Radiotherapy for stage I/II follicular lymphoma (FL): is it time for a reappraisal?

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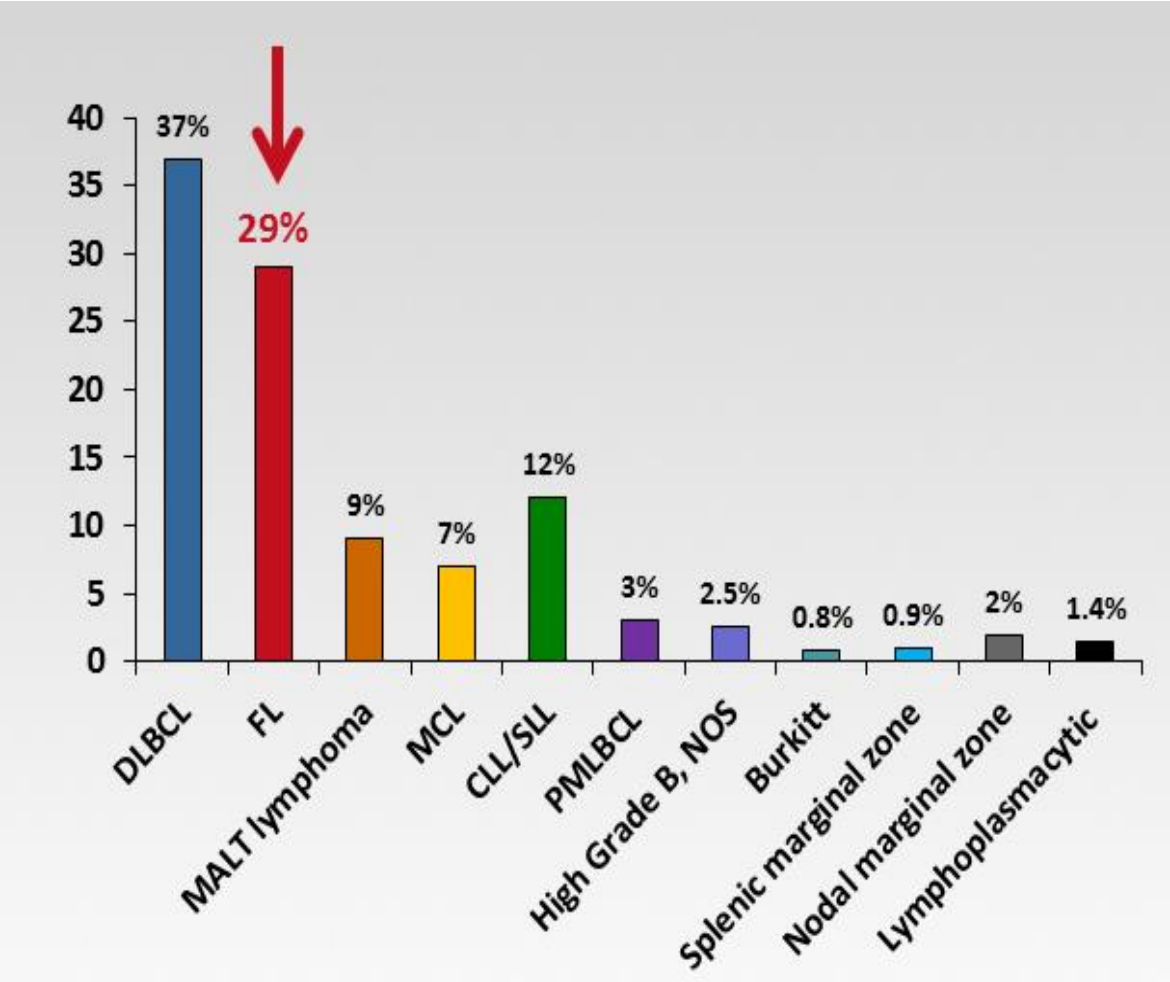
Background



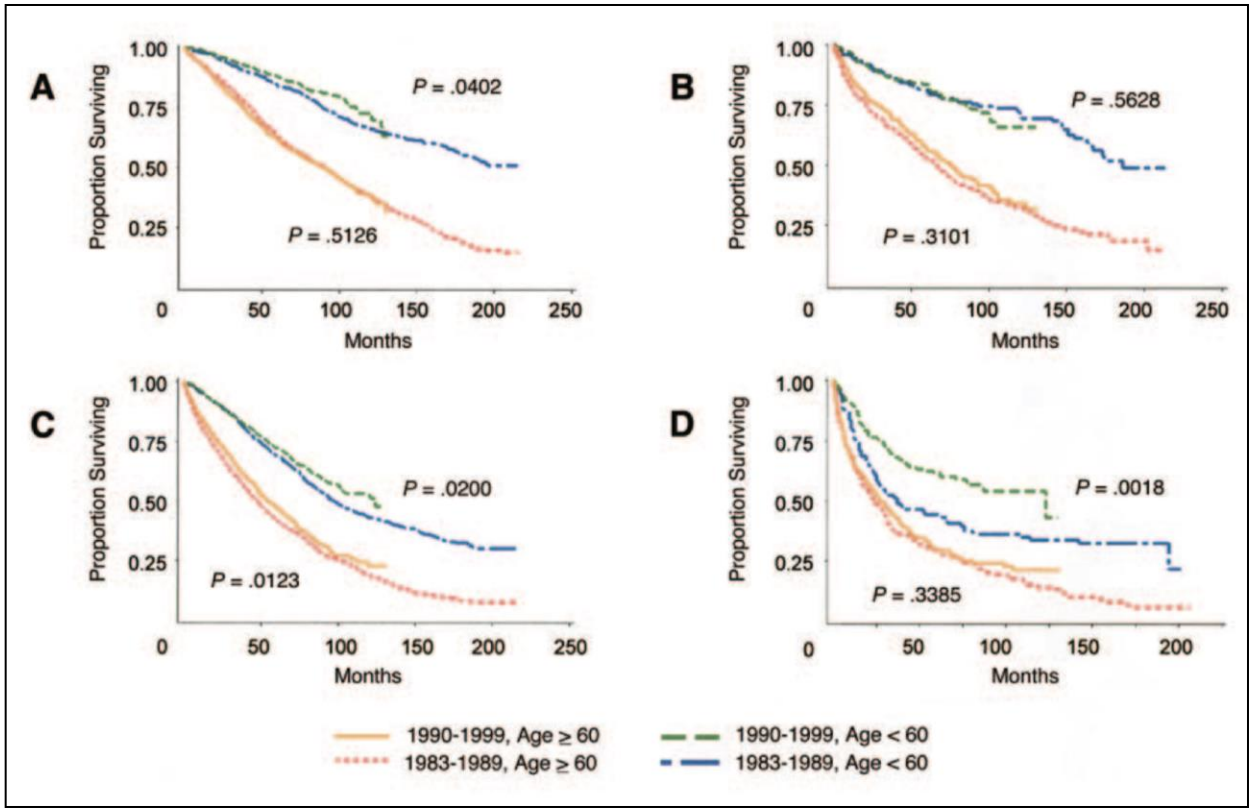
Follicular lymphoma (FL) is the second most common non-Hodgin lymphoma (NHL), representing **about 30%** of all new diagnoses

Most patients present with advanced disease, while **15-20%** have **stage I-II**

The median age is the **6th** and **7th decade**

Jaffe ES, et al In: Swerdlow SH, et al. World Health Organization (WHO) Classidication of Tumours of Haematopoietic and Lymphoid Tissues, Fourth edition. Lyon, France: IARC Press; 2008:158-166.

Background



FSC= small cleaved-cell follicular lymphoma; FM= mixed follicular lymphoma; FLC= large-cell follicular (A) Limited/regional stage FSC+ FM; (B) limited/regional stage FLC; (C) advanced stage FSC + FM; (D) advanced stage FLC.

- indolent clinical course
- **continuous pattern of relapse**
- **very long overall survival** both in early and advanced stages

Tan D, et al. Blood. 2013 Aug 8;122(6):981-7.

NCCN Guidelines Follicular Lymphoma

National Comprehensive Cancer Network®

STAGE	INITIAL THERAPY
Stage I, II →	ISRT[i] (preferred for clinical stage I or contiguous stage II) or Immunotherapy ± chemotherapy or Immunotherapy ± chemotherapy + ISRT (category 2B) or Observation (selected cases)

ISRT= Involved-site radiation therapy

NCC Network: Non-Hodgkin's Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2011). Follicular Lymphoma (Grade 1-2) Guidelines, p. 27. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf. Accessed August 25, 2011

Nowadays, for patients with stage I-II disease, **RT alone** is the **treatment of choice**

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

	Stage I-II
First line	IFRT 30-35 Gy
	(WW)
	(Systematic therapy)

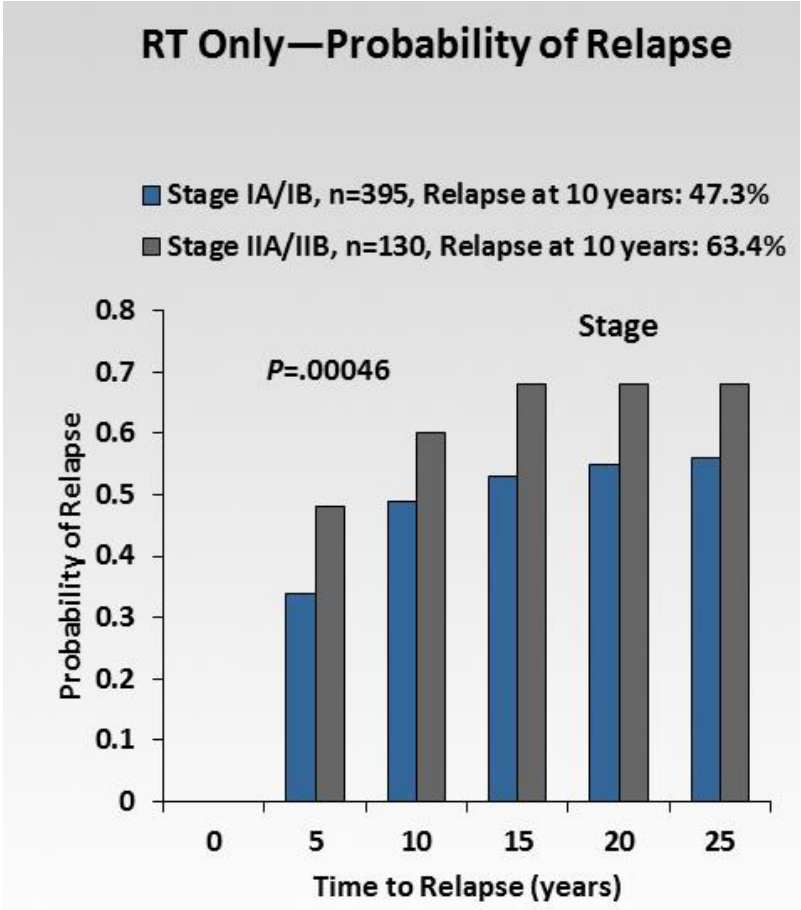
IFRT= Involved field radiation therapy

Ghielmini M , et aL. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), **follicular** lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol 2013; 24 (3): 561-576.

Follicular lymphoma, stage I–II radiation therapy alone.

Center	N	Stage	FFR/DFS (yrs)	Survival (yrs)
PMH [1]	460	I–II	41% (10)	62% (10)
BNLI [2]	208	I	49% (10)	64% (10)
Stanford [3]	177	I–II	44% (10)	64% (10)

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



NCCN = National Comprehensive Cancer Network

Charpentier A, et al. ICML-12 2013. Abstract 62.

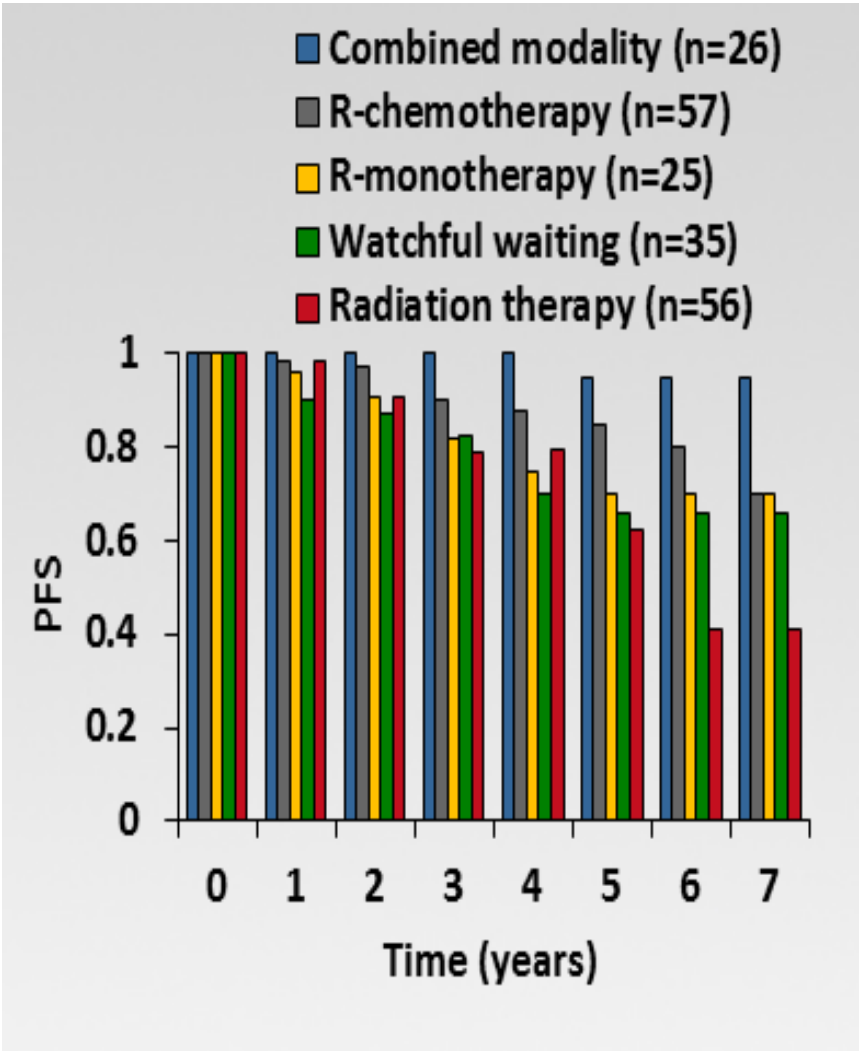
- nearly **50%** of pts **relapse** within 10 years[1-3]
- **disease recurrence** mostly occurs **outside** the primary irradiation field
- **side effects**:

  Acute: skin irritation, nausea and vomiting, fatigue, bone marrow toxicity;

  Late: fibrosis, heart disease, secondary cancer;
- 20–30% of patients will show evidence of **histologic transformation** at the time of or shortly following relapse

1. Petersen PMGM, et al. J Clin Oncol 2004;22(14S):652.
2. Denham JW, et al. Eur J Cancer 1996 Mar;32A(3):470–9.
3. Mac Manus MP, et al. J Clin Oncol 1996 Apr;14(4):1282–90.

US: Lymphocare Survey



Patients on **systemic therapy +/- RT** had **improved PFS** compared to RT alone.

No difference in OS between treatment groups.

Anthracycline containing chemotherapy

- **acute toxicities**
- **secondary malignancies**

Rituximab

- **eradicate minimal residual disease** (MRD)
- **favorable toxicity profile**

Combined modality treatment (R plus IFRT)

- **Rituximab enhances radiosensitivity** of lymphoma cells
- **reduces the rate of distant recurrences**.

Friedberg JW, et al. J Clin Oncol 2012;30(27):3368-3375

Retrospective “real-life” analysis

•from **1995** to September **2012**

•**108** consecutive **early stage FL** patients (grade 1-3A)

•University Hospital “G. Martino” in Messina, Italy
and the Medical University of Innsbruck, Austria

•patients with **bulky disease** were **excluded** from the study

End points:

•Progression-free survival (PFS)

•Time to next therapy (TTNT)

•Overall survival (OS)

All these data were plotted as curves using the Kaplan-Meier method.

Chi-square test was performed to assess the significance of differences between categorical variables.

Clinical characteristics at time of diagnosis

Parameter	IFRT (n=36)		R (n=38)		R+IFRT (n=34)		*p*-value
	N	%	n	%	n	%	
B-Symptoms	2	5.5	6	15.8	14	41.1	0.001
LDH>UNL	8	22.2	10	26.3	18	52.9	0.013
B2-microglobulin	12	33.3	18	47.3	21	62	0.059
FLIPI							0.015
0	28	77.8	20	52.6	16	47	
1	8	22.2	18	47.4	18	53	
Stage							0.715
I	19	52.7	17	44.7	15	44.1	
II	17	47.3	21	52.3	19	55.9	

Abbreviations: LDH, lactate dehydrogenase; UNL, upper normal limit; FLIPI, follicular lymphoma international prognostic index; IFRT, involved-field radiation therapy; R, rituximab.

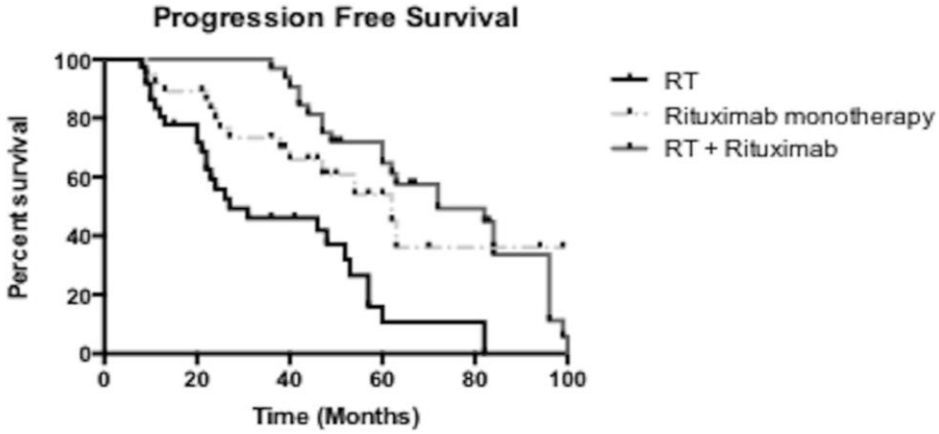
- IFRT group: Radiation doses were ≥ 24Gy in all cases;
- R group: Rituximab weekly at the standard dose of 375mg/sqm for a median of 5 administrations (range 4-8);
- R+IFRT group: Rituximab weekly at the standard dose of 375mg/sqm for 4 cycles after IFRT.

Parameter	IFRT (n=36)		R (n=38)		R+IFRT (n=34)		All patients (n=108)		p-value
	n	%	n	%	n	%	n	%	
Treatment Response									
CR	30	84	33	87	33	97	96	88.8	0.1
PR	6	16.6	5	13.1	1	2.9	12	11.1	0.4
Relapse	27	75	18	47.3	19	55.8	64	59.2	0.03
Status at last follow-up	9	25	16	42.1	16	47	42	38.8	
Alive in CR	20	55.5	16	42.1	18	52.9	52	48.1	
Alive with disease	2	5.5	1	2.6	1	2.9	4	3.7	
Death in CR	5	13.8	2	5.2	1	2.9	8	7.4	
Death with disease									

Abbreviations: CR: complete response, PR: partial response, IFRT: involved-field radiation therapy; R: rituximab

Administration of **Rituximab** translated into a **significantly lower relapse rate** (≥20% less) suggesting it has an important role in the elimination of persistent occult MRD.

A



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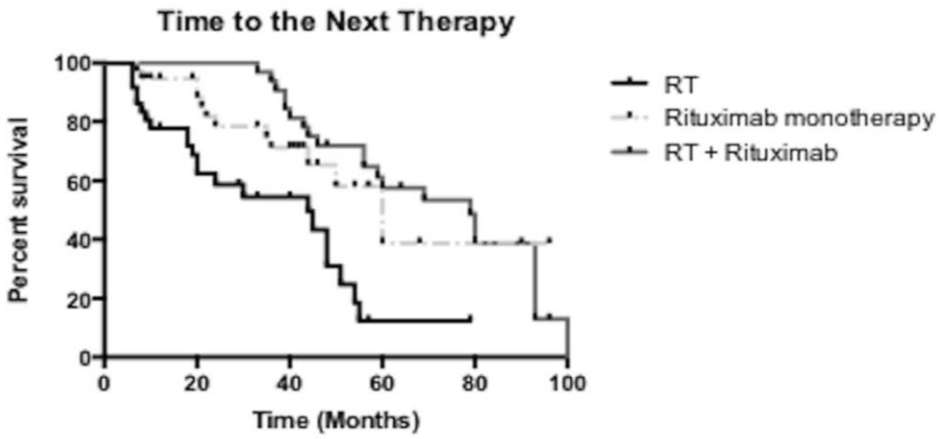

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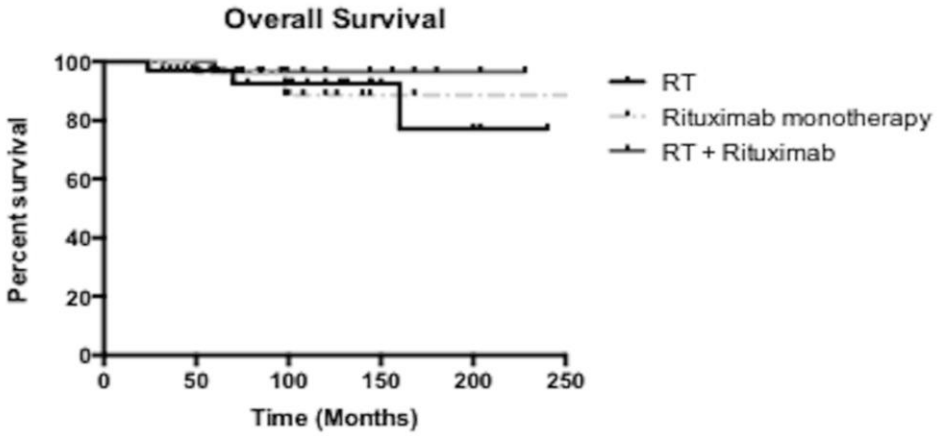

Parameter	IFRT (n=36)	R (n=38)	R+IFRT (n=34)	*p*-value
	yrs	yrs	yrs	
PFS	2.3	5	6	< 0.001
TTNT	2	5	6.6	< 0.001
OS	und	und	und	0.059

Abbreviations: IFRT: involved-field radiation therapy; R: rituximab; PFS: progression free survival; TTNT: time to next therapy; OS: overall survival; und: undefined.

- **PFS** and **TTNT** were significantly **higher in both rituximab arms** with respect to IFRT alone
- No difference in OS among all treatment arms

Conclusions

- The **IFRT-group** showed the **highest relapse rate** with the **worst PFS** and **TTNT**;
- **Rituximab-based therapy** induced a **better long-term disease control**;
- In **the R+IFRT group** results were **even better than in the Rituximab** group, probably thanks to the combined therapeutic activity on local disease as well as on persistent occult MRD;
- **No difference in OS** among the three treatment groups, probably due to the indolent course of this disease.

A prospective, randomized clinical trial is warranted in order to confirm the superiority of combined therapy in comparison to the current standard of care.

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