Radioterapia a basse dosi nei linfomi indolenti

Umberto Ricardi

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Indolent lymphomas

- Approximately 40–45 % of all NHL (follicular lymphoma 25%; SLL 6%, Marginal zone 10%)
- Thorough staging with bone marrow biopsy and FDG-PET essential
- Minority of patients present with localised disease
- Highly radiosensitive
- Therapy guidelines
  - Stage I/II: radiotherapy
  - Stage III/IV: systemic treatment, when needed

Follicular 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 (Stanford, 177 pts):

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

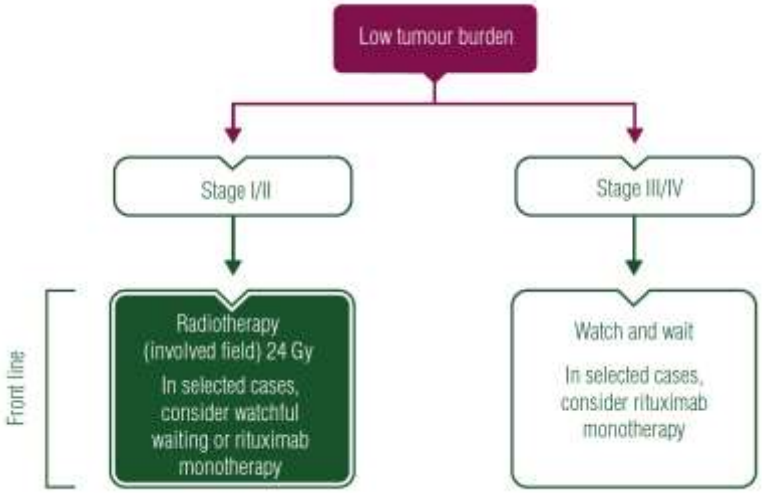
Ref.: MacManus,MP et al.; JCO 14: 1282-90 (1996)

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*



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

STAGE | **INITIAL THERAPY** | **RESPONSE TO THERAPY[n]** | **FOLLOW-UP**

See monoclonal antibody and viral reactivation (NHODG-B)

Stage I, II

- **ISRT[k] (preferred for clinical stage I or contiguous stage II)**
  - CR or PR → **FOLLOW-UP**
  - NR → See Stage II bulky, III, IV (FOLL-4)
- **or**
- **Immunotherapy ± chemotherapy (See FOLL-B)[l]**
  - CR → **FOLLOW-UP**
  - PR or NR → Consider ISRT
    - CR or PR → **FOLLOW-UP**
    - NR → See Stage II bulky, III, IV (FOLL-4)
- **or**
- **Immunotherapy ± chemotherapy (See FOLL-B) + ISRT (category 2B)[l]**
  - CR or PR → **FOLLOW-UP**
  - NR → See Stage II bulky, III, IV (FOLL-4)
- **or**
- **Observation (selected cases)[m]** → **FOLLOW-UP**

FOLLOW-UP

Clinical
- **H&P and labs every 3–6 mo for 5 y and then annually or as clinically indicated**

Surveillance imaging[o]
- **Up to 2 y post completion of treatment: CT scan no more than every 6 mo**
- **>2 y: No more than annually**

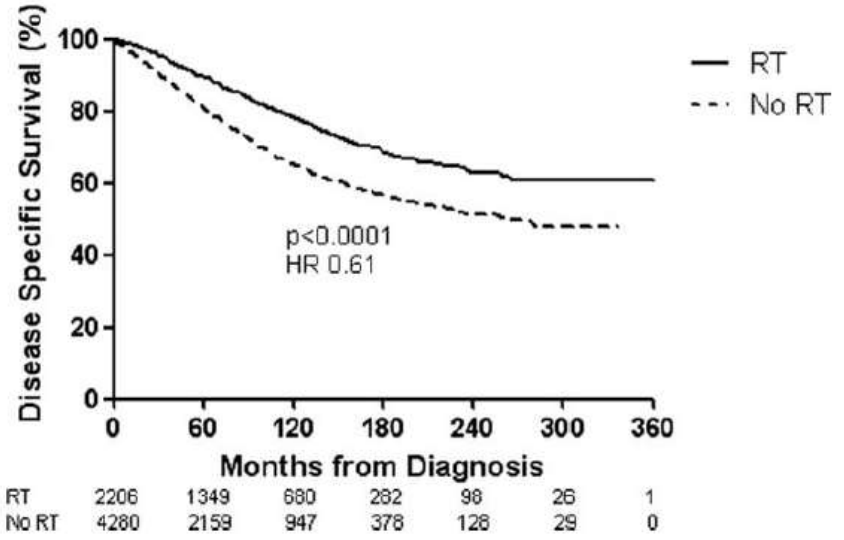
→
- **Progressive disease,[n,p] see Stage II bulky, III, IV (FOLL-4)**
- **For transformation, see FOLL-6**

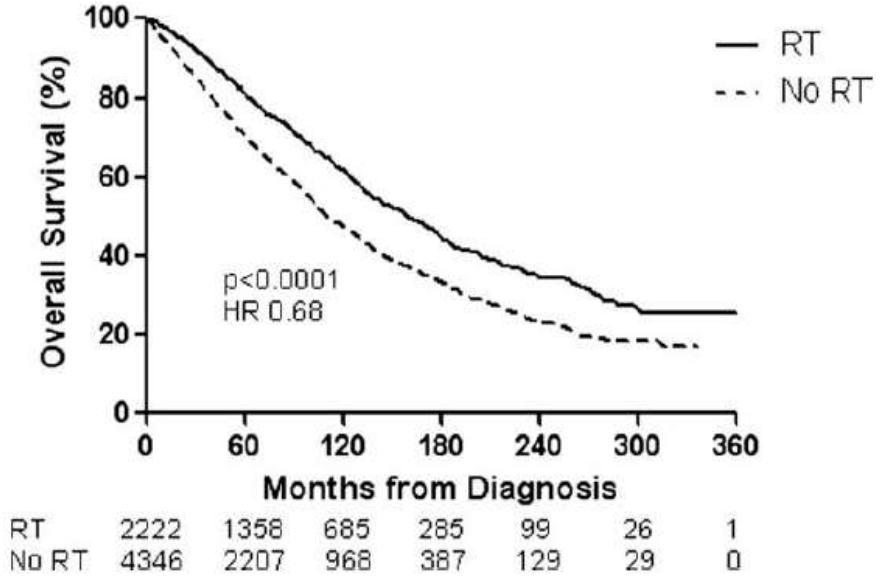
Improved Survival in Patients With Early Stage Low-Grade Follicular Lymphoma Treated With Radiation

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





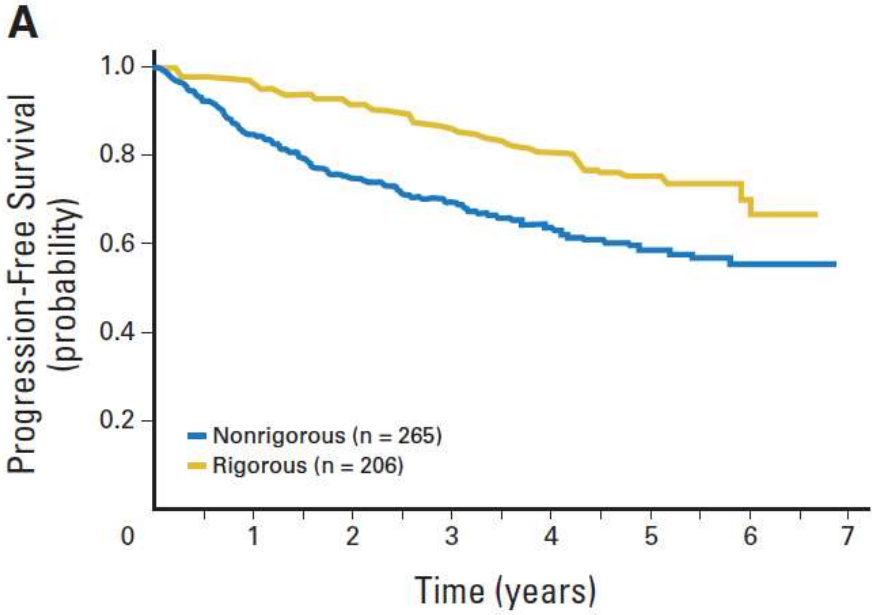
Radiation Therapy has low toxicity, high efficacy (but under-utilised)

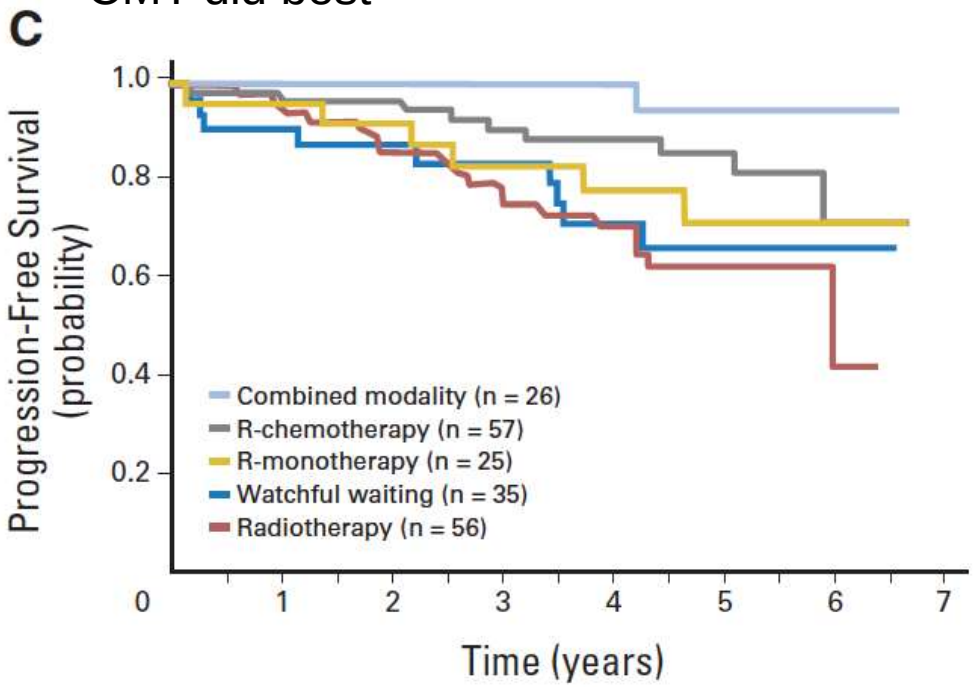
Effectiveness of First-Line Management Strategies for Stage I Follicular Lymphoma: Analysis of the National LymphoCare Study

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

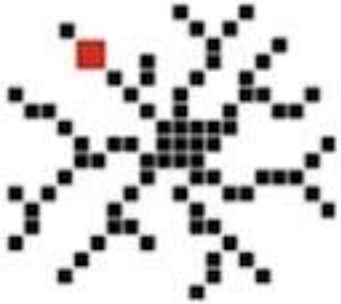
J Clin Oncol 30:3368-3375. © 2012

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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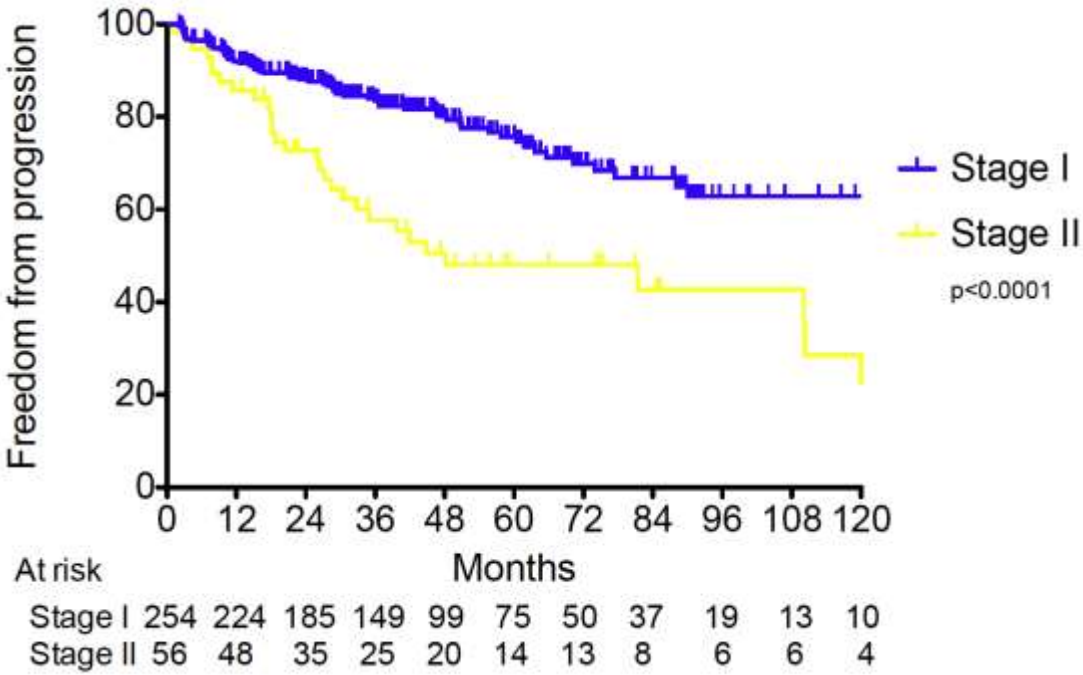
RESULTS

- **310 pts** treated from 2000-2016 at 11 centres were eligible
- **Pre-treatment characteristics**:
  - age (median 58 yrs, range 20-84)
  - female sex (n=160, 51.6%)
  - stage I disease (n=254, 81.9%)
  - FLIPI score (median 1, range 0-3)
  - B-symptoms (n=2, 0.6%)
  - bulk of disease (median 2.5 cm, range 0.2-10)
  - extranodal disease (n=83, 26.8%)

- 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)

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Treatment with 6 cycles of CVP or R-CVP after Involved Field Radiation Therapy (IFRT) Significantly Improves Progression-free Survival Compared to IFRT alone in Stage I-II Low Grade Follicular Lymphoma

Results of an International Randomized Trial

TROG CANCER RESEARCH

ALG AUSTRALASIAN LEUKAEMIA & LYMPHOMA GROUP

Presented ASTRO 2016 and ICML 2017

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Study Schema

- 150 patients from 21 centres in Australia NZ and Toronto enrolled from Feb 2000 to July 2012
- Protocol amendment 2006 mandated Rituximab in Arm B

Eligibility:
-Follicular Lymphoma
-Grades 1, 2 or 3a
-Stage I or II

Randomize

Stratify:

- Treating Centre
- Stage (I or II)
- Age (<60 or ≥ 60)
- PET Staging

Arm A:

IFRT 30 Gy

Arm B:

IFRT 30 Gy
+ (R)-CVP x 6

Follow up with annual CT

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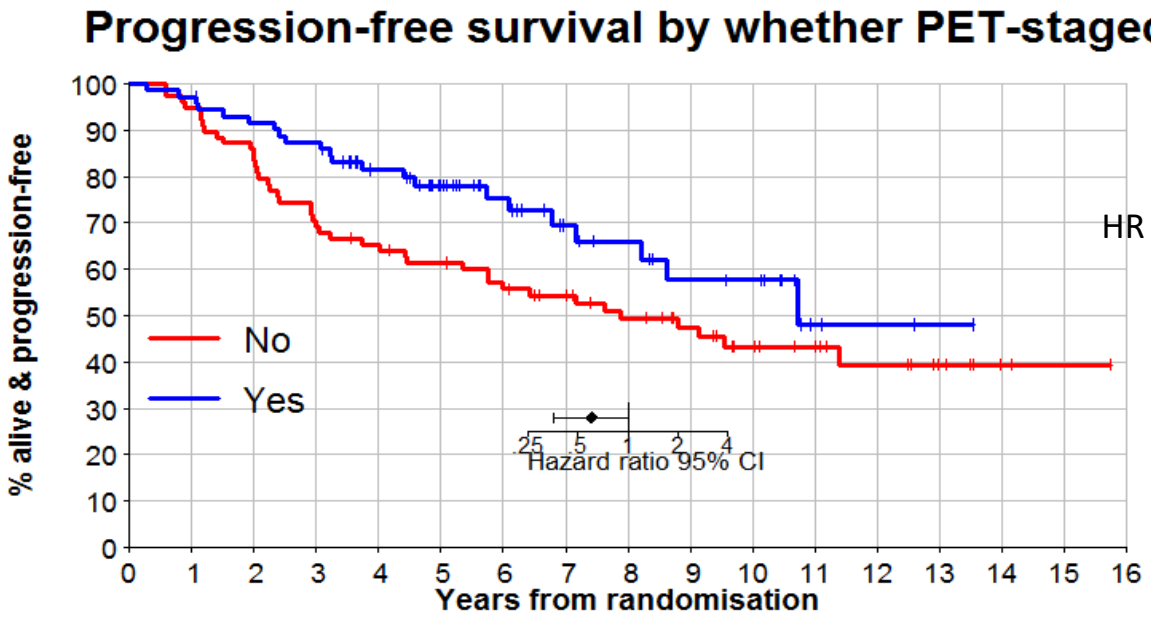
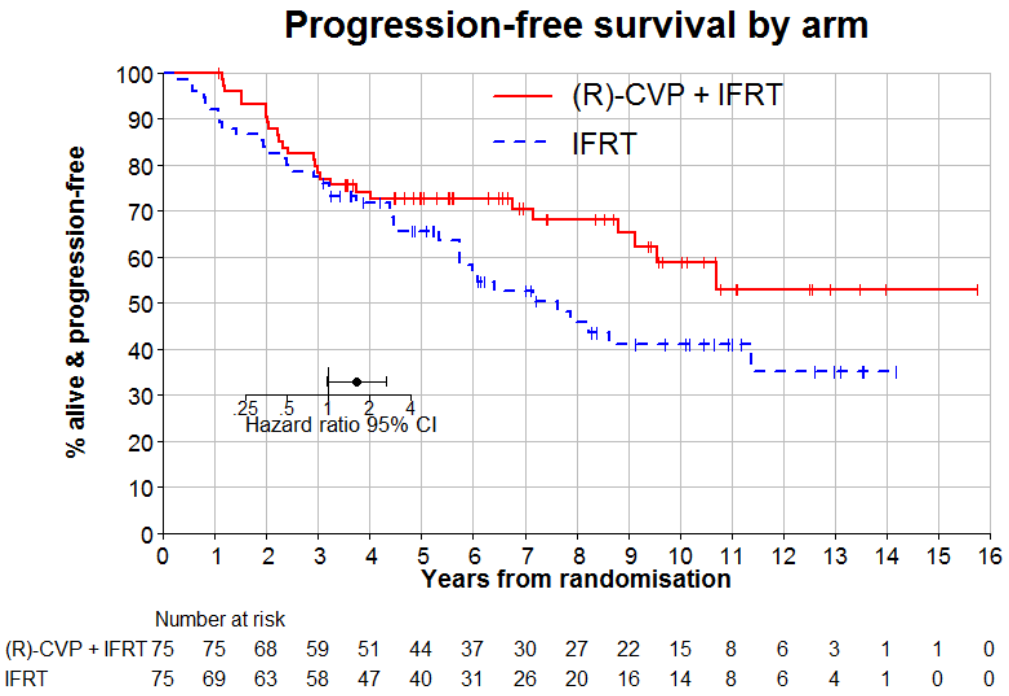
Effect of PET



HR 0.61 P = 0.056

Results: Primary Objective: PFS



10 Yrs 59%
10 Yrs 41%

Factor	Level	N	O	O/E	HR	95% CI	P
Arm	(R)-CVP+IFRT	75	26	0.758	0.57	0.34 to 0.95	0.033
Strata (8 strata):	IFRT	75	38	1.280	1.77	1.05 to 2.95	

What Volume should be treated with radiotherapy?

Extended Field vs Involved Field vs Involved Site/Node

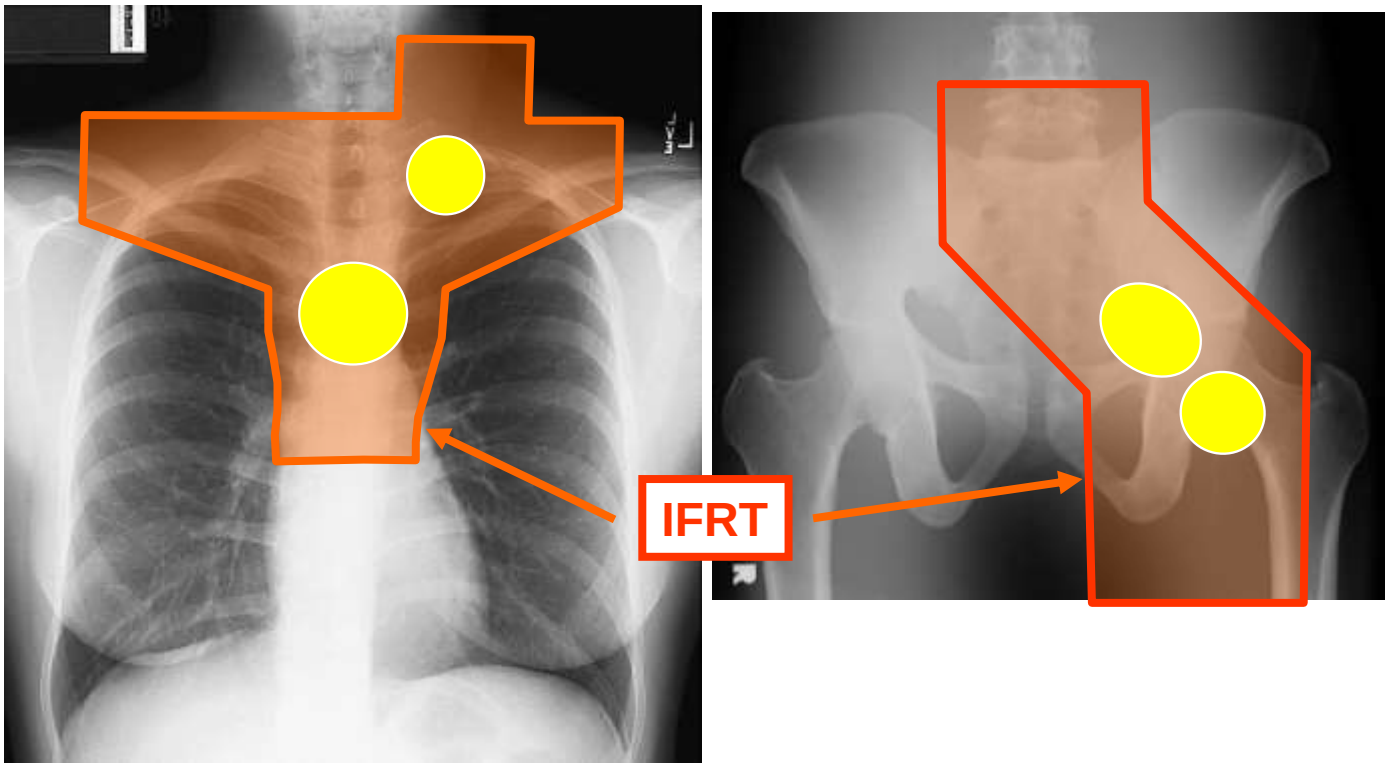
No effect of field size on PFS or OS

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

Development of Radiation Volumes

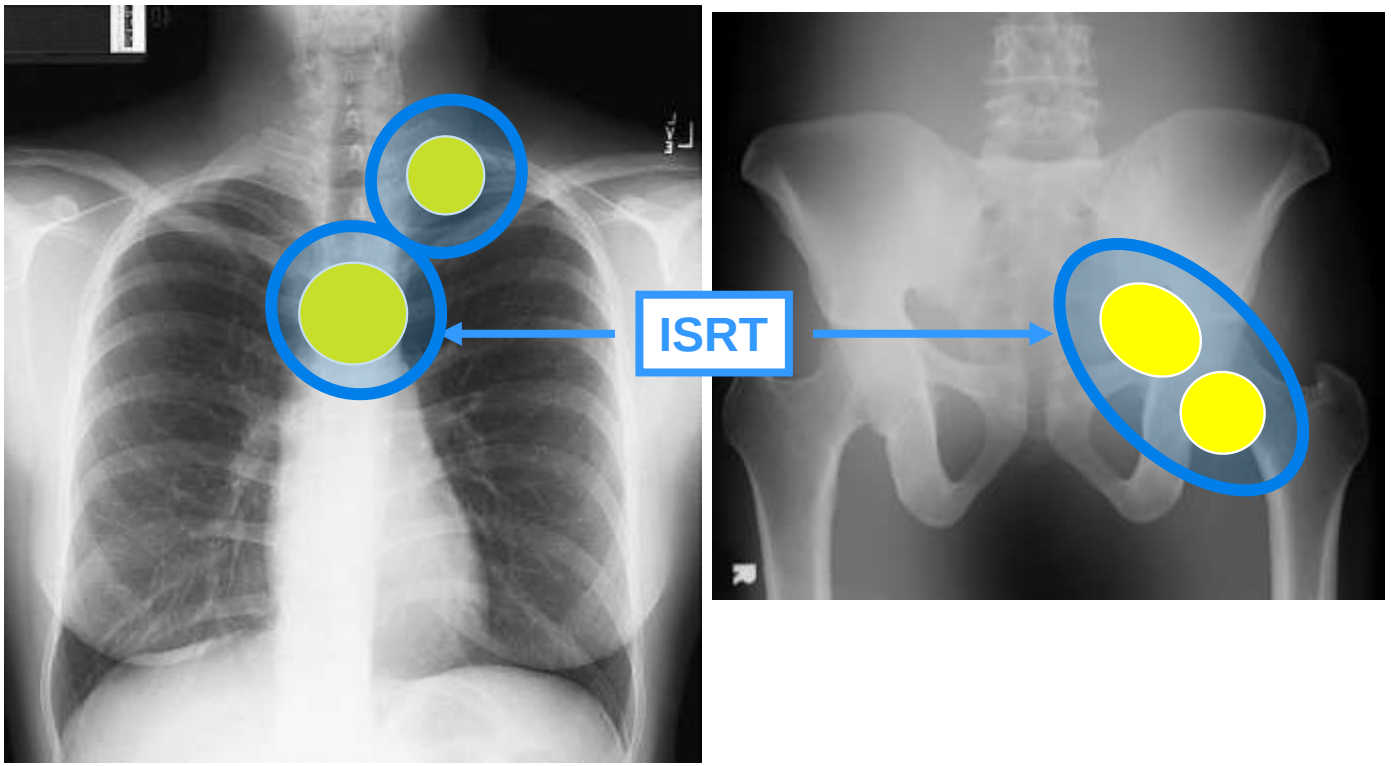
Involved Field:

2D planning, based on bony landmarks



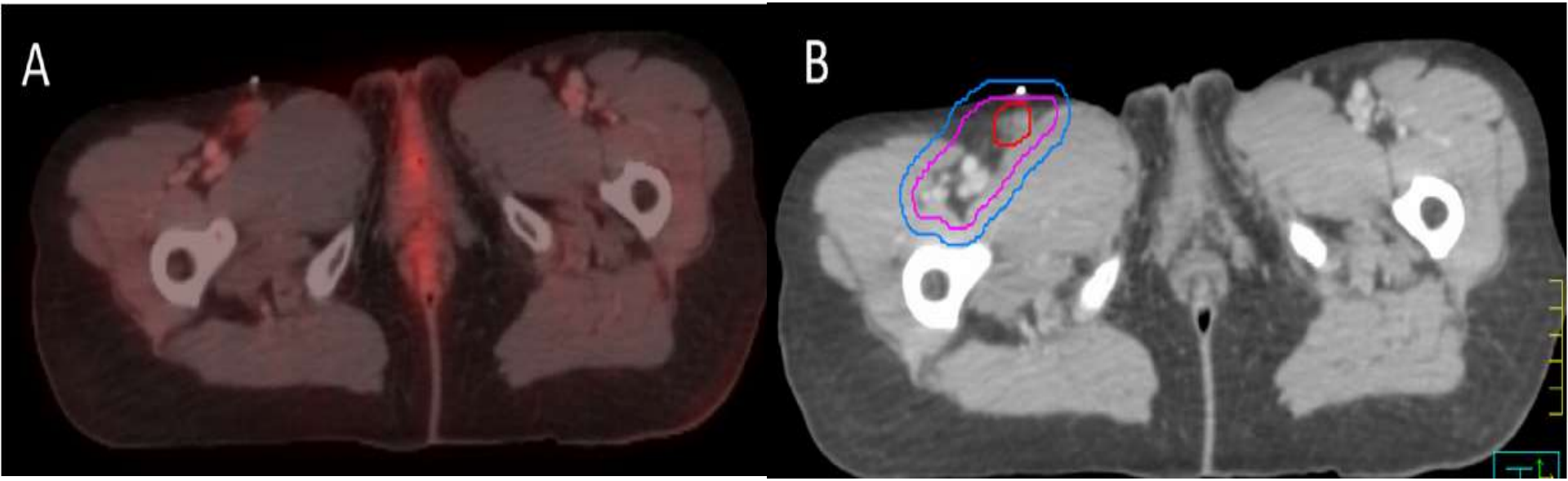
Involved Site

3D planning, based on lymphoma volume



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

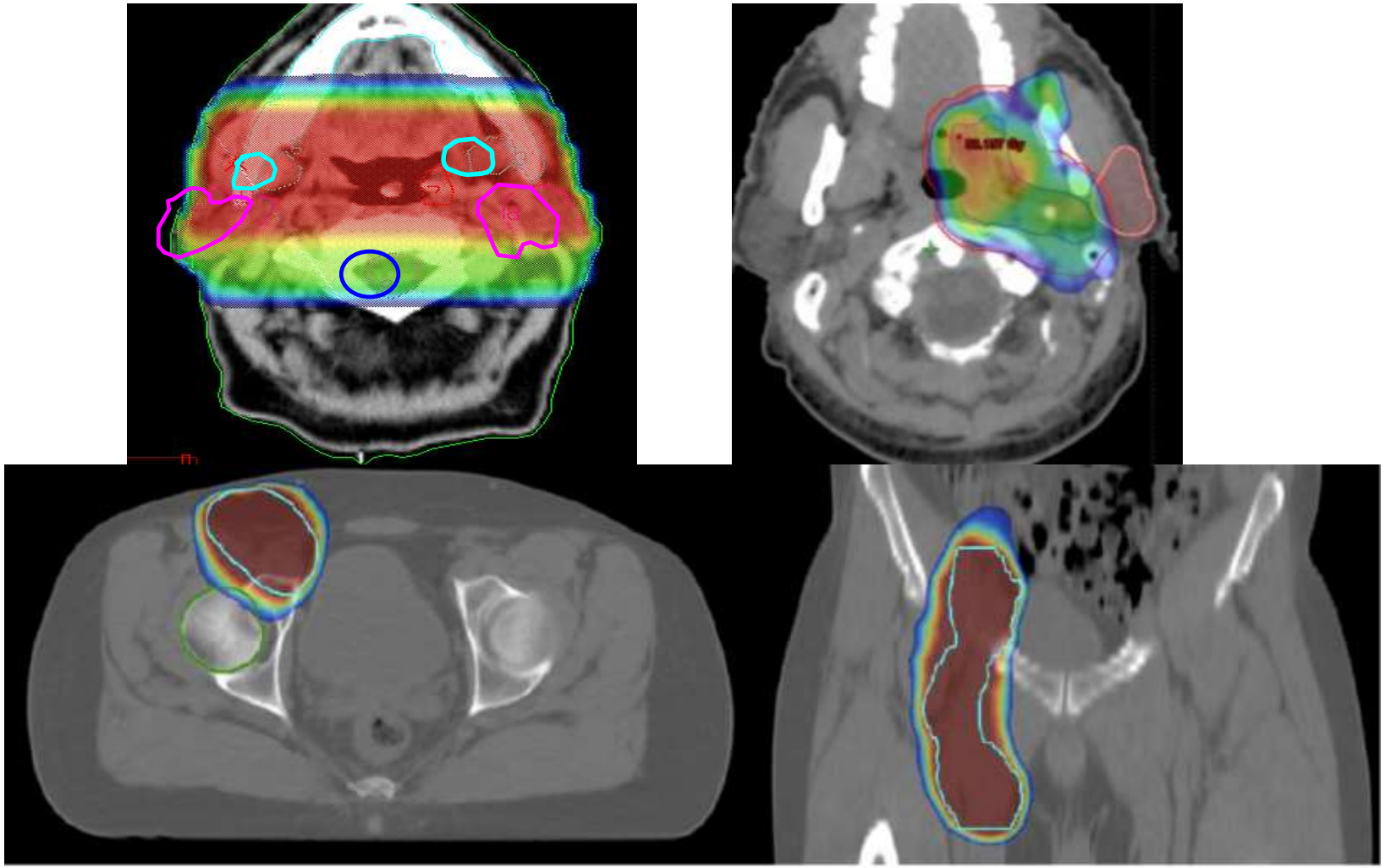
The CTV should incorporate GTV and include adjacent lymph nodes in that site and margin dictated by the clinical situation

Illidge et al, IJROBP, 2014

Conformal planning and precise delivery

Conventional RT

Intensity modulated RT

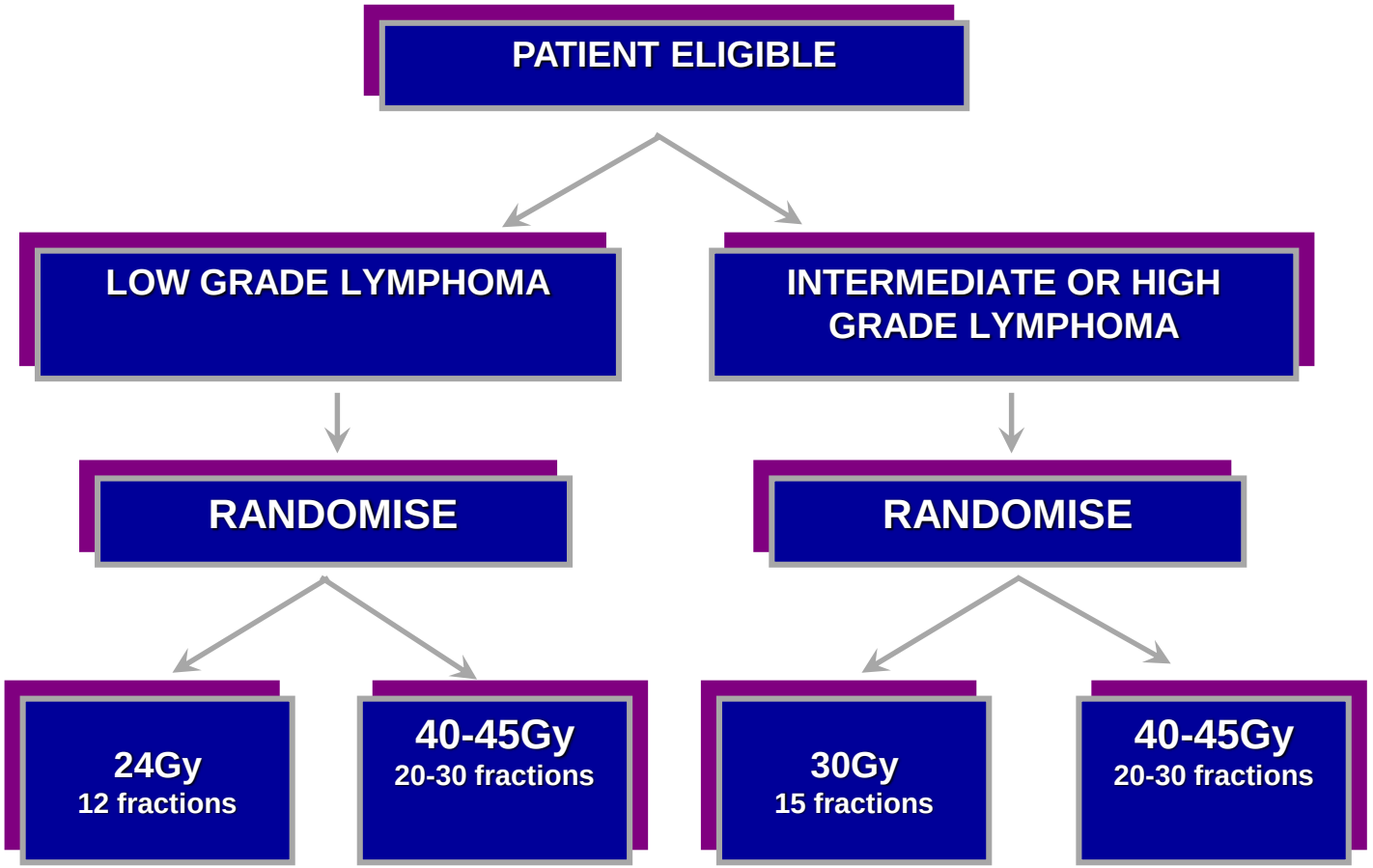


What Radiation Dose?

Hypothesis: Is more dose better?

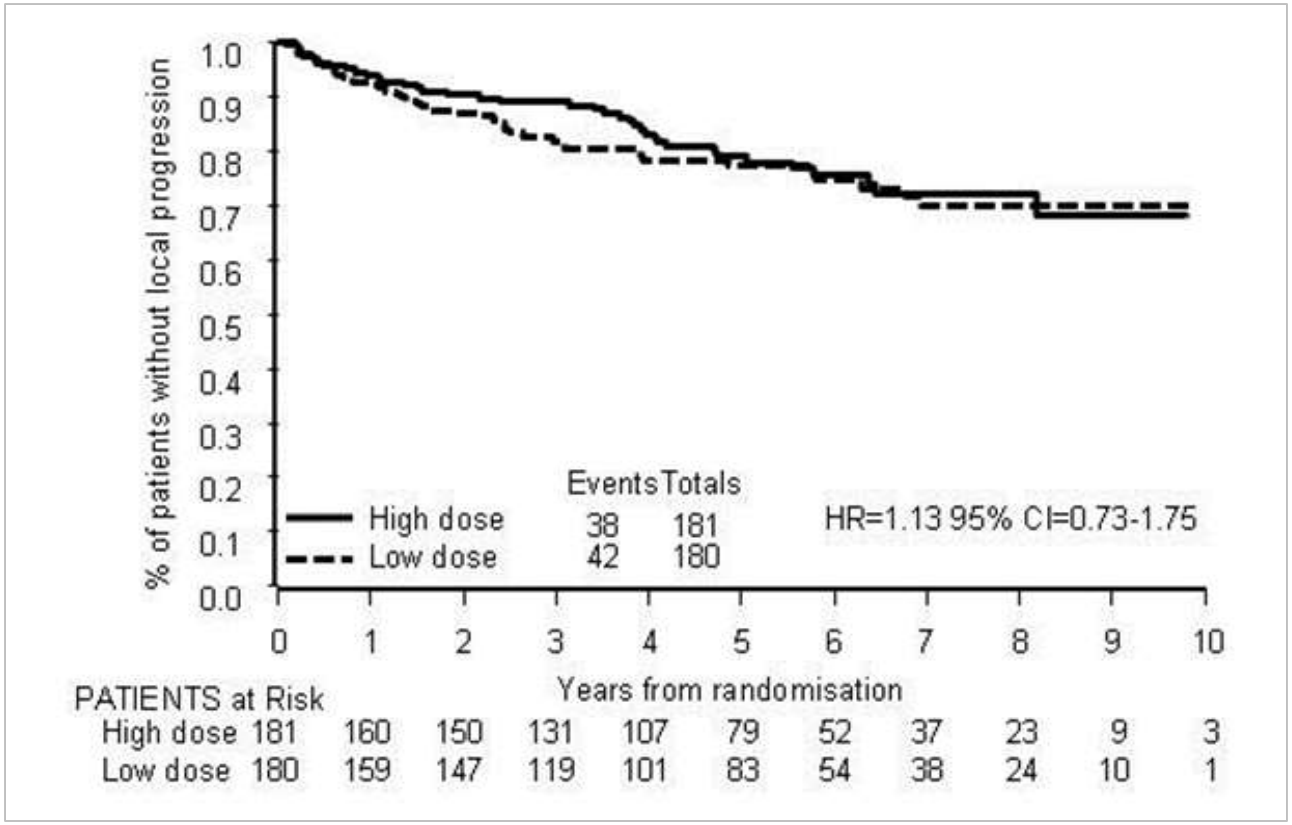
Reduced dose radiotherapy for NHL : A randomised phase III trial

360 indolent NHL (mostly follicular and MZL) randomized



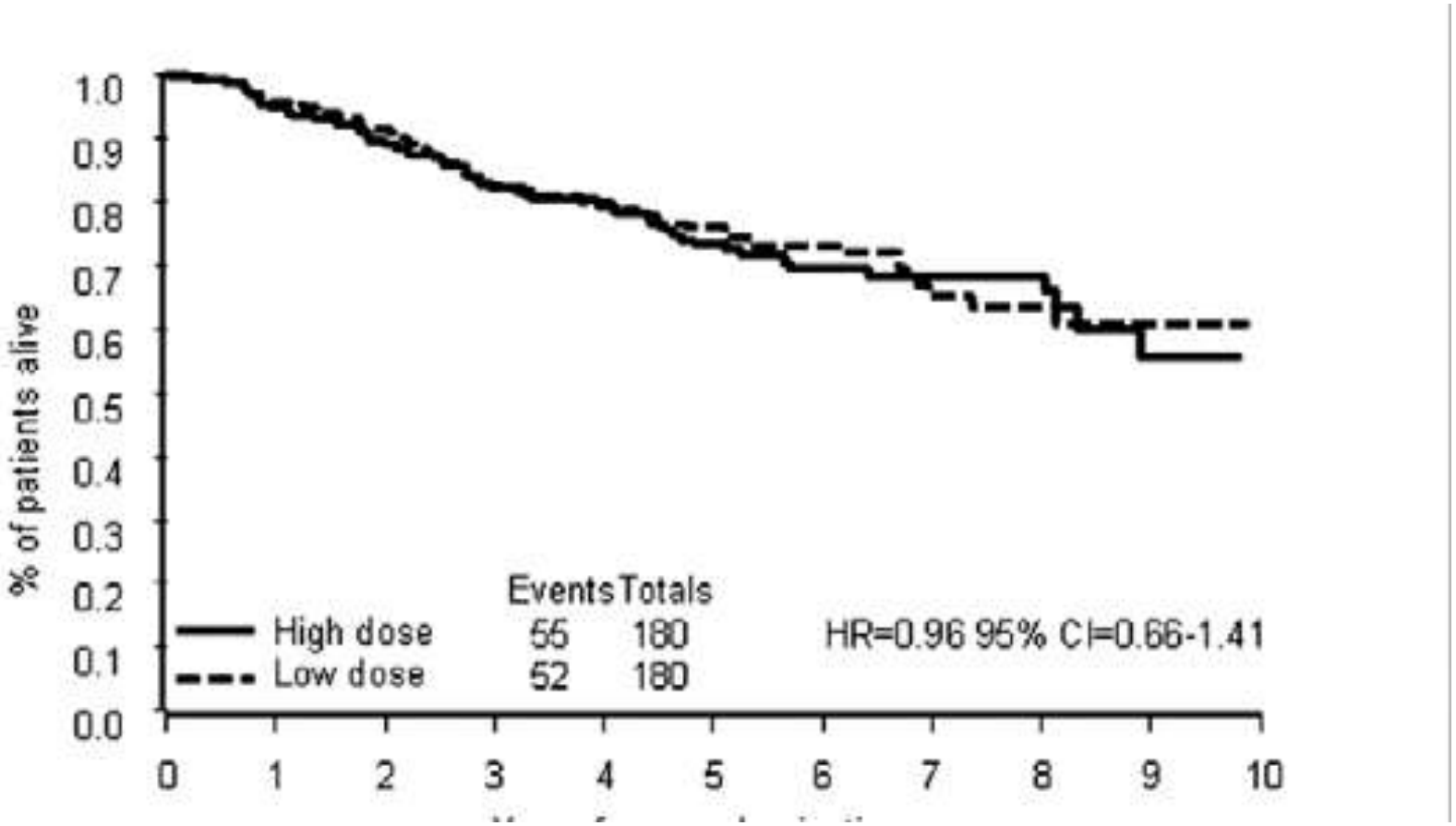
Lowry L et al Radiother Oncol, 100, 86-92, 2011

RT dose 24 Gy vs 40-45 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

The discovery that small doses of radiotherapy could eradicate low-grade lymphomas was purely due to serendipity

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

- At follow-up found to be in CR

Girinsky et al. Int J Radiat Oncol Biol Phys 51 (1), 148-155. 2001

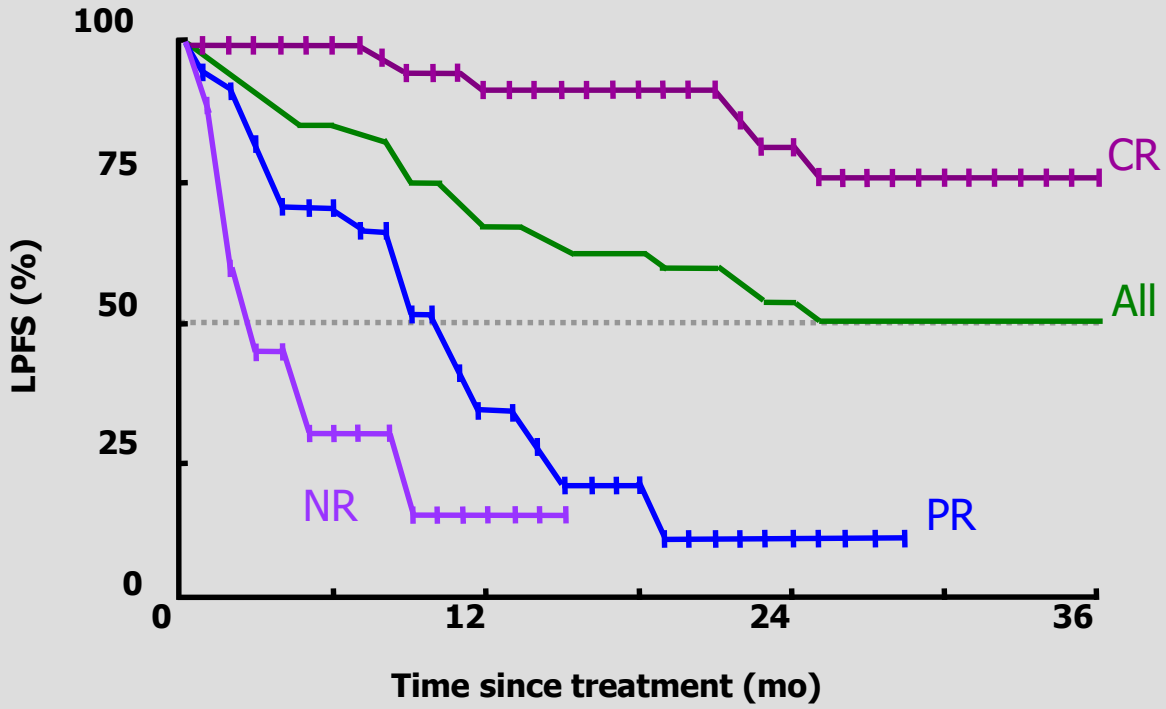
Advantages of "Boom-Boom"

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

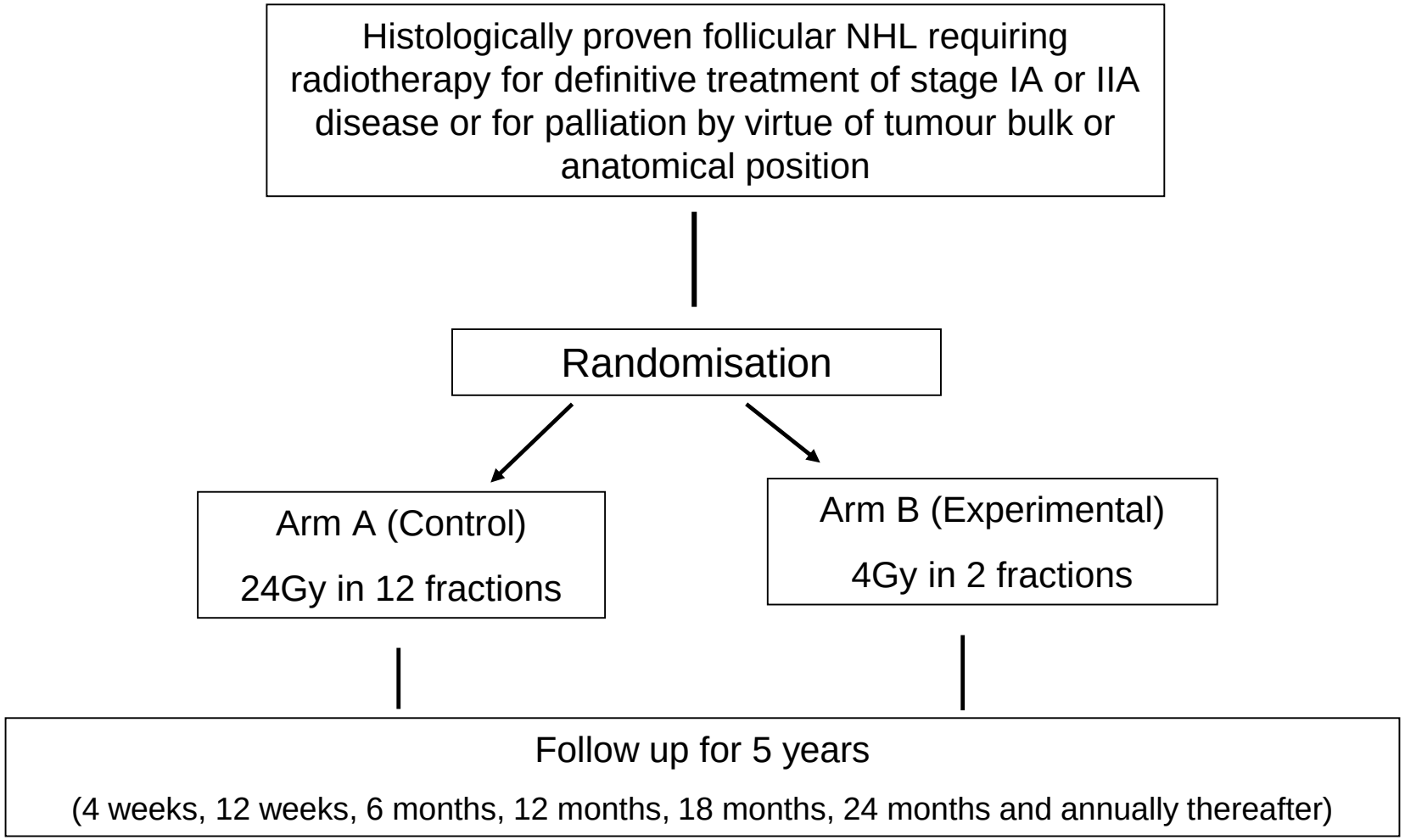
High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

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

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



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



Histology confirmed by central review		
Follicular	157 (53%)	176 (56%)
Marginal zone	24 (8%)	22 (7%)
Other	18 (6%)	18 (6%)
Chronic lymphocytic leukaemia	1 (<1%)	1 (<1%)
Classical Hodgkin's lymphoma	0	1 (<1%)
Nodular lymphocyte predominant Hodgkin's lymphoma	1 (<1%)	0
Diffuse large B-cell lymphoma	9 (3%)	9 (3%)
Diffuse large B-cell lymphoma with underlying follicular	5 (2%)	4 (1%)
Soft-tissue plasmocytoma	1 (<1%)	1 (<1%)
Diffuse follicle centre lymphoma	1 (<1%)	2 (<1%)
Tested, no diagnosis	35 (12%)	32 (10%)
Insufficient material or unclear diagnosis	25 (8%)	23 (7%)
No definitive evidence of lymphoma	5 (2%)	6 (2%)
Reactive changes only	5 (2%)	3 (1%)
No central review	65 (22%)	67 (21%)

Radiological stage at randomisation		
IA	124 (41%)	135 (43%)
IB	1 (<1%)	2 (<1%)
II	55 (18%)	53 (17%)
III	54 (18%)	57 (18%)
IV	34 (11%)	30 (10%)
Missing	31 (10%)	38 (12%)
Previous treatment		
Previous chemotherapy	97 (32%)	110 (35%)
Previous radiotherapy	77 (26%)	74 (23%)
Reason for radiotherapy		
Curative	119 (40%)	129(41%)
Palliative	180 (60%)	186 (59%)

Clinical Applications

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 Cottart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

Lancet Oncol 2014

	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

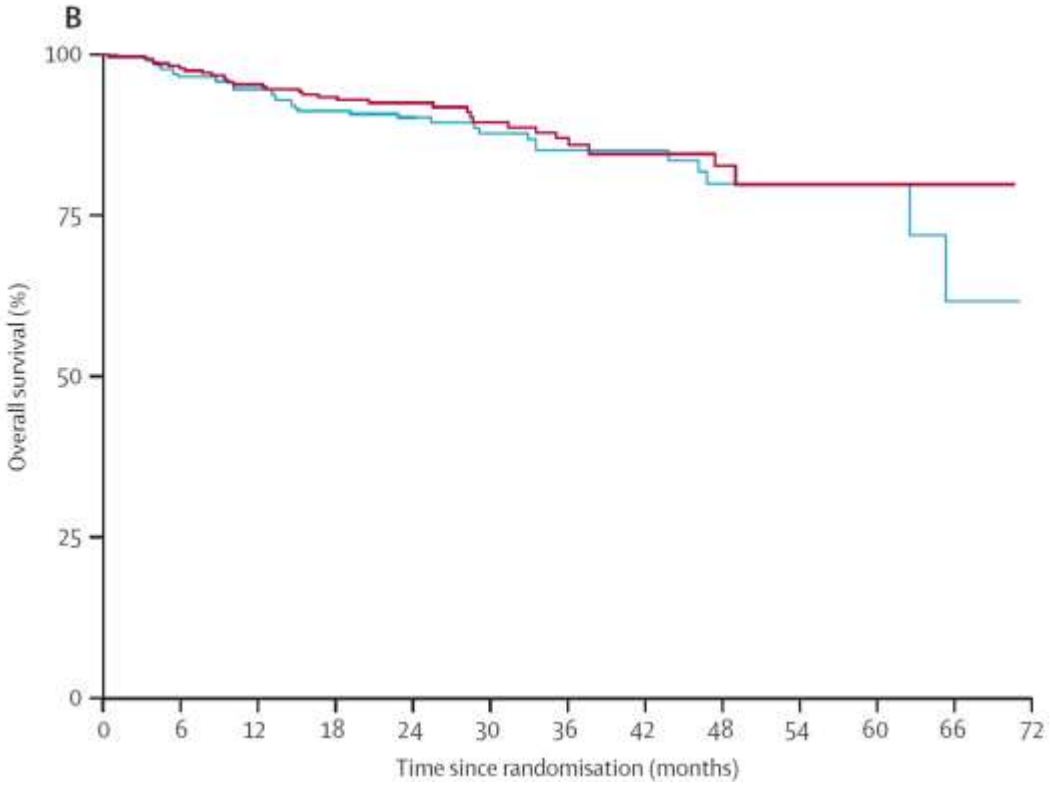
	24 Gy		4 Gy		p value*
	Complete response (%)	Complete response plus partial response (%)	Complete response (%)	Complete response plus partial response (%)	
All patients	176/260 (68%)	236/260 (91%)	137/281 (49%)	227/281 (81%)	0·0095
Follicular lymphoma	152/226 (67%)	205/226 (91%)	116/243 (48%)	194/243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

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

Radical or palliative FL or MZL
299 sites assigned to 24 Gy and 315 sites to 4 Gy



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

UK NCRI FORT trial
Summary and conclusion

- 4 Gy in 2 fractions is effective (ORR 74.1%; CR rate: 44.3%, PR rate: 29.8%) and may be considered for palliative treatment or retreatment

BOOM **BOOM**

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Whom to Boom-Boom?

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

- Relapsed, refractory to systemic therapy
- As an alternative adequate first-line ?

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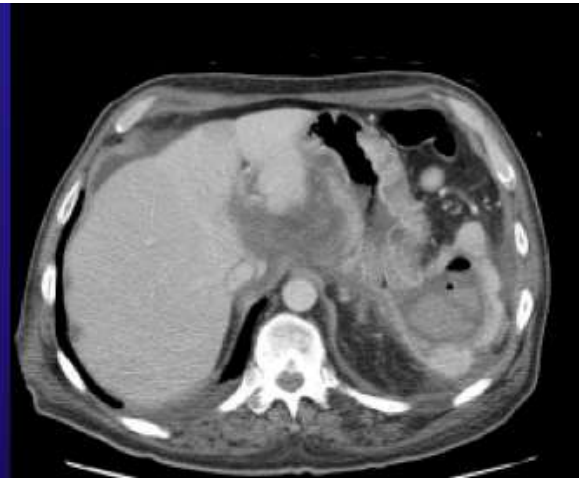
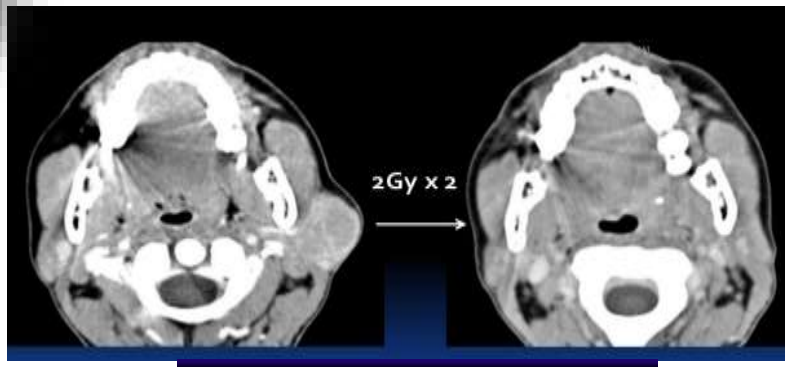
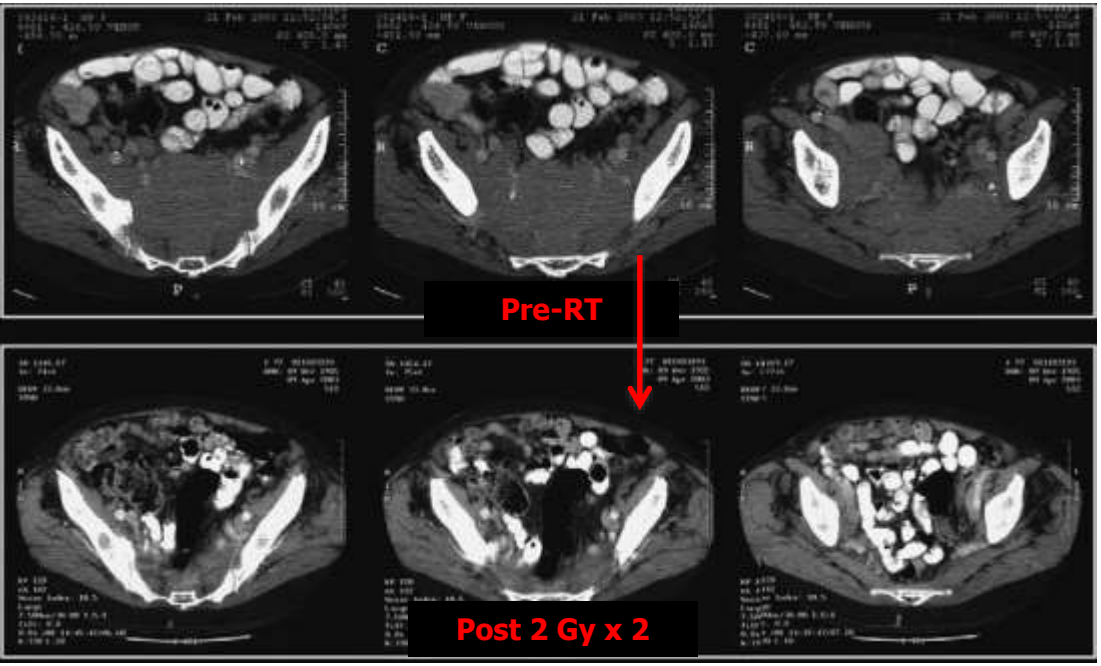
Clinical Applications

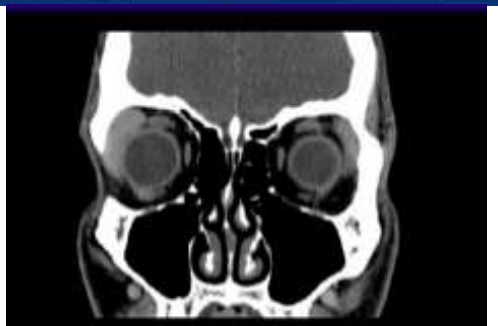
Author/year	N° pts	Primary disease	Primary endpoints	Secondary endpoints
Ganem /1994	27	FL 74%	CR 37%, PR 52%	Median duration of CR 17 mo
Sawyer/1997	11	FL 54%	CR 36%, PR 54%	
Girinsky/2001	48	FL 66%	CR 57%, PR 24%	Median duration of CR 24 mo
Johannson/2002	22	FL 68%	CR 61%, PR 31%	Median duration of CR 22 mo
Haas/2003	109	FL 88%	ORR 92%, CR 61%, PR 42%	Median time to PD 14 mo; Median duration of CR 42 mo
Haas/2005	71	CLL 23, MCL 17, DLBCL 13, FL 18	ORR 87%, CR 48%, PR 39%	Median time to progression 12 mo ; median time to local progression 22 mo
Ng/2006	10	Indolent NHL	CR 70%, PR 20%	
Luthy/2008	33	FL 85%	ORR 95%, CR 84%, PR12%	
Haas/2005	71	FL 0%	CR 48%, PR 39%	Median duration of CR 23 mo
Murthy/2008	36	FL 44%	ORR 75%, CR 44% for indolent, 23% for aggressive	Median duration of CR 15 mo
Haas/2009	9	NLPHL	ORR 89%, CR 67%, PR 22%, SD 11%	
Rossier/2011	43	FL 56%, CLL 44%	ORR 90%, CR 28%, PR 35%, SD 26%	Median time to in-field progression 21 mo, median time to out-field progression 8 mo
Chan/2011	54	56% Indolent NHL	ORR 81%, CR 49%, PR 32%	2yr-LPFS 50%
Russo/ 2012	127	FL 66%	ORR 82%, CR 57%, PR 25%	Median time to first recurrence 13.6 mo
Girinsky/2012	10	Pulmonary MALT	CR 60%	5-yr PFS 87.5%
Fasola/2013	27	Orbital MALT	ORR 100%, CR 85%	2yr-LPFS 100%
Konig/2016	45	Orbital MALT	ORR 100%	2yr-LPFS 100%
Pinnix /2016	22	Orbital MALT 64%; FL 23%	ORR 100%, CR 86%, PR 14%	Median time to CR 3.76 mo; 1 and 2yr-LPFS 100% and 75%
Furlan/2016	23	DLBCL	ORR 70% , CR 30%, PR 39%	Median duration of response 6 mo (range, 1-39 mo)
Tanaka/2016	30	DLBCL	CR 45% , PR 36%	
OVERALL	**829**	**FL 45%**	**0RR 89%, CR 56%**	**Median duration of response 20 mo.**

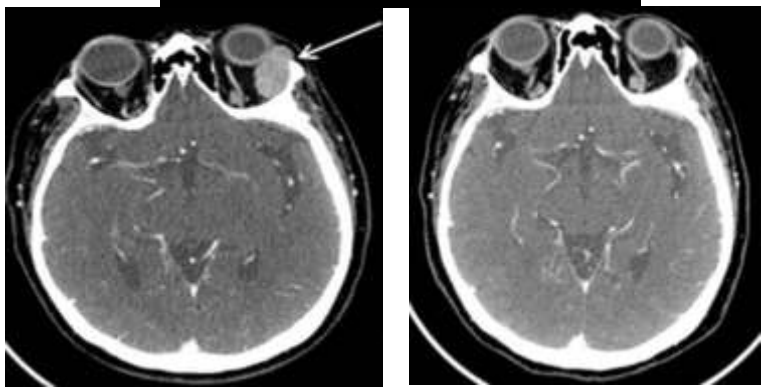
Clinical Applications







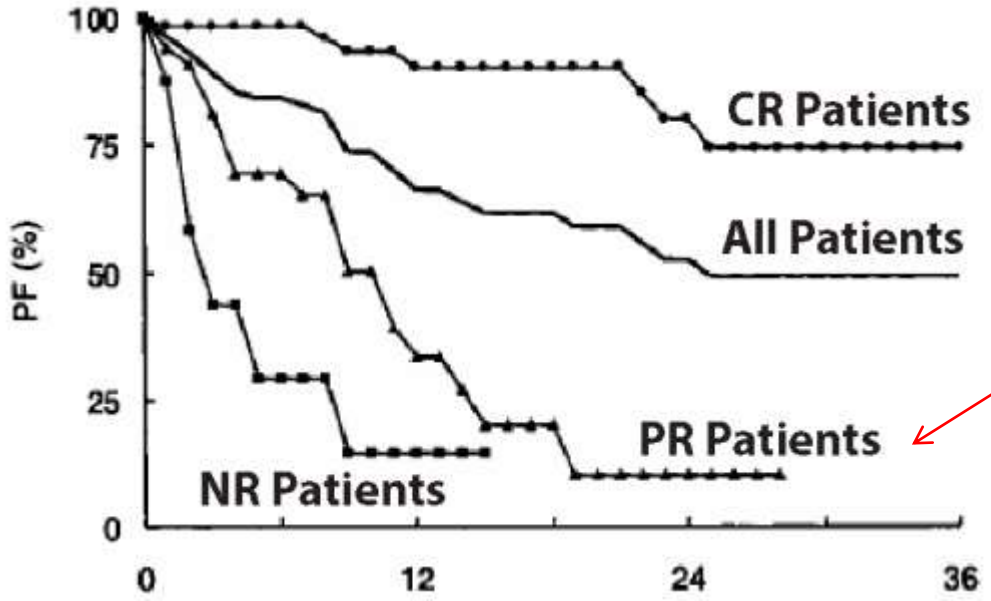




Response to very low dose RT is variable

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?

*The wide spectrum of RT responses**

0.1 μSv

Lymphoma	**Medullo**	**Breast Cancer**	**Lung Cancer**	**Prostate Cancer**	**GBM**
4-45 Gy	23.4-36 Gy	50 Gy	60-70 Gy	74-80 Gy	>100 Gy

Outliers… ***Outliers…***

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

Our Central Hypothesis:

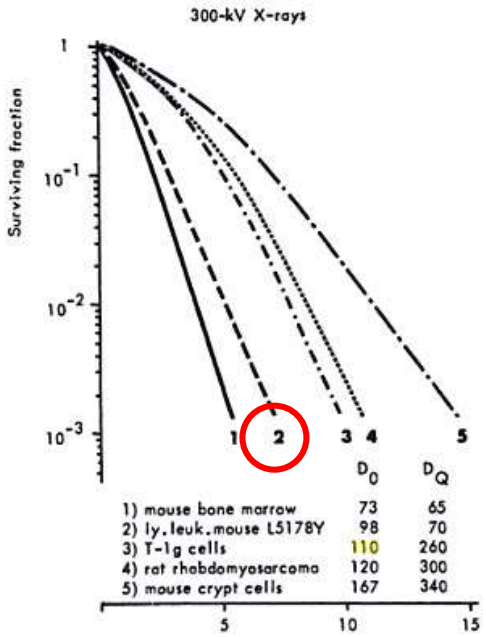
1. Dramatic variations in radiosensitivity can be explained by molecular differences in the tumor
2. Gene expression signatures can be used to predict RT response and to better stratify patients

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

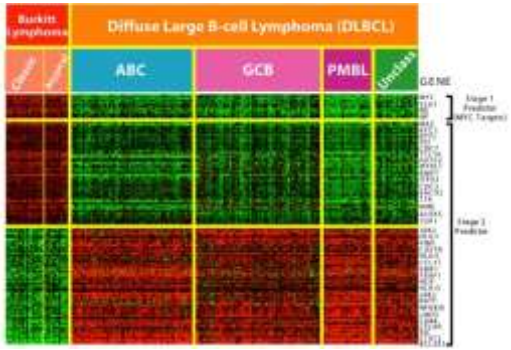
What Drives Radiation Sensitivity in Lymphoma?

The old radiobiology view of RT sensitivity in lymphoma

Lymphoma = Apoptosis = Radiosensitive



RT sensitivity in lymphoma, in the molecular age…

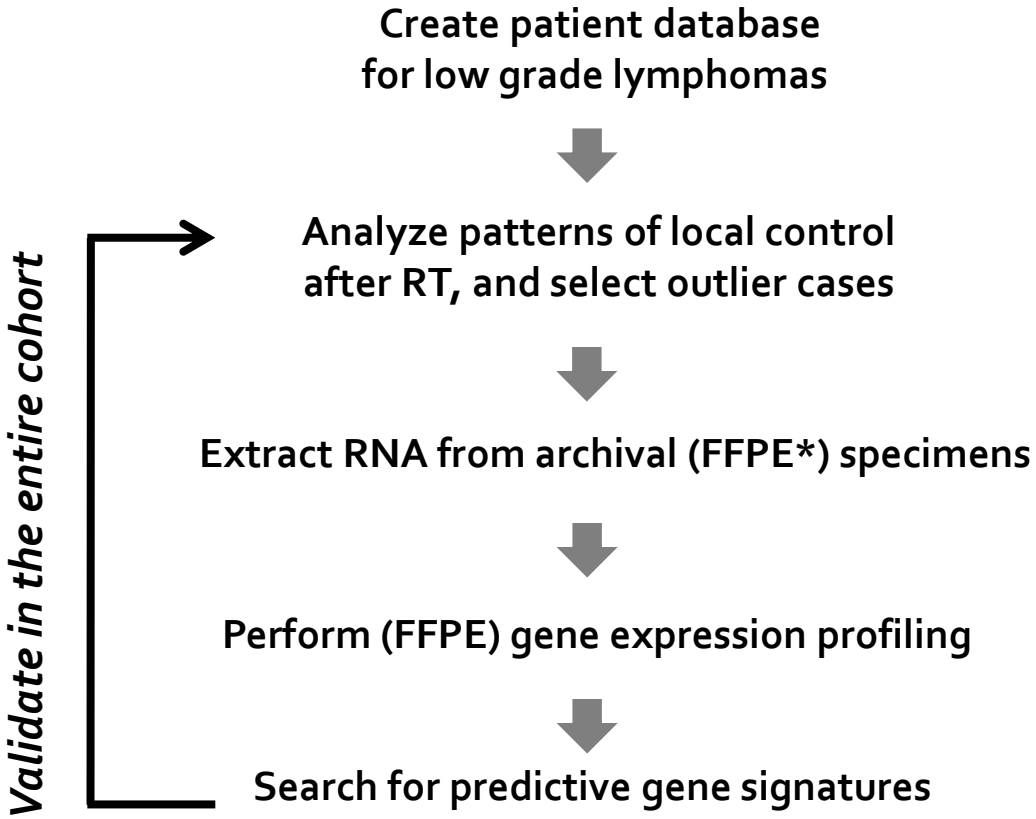


Lymphoma gene expression profiles may predict differences in radiosensitivity

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

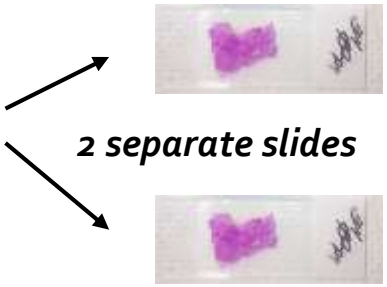
Materials and Methods: Our Approach

The Yale/MSK Lymphoma GEP Collaboration



*FFPE=Formalin-fixed, paraffin-embedded tissue

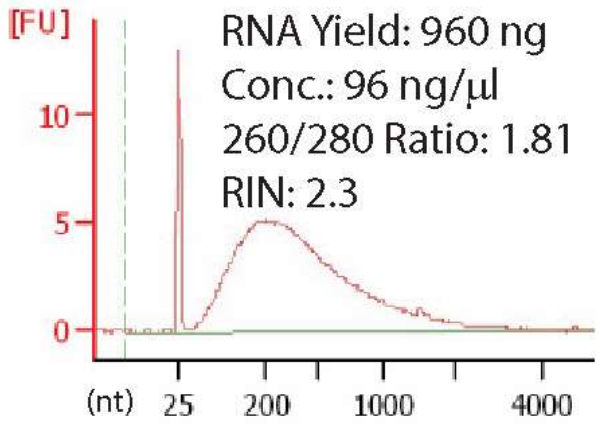
Whole transcriptome profiling with FFPE extracted RNA samples



2 separate slides

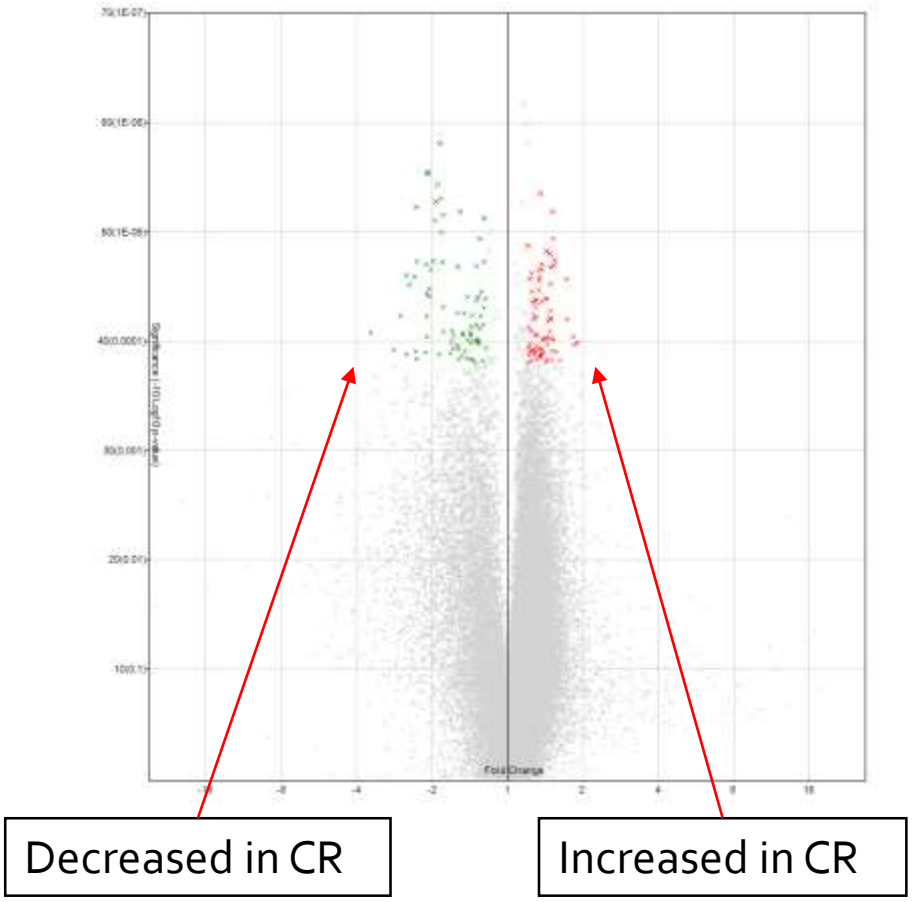
→ ***Extract RNA*** →

AFFYMETRIX®



Whole transcriptome profiling with FFPE extracted RNA samples

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



Increased expression in CR vs. PR/NR

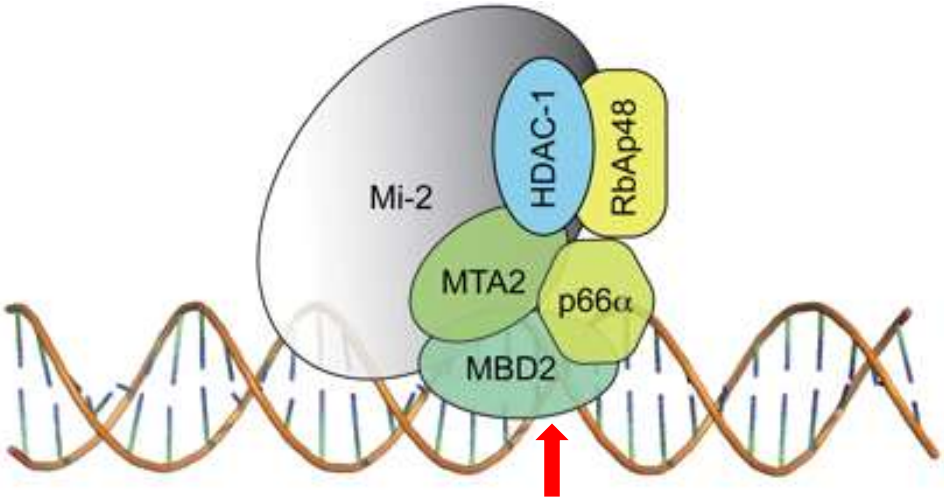
Gene	CR Avg Exp.	NR Avg. Exp	Fold Change	Gene Description
MIR517B	4.94	4.15	1.73	microRNA 517b
MGC13053	5.89	5.19	1.62	uncharacterized MGC13053
OR10J1	4.92	4.32	1.52	olfactory receptor, family 10, subfamily J, member 1
C17orf112	5.06	4.48	1.49	chromosome 17 open reading frame 112
PART1	5.99	5.42	1.48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

Decreased expression in CR vs. PR/NR

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

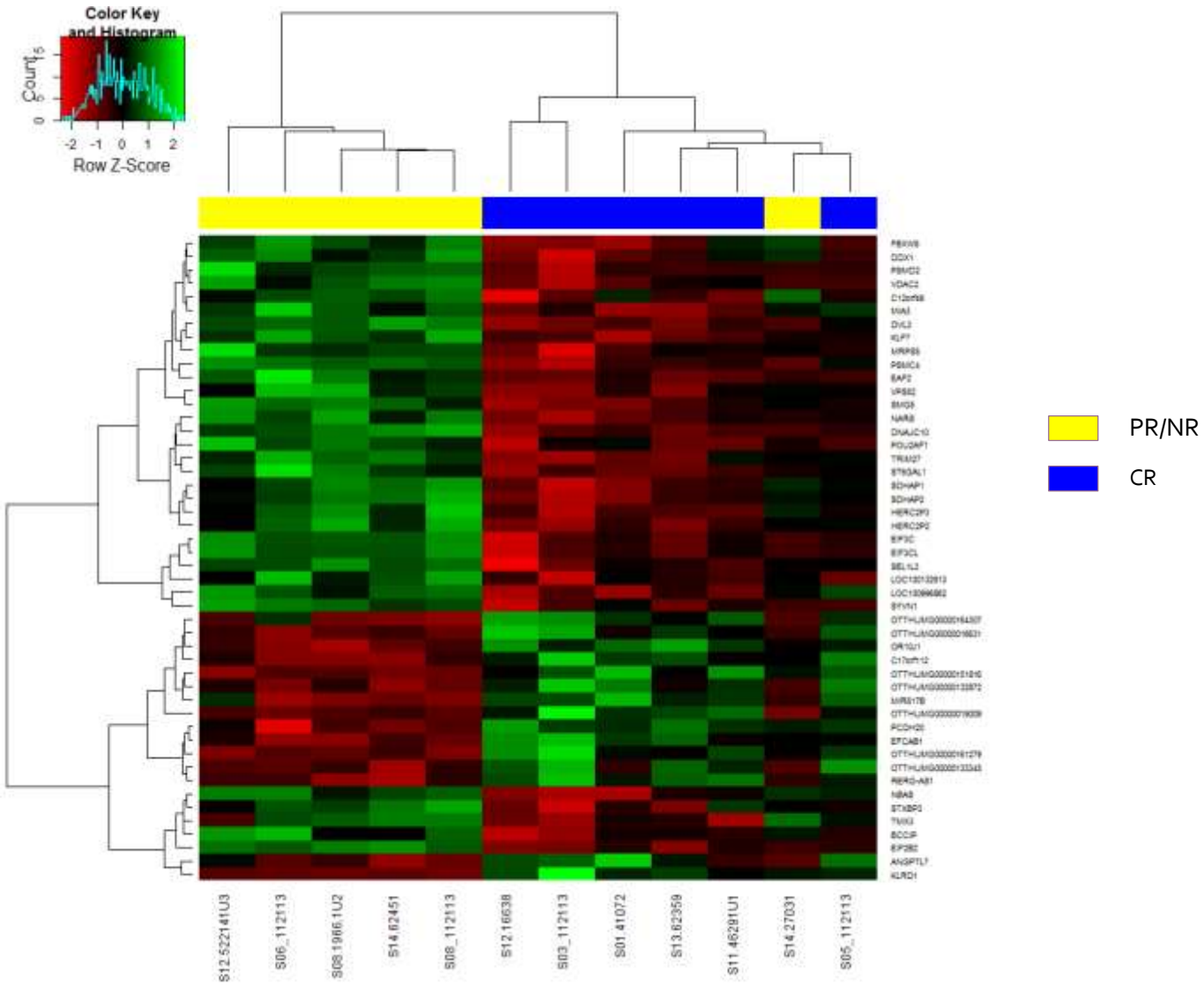
Associated with chromatin modification in cancers

Are the genes relevant to radiosensitivity?



4-fold reduction in MBD2 mRNA in CR patients

CR vs. PR/NR Gene Pathways



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

Studies are ongoing and we are actively seeking collaborators!

Yale CANCER CENTER
SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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