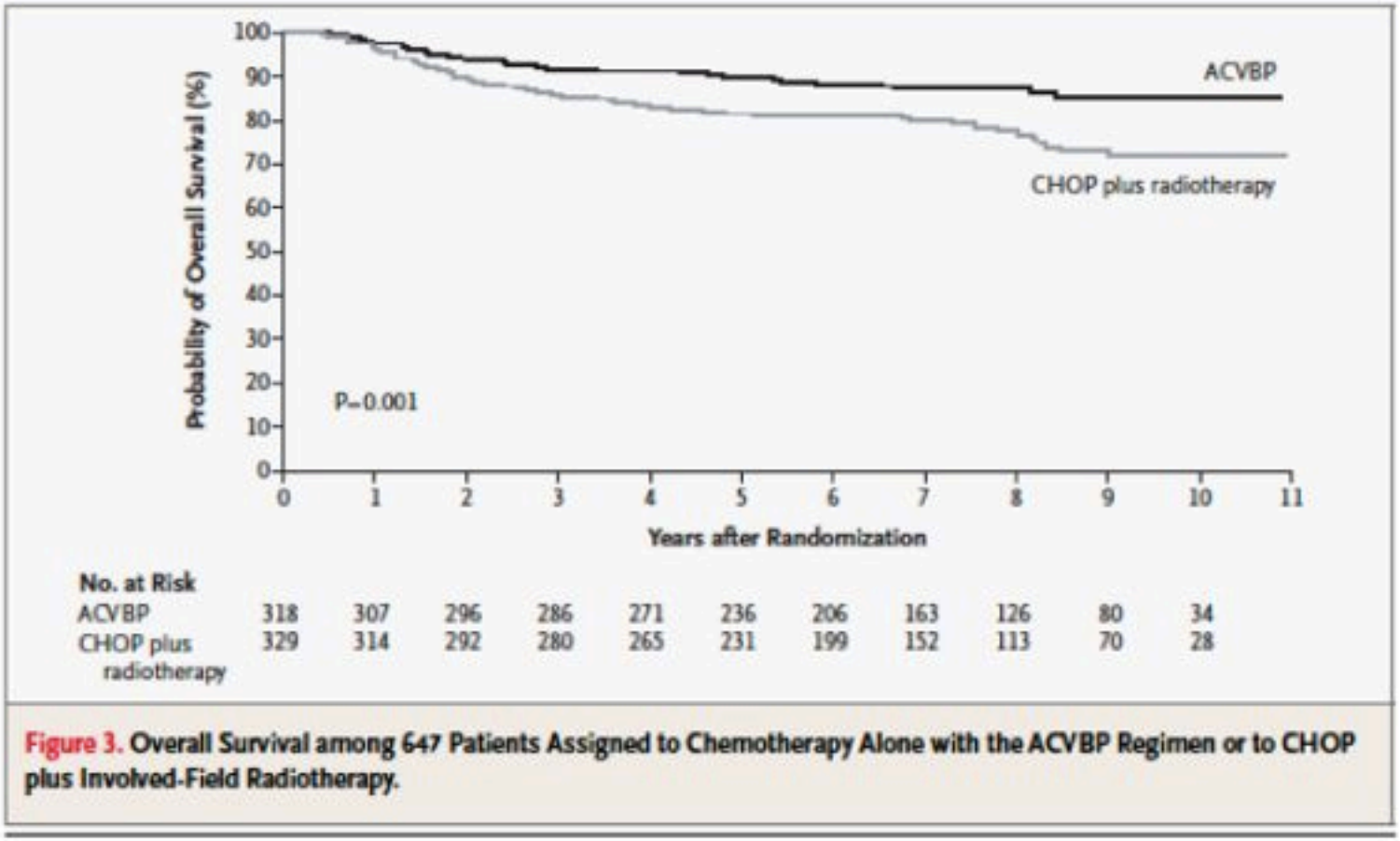
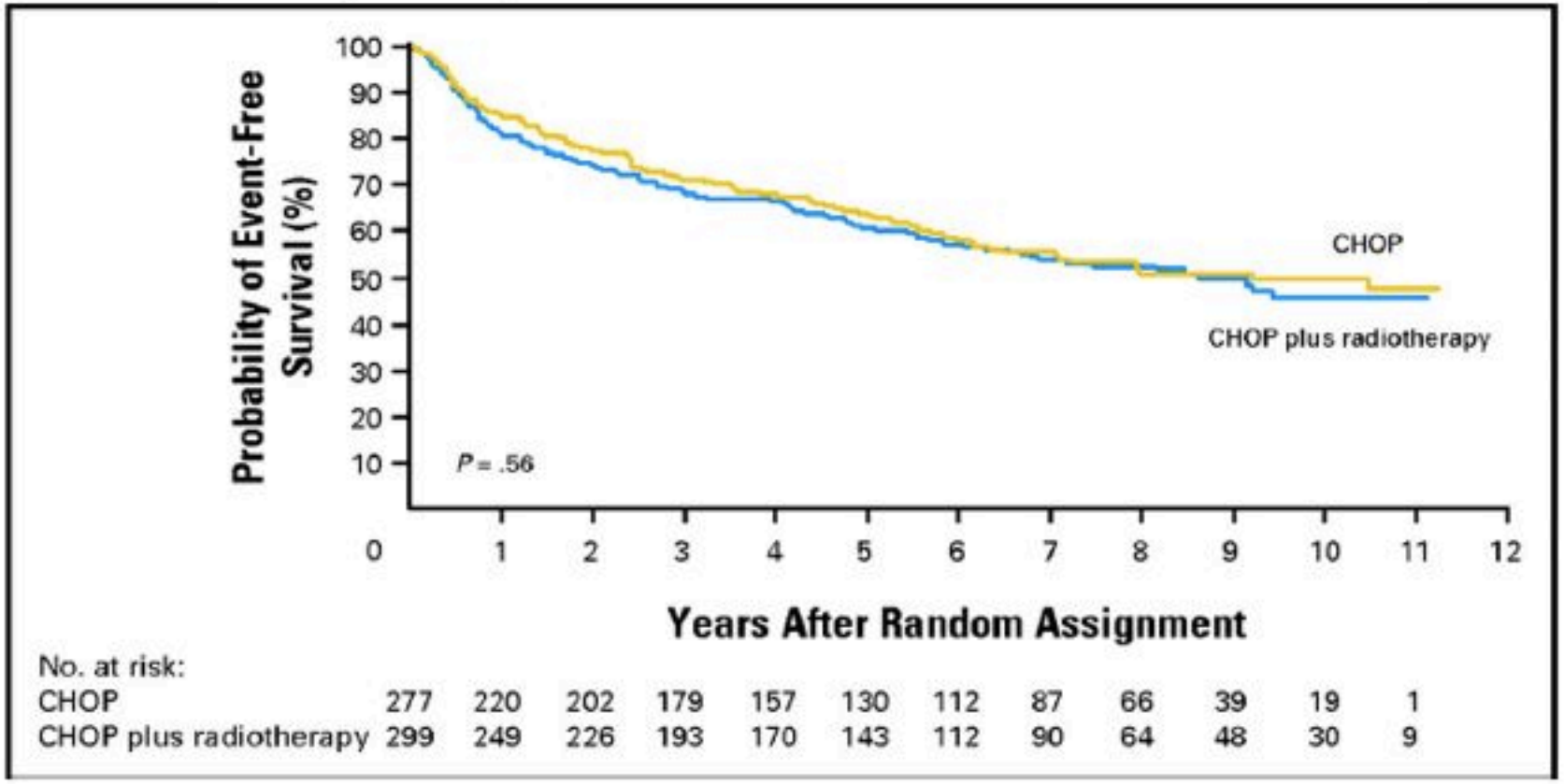


Figure 3. Overall Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

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†



GELA LNH 93-4

Bonnet C et al. JCO 2007;25:787-792

CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

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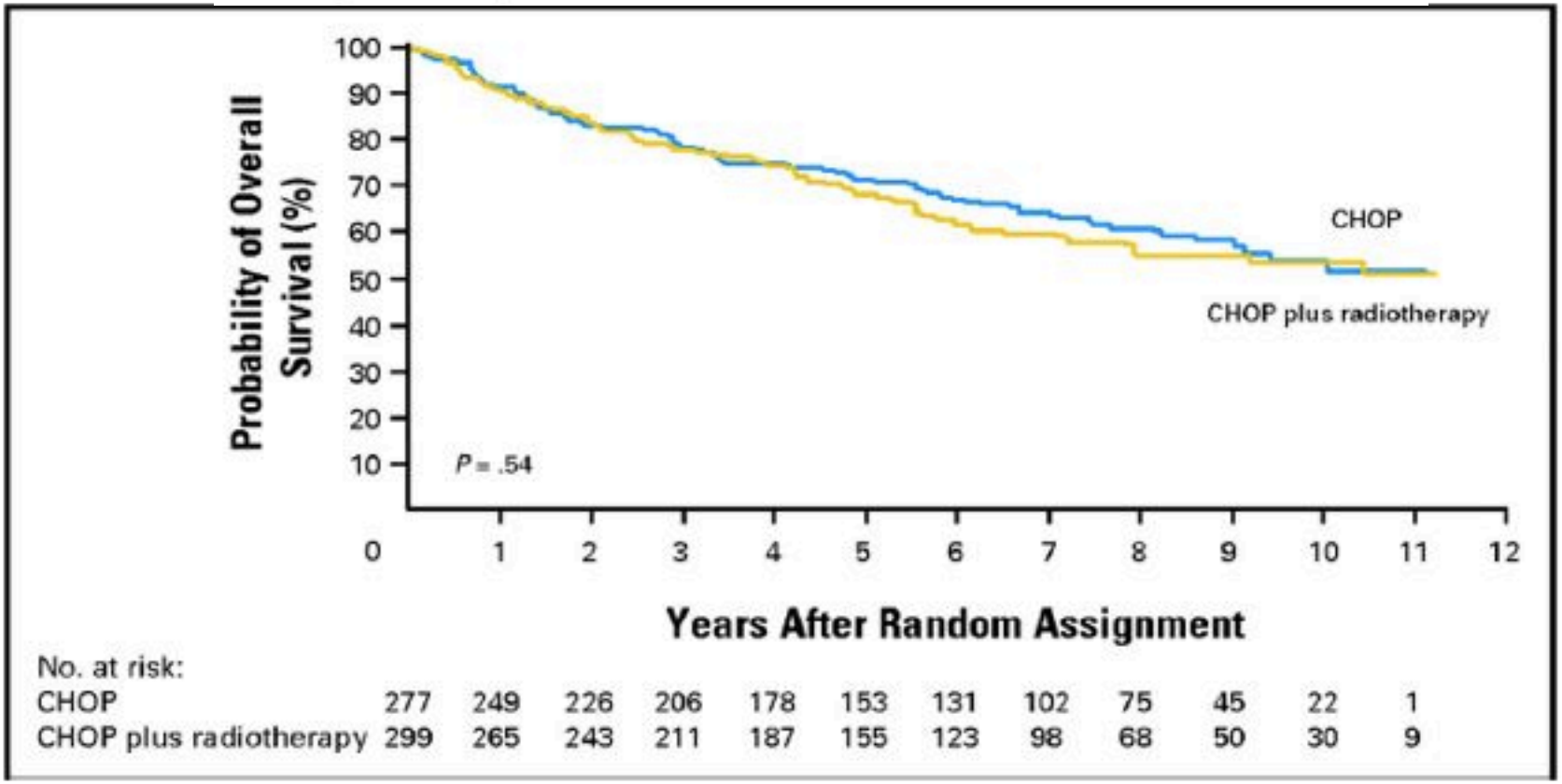


GELA LNH 93-4

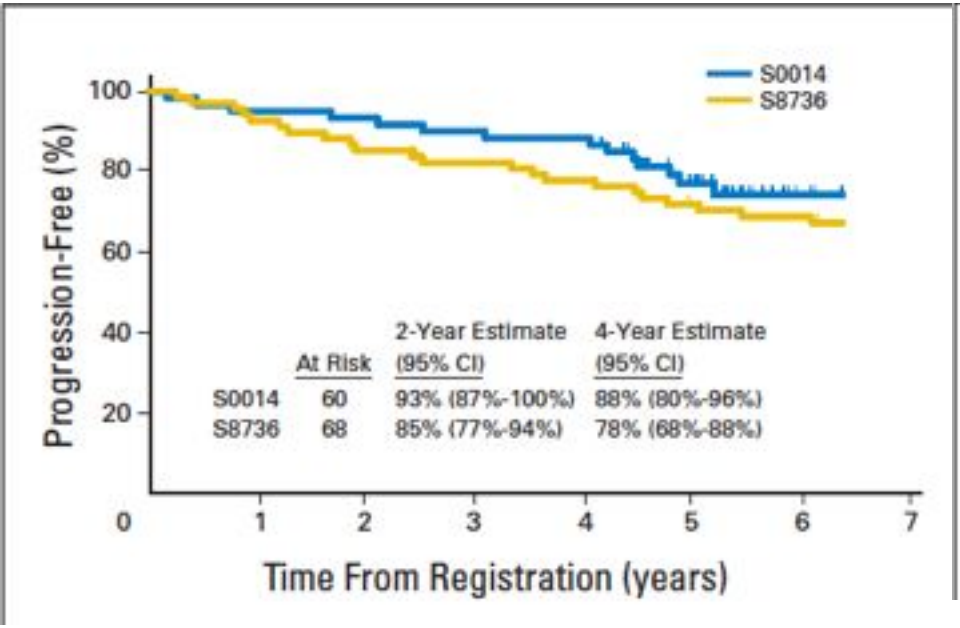
Bonnet C et al. JCO 2007;25:787-792

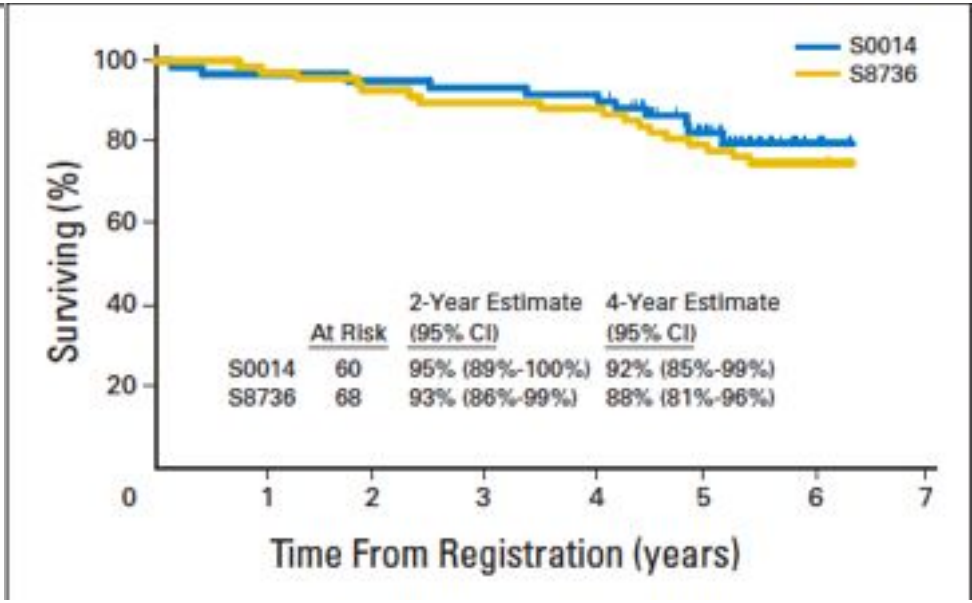
Will Rituximab markedly change the results of CHOP+RT?

Rituximab is routinely given to all DLBCL - A randomized study of:

R-CHOP vs R-CHOP+RT vs CHOP+RT is unlikely

3 R-CHOP + RT compared with an historical group of 3 CHOP + RT

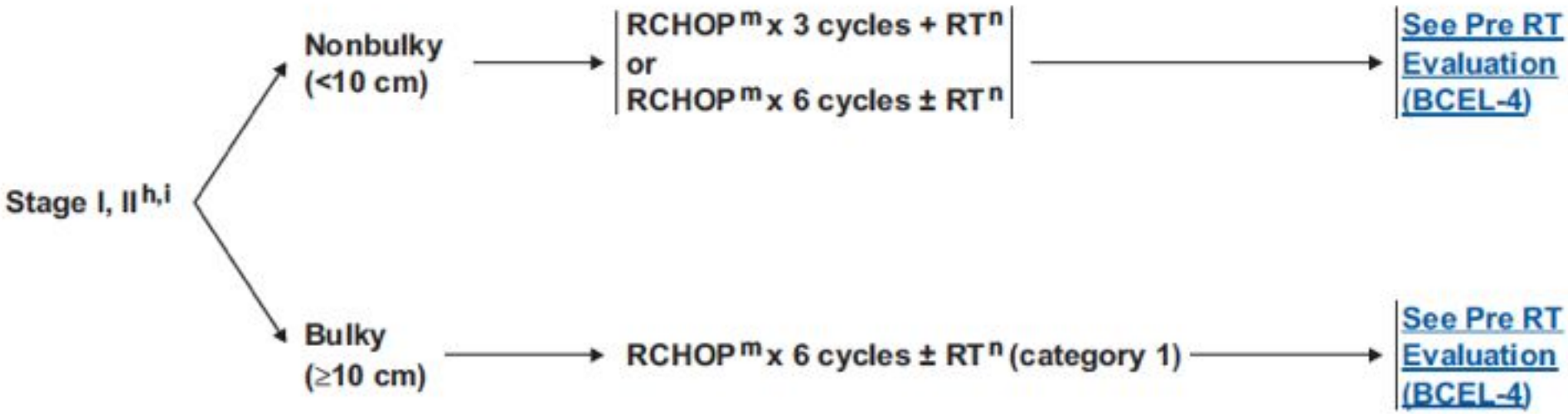


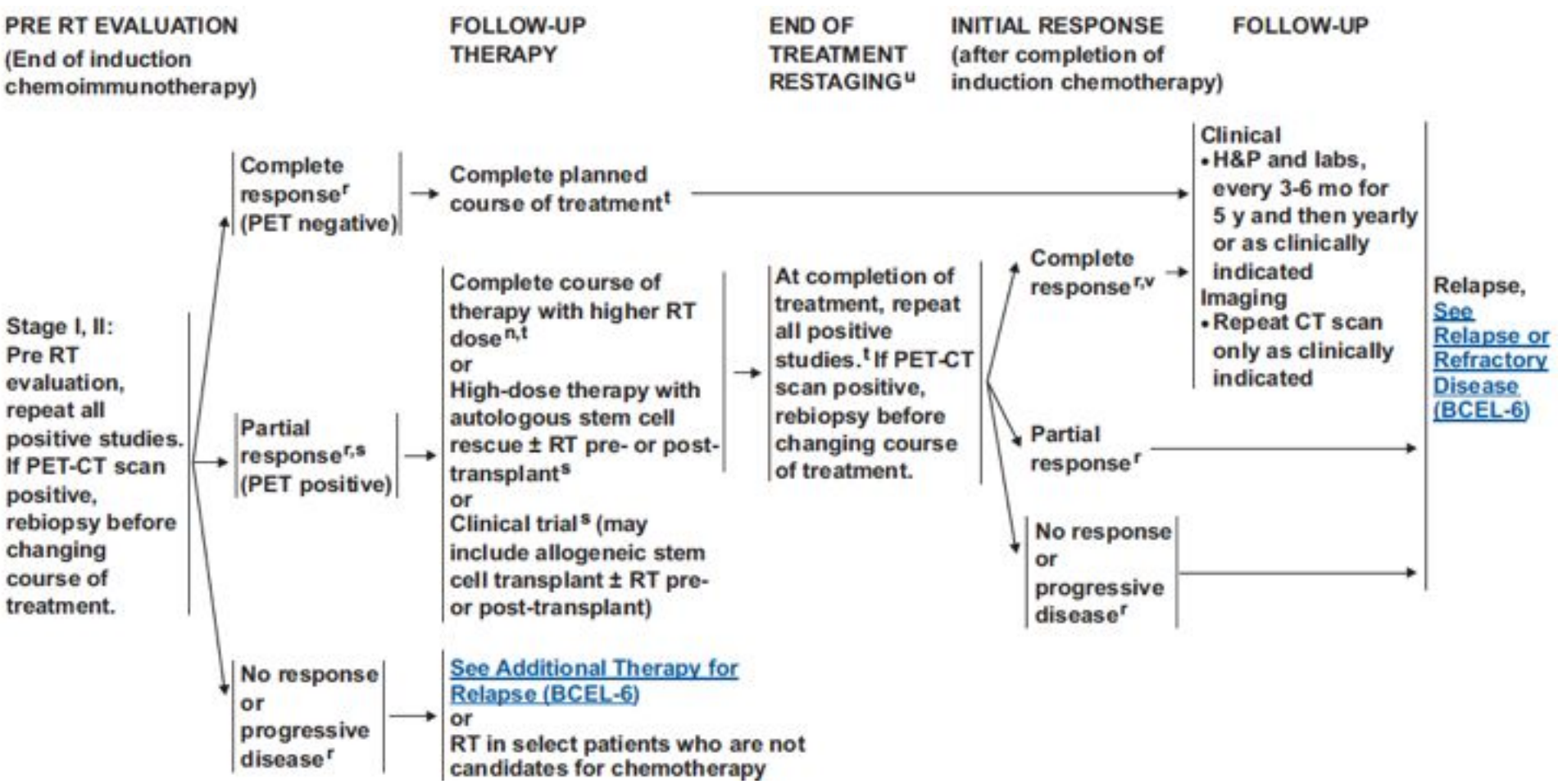


Persky et all, J Clin Oncol 2008

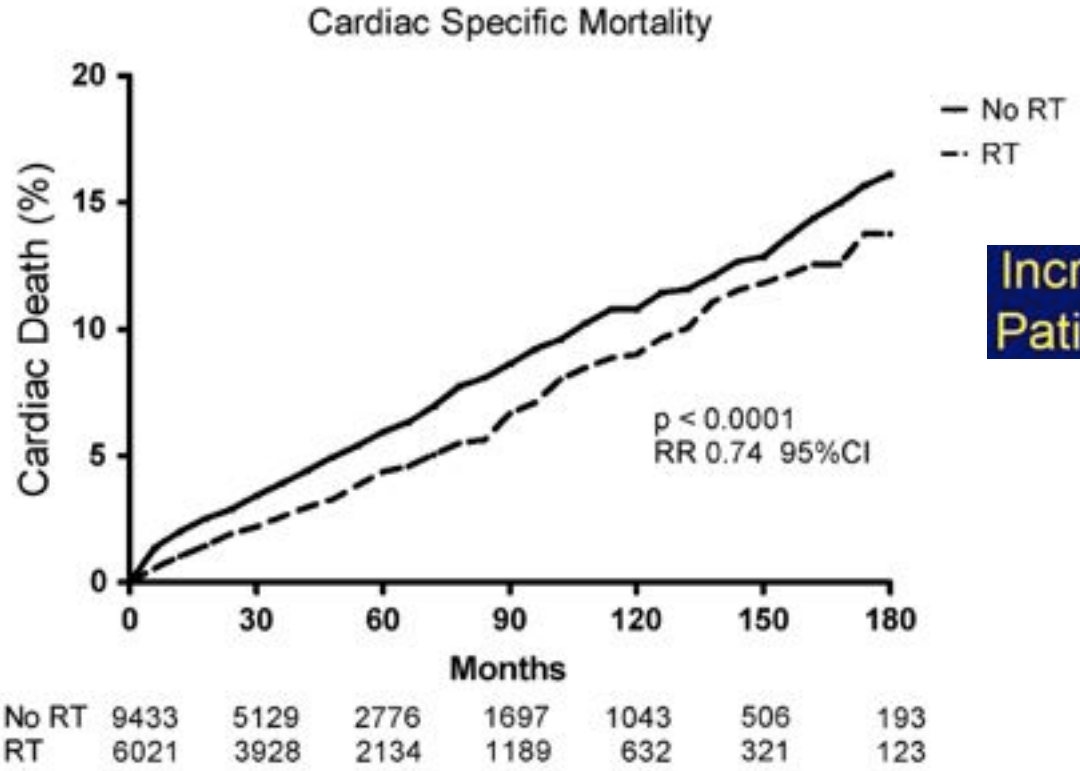
National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2014
Diffuse Large B-Cell Lymphoma





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



Increased Cardiac Death in Patients Treated without RT

Fig. 1. Cardiac death in patients with stage I–II DLBCL. A comparison between patients treated with and without RT.

Annals of Oncology 22: 1845–1858, 2011
doi:10.1093/annonc/mdq697
Published online 10 February 2011

Risk for second malignancies in non-Hodgkin's lymphoma survivors: a meta-analysis

M. Pirani, R. Marcheselli*, L. Marcheselli, A. Bari, M. Federico & S. Sacchi

Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy

Type of study	Model used	No. of studies (reference)	Q test (P value)	I^2, %	RR	95% CI
Secondary malignancy						
Clinical trial	Fixed effects	6 [17F, 17M, 18, 71, 73, 74]	<0.001	97.1	1.43	1.26–1.62
	Random effects	6 [17F, 17M, 18, 71, 73, 74]	<0.001	97.1	2.36	1.08–5.14
Hospital- or specialist center-based study	Fixed effects	11 [21, 23, 27, 75–82]	<0.001	96.2	2.42	2.19–2.69
	Random effects	11 [21, 23, 27, 75–82]	<0.001	96.2	2.11	1.18–3.77
Population-based study	Fixed effects	3 [19, 83, 84]	<0.001	98.8	1.29	1.26–1.31
	Random effects	3 [19, 83, 84]	<0.001	98.8	1.27	1.04–1.56
Overall study	Fixed effects	20 [17F, 17M–19, 21, 23, 27, 75–84]	<0.001	97.5	1.31	1.29–1.34
	Random effect	20 [17F, 17M–19, 21, 23, 27, 75–84]	<0.001	97.5	1.88	1.58–2.22
Solid tumors						
Overall study	Fixed effects	10 [17F, 17M, 18, 19, 21, 23, 76, 78, 79, 85]	<0.001	97.2	1.25	1.23–1.29
	Random effect	10 [17F, 17M, 18, 19, 21, 23, 76, 78, 79, 85]	<0.001	97.2	1.32	1.07–1.63

Treatment	No. of studies (reference)	Heterogeneity statistics		Model used	Pooled effect	
		Q test (P value)	I^2, %		RR	95% CI
Chemotherapy, any type of drugs[a,b]						
All malignancies	7 [18, 19, 73–76, 78]	<0.001	80.5	Random effect	**1.49**	**1.11–2.10**
Solid tumors	3 [18, 19, 76]	0.317	13.1	Fixed effect	**1.10**	**1.07–1.13**
Alkylating[b]						
All malignancies	2 [18, 73]	0.802	0.0	Fixed effect	**1.43**	**1.07–1.90**
Solid tumors	0					
CHOP or CHOP-like[b]						
All malignancies	4 [17, 18, 74, 76*]	<0.001	84.0	Random effect	1.28	0.79–2.05
Solid tumors	3 [17, 21, 76*]	<0.001	91.1	Random effect	1.16	0.58–2.30
Radiotherapy, only therapy						
All malignancies	4 [18, 75, 76, 78]	<0.898	0.0	Fixed effect	1.18	0.84–1.64
Solid tumors	2 [18, 76]	<0.514	0.0	Fixed effect	1.23	0.88–1.70
Additional radiotherapy to any type of chemotherapy						
All malignancies	8 [18, 19, 73–76, 78, 80*]	<0.001	77.6	Random effect	**1.50**	**1.03–2.20**
Solid tumors	5 [18, 19, 21, 72, 80*]	<0.001	87.5	Random effect	1.29	0.87–1.92

Modern, better targeted, safer and lower-dosage consolidative RT

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Original Article

Limited-Stage Diffuse Large B-Cell Lymphoma Treated With Abbreviated Systemic Therapy and Consolidation Radiotherapy

Involved-Field Versus Involved-Node Radiotherapy

Belinda A. Campbell, MBBS[1,2,3]; Joseph M. Connors, MD[2]; Randy D. Gascoyne, MD[2,4]; W. James Morris, MD[3]; Tom Pickles, MD[3]; and Laurie H. Sehn, MD[2]

	Total (n = 288)	IFRT (n = 138)	INRT≤5 cm (n = 150)
Total number of relapses	64 (22%)	32 (23%)	32 (21%)
Infield relapse only	4 (2%)	2 (2%)	2 (1%)
Distant relapse without infield relapse	50 (17%)	24 (17%)	26 (17%)
Distant only	44	24	20
Marginal only	3	–	3
Marginal + distant	3	–	3
Distant and infield relapse	10 (3%)	6 (4%)	4 (3%)

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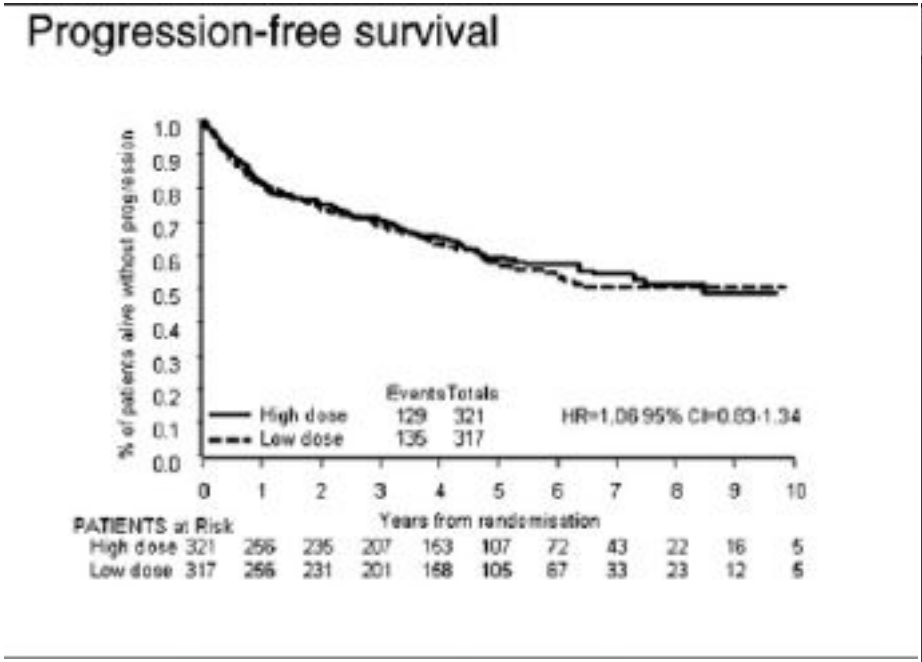
Phase III randomised trial

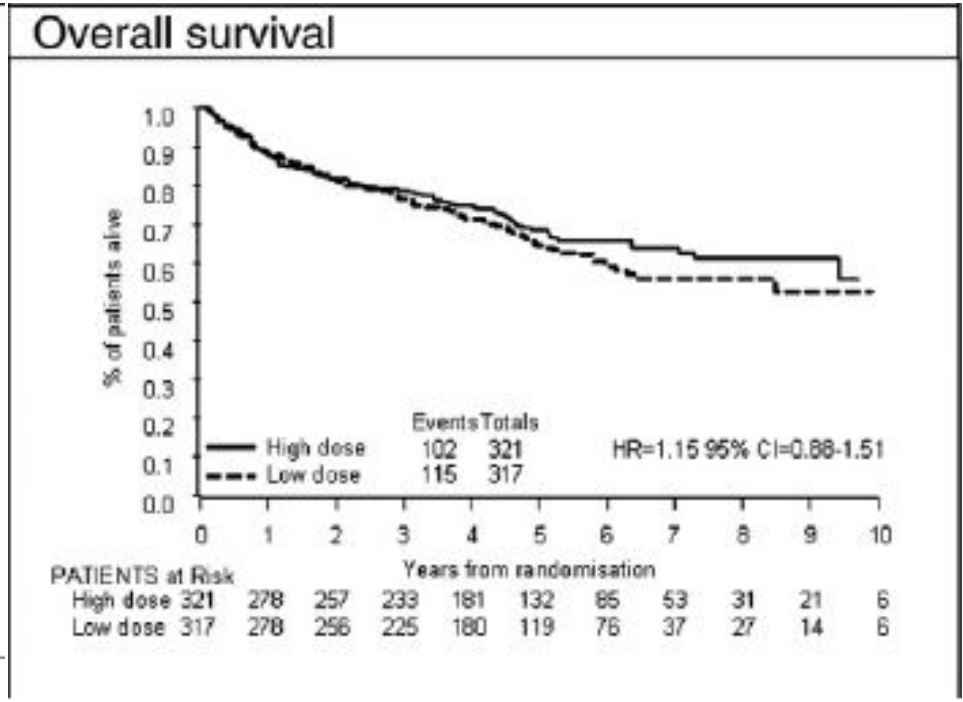
Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

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

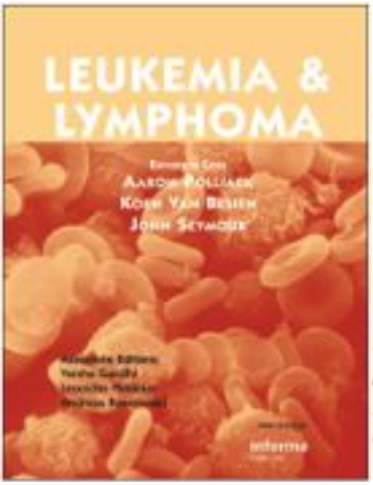
	Indolent		Aggressive		Total
	24 Gy *N* = 180	40–45 Gy *N* = 181	30 Gy *N* = 319	40–45 Gy *N* = 321	
Age median (range)	62 (29–85)	64 (30–89)	65 (18–91)	65 (23–92)	64 (18–92)
Male gender N (%)	84 (47)	97 (54)	179 (56)	168 (52)	528 (53)
First-line treatment: stage N (%)					
I	69 (40)	72 (41)	77 (24)	68 (21)	286 (29)
IE	38 (22)	47 (27)	55 (17)	56 (18)	196 (20)
II/IIE	11 (6)	13 (7)	79 (25)	93 (30)	216 (20)
III/IV	6 (3)	12 (7)	45 (14)	45 (14)	108 (11)
Relapsed/refractory; any stage N (%)	50 (29)	30 (17)	44 (14)	41 (13)	165 (17)
Not known N	6	7	19	18	50
B symptoms N (%)	13 (8)	4 (2)	43 (15)	40 (15)	100 (11)
Time from diagnosis to randomisation; median months (range)	3.1 (0.2–220)	2.8 (0–179)	4.6 (0–352*)	4.5 (0–164)	4.1 (0–352)
Indication for RT radical	119 (66)	130 (72)	36 (12)	35 (12)	320 (32)
Palliation	56 (31	46 (25)	25 (8)	29 (9)	156 (16)
Consolidation	5 (3)	5 (3)	257 (81)	255 (79)	522 (52)
Previous/contemporaneous chemotherapy N (%)	46 (26)	36 (20)	256 (80)	252 (79)	590 (59)
Previous radiotherapy N (%)	15 (8)	24 (13)	32 (10)	29 (9)	100 (10)
Previous rituximab exposure N (%)	2 (1)	2 (1)	34 (11)	33 (10)	71 (7)
Karnofsky scale N (%)					
60–80	16 (12)	16 (11)	67 (30))	61 (30)	160 (23)
90	44 (34)	34 (24)	66 (29)	67 (32)	211 (30)
100	70 (53)	90 (64)	92 (41)	80 (38)	332 (47)
Not known	50	41	94	113	298

40-45 Gy vs 30 Gy





Lowry et al, Radiother Oncol 2011



Renewed Interest In The Role Of Consolidative Radiotherapy In Advanced Stage Diffuse Large B-Cell Lymphoma (DLBCL)

Zheng Shi, Natia Esiashvili, Christopher Flowers, Satya Das, and Mohammad K Khan

Leukemia&Lymphoma 2013

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Why Radiation Therapy for Early Stage FL?

- Indolent B-cells lymphomas are highly radiosensitive
- Local recurrences are unusual
- Low toxicity, high feasibility
- Possibility to cure a significant proportion of patients

Historical data

Table 1
Follicular lymphoma, stage I–II radiation therapy alone.

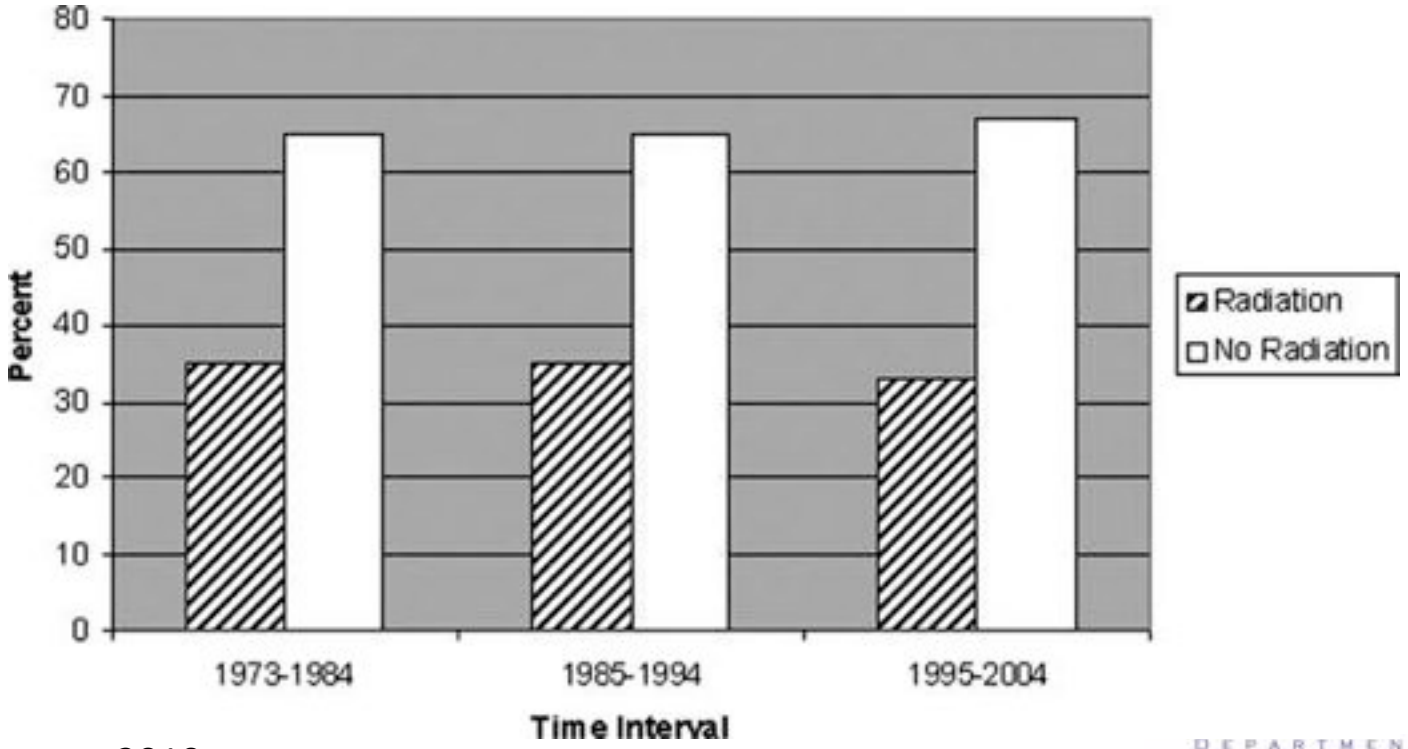
Center	N	Stage	FFR/DFS (yrs)	Survival (yrs)
PMH [34]	460	I–II	41% (10)	62% (10)
BNLI [7]	208	I	49% (10)	64% (10)
Stanford [10]	177	I–II	44% (10)	64% (10)

FFR-Freedom-from-Relapse; DFS-Disease Free Survival; PMH-Princess Margaret Hospital; BNLI-British National Lymphoma Investigation.

Hoppe RT, Best Pract Res Clin Hematol 2011

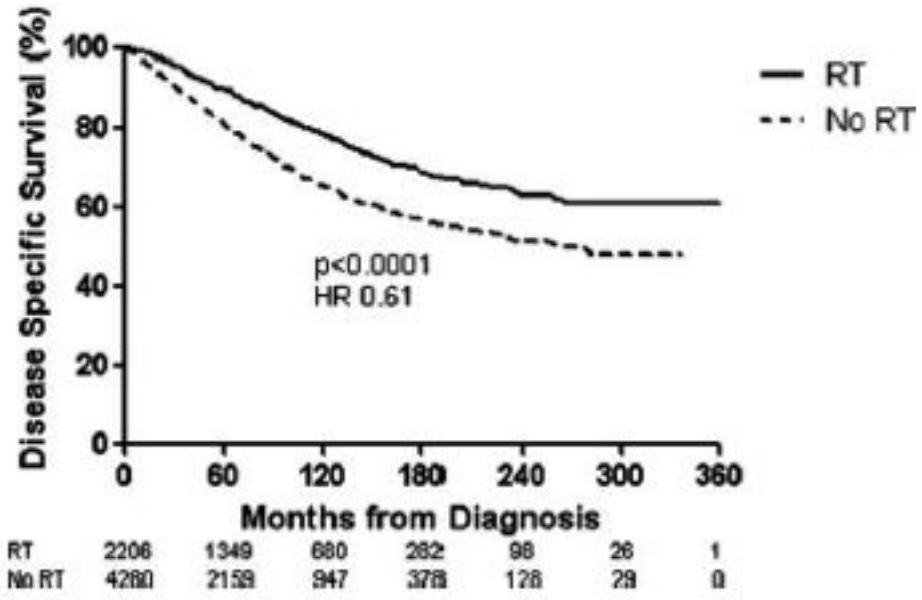
Long-term outcome: SEER data

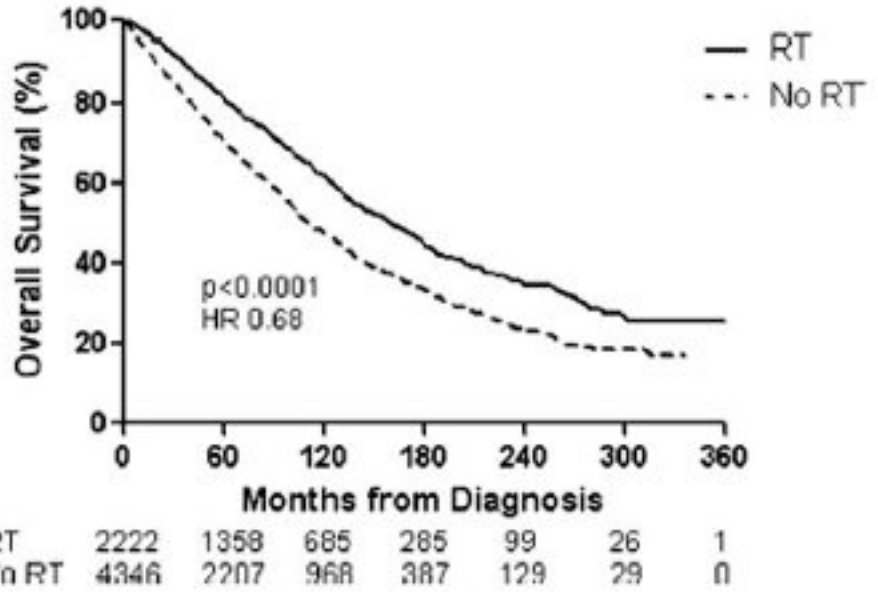
- 6568 pts with stage I-II follicular lymphoma diagnosed between 1973 and 2004
- 2222 pts (34%) treated with upfront RT



Pugh et al, Cancer, 2010

Long-term outcome: SEER data



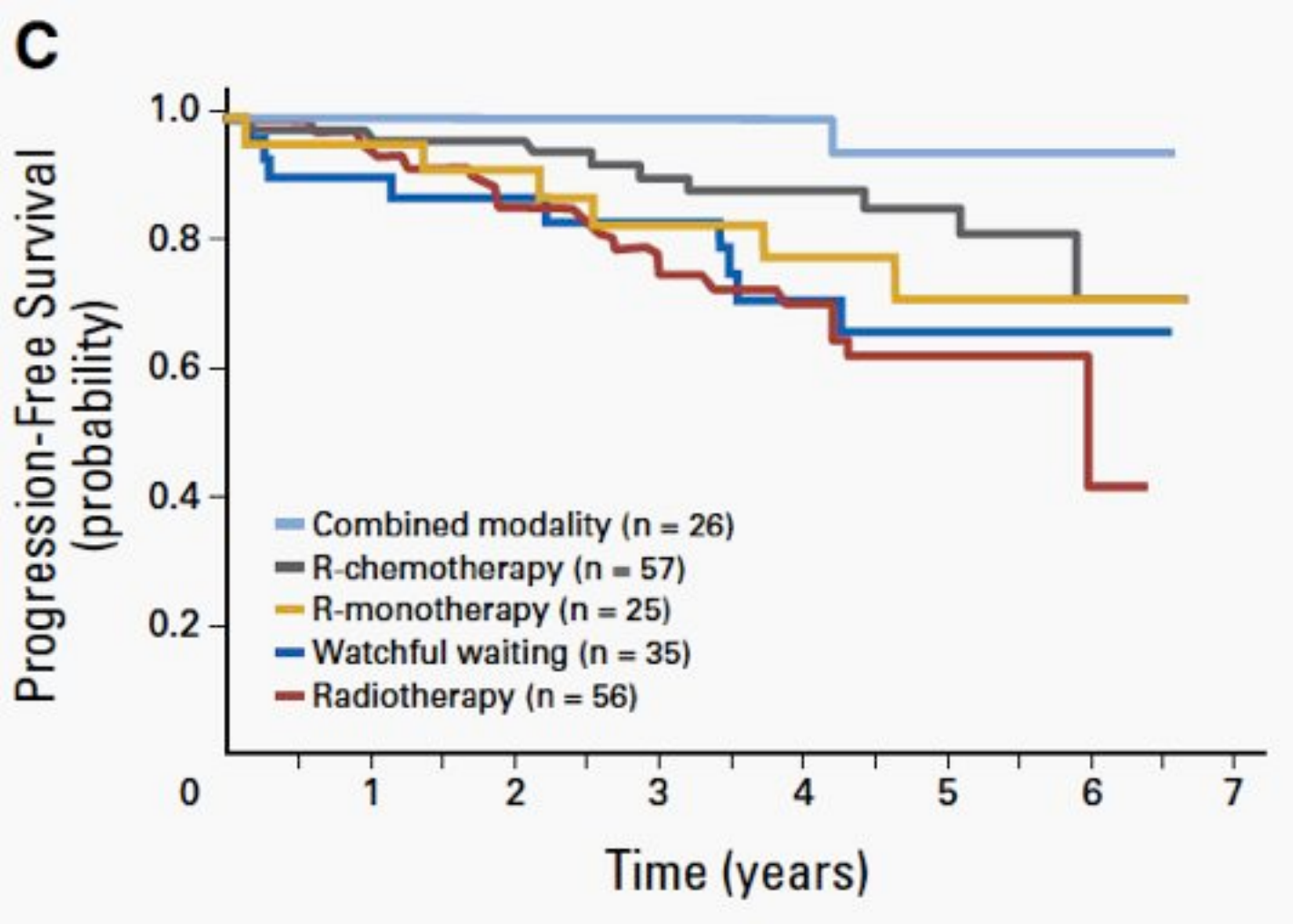


Pugh et al, Cancer, 2010

Lymphocare study

- 471 pts with stage I follicular lymphoma
- 206 pts rigorously staged (bone marrow aspirate and biopsy and an imaging study – CT, PET or both)
- **Treatment:**
  - R-chemo 28%
  - RT 27%
  - observation 17%
  - systemic therapy + RT 13%
  - rituximab monotherapy 12%
  - other 3%

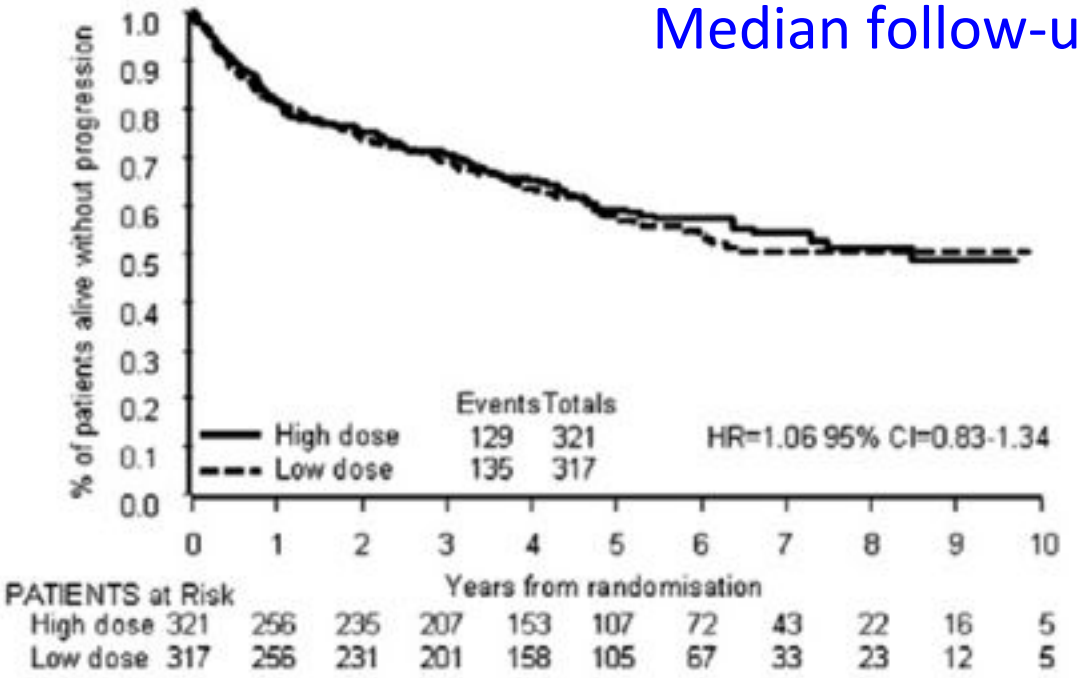
Friedberg et al, JCO, 2012



Friedberg et al, JCO, 2012

Reduced RT dose 40 Gy vs 24 Gy : a phase III randomized trial

Progression-free survival



Median follow-up time: 5.6 years

Lowry L, Radiother Oncol 2011

Reduced RT dose in NHL FORT trial: 4 Gy vs. 24 Gy

614 sites in 548 pts with FL and some with MZL

Random to 24 Gy (299 sites) and 4 Gy (315 sites)

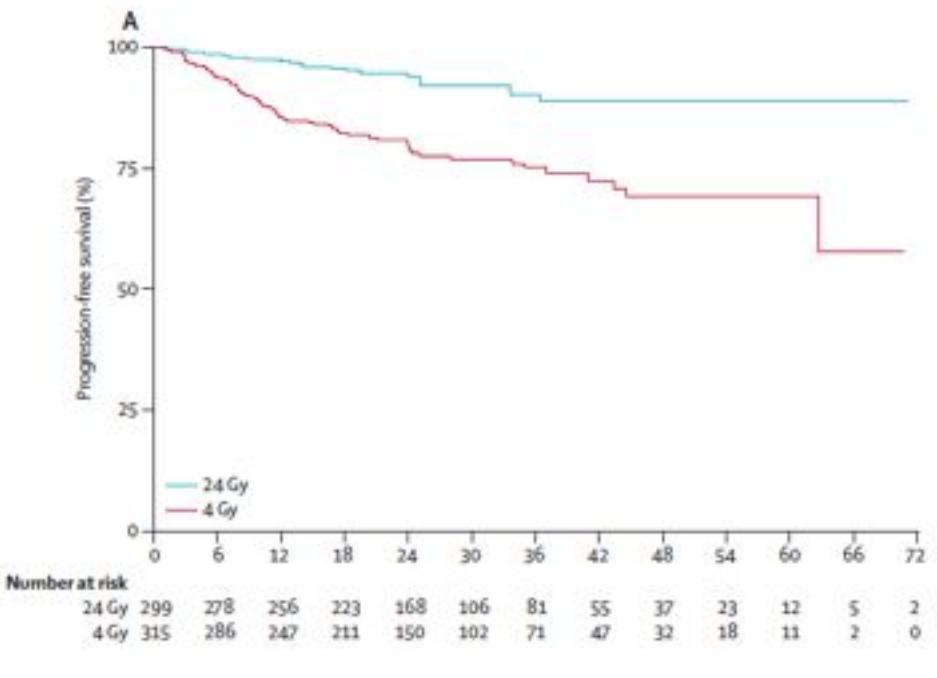
	24 Gy		4 Gy		p value*
	Complete response (%)	Complete response plus partial response (%)	Complete response (%)	Complete response plus partial response (%)	
All patients	176/260 (68%)	236/260 (91%)	137/281 (49%)	227/281 (81%)	0·0095
Follicular lymphoma	152/226 (67%)	205/226 (91%)	116/243 (48%)	194/243 (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

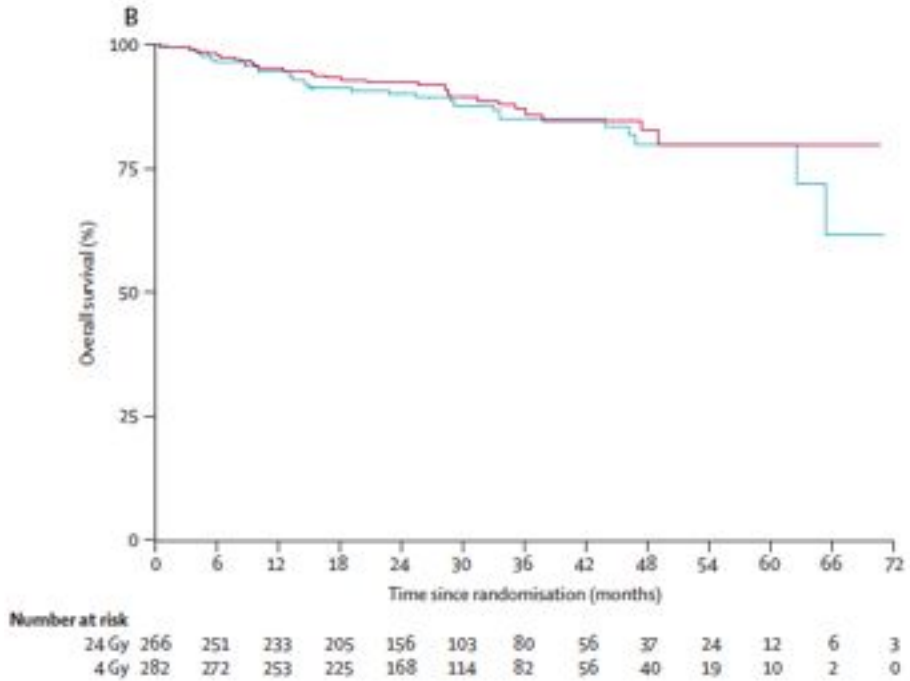
*p value for responders (complete response plus partial response) versus non responders. †Confirmed by central review.

Table 3: **Response by subgroup**

Hoskin et al, Lancet Oncol, 2014

Reduced RT dose in NHL FORT trial: 4 Gy vs 24 Gy





Hoskin et al, Lancet Oncol, 2014

"Regional" RT *vs* Involved Nodal RT≤5cm

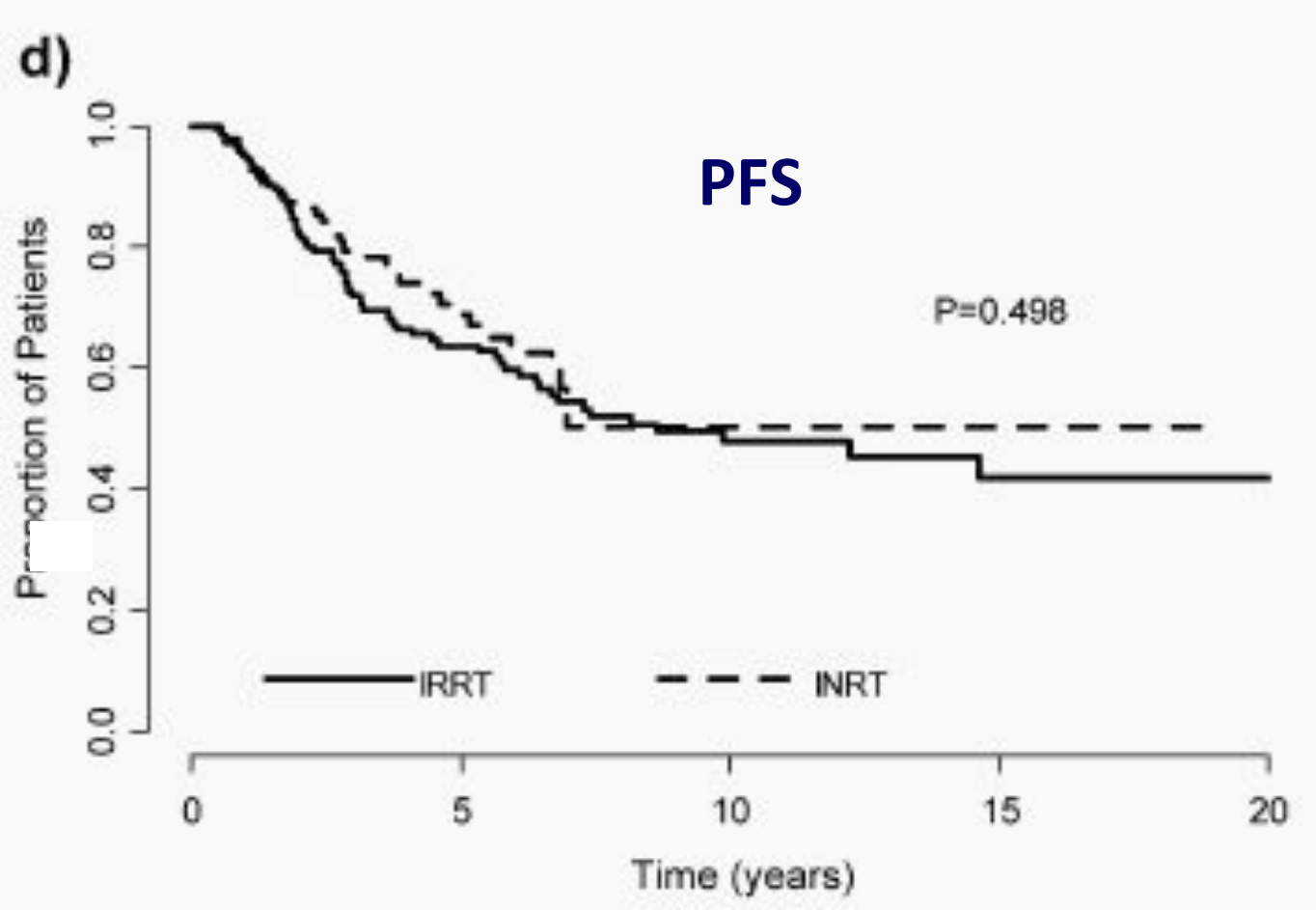
Characteristic	No. of Patients (%) Total, n=237	IRRT, n=142	INRT≤5 cm, n=95	P
Median age, y	61	59	64	.021[a]
Age >60 y	128 (54)	70 (49)	58 (61)	.075
Sex, men	113 (48)	68 (48)	45 (47)	.938
Performance state, ECOG				.700
0	179 (75)	106 (75)	73 (77)	
1-2	60 (25)	36 (25)	22 (23)	
Grade				.948
1	129 (54)	78 (55)	51 (54)	
2	80 (34)	48 (34)	32 (34)	
3A	28 (12)	16 (11)	12 (13)	
Stage				.004[a]
IA	179 (76)	98 (69)	81 (85)	
IIA	58 (24)	44 (31)	14 (15)	
Nodal size				.001[a]
Completely excised	18 (8)	18 (13)	0 (0)	
<5 cm	173 (73)	98 (69)	75 (79)	
≥5 cm	46 (19)	26 (18)	20 (21)	
Extranodal disease	55 (23)	16 (11)	39 (41)	<.001[a]
Serum LDH level				.130
Elevated	16 (7)	7 (5)	9 (10)	
≤Normal	210 (89)	132 (95)	78 (90)	
Unknown	11 (5)	3	8	
Radiotherapy dose				<.001[a]
30 Gy in 10 fractions	78 (33)	49 (35)	29 (31)	
35 Gy in 20 fractions	79 (33)	59 (42)	20 (21)	
Other	80 (34)	34 (24)	46 (48)	

IRRT indicates involved regional radiotherapy; INRT≤5 cm, involved node radiotherapy with margins up to 5 cm; LDH, lactate dehydrogenase; Gy, grays.

Campbell et al, Cancer, 2010

Median follow-up time: 7.5 years

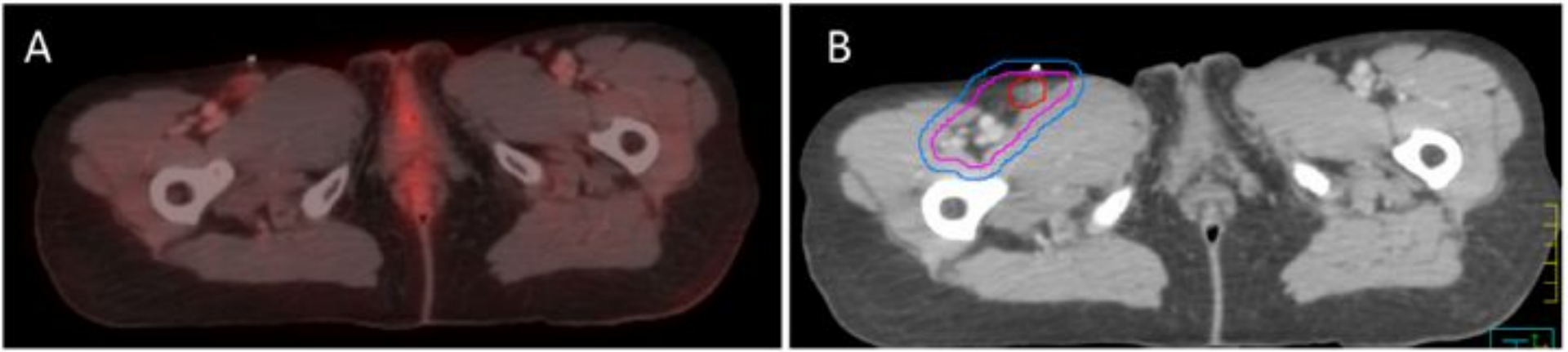
“Regional” RT *vs* INRT≤5cm



Campbell et al, Cancer, 2010

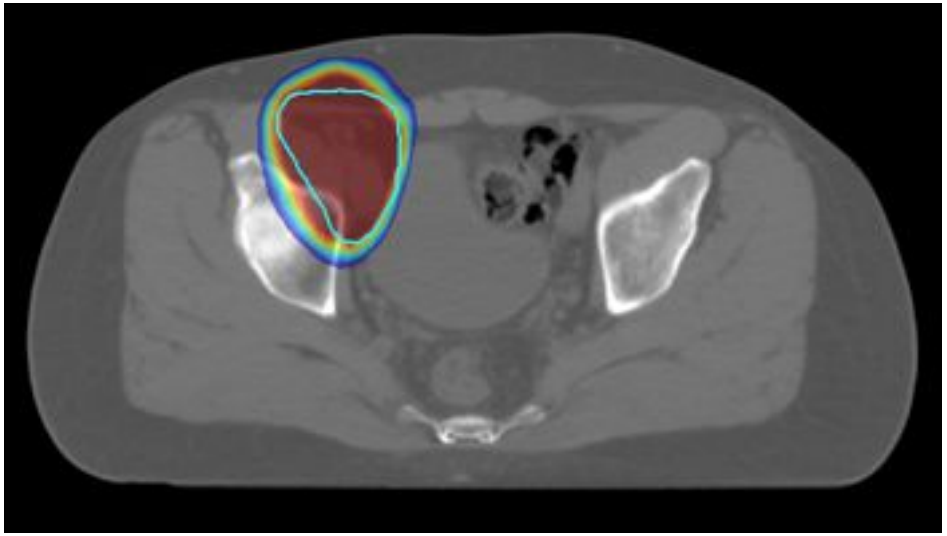
Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

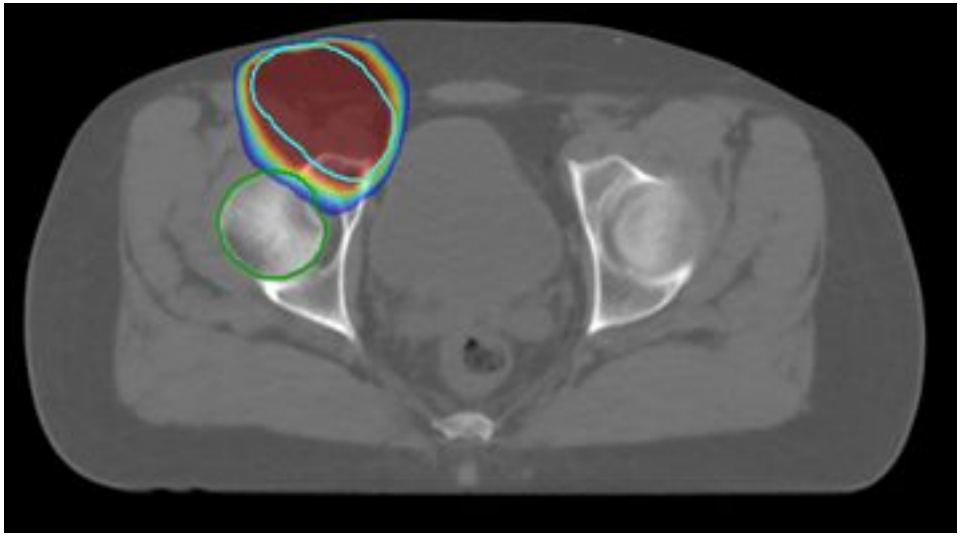
Tim Illidge, MD, PhD,* Lena Specht, MD,† Joachim Yahalom, MD,‡ Berthe Aleman, MD, PhD,§ Anne Kiil Berthelsen, MD,‖ Louis Constine, MD,¶ Bouthaina Dabaja, MD,# Kavita Dharmarajan, MD,‡ Andrea Ng, MD,** Umberto Ricardi, MD,†† and Andrew Wirth, MD,‡‡, on behalf of the International Lymphoma Radiation Oncology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

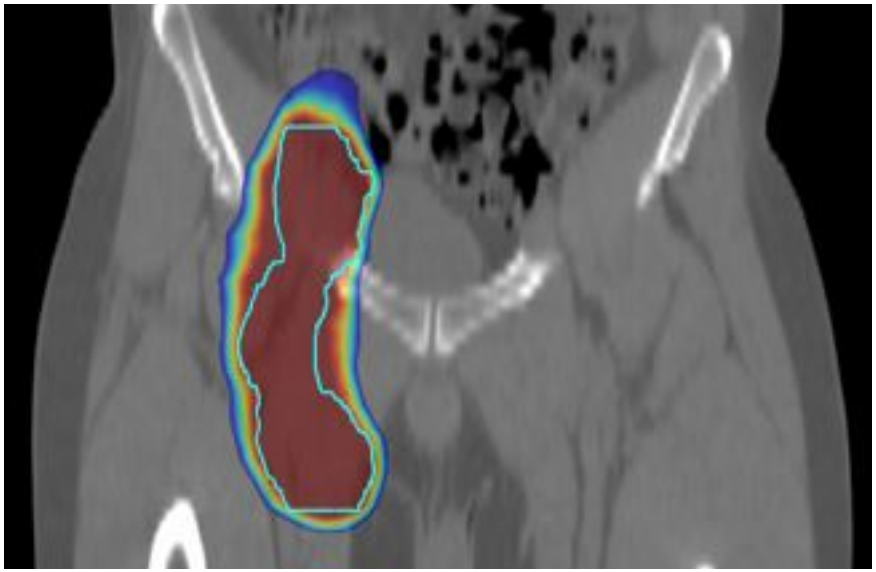


Illidge et al, IJROBP, 2014

- M. L., 43 years old, follicular NHL IA





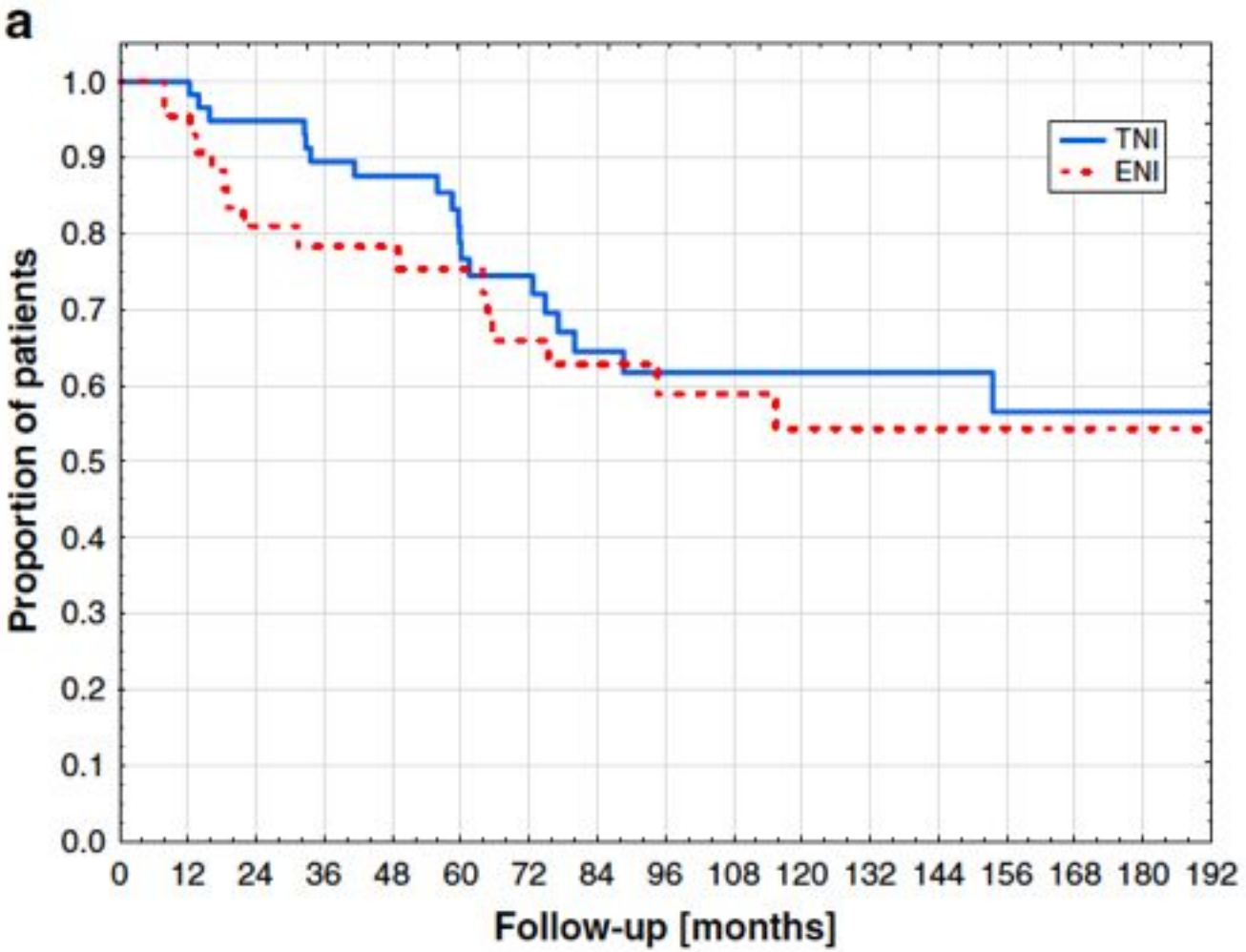


How to improve results?

Study	Institution	Patient No.	Treatment	10-Year FFR	10-Year OS	10-Year DSS
Soubeyran 1988[7]	Fondation Bergonié	103	RT ± Chemo	49%[a]	56%	NA
Kelsey 1994[11]	British National Lymphoma Investigation (RCT)	148	RT	33%	52%	NA
			RT + Chemo	42%	42%	NA
Vaughan Hudson 1994[6]	British National Lymphoma Investigation	208	RT	47%	64%	70%
Pendlebury 1995[26]	Royal Marsden, England	58	RT	43%[b]	79%	NA
MacManus & Hoppe 1996[4]	Stanford	177	RT	44%	64%	NA
Seymour 2003[27]	M. D. Anderson	83	RT+ Chemo	72%	80%	NA
Petersen 2004[5]	Princess Margaret Hospital, Canada	460	RT	51%	62%	79%
Advani 2004[12]	Stanford	43	WW	NA	85%	NA
Guadagnolo 2006[8]	Joint Center	106	RT ± Chemo	46%	75%	NA
Current study	NCI SEER	2222	RT	NA	62%	79%
		4346	No RT	NA	48%	65%

Pugh et al, Cancer 2010

EFRT/TNI does not protect from relapses



Guckenberger et al, Radiat Oncol, 2012

Rituximab-Radiotherapy Combination

Department of Oncology
University of Turin

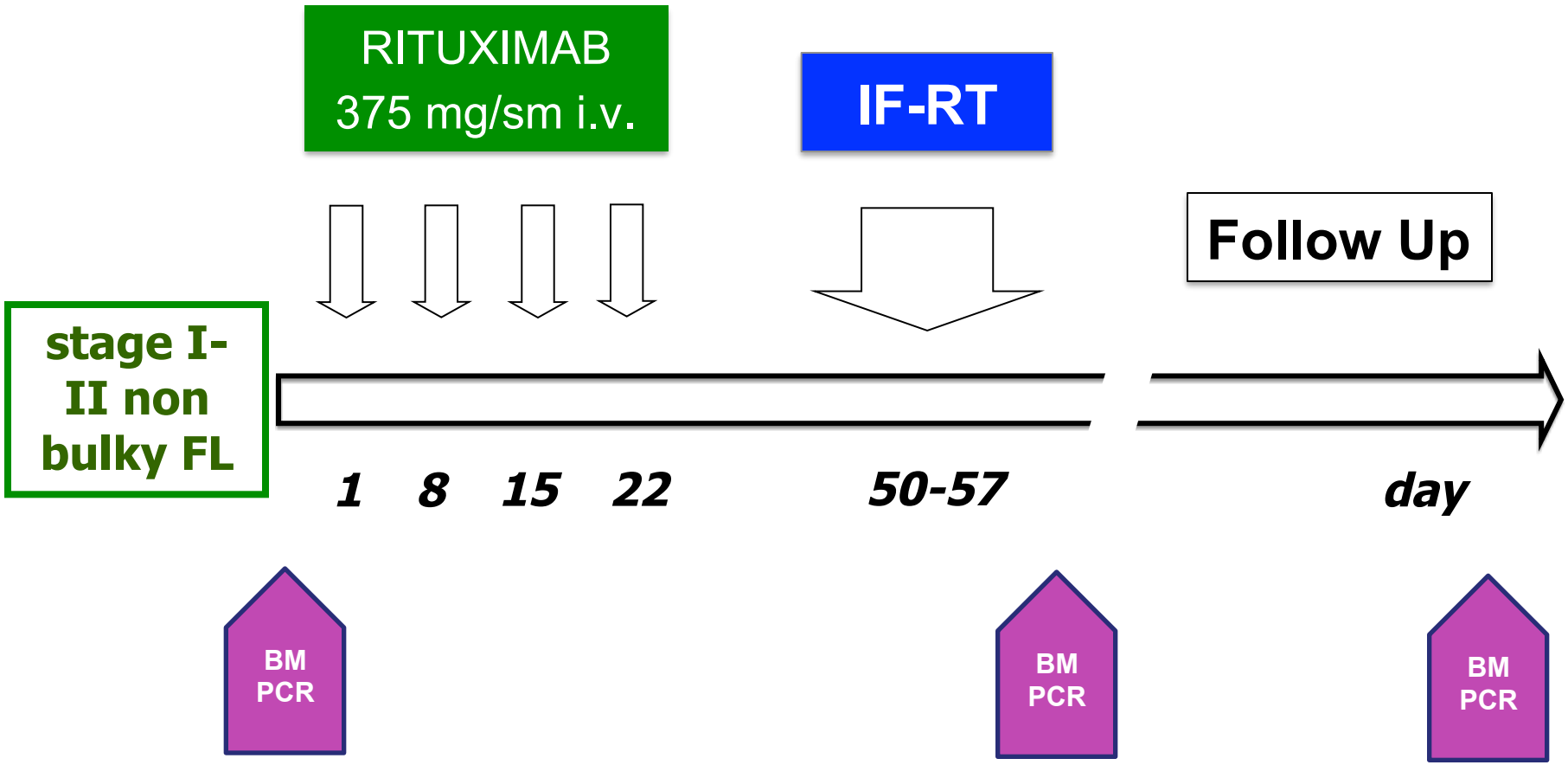
Rituximab-RT: case-control study

(PI: C. Tarella, L. Devizzi, A.M. Gianni)

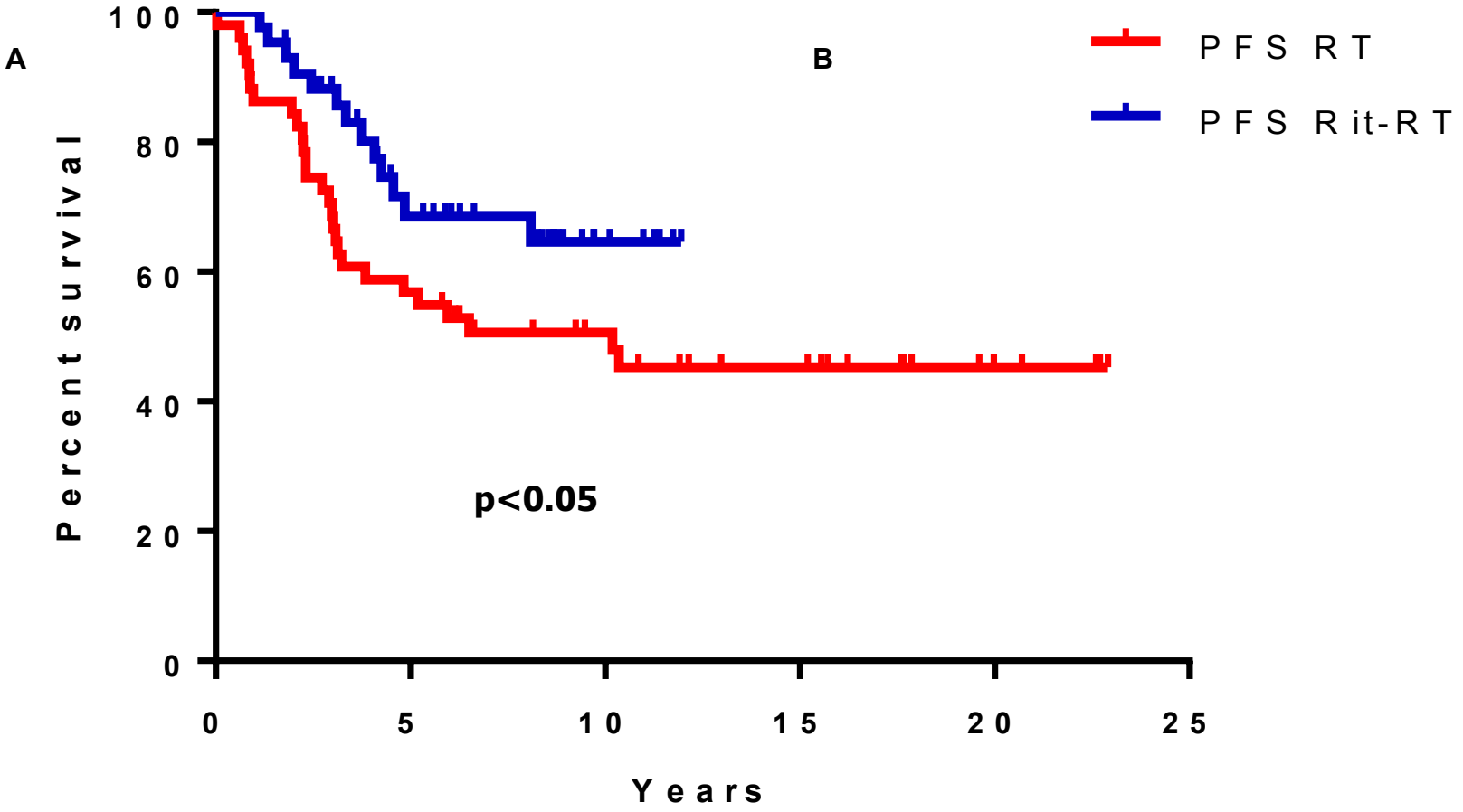
Weekly Rituximab X 4 followed by IFRT

Parameters:	Whole group	Rit-RT group*	Controls^	*p*
All patients, n=	94	43	51	-
Gender, M/F	55 / 39	26 / 17	29 /22	*NS*
Median age (years), median (range)	54 (25-82)	54 (25-82)	53 (28-79)	*NS*
Stage I / II	75 / 19	38 / 5	37 / 14	*NS*
FLIPI 0 / 1	75 / 19	34 / 9	41 / 10	*NS*
Molecular probe°, n=	33	33	not performed	-
BM PCR + ˜, n=	10	10	not performed	-
RT dose (Gy) median (range)	37 (20-50)	33 (20-45)	40 (30-50)	*<0,0001*
Median follow-up time (years)	10.9 (1.8-22.9)	8.6 (1.8-14.0)	16.7 (1.8-22.9)	

Ruella M, Fillippi AR et al, under submission



Ruella M, Fillippi AR et al, under submission



Ruella M, Fillippi AR et al, under submission

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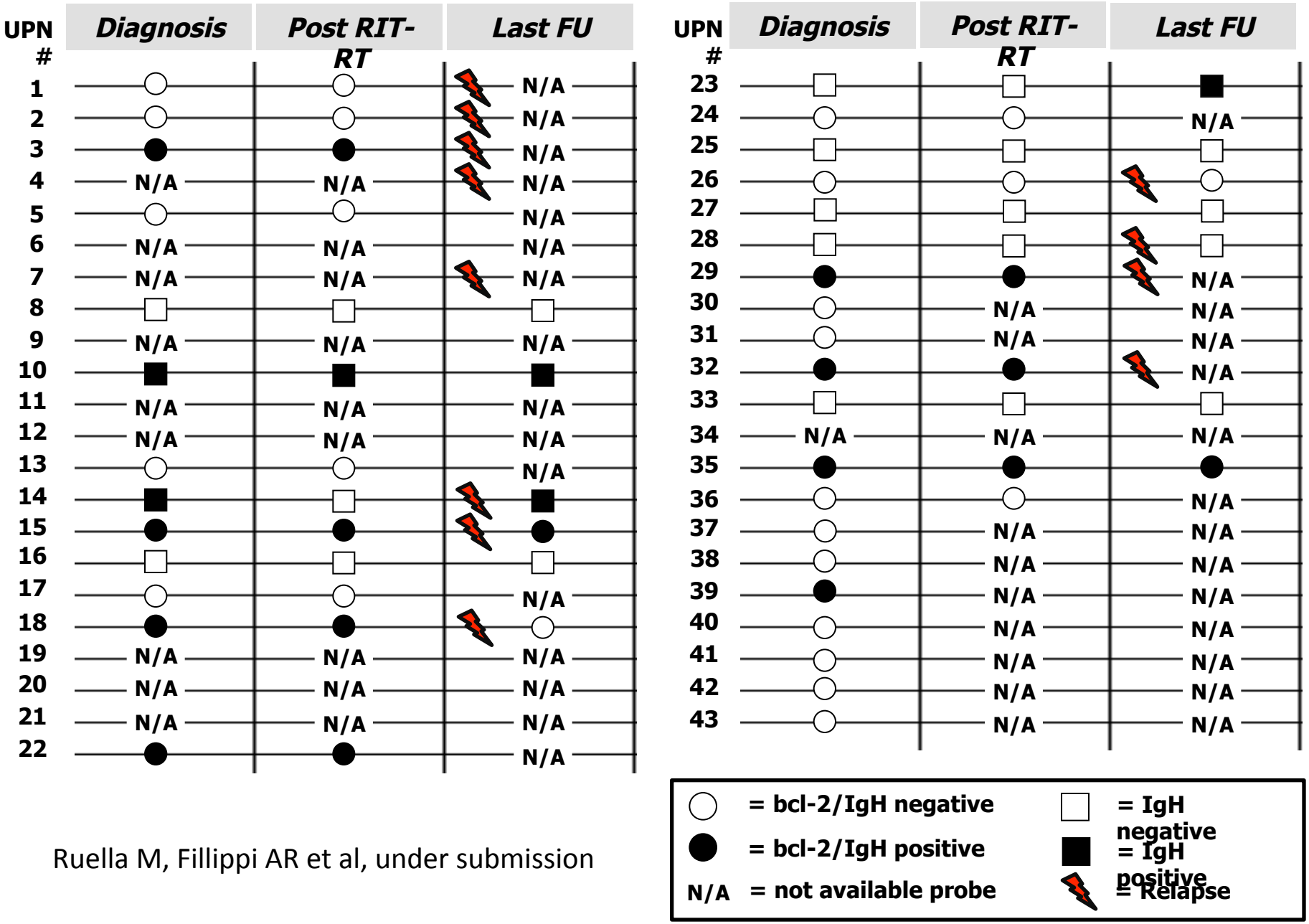

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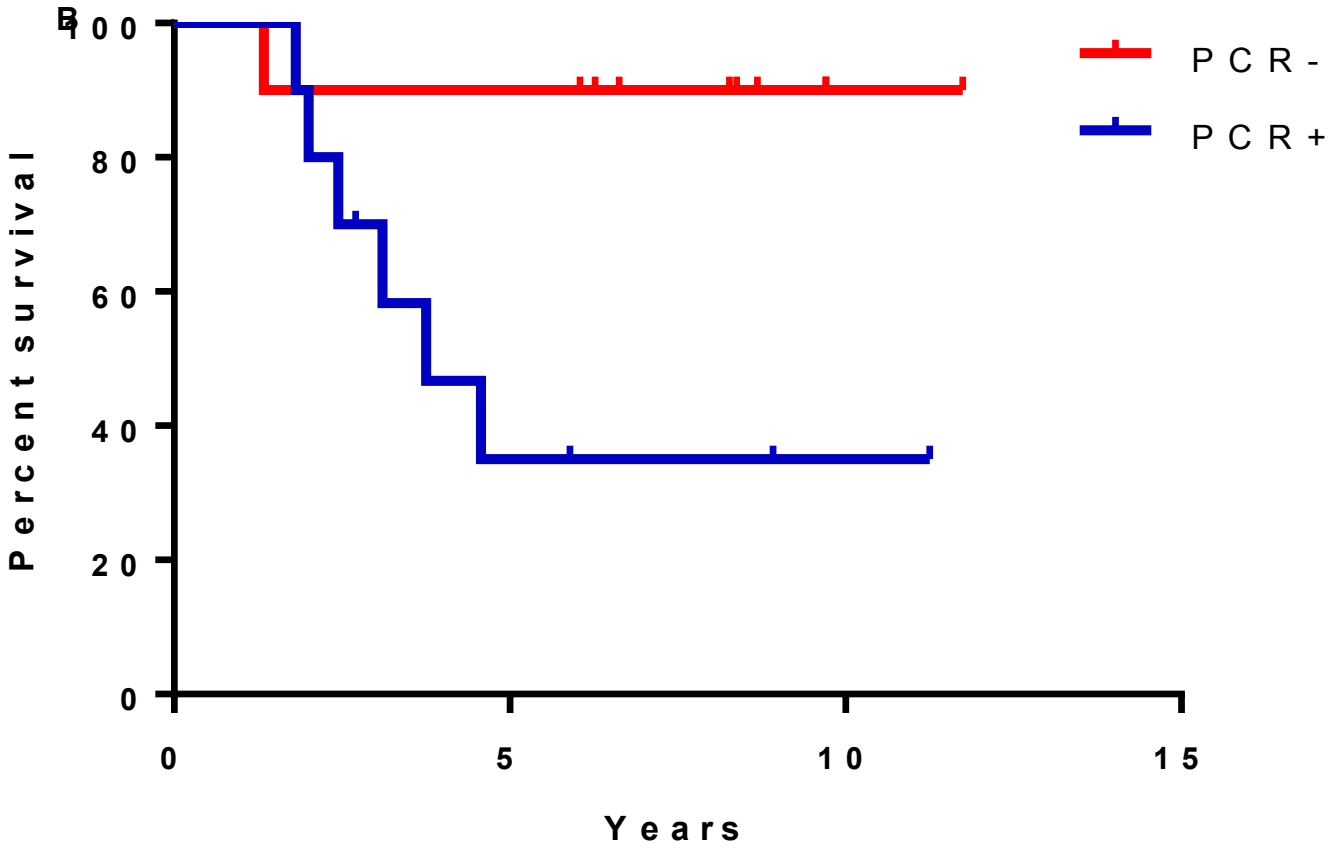
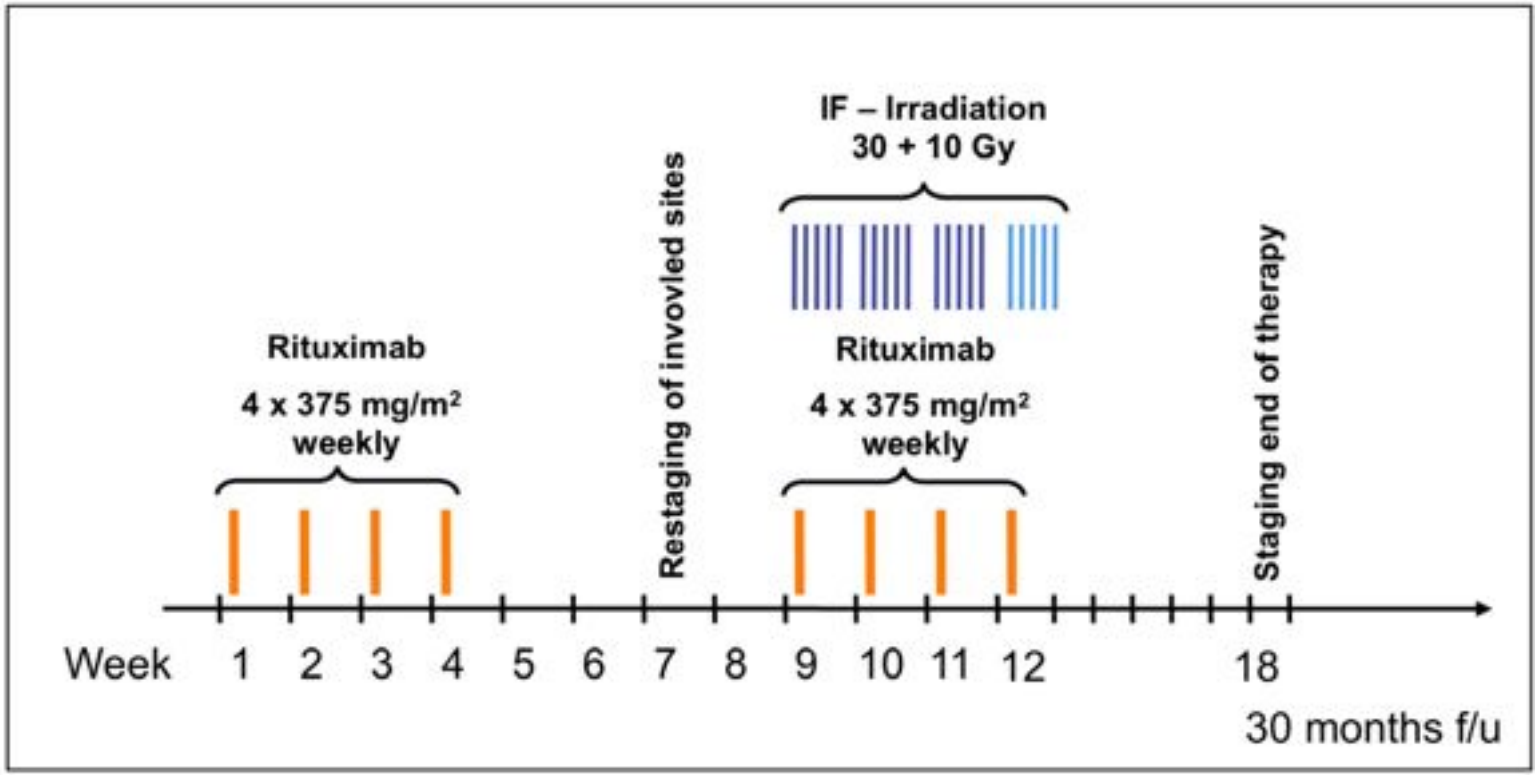


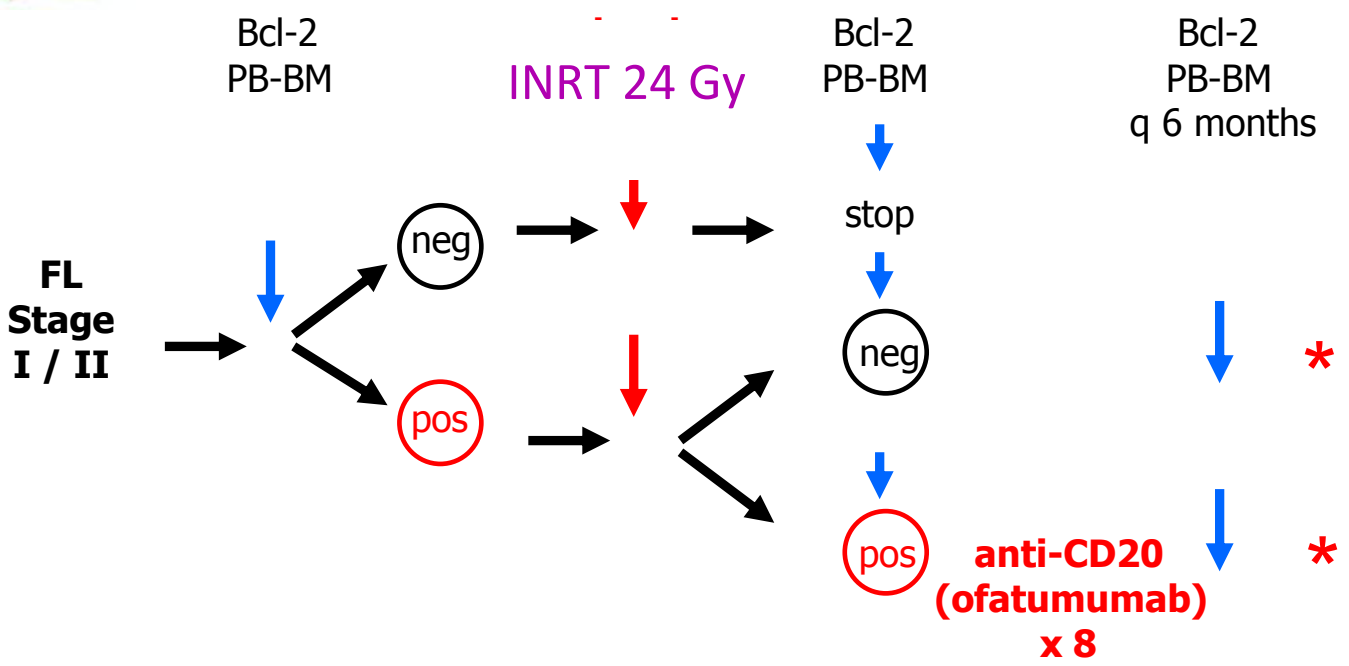
Ruella M, Fillippi AR et al, under submission

Rituximab and RT: Phase II MIR trial



Witzens-Harig et al, BMC Cancer, 2011

"MIRO'" study (Molecularly Immuno-Radiotherapy Oriented)



* In case of conversion from (neg) to (pos) → **anti-CD20 (ofatumumab) x 8**

Courtesy A. Pulsoni, FIL Follicular Lymphoma Group

Considerations on the role of RT in FL

- RT may cure a proportion of patients, however prospective data are lacking on its role vs. other options
- Discrepancy between guidelines and “real life”
- Low-dose/smaller fields are now widely accepted as the standard
- The addition of Rituximab may prolong PFS and probably increase curability rate
- Treatment choice should be individualized