Front line therapy – How I approach

Role of radiotherapy

Umberto Ricardi

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Follicular Lymphoma

Role of Radiation Therapy in Curative-Intent Management

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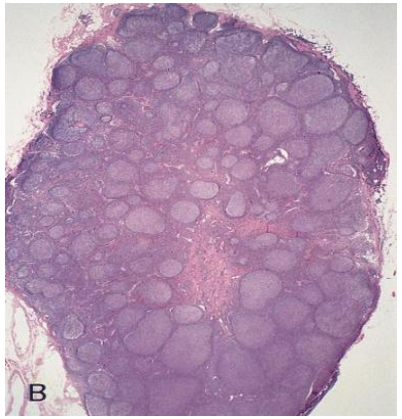
Low Grade Follicular Lymphoma



- 20-25% FL have Ann Arbor stage I-II (A)
- Most stage I-II patients have nodal disease only
- Highly radiosensitive

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)

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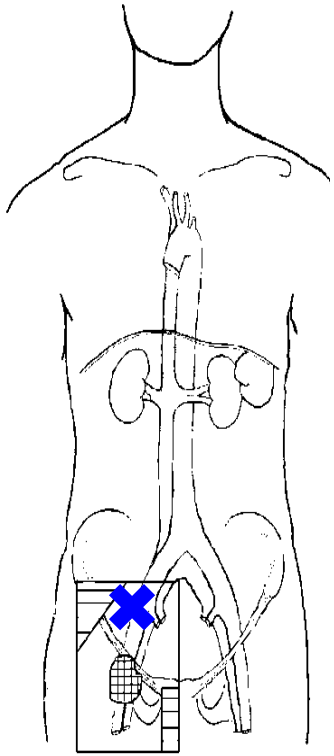
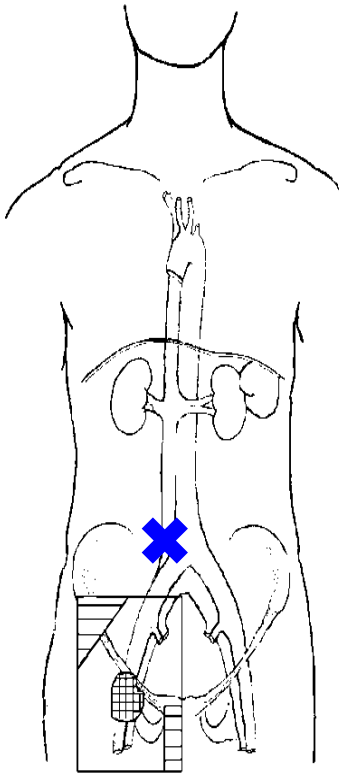
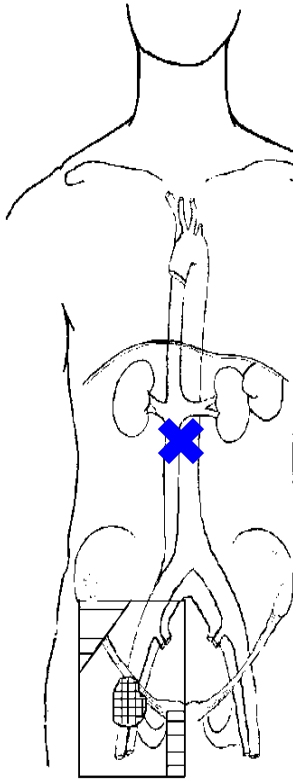
Relapse Locations in Relation to RT Fields



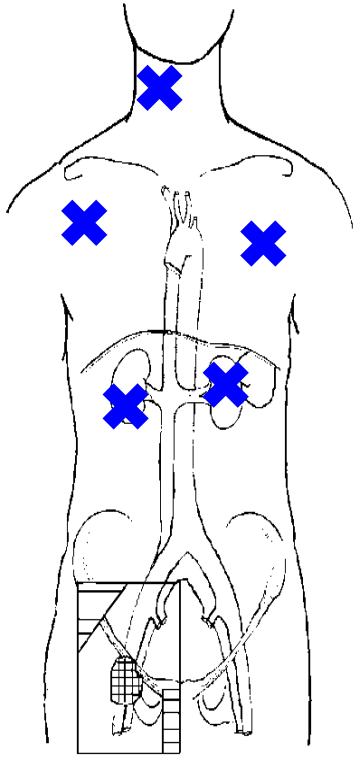
In-Field



Marginal (<5cm)



Next Echelon (contiguous)



Distant

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RT as Single Modality

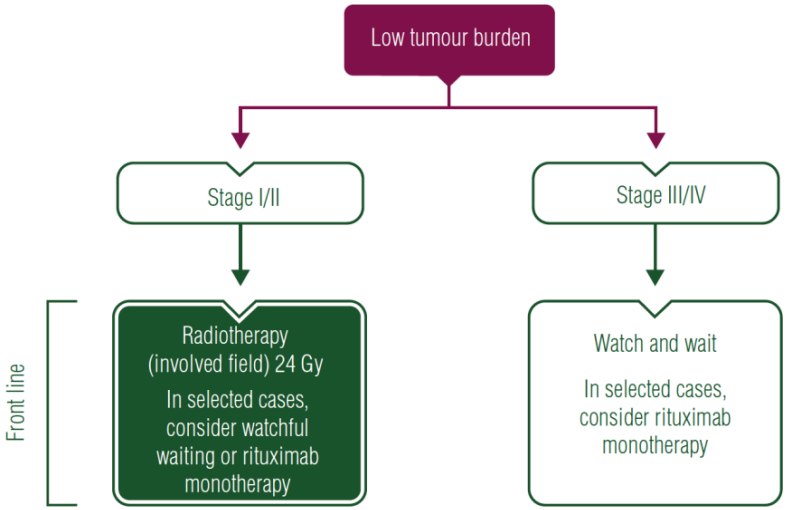
Centre, year	# pts	Median Age (y)	10y RFS (%)	10y OS (%)
PMH, 1993	285	57	52	65
Marsden, 1995	58	55	43	79
Stanford, 1996	177	52	44	64
BNLI, 1996	208	60	49	64

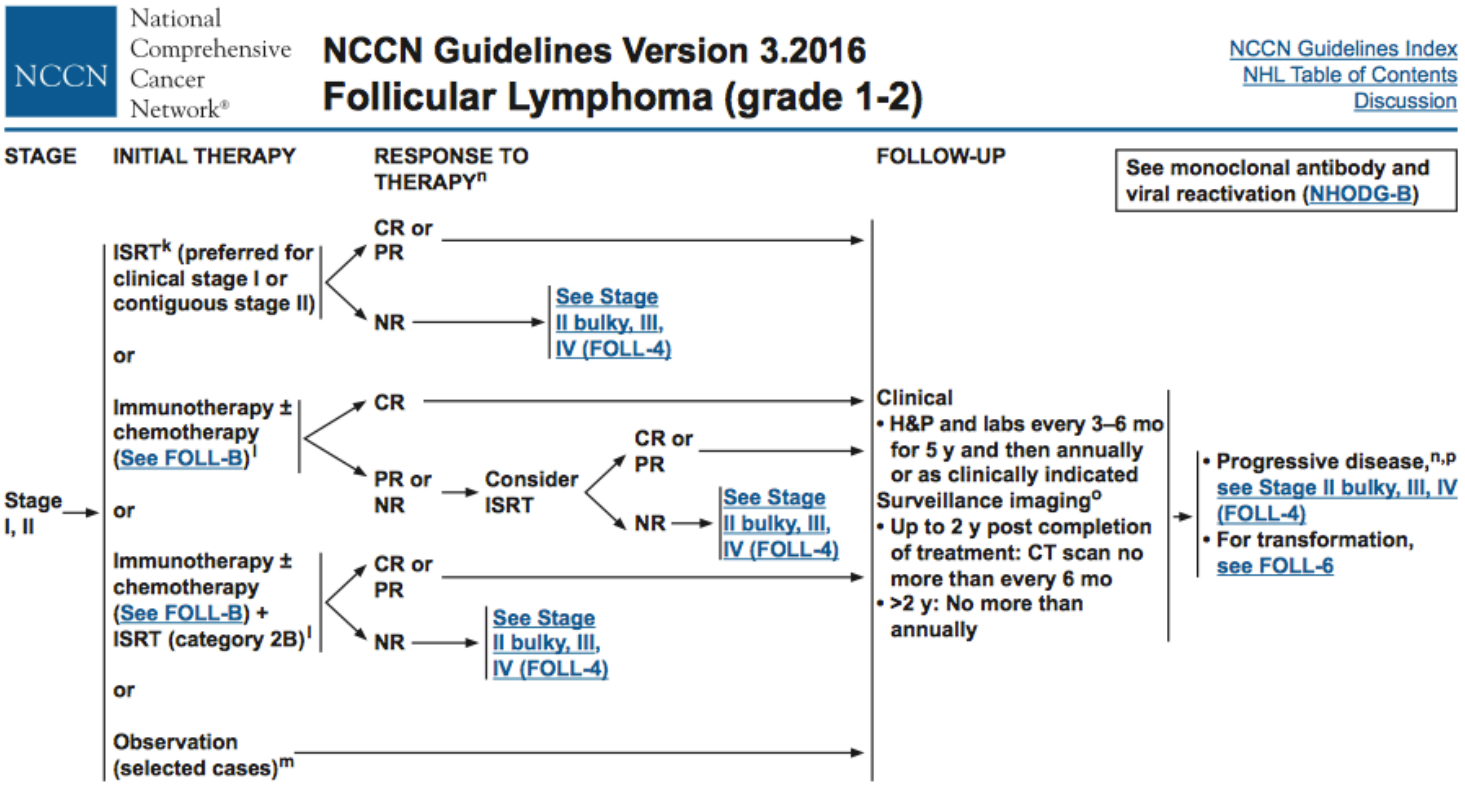
clinical practice guidelines

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*



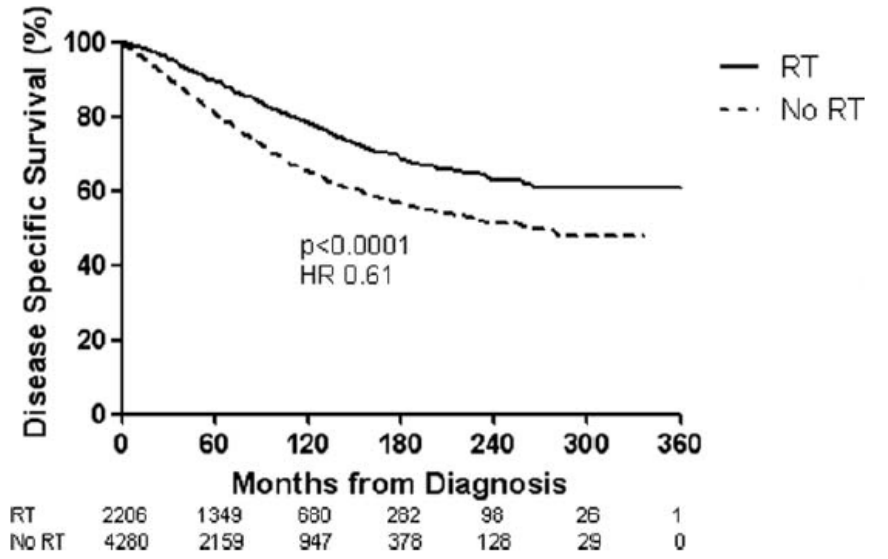


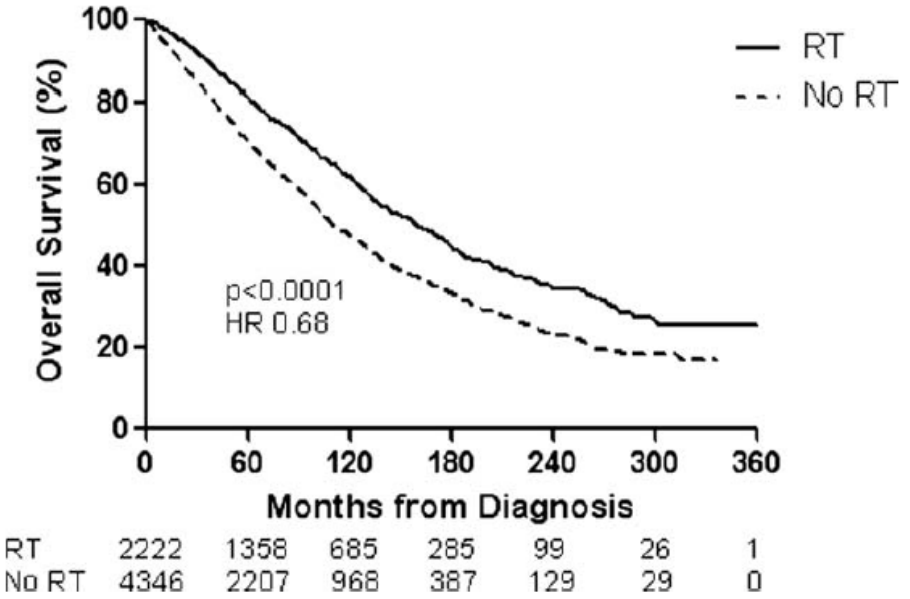
Improved Survival in Patients With Early Stage Low-Grade Follicular Lymphoma Treated With Radiation

Cancer 2010;116:3843–51

A Surveillance, Epidemiology, and End Results Database Analysis

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





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

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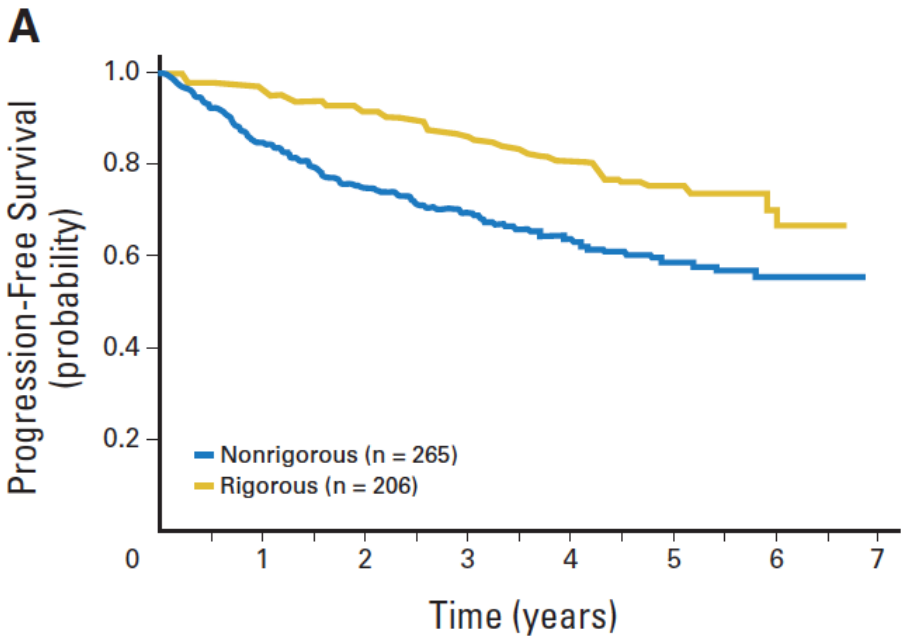
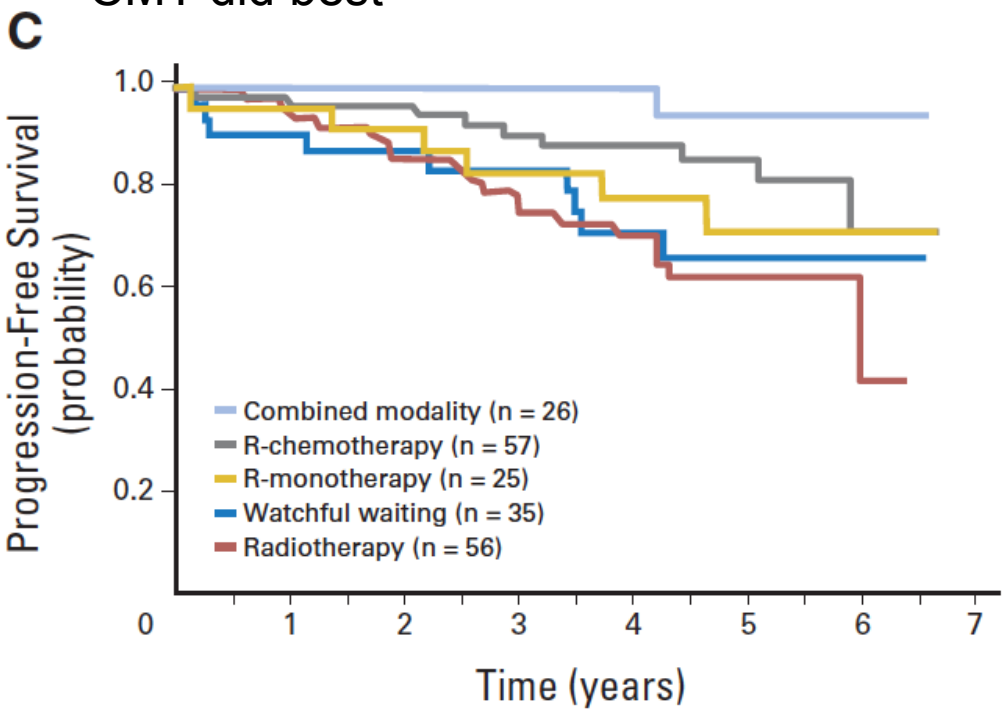
Effectiveness of First-Line Management Strategies for Stage I Follicular Lymphoma: Analysis of the National LymphoCare Study

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

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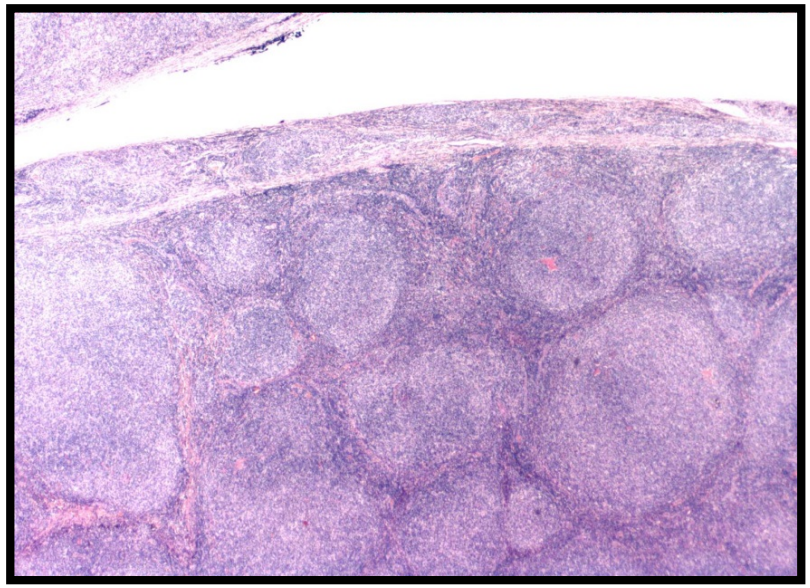
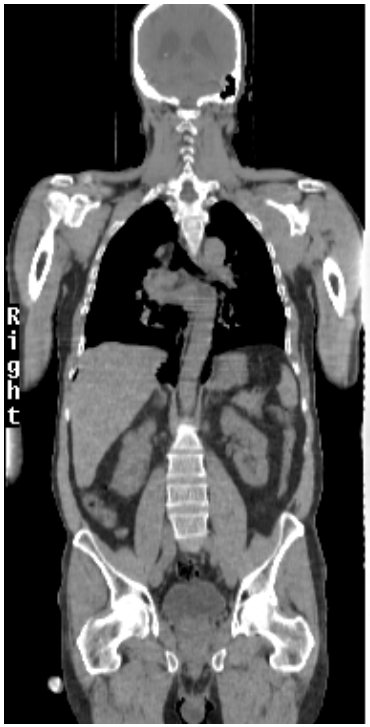
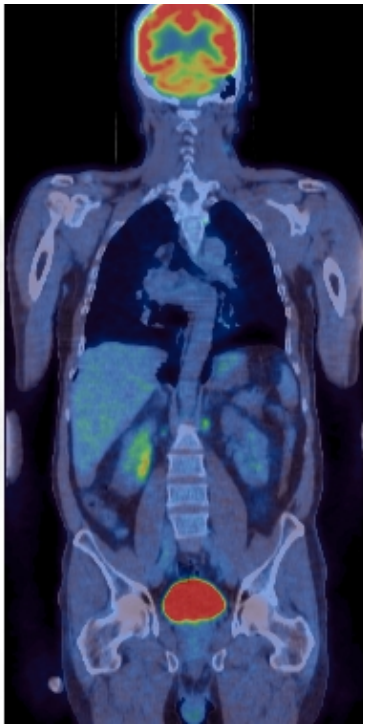
Follicular lymphoma: what staging?







Thorough staging with bone marrow biopsy
and FDG-PET essential

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PET in Early stage FL

- 42 patients
- 97% with gross disease had +ve PET
- PET upstaged in 19 (45%) to III/IV
- 6 (14%) had RT field enlarged
- 1 false positive PET

Wirth A et al. Int J Radiat Oncol Biol Phys 71,213, 2010

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 treatment with RT, with consequent improvement in clinical results

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What Volume should be treated with radiotherapy?

Extended Field vs Involved Field vs Involved Site/Node

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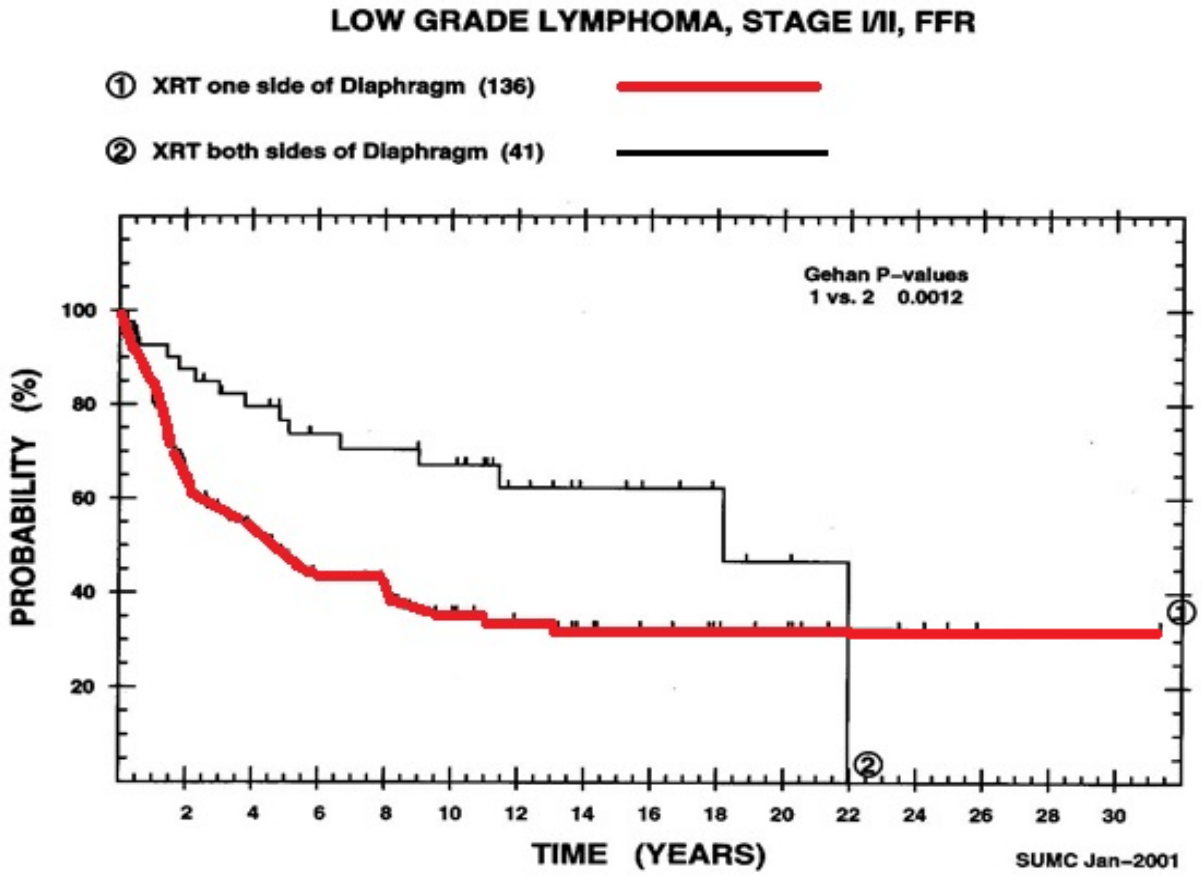
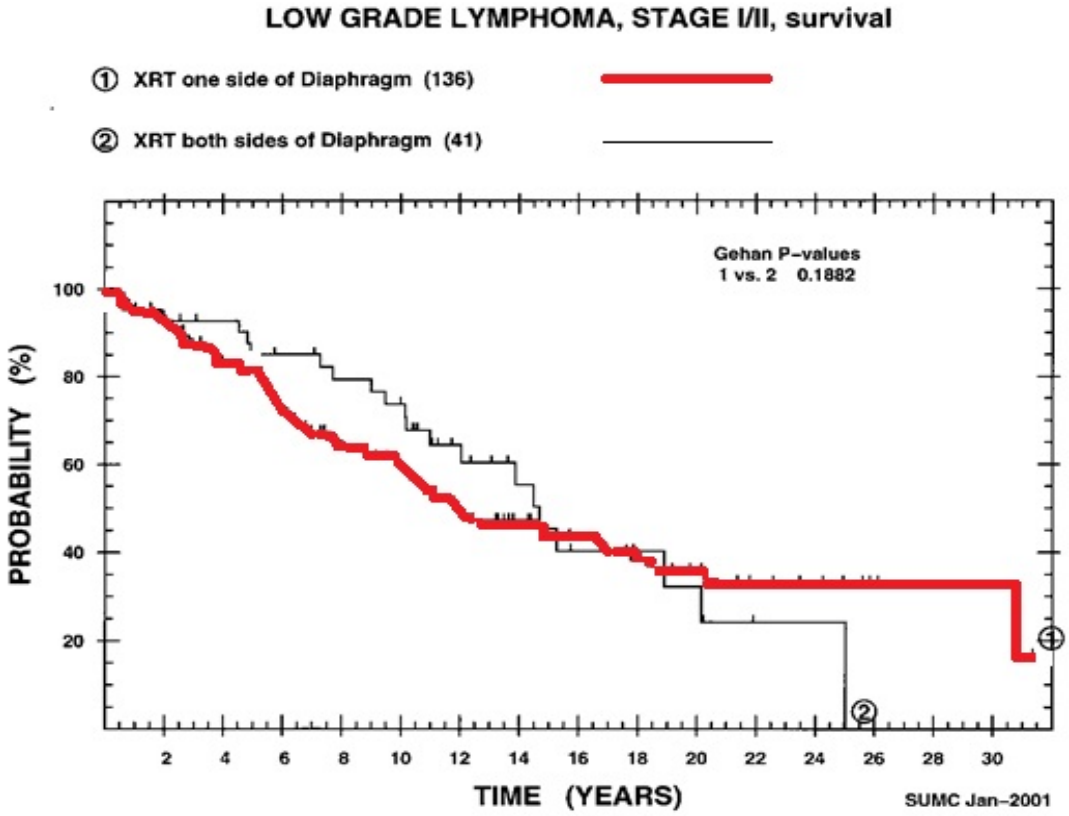
Stanford Follicular Lymphoma:
Effect of Treatment Volume on Freedom from Relapse



Approx 30% difference at 10y

Mac Manus and Hoppe JCO 14; 1282-1290 1996

Stanford Follicular Lymphoma: Effect of Treatment Volume on Overall Survival



Mac Manus and Hoppe JCO 14; 1282-1290 1996

Involved Node vs Involved Region in FL

- IRRT = involved lymph node group plus ≥1 adjacent, uninvolved lymph node group(s).
- INRT=involved lymph node(s) with margins ≤5 cm.
- 237 pts: INRT 95, IRRT 142
- Median follow-up, 7.3 years
- After INRT, 1% of patients had a regional-only recurrence
- No effect of field size on PFS or OS

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

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What Radiation Dose?

Reducing doses for FL

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

- Informative RCTs needed to answer dose question

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Hypothesis: Is more dose better?

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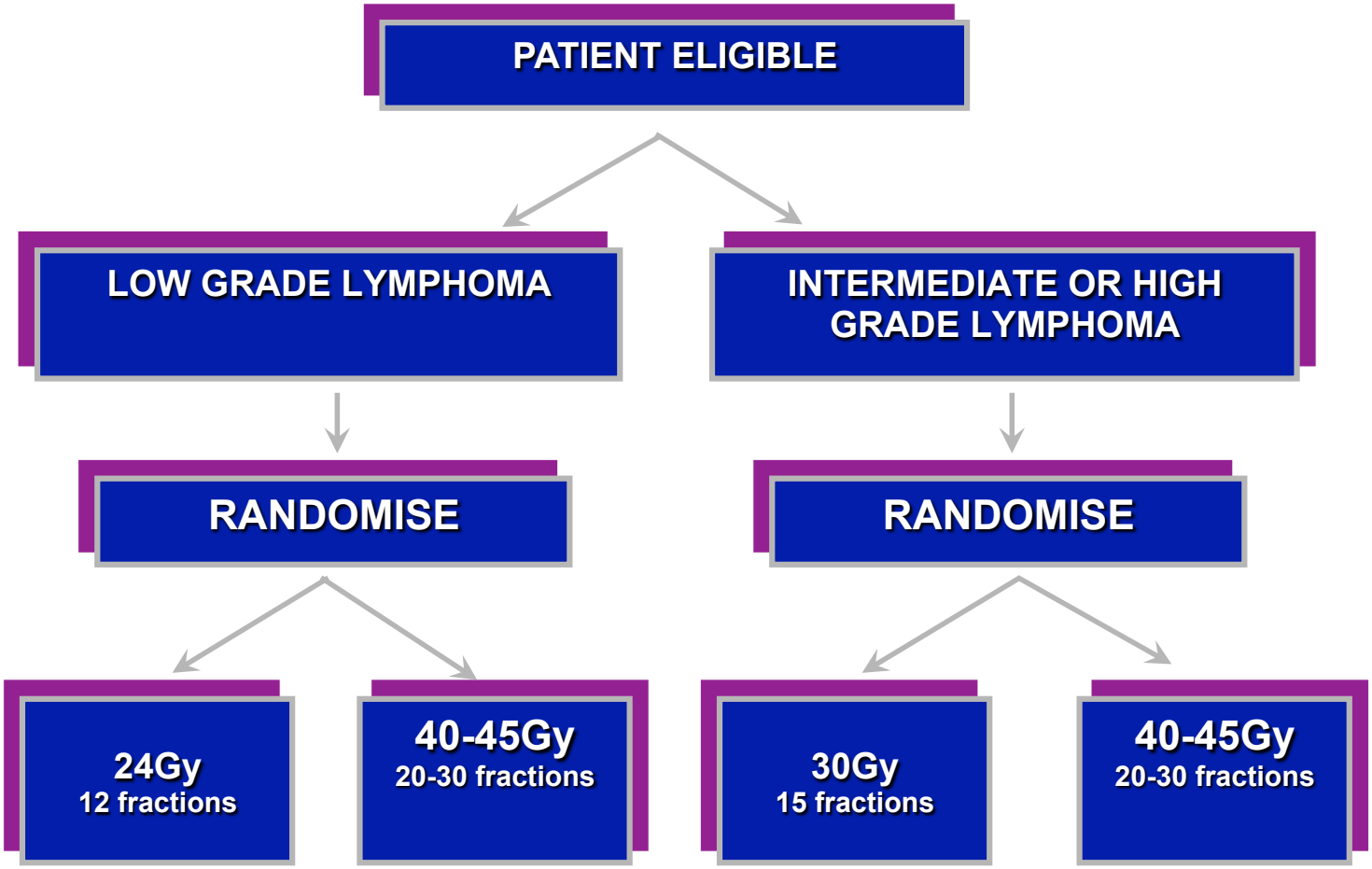
Reduced dose radiotherapy for NHL : A randomised phase III trial

360 indolent NHL (mostly follicular and MZL) randomized



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

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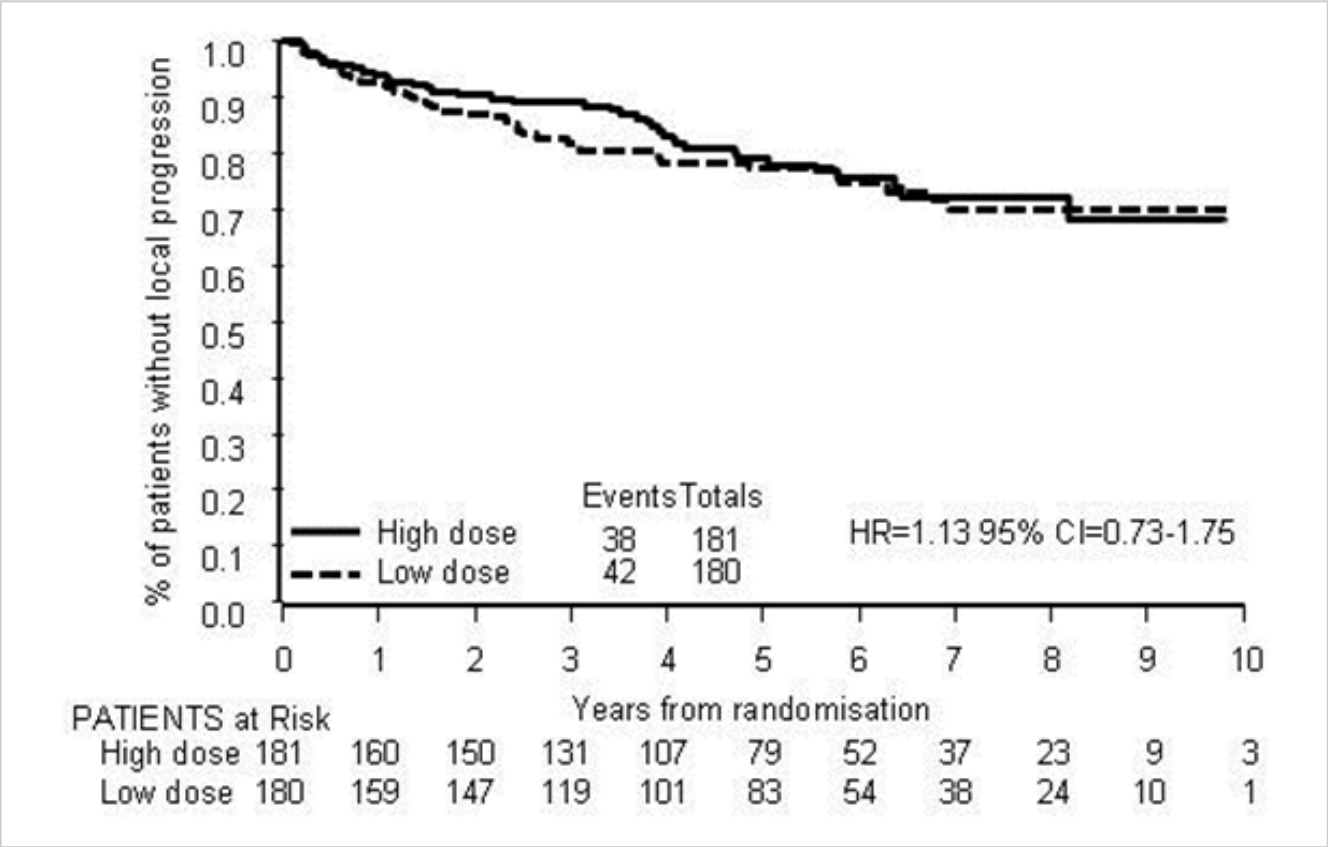
RT dose 24 Gy vs 40-45 Gy in indolent NHL



[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

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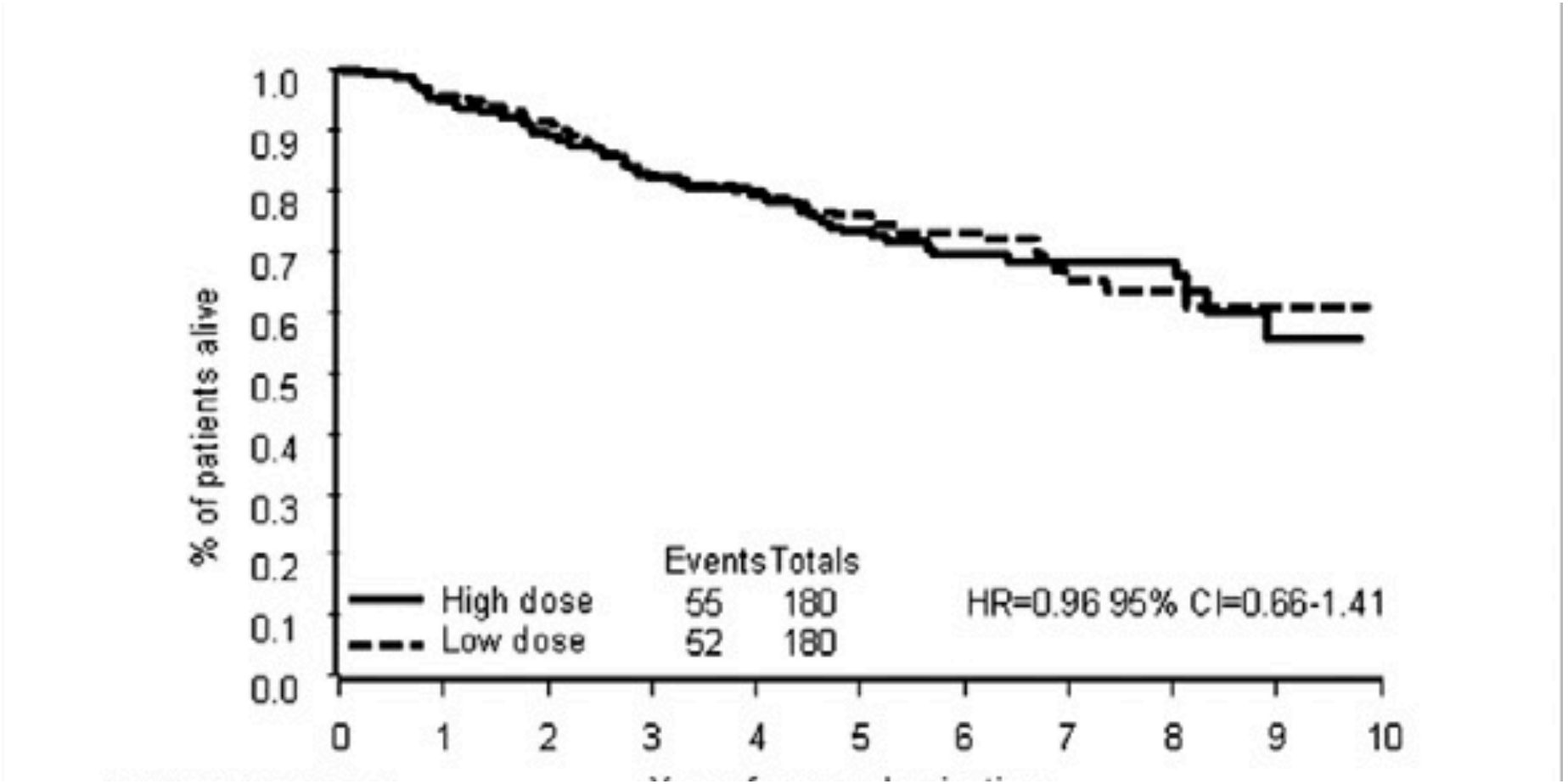
INDOLENT LYMPHOMAS:

Overall Survival



Lowry et al. 2011

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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

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

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

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

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

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

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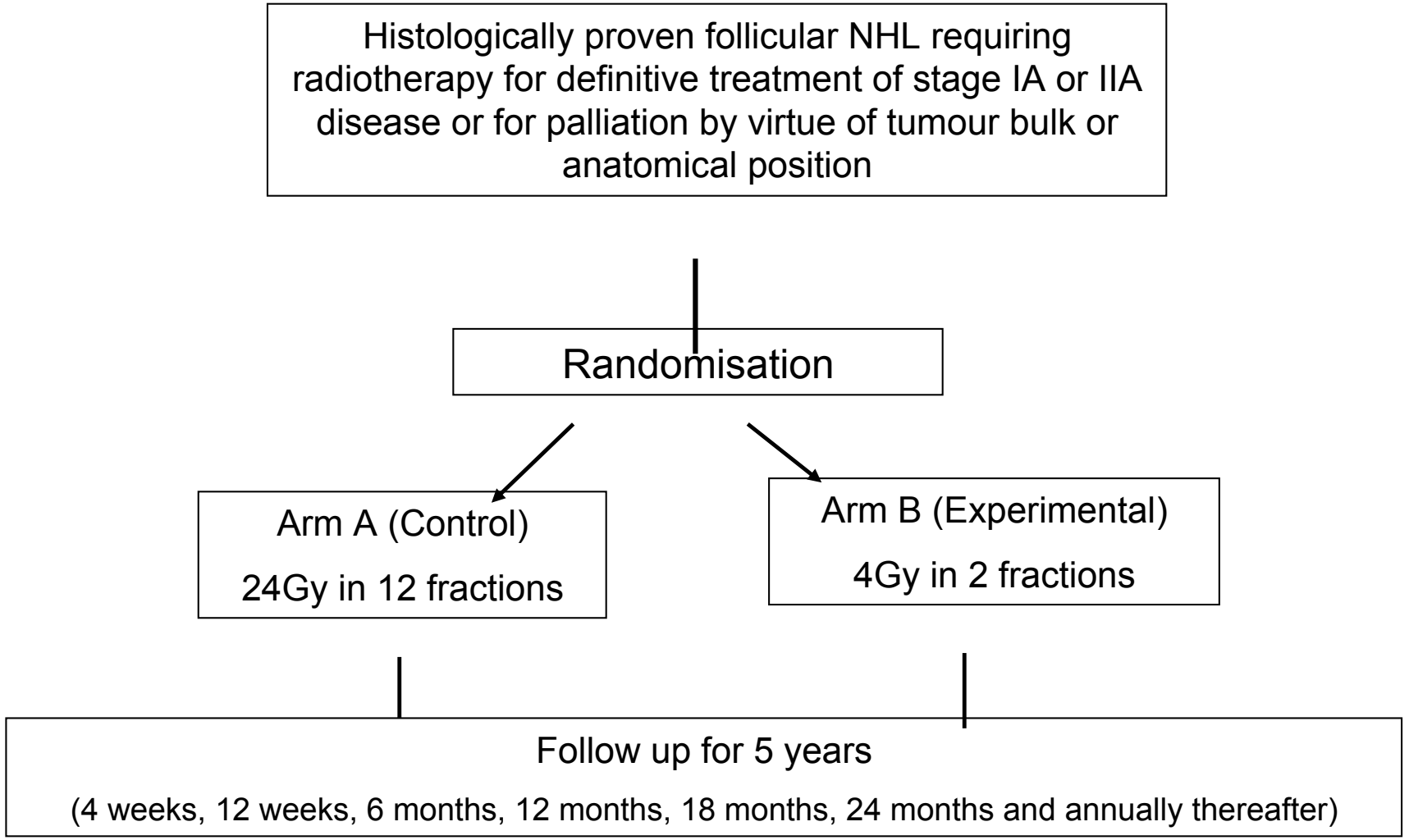
FoRT: Study design : A randomised trial of low dose radiotherapy for follicular lymphoma



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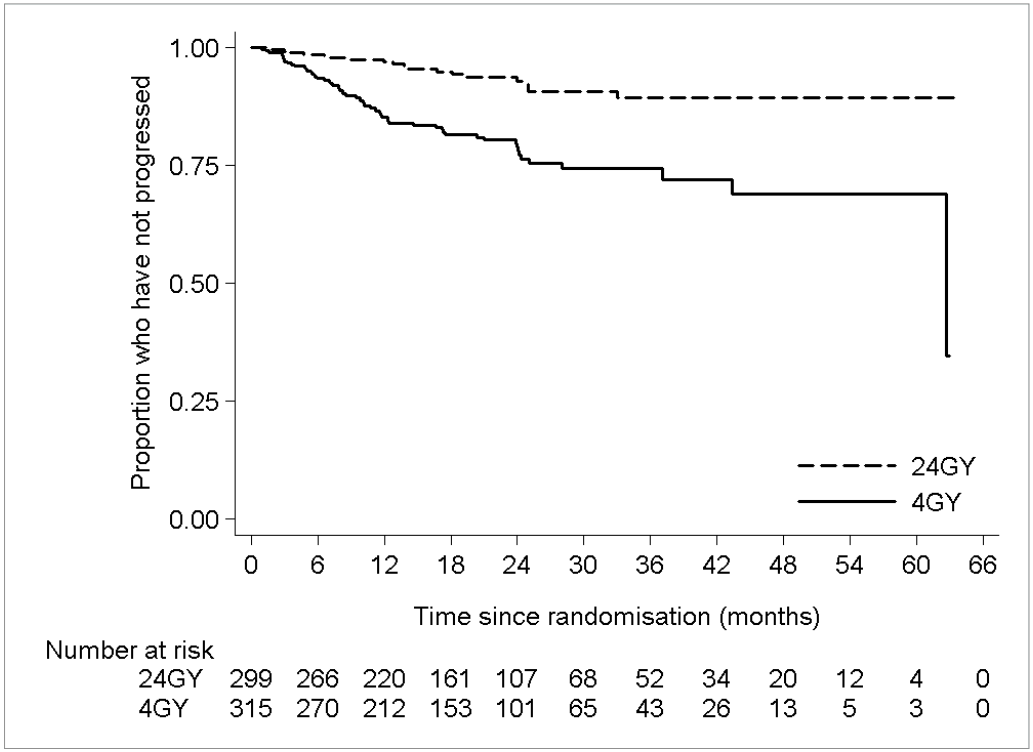
4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

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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SIE, SIES, GITMO revised guidelines for the management of follicular lymphoma

Pier Luigi Zinzani,[1] Monia Marchetti,[2] Atto Billio,[3] Giovanni Barosi,[4]* Angelo Michele Carella,[5] Mario Lazzarino,[6] Maurizio Martelli,[7] Alessandro Rambaldi,[8] Luigi Rigacci,[9] Corrado Tarella,[10] Umberto Vitolo,[11] and Sante Tura[12]

Am. J. Hematol. 88:185–192, 2013

Recommendations Patients with Stage I–II disease, a low tumor burden, and with documented contiguity of involved lymph-nodes treatable in the same radiotherapy field, should receive external involved field radiotherapy, at the dose of 24 Gy (quality of evidence, low; strength of recommendation, strong).

Modern RT in lymphoma

- Radiation therapy has changed dramatically over the last few decades in terms of both irradiated volumes and dose

- Advanced conformal techniques (3D-CRT, IMRT) can certainly allow a safer radiation delivery

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INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

- Worldwide organization
- Steering committee members from Europe, America, Asia, and Australia
- Promoting Education and Collaboration on Radiotherapy for Lymphoma

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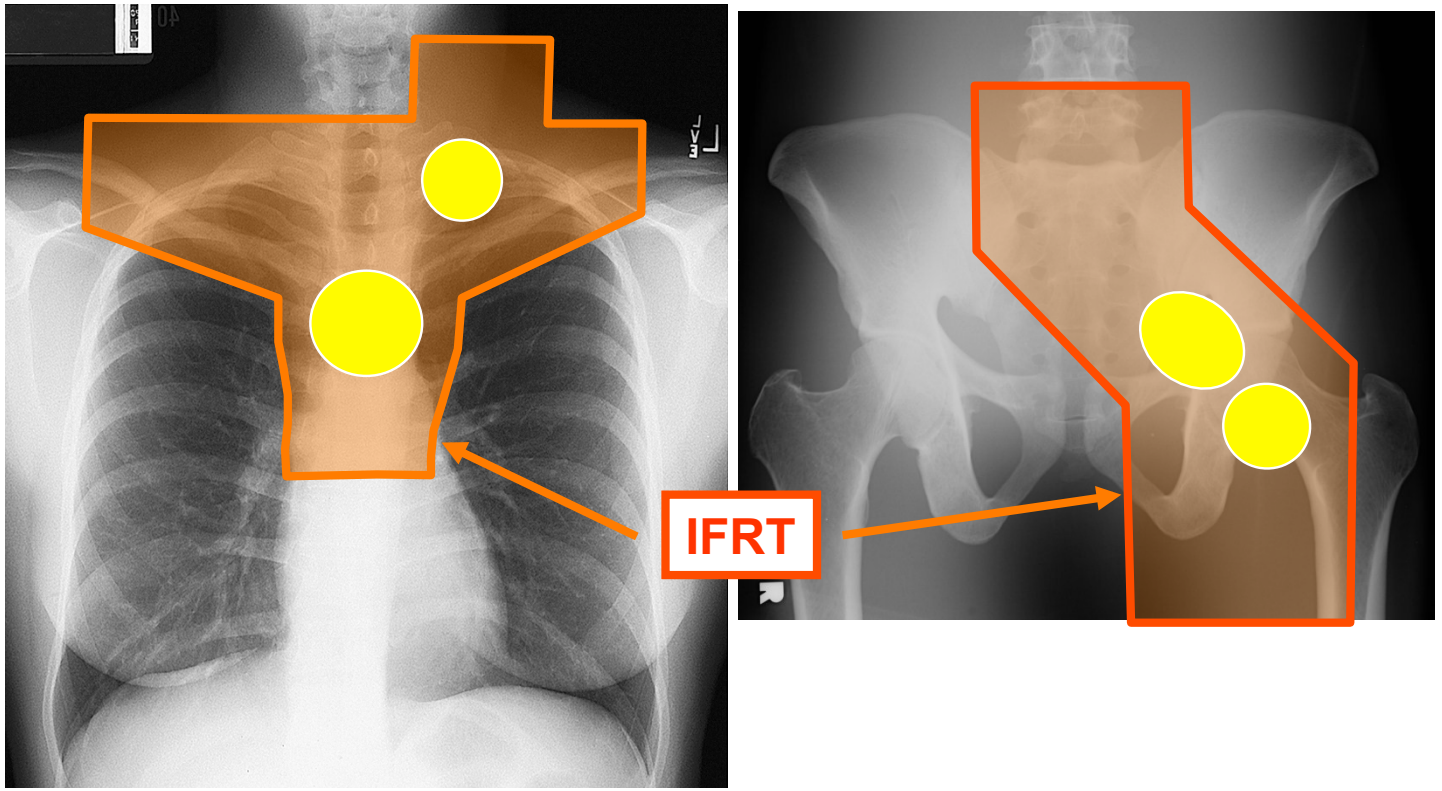
Development of Radiation Volumes

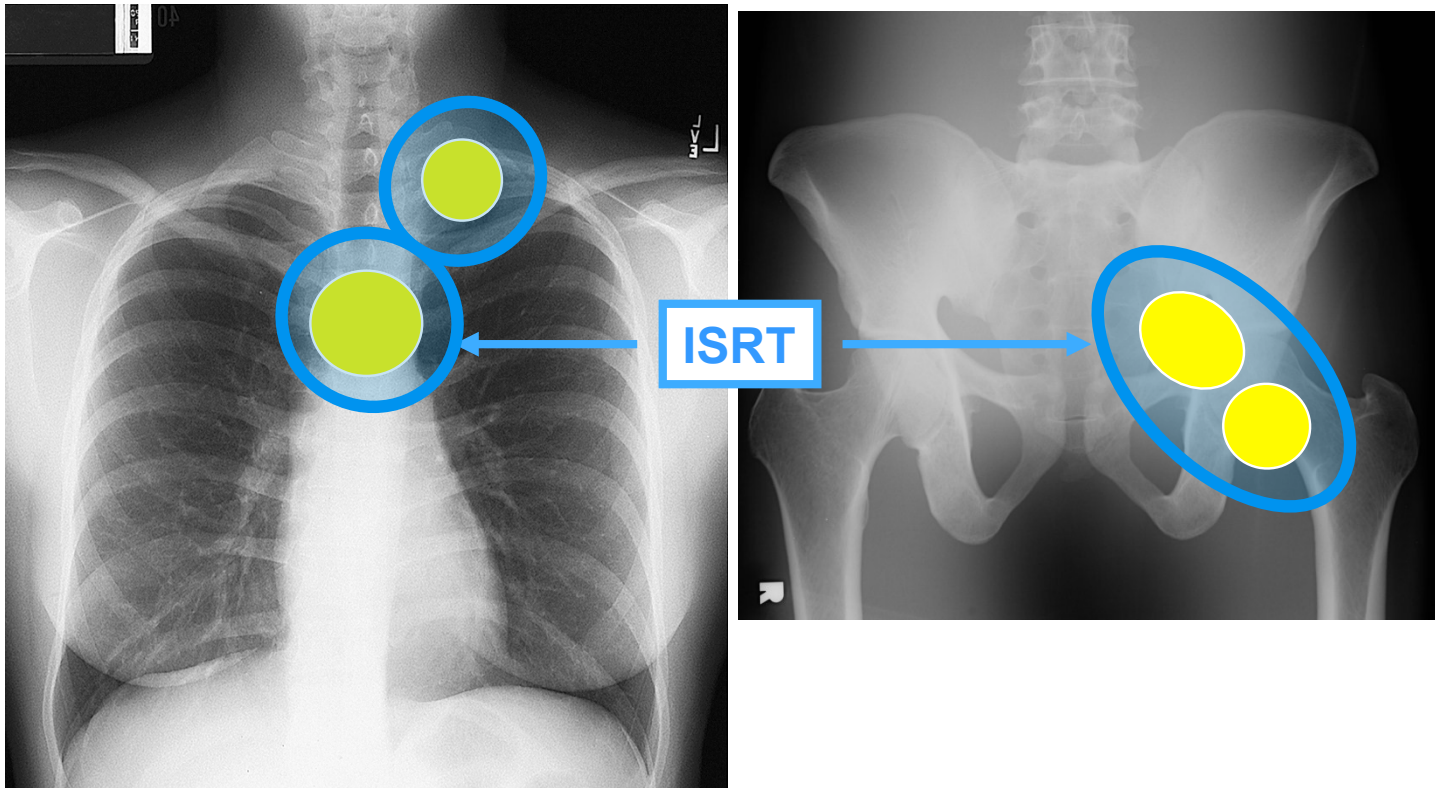
Involved Field:

2D planning, based on bony landmarks

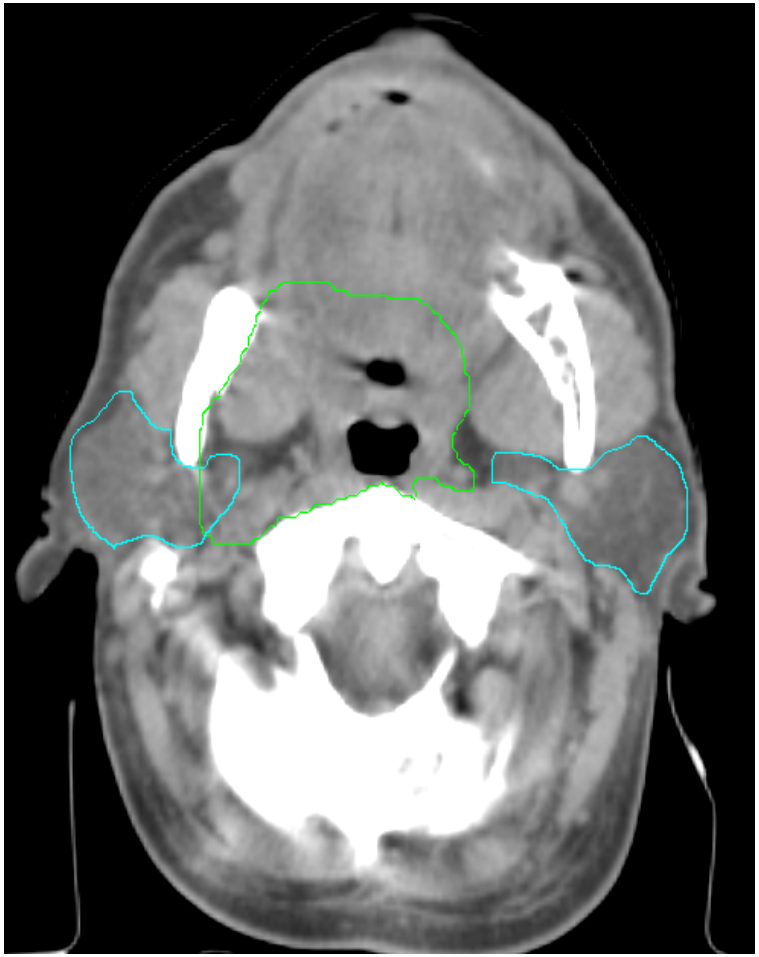


Involved Site

3D planning, based on lymphoma volume



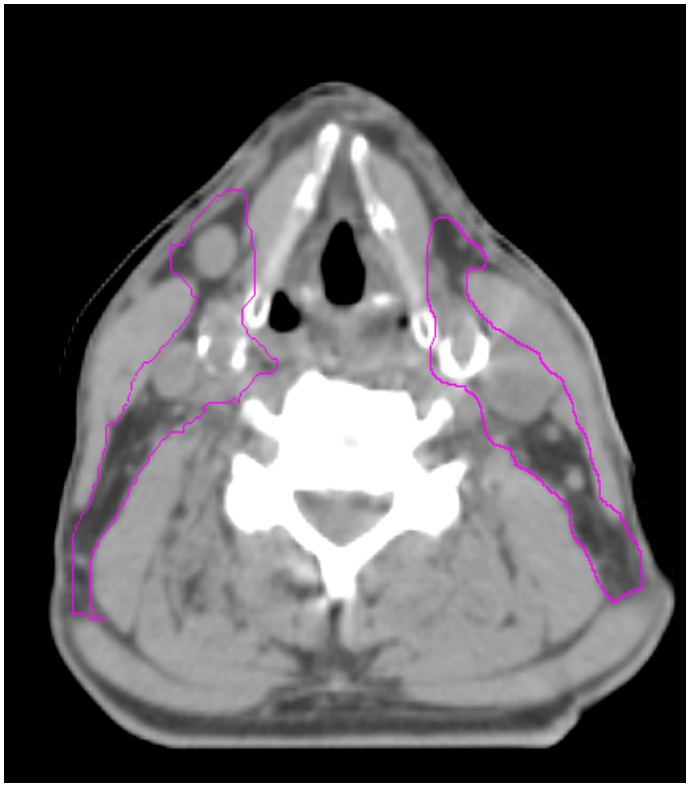
3D CT based planning



Outlining of tumour

+ normal organs

1.25 mm slices



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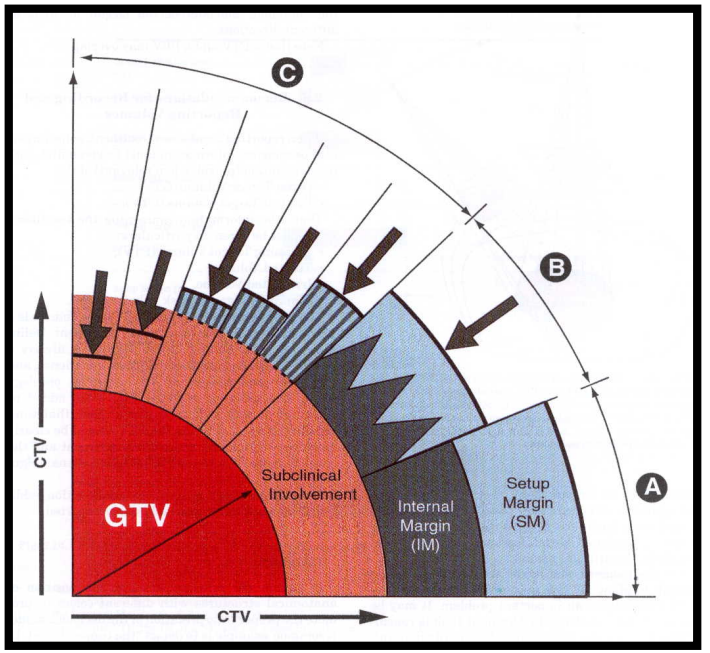
Gross tumor volume (GTV) (ICRU 83)

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

Clinical target volume (CTV)

- Volume of tissue that contains subclinical malignant disease with a certain probability of occurrence considered relevant for therapy



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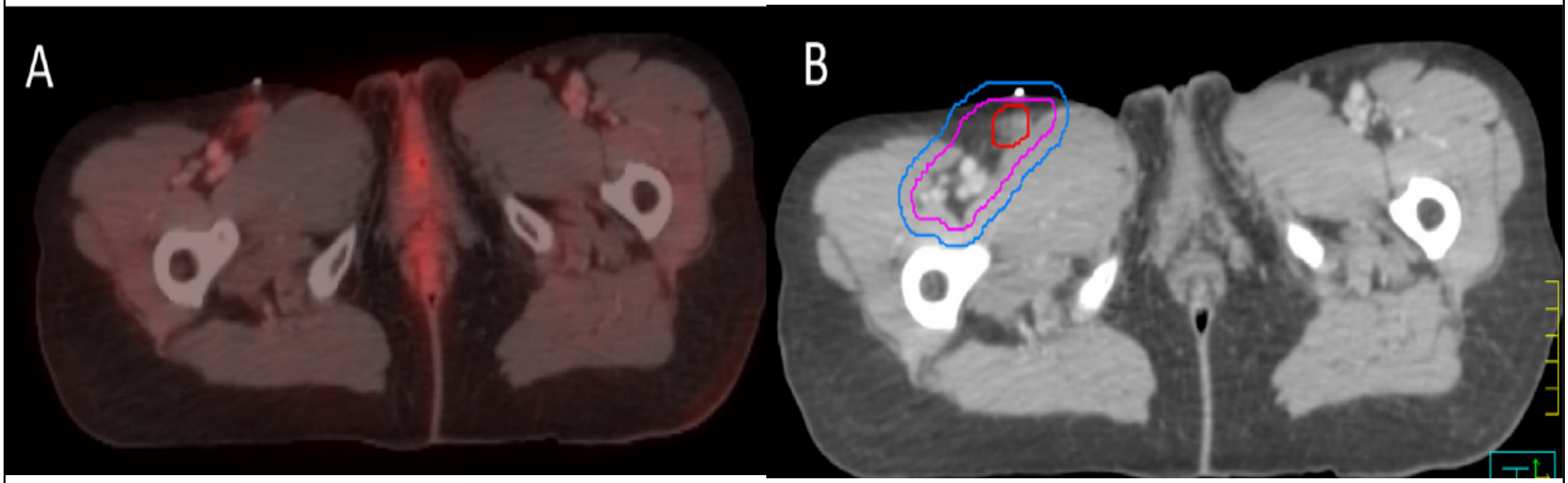
Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

ISRT: Localized indolent lymphoma



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

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

Illidge et al, IJROBP, 2014

Responsibilities of the radiation oncologist

- Ensure that the advantages that can be obtained with modern radiotherapy are used to the benefit of the patient:
  - Optimal target coverage
  - Lowest target dose necessary for the highest chance of local lymphoma control
  - Lowest possible risk of significant long-term side effects

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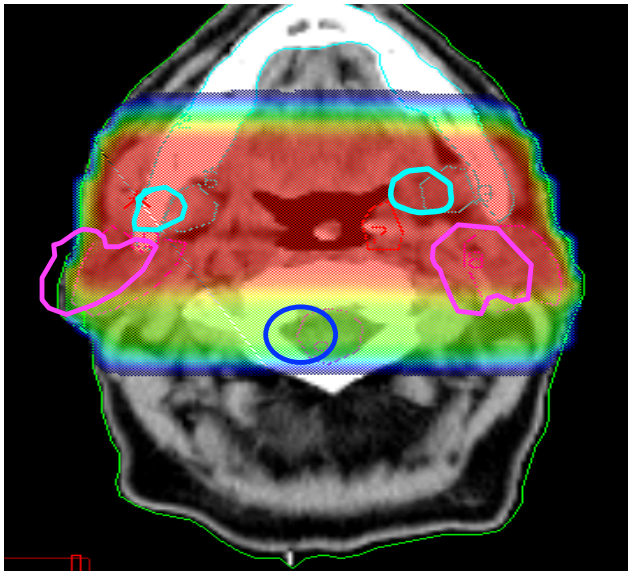
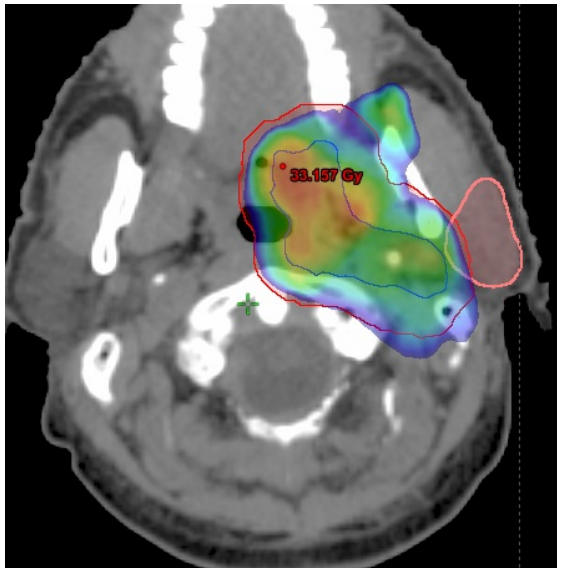
Conformal planning and precise delivery

Conventional RT



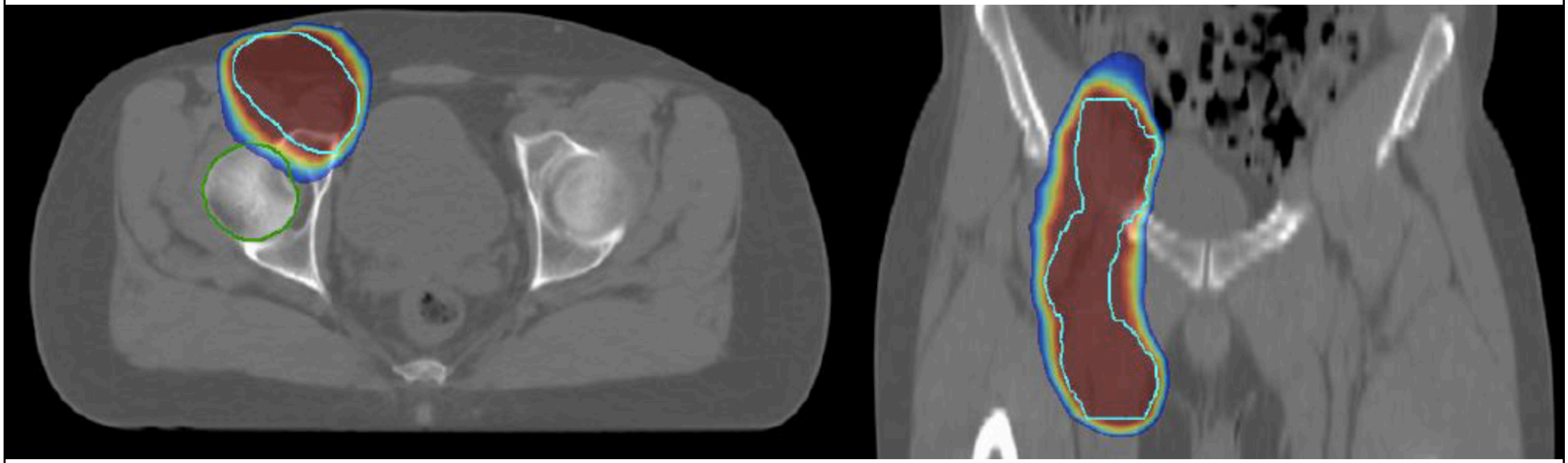
Intensity modulated RT



Review article

Limited Stage Follicular Lymphoma: Current Role of Radiation Therapy

Andrea Riccardo Filippi[1], Patrizia Ciammella[2] and Umberto Ricardi[1]



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Combined Modality Therapy in Stage I-II FL?

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Prospective Combined-Modality Therapy RCTs

4 randomized studies of IF XRT ± CVP / CHOP:

– Finsen institute	17 pts	No diff
– EORTC	28 pts	92% vs 67% 5y RFS
– Milan	26 pts	63% vs 55% 5y RFS
– MSKCC	16 pts	83% vs 54% 10y RFS

BNLI; IF XRT ± low-dose chlorambucil *(Med Oncol 1994)*

– IF XRT	82 pts	37% 10y RFS
– XRT + chlb	66 pts	46% 10y RFS *(P = 0.14)*

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: Submitted to Lugano 2017

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TROG 99.03/ALLG NHLLOW5: Objectives

Primary
To test hypothesis that 6 cycles of systemic therapy after IFRT will improve PFS in stage I-II low-grade FL

Secondary
To compare overall OS and FFP between arms
To compare location of 1st relapse between study arms.
To compare time to transformation to higher grade
Study effect of PET staging
Evaluate effect of Rituximab

Translational studies (stored blood, marrow, biopsy specimens)

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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

Arm A:

IFRT 30 Gy

Randomize

Stratify:

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

Arm B:

IFRT 30 Gy
+ (R)-CVP x 6

Follow up with annual CT

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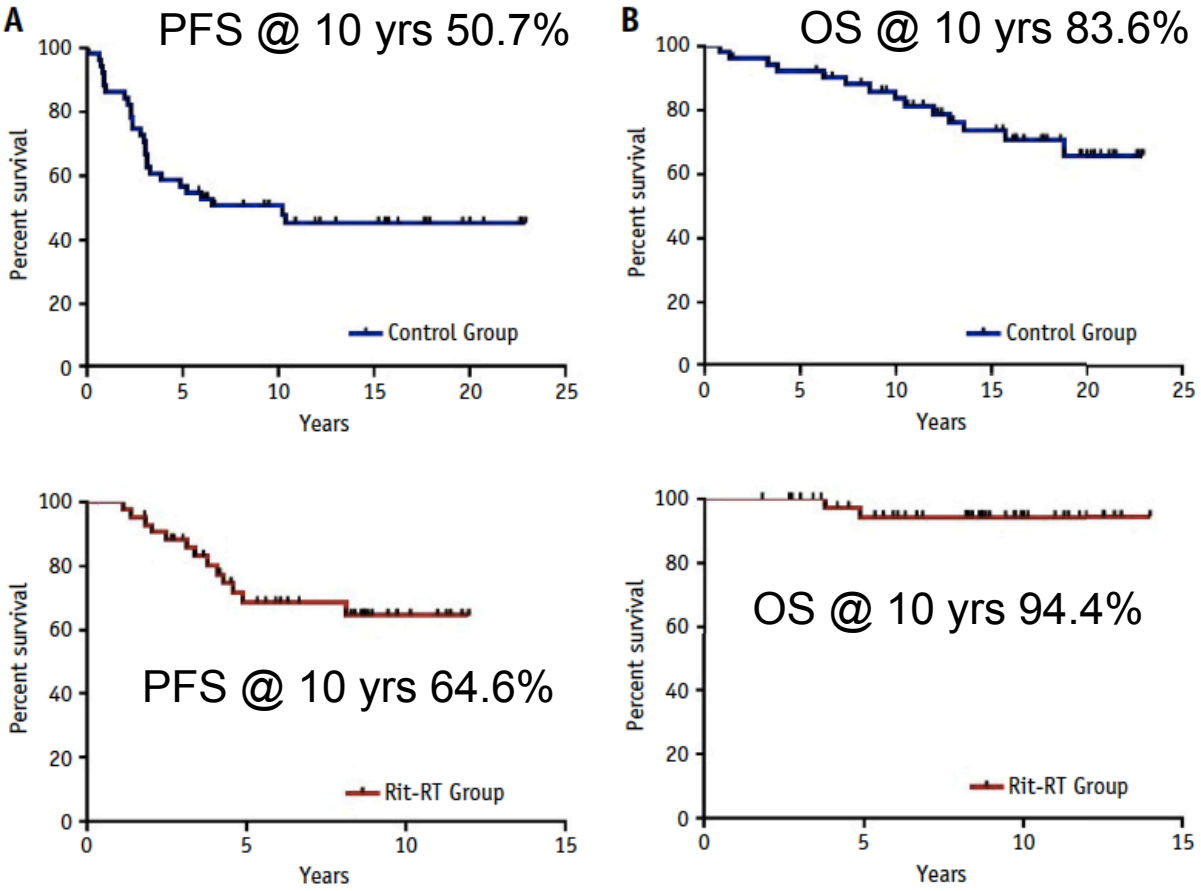
Addition of Rituximab to Involved-Field Radiation Therapy Prolongs Progression-free Survival in Stage I-II Follicular Lymphoma: Results of a Multicenter Study

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



4 rituximab courses (375 mg/m^2 , days 1, 8, 15, 22) before RT (Rit-RT)

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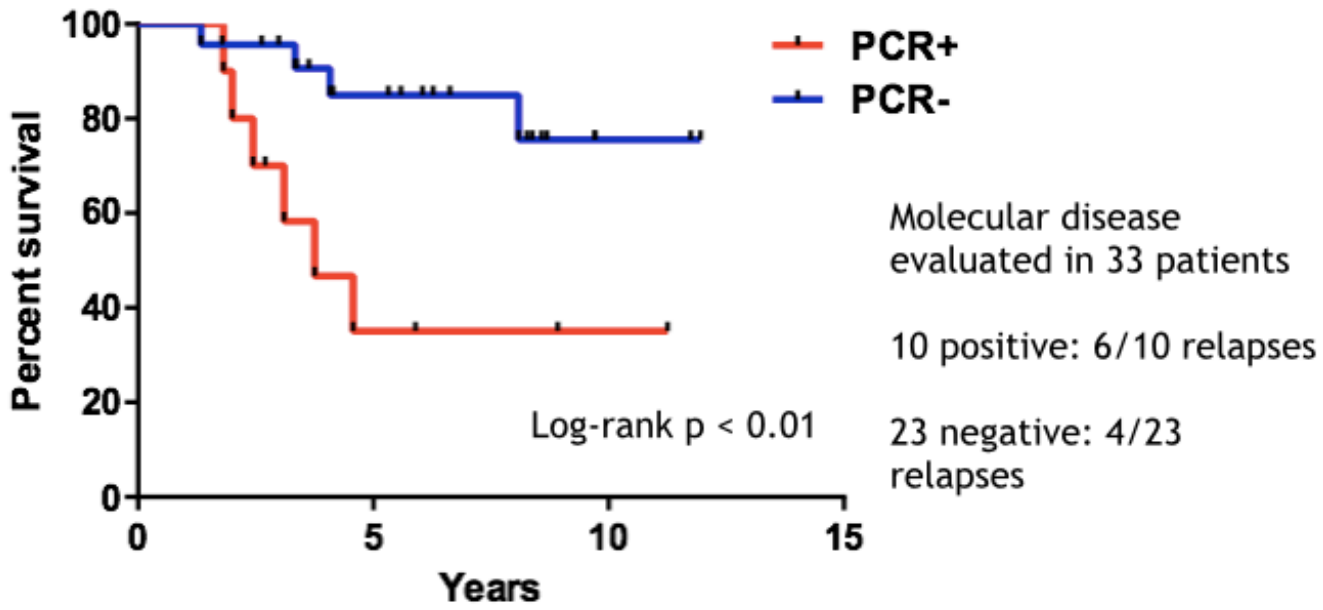
Rituximab-RT

PFS according to bone marrow PCR positivity at baseline

PFS: PCR positive vs. PCR negative

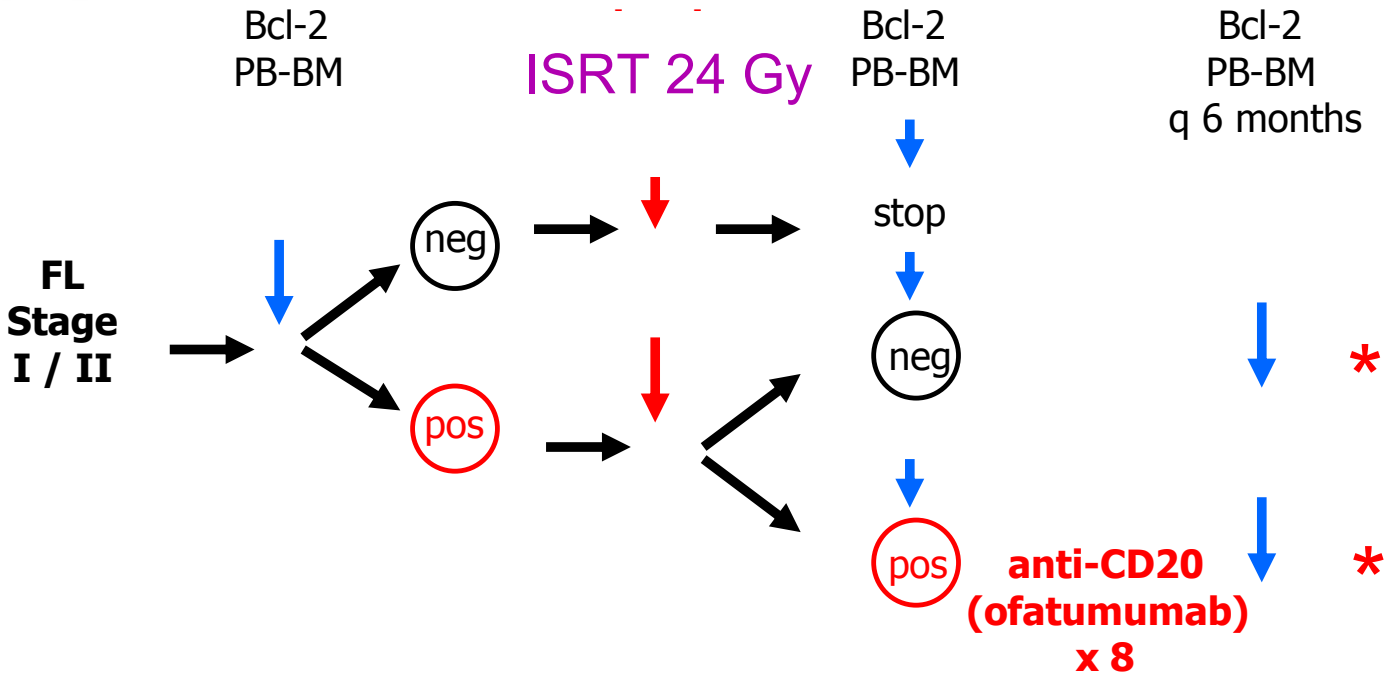


Ruella M, Fillippi AR

Department of Oncology
University of Turin

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

FLOW CHART



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

Courtesy A. Pulsoni

Conclusions

•RT remains treatment of choice for majority of stage I/II follicular lymphomas, resulting in long term progression free survival and possible “cure” achievable with very low morbidity[1]

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

James O. Armitage

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