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RETE ONCOLOGICA
GRUPPO LINFOMI

La radioterapia a basso dosaggio nei linfomi indolenti

Torino, 13 aprile 2018

Mario Levis

Radioterapia Universitaria – A.O.U. Città della Salute e della Scienza

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%

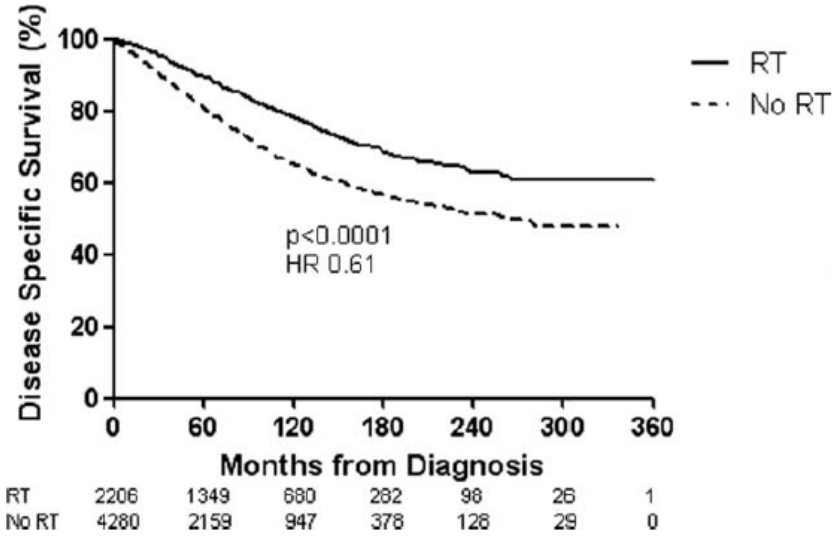
Ref.: MacManus,MP et al.; JCO 14: 1282-90 (1996)

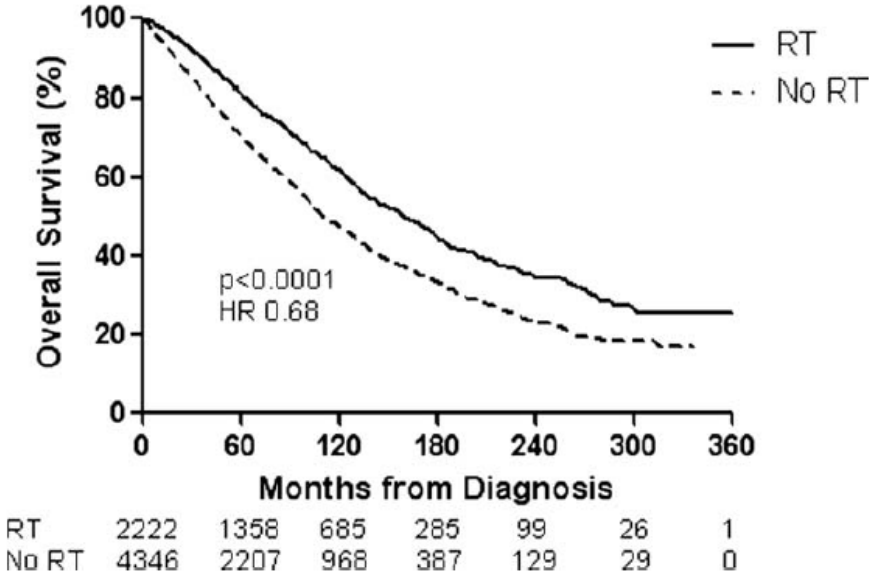
Improved Survival in Patients With Early Stage Low-Grade Follicular Lymphoma Treated With Radiation

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)

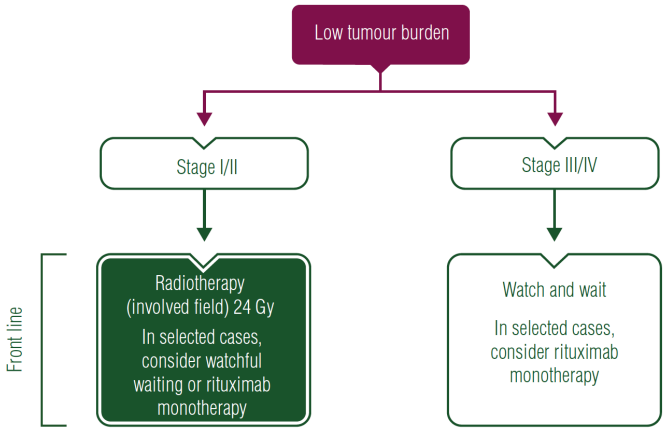
ESMO GUIDELINES

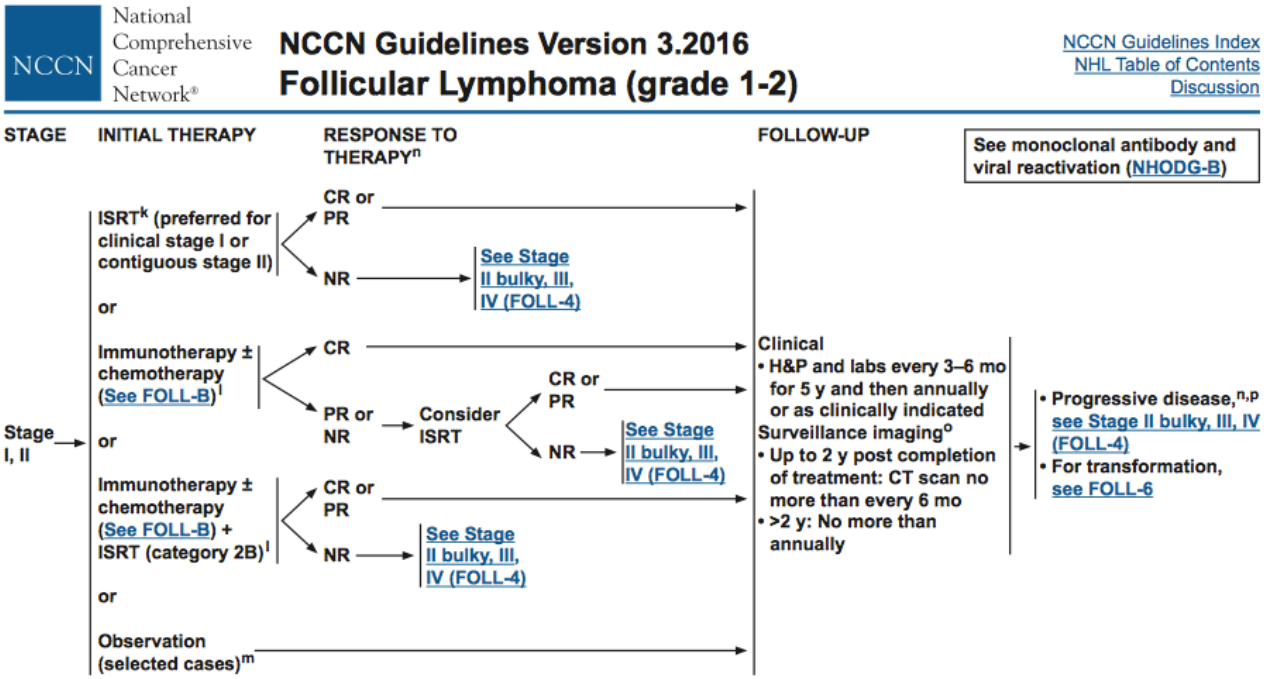
clinical practice guidelines

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†

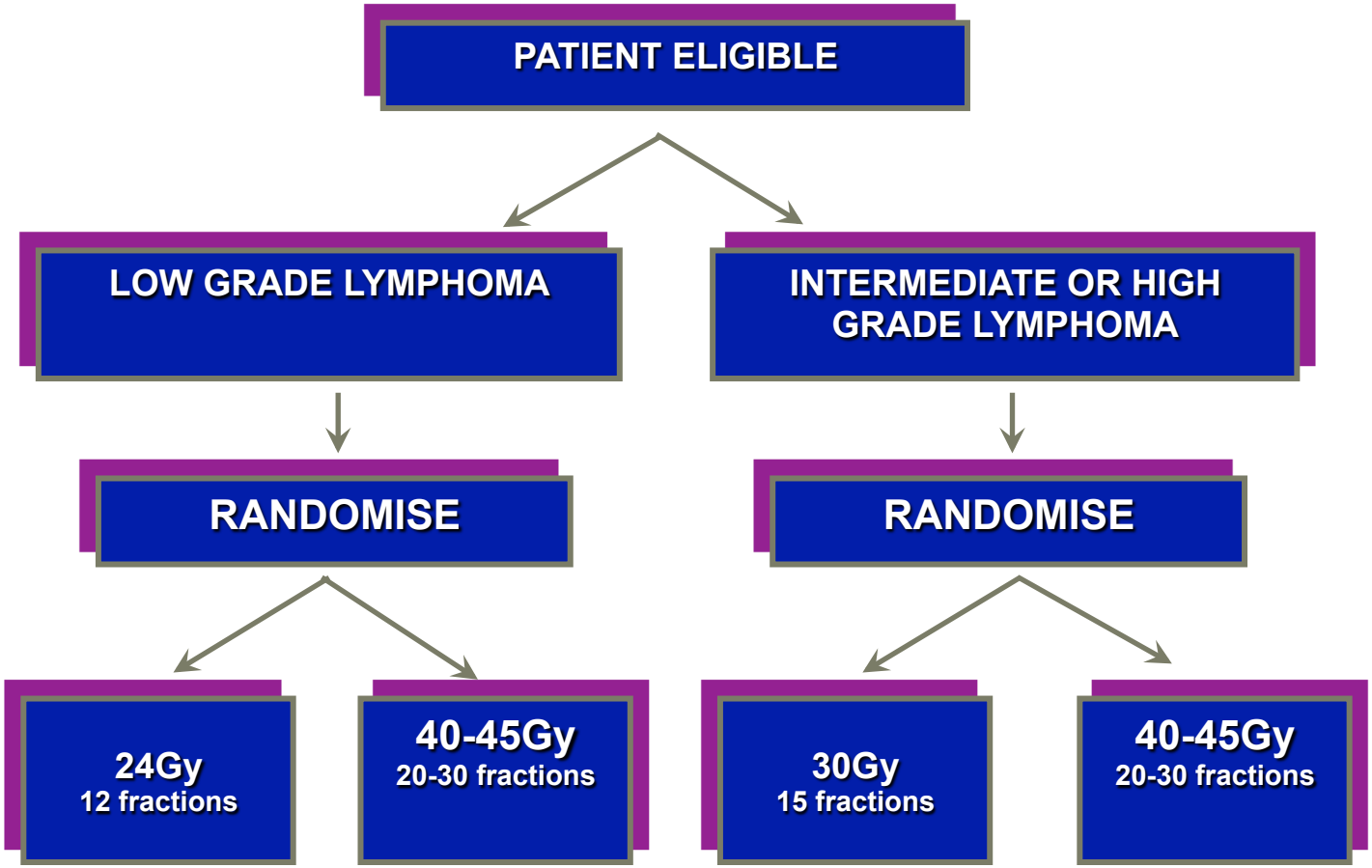
M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4], U. Vitolo[5] & M. Ladetto[6], on behalf of the ESMO Guidelines Committee*





REDUCED DOSE RADIOTHERAPY FOR NHL : A RANDOMISED PHASE III TRIAL

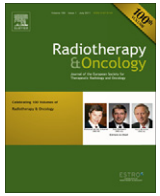
360 INDOLENT NHL (MOSTLY FOLLICULAR AND MZL) RANDOMIZED



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

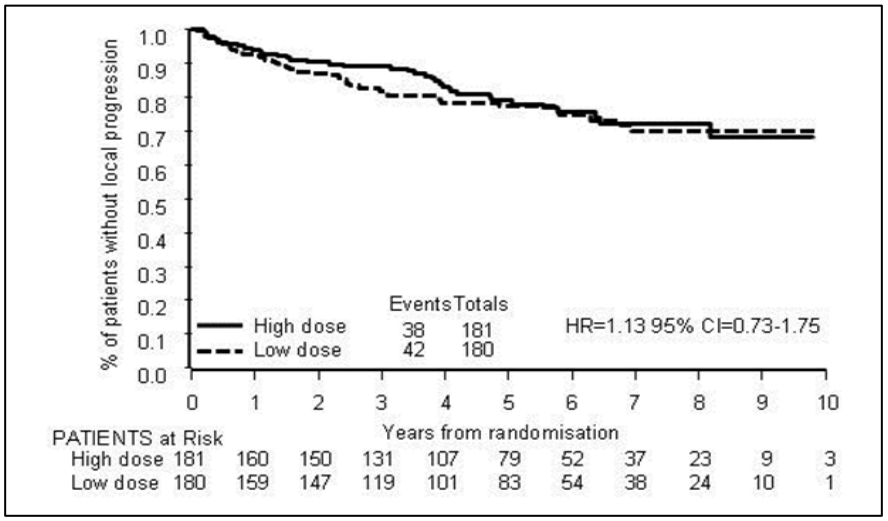
Phase III randomised trial

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

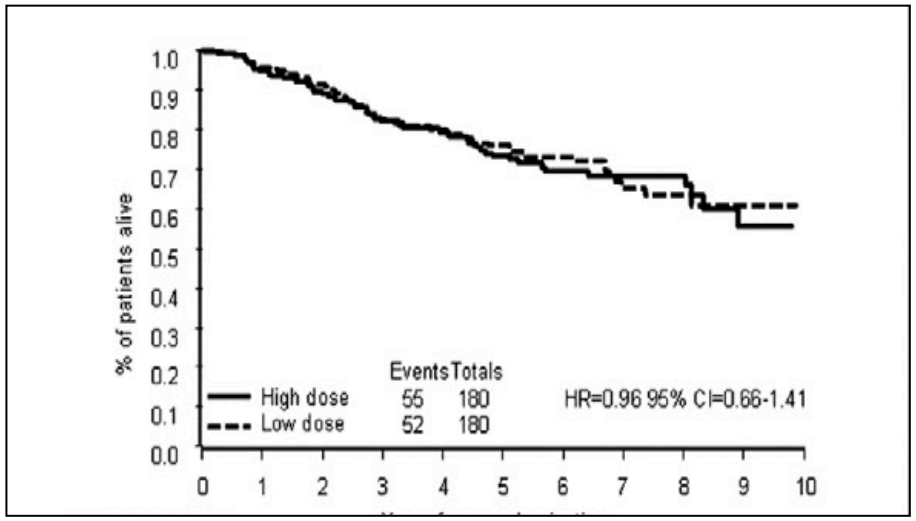


45 vs 24 Gy in indolent B cell lymphoma

Local Control



Overall Survival



Conclusion: In a large, randomised trial, there was no loss of efficacy associated with radiotherapy doses of 24 Gy in indolent NHL and 30 Gy in aggressive NHL, compared with previous standard doses of 40–45 Gy.

Lowry et al. Radiotherapy and Oncology 2011;100

What Volume should be treated with radiotherapy?

EXTENDED FIELD VS INVOLVED FIELD VS INVOLVED SITE/NODE

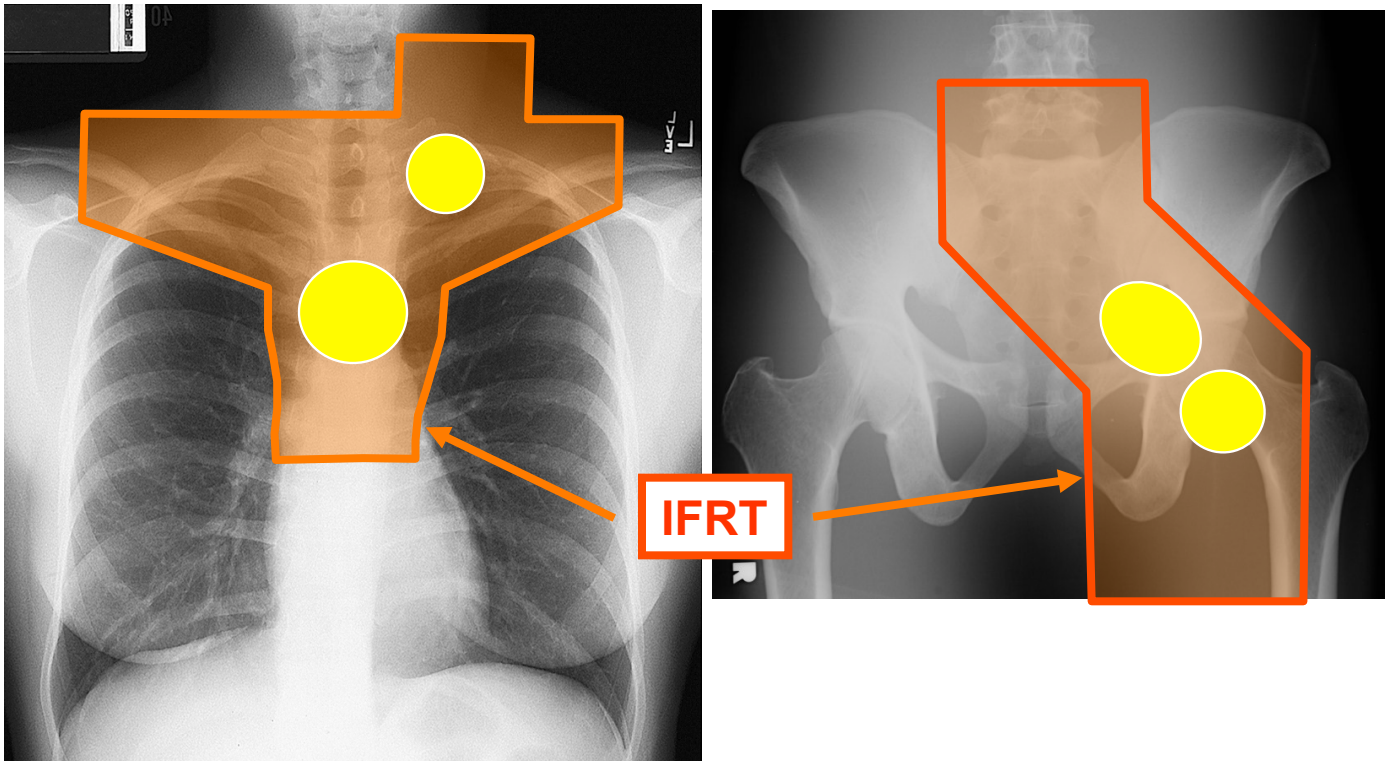
NO EFFECT OF FIELD SIZE ON PFS OR OS

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

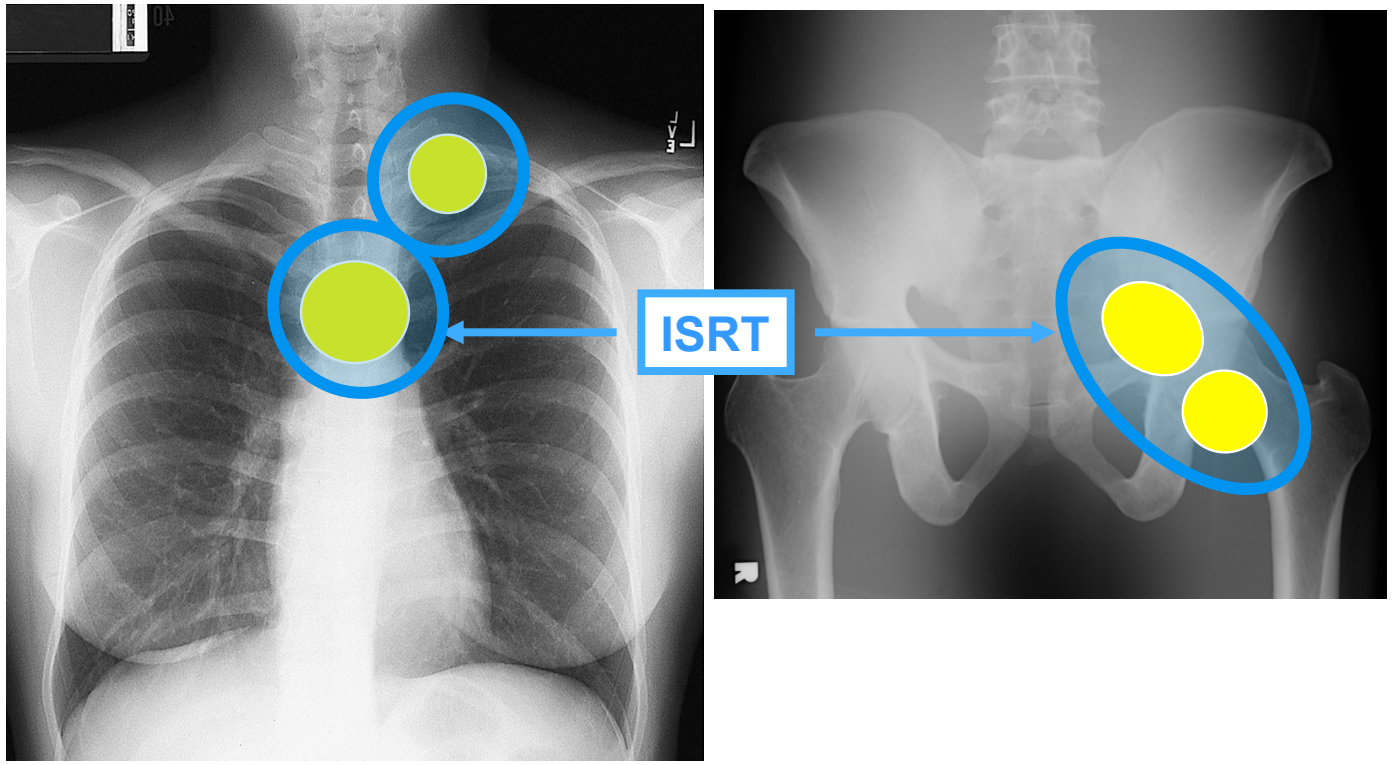
Development of Radiation Volumes

Involved Field:

2D planning, based on bony landmarks

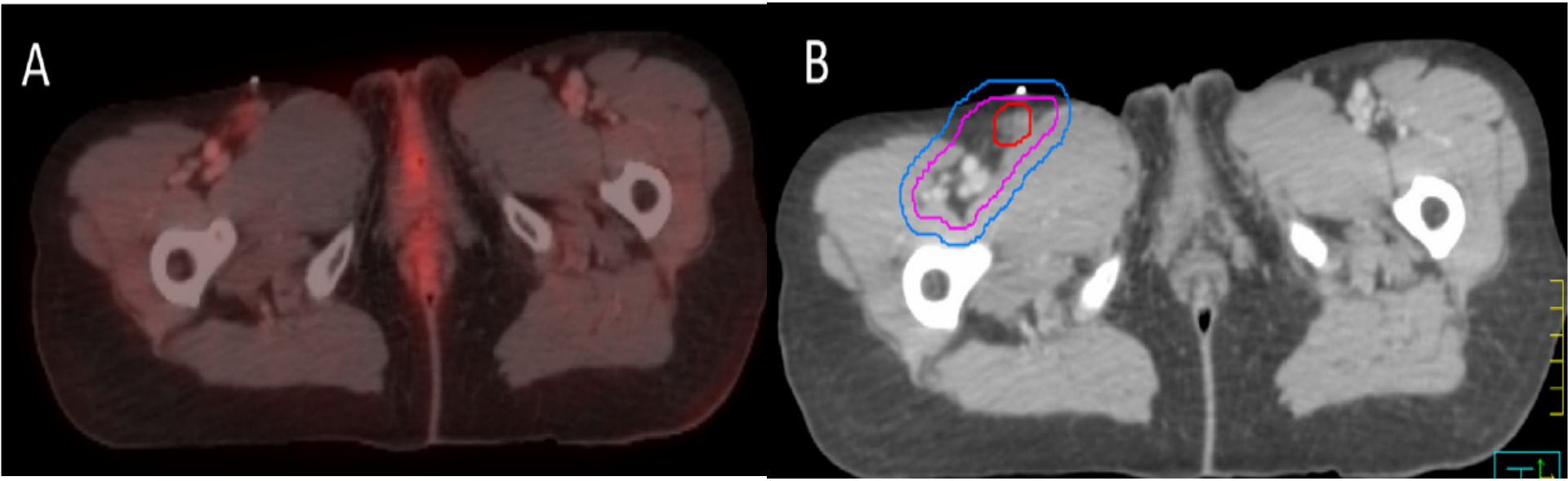


Involved Site
3D planning, based on lymphoma volume



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

ISRT: Localized indolent lymphoma



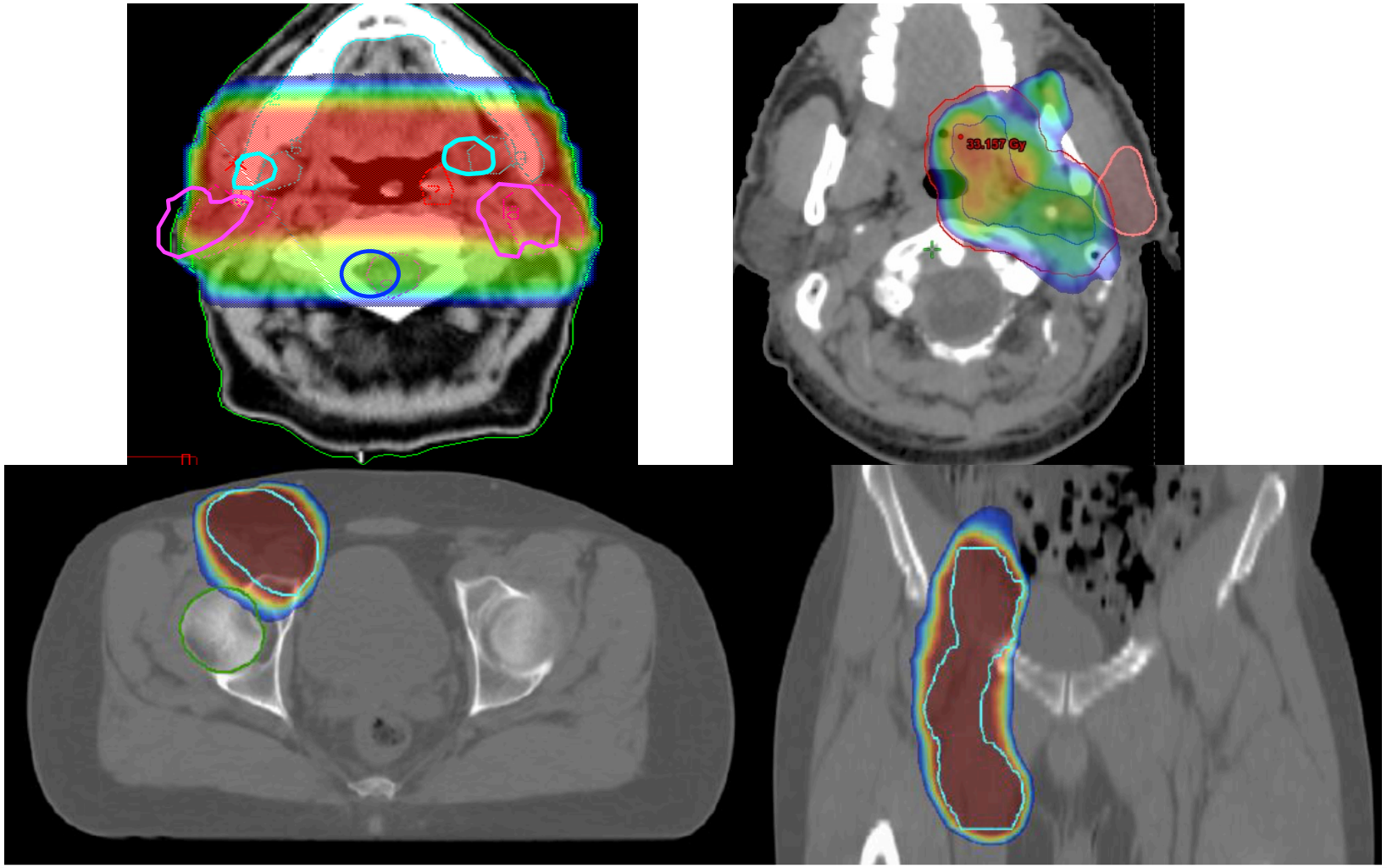
The CTV must be designed to encompass suspected subclinical disease based on the pre intervention GTV imaging
The CTV should incorporate GTV and include adjacent lymph nodes in that site and margin dictated by the clinical situation

Illidge et al, IJROBP, 2014

Conformal planning and precise delivery

Conventional RT

Intensity modulated RT



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

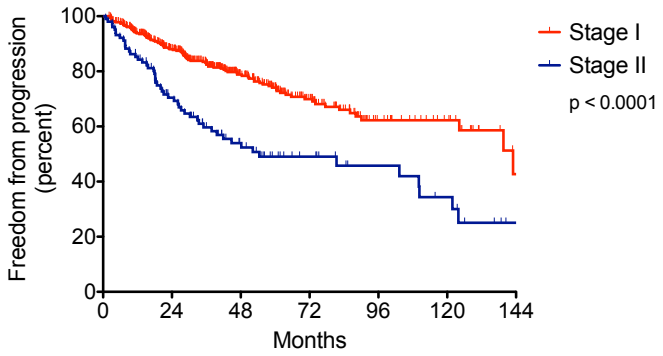
Outcome of curative radiotherapy for localised follicular lymphoma in the era of ^{18}F-FDG PET-CT staging: an international collaborative study on behalf of ILROG.

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

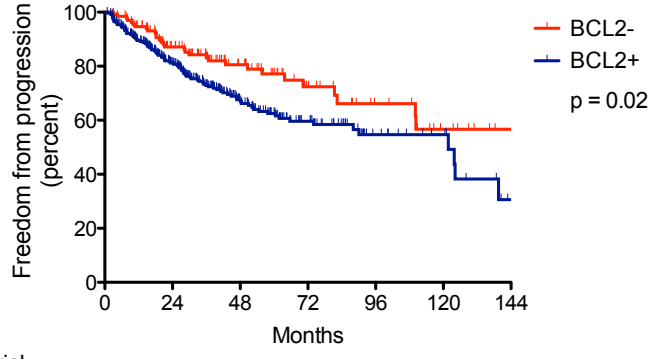
RESULTS

Stage I vs II



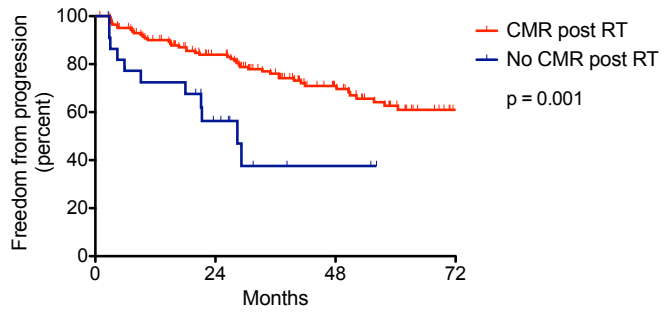
At risk							
Stage I	410	305	165	84	34	20	5
Stage II	102	61	34	19	12	8	1

BCL2 status



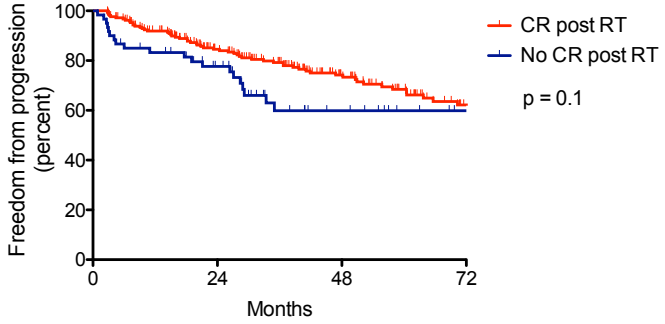
At risk							
BCL2-	133	94	54	27	16	8	2
BCL2+.	281	191	98	51	19	12	2

Metabolic Response



At risk				
CMR	143	102	57	25
No CMR	23	10	3	1

CT response



At risk				
CR	213	150	85	43
No CR	60	39	15	6

Manuscript submitted to Blood

Can we further reduce RT Dose…?

HYPOTHESIS: IS MORE DOSE BETTER?

Low Dose Radiotherapy

BOOM BOOM

Basis For Boom-Boom Palliation

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

Advantages of “Boom-Boom”

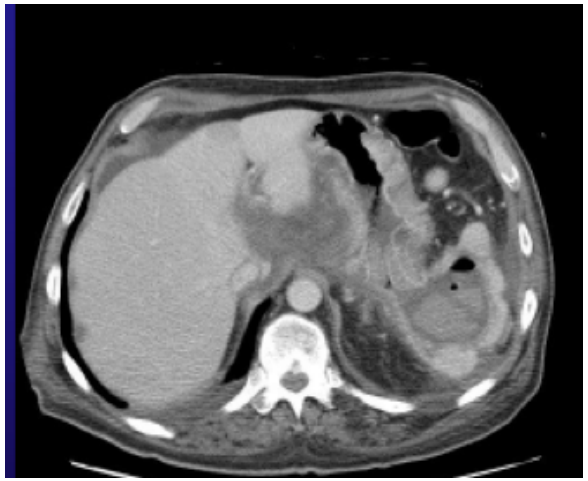
- Short treatment duration.
- Minimal morbidity. No myelosuppression.
- High response rate similar to that obtained with primary therapy.
- Effective and simple re-treatment
- Rapid response onset.
- Significant LPFS interval.

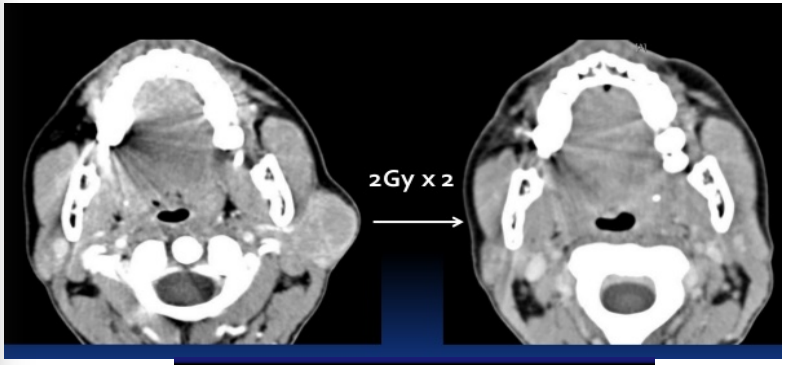
"Boom-Boom" Palliation of Recurrent/Refractory NHL

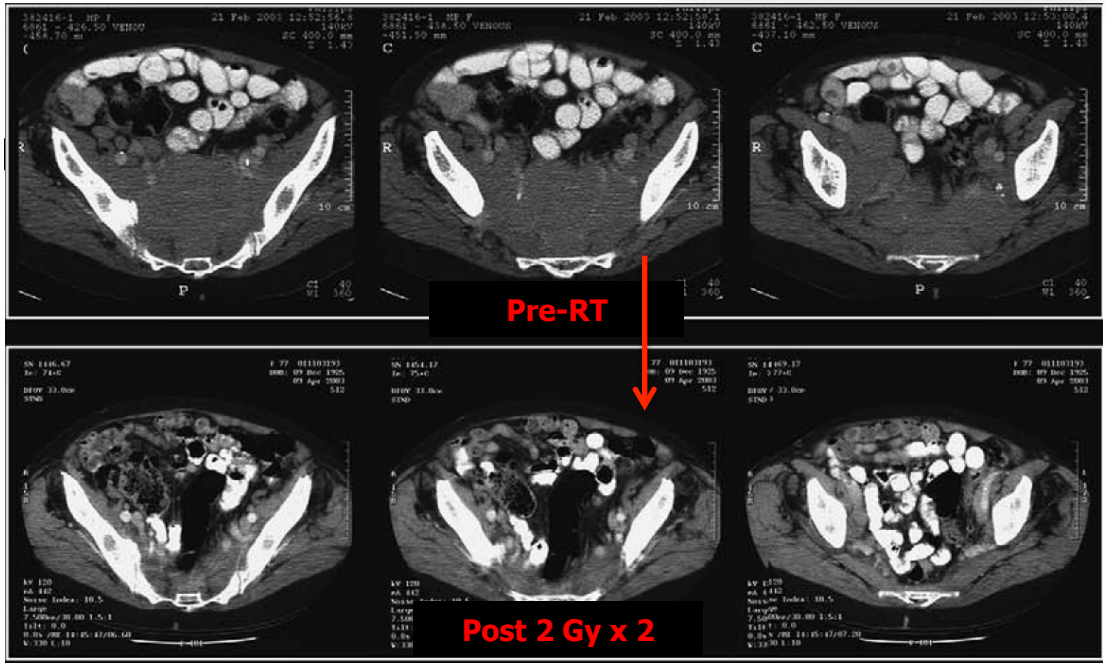
Study	N (pts)	N (sites)	PR	CR	Overall RR	Response duration	Comment
Ganem 1994	27	N/A	52%	37%	89%	Range: 4 – 35 mo	
Sawyer 1997	11	16	38%	56%	94%	Median: 7 mo	
Girinsky 2001	48	135	24%	57%	81%	2 yr actuarial: 56%	
Johannsson 2002	22	31	22%	65%	87%	Median: 22 mo	Prospective Phase II
Haas 2003	109	304	31%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

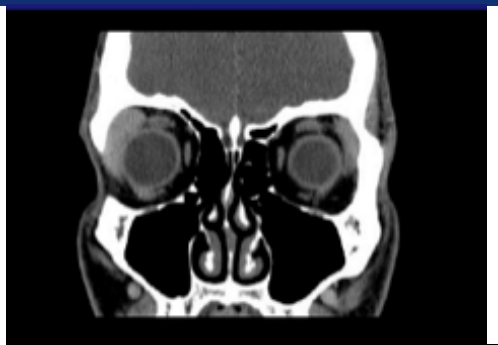
†Includes 30 patients (42%) with aggressive NHL.

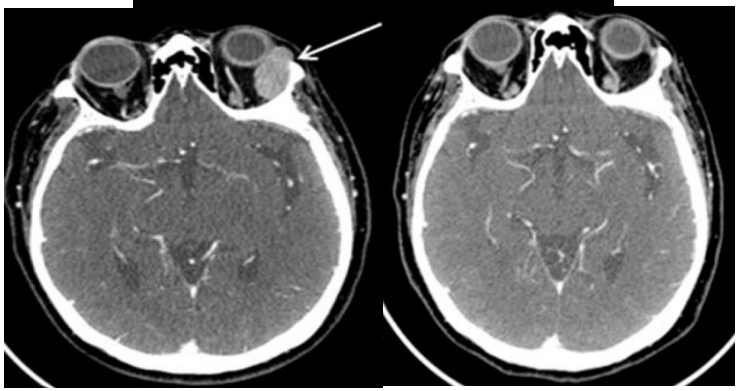
Clinical Applications









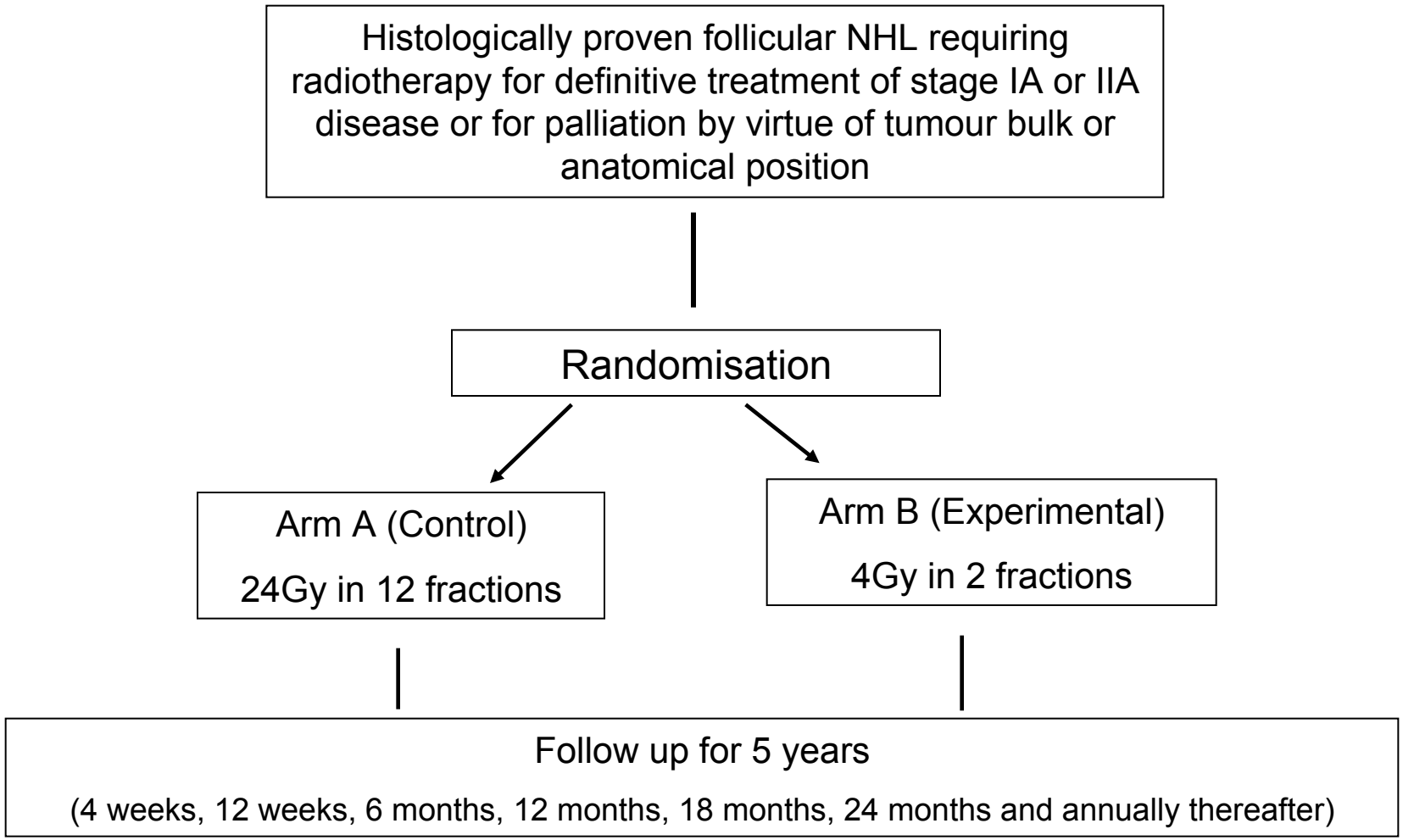


WHOM TO BOOM-BOOM?

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

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

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

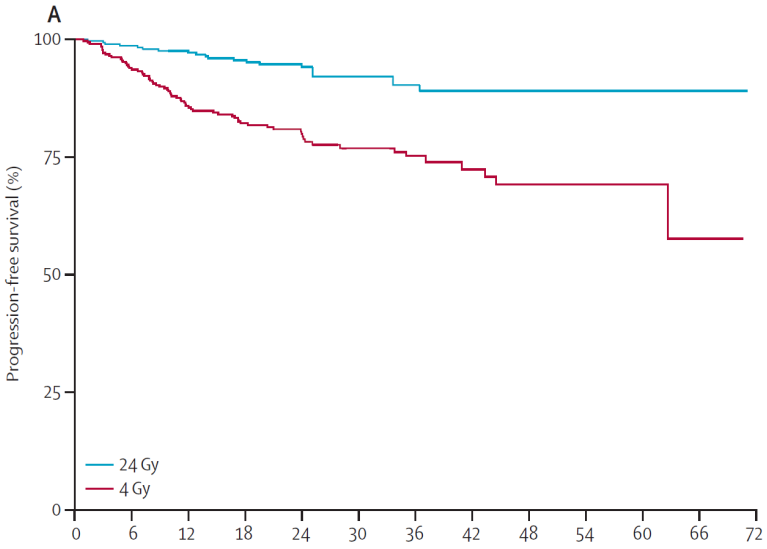


4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

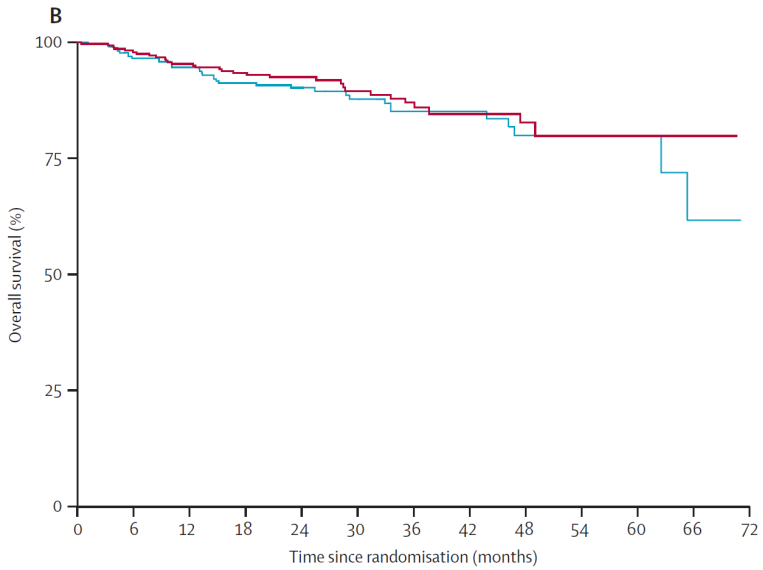
Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

Lancet Oncol 2014

Progression Free Survival



Overall Survival



Conclusion:

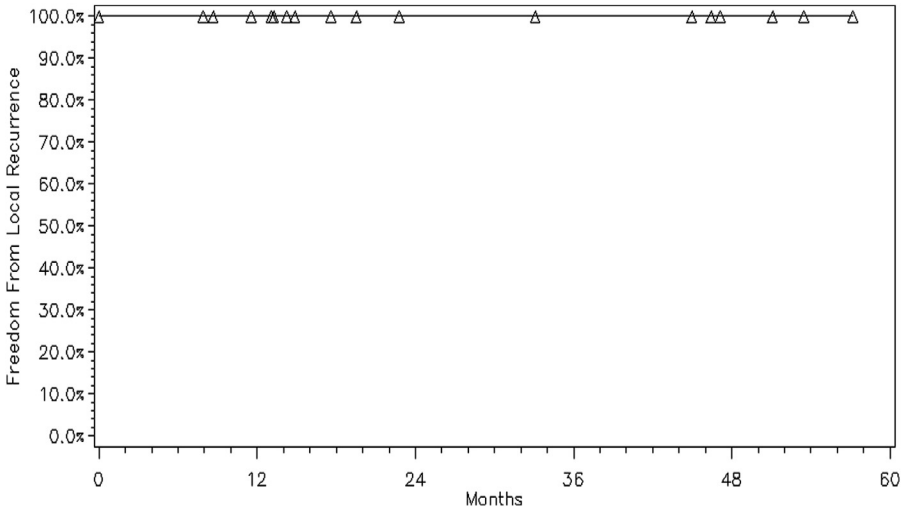
24 Gy in 12 fractions is more effective and remains the standard of treatment. "Boom boom" RT (2 Gy x 2) achieves high response rates (ORR 74%) and is a feasible option for palliation or retreatment

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*



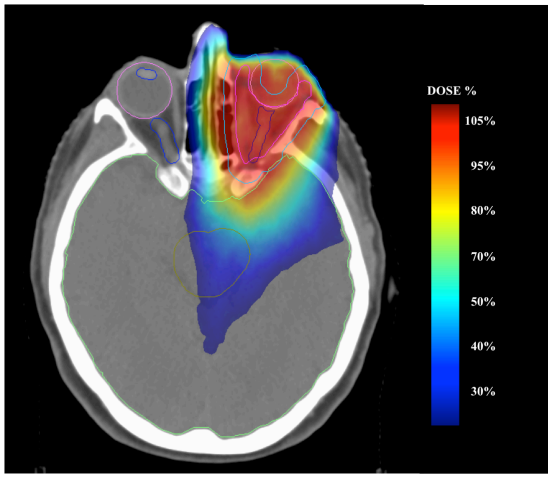


Fig. 1. Freedom from local relapse for all sites with complete response treated with low-dose radiation therapy (N = 23).

LOCAL CONTROL: 100%

Can we predict the response to Low dose RT…?

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…

Central Hypothesis:

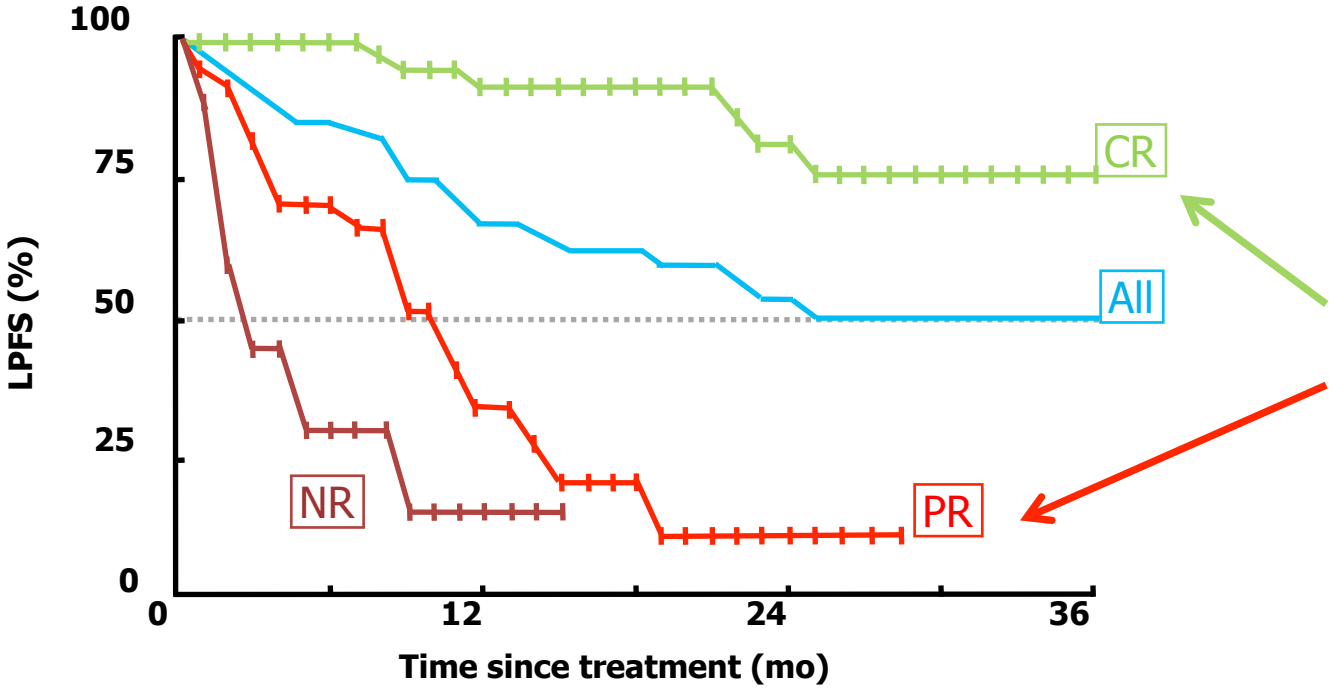
1. Dramatic variations in radiosensitivity can be explained by molecular differences in the tumor
2. Do we have any signature to be used to predict RT response and to better stratify patients?

Response to very low dose RT is variable

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



Can we identify these patients up-front?

Our key questions:

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

CONCLUSIONS

- **RT remains treatment of choice** for majority of stage I/II_1 indolent lymphomas (PET-staged), resulting in long term progression free survival and possible “cure” achievable with very low morbidity
- Intrinsic radiosensitivity exists, but **molecular features** may trump histology
- Archival FFPE tissue now can be used readily for gene expression profiling
- RT **gene signatures** could help better **direct treatment** choices in lymphoma