

Follicular Lymphomas Workshop

Bologna
Royal Hotel Carlton
May 7, 2024

President: *Pier Luigi Zinzani*



Front line therapy – How I approach
Newly diagnosed early-stage patients

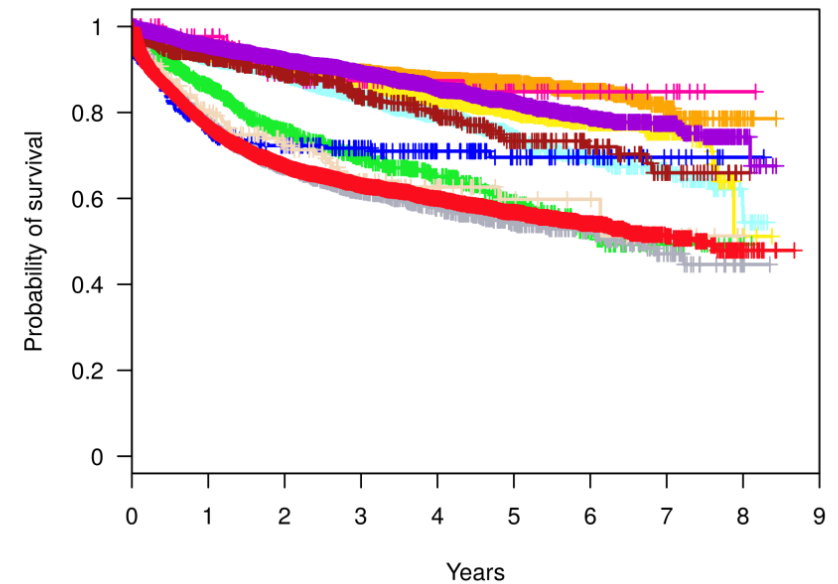
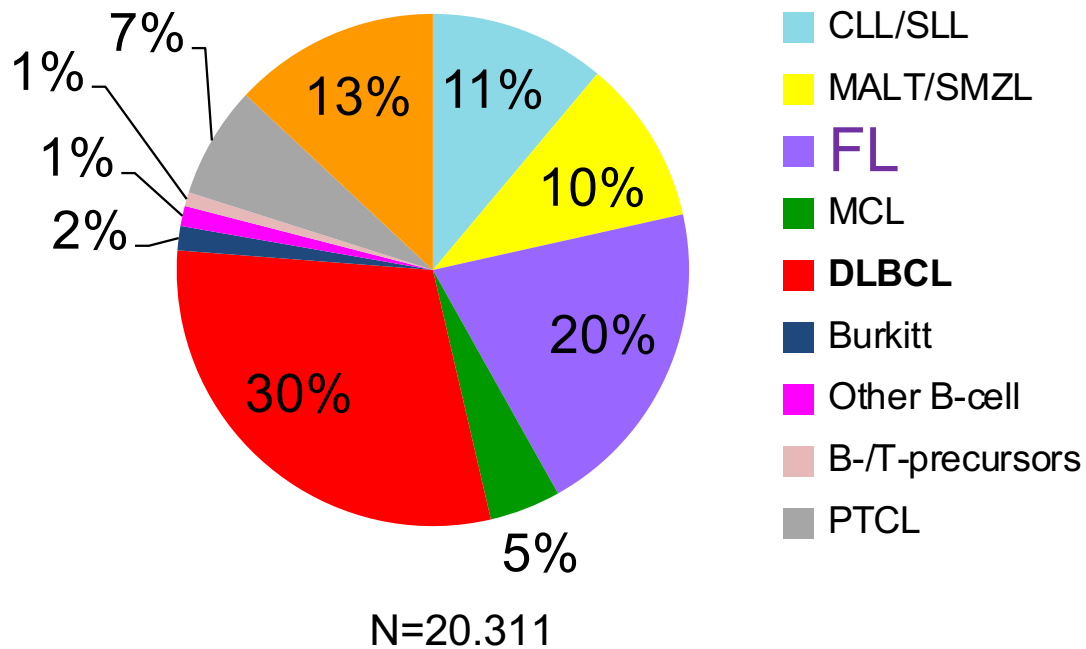
Armando López-Guillermo, Barcelona, Spain

Disclosures of Armando López-Guillermo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche	X		X			X	
Gilead/Kite	X		X			X	X
BMS/Celgene	X					X	
Janssen						X	
Incyte						X	
Abbvie						X	



Histologic distribution of lymphomas

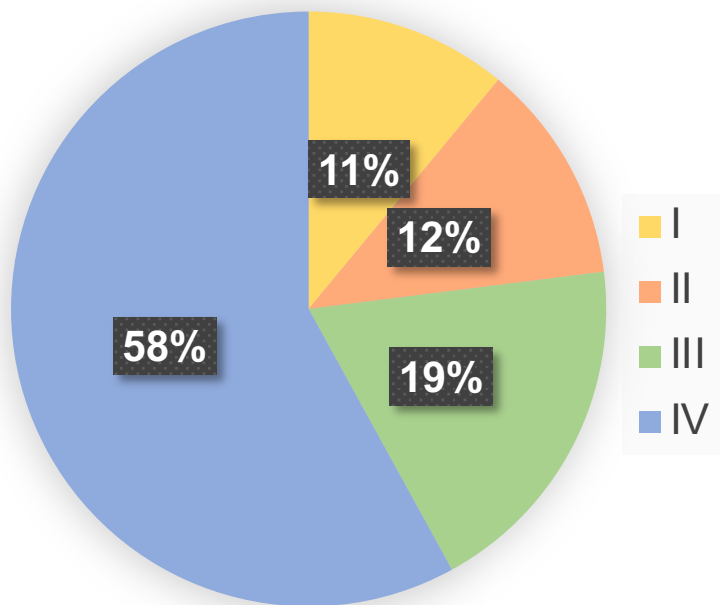


GELTAMO 2014/21

Early stage follicular lymphoma (FL)

- “Limited”, “localized” or “early” stage occurs in ~10-15% of FL
- Overall, the outcome of these patients is particularly good (10-yr OS 90%)
- No standard definition of early stage
 - In general: stages I or II adjacent sites, in absence of symptoms and bulky disease (7-10cm?)
- Few specific studies on prognosis or treatment

Ann Arbor stage distribution in follicular lymphoma



GELTAMO registry 2000/14
N=2150 (excluding 43 missing)

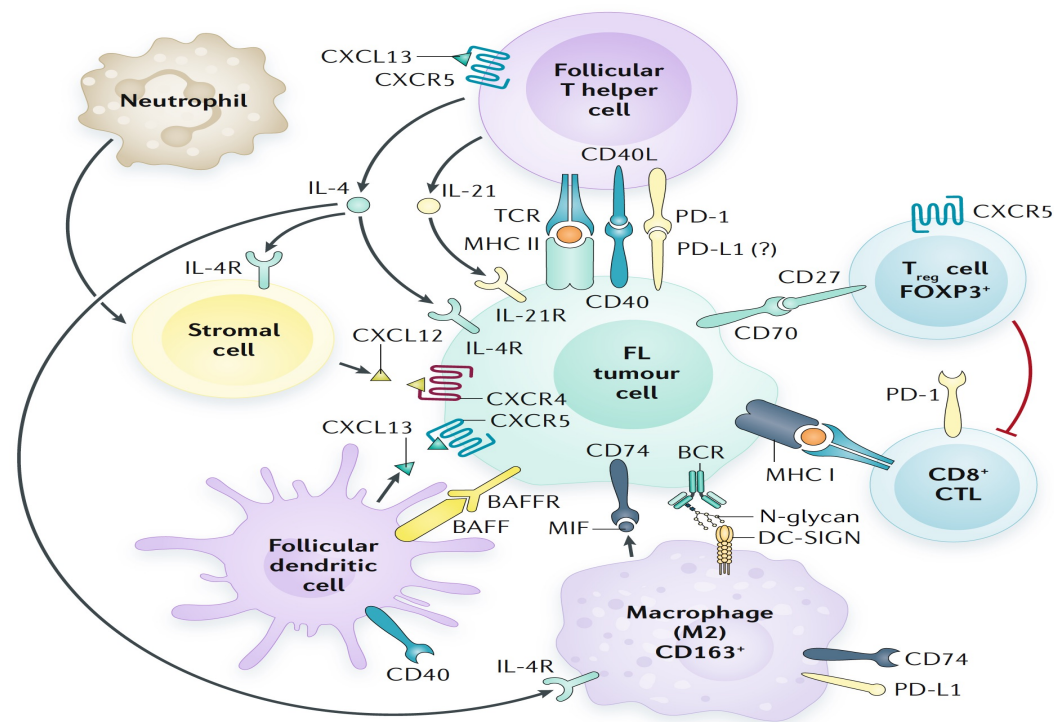


Features in biology of follicular lymphoma (FL)

Table 1 | Genetic alterations affecting at least 10% of cases of FL

Gene	Alterations (effect)	Frequency in FL (%)	Effect or function
Proliferation			
KMT2D	Mutation (↓)	80–90	Histone modification; tumour suppressor
IgHV, IgLV	Mutation (↑)	75–90	N-glycosylation of IgV region of BCR; BCR signalling
RB1	Deletion (↓)	12	Impairment of cell cycle control
CDK4	Copy number gain (↑)	29	Impairment of cell cycle control
BCL6	Translocation (↑) Mutation (↑)	6–15 47	Transcription factor; tumour progression
H1–2, H1–4	Mutation (↓)	44	Chromatin remodelling
MEF2B	Mutation (↓)	13–15	Transcription factor; transcriptional activator
EP300	Mutation (↓)	10–20	Histone modification
SESN1	Epigenetic silencing (↓)	~20	Promotion of mTOR activity
RRAGC ^{ATP10B, ATP10A1}	Mutation (↑)	17	mTORC1 survival signal
EZH2	Mutation (↑)	7–30	Histone modification
ARID1A	Mutation (↓)	15	Chromatin remodelling
GNA13	Mutation (↓)	~10	B cell growth and lymphoma cell dissemination
SGK1	Mutation (↓)	~10	Deregulation of FOXO transcription factors and NF-κB
FOXO1	Mutation (↑)	~10	Transcription factor; survival and proliferation
CARD11	Mutation (↑)	10	Increased BCR signalling
STAT6	Mutation (↑)	10	Activation of JAK–STAT signalling
Survival			
BCL2	Translocation (↑) Mutation (↑)	80–90 50	Suppression of apoptosis
TNFAIP3	Mutation (↓)	2–26	Loss of tumour suppressor
Immune evasion			
EPHA7	Deletion (↓) Epigenetic silencing (↓)	70	Tumour suppressor
TNFRSF14	Mutation (↓)	18–50	Tumour suppressor; increased BCR signalling
CREBBP	Mutation (↓)	33–70	Histone modification; tumour suppressor

↑, gain of function; ↓, loss of function; BCR, B cell receptor; FL, follicular lymphoma; FOXO, Forkhead box O; JAK, Janus kinase; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; NF-κB, nuclear factor-κB; STAT, signal transducer and activator of transcription



FL tumor microenvironment

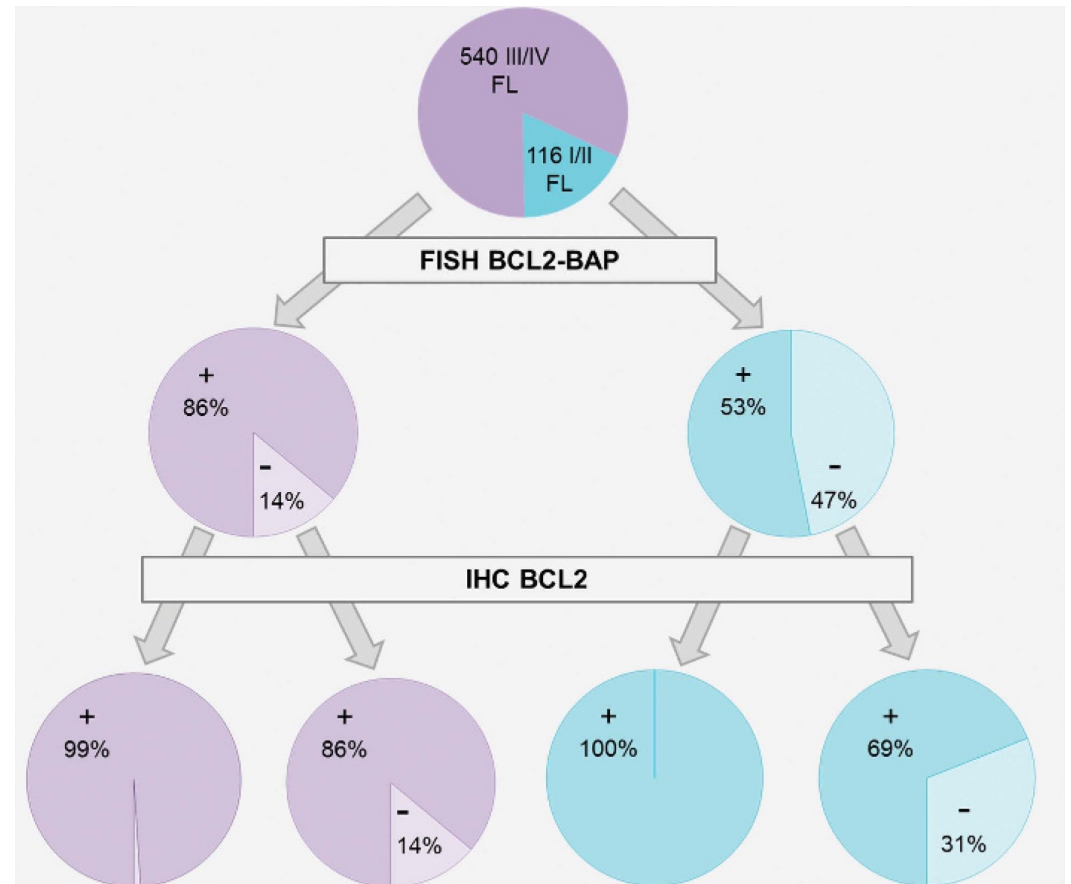
Early-stage follicular lymphoma (FL)

- Differences between early and advanced-stage FL are only due to the degree of dissemination?
- Evidences of distinct biological features in early-stage FL?
 - Copy number alterations (CNA), including t(14;18)
 - Mutational landscape
 - Gene expression profiling

Assessment of *BCL2*-breakpoint/t(14;18) status and *BCL2* expresión in early- and advanced-stage FL

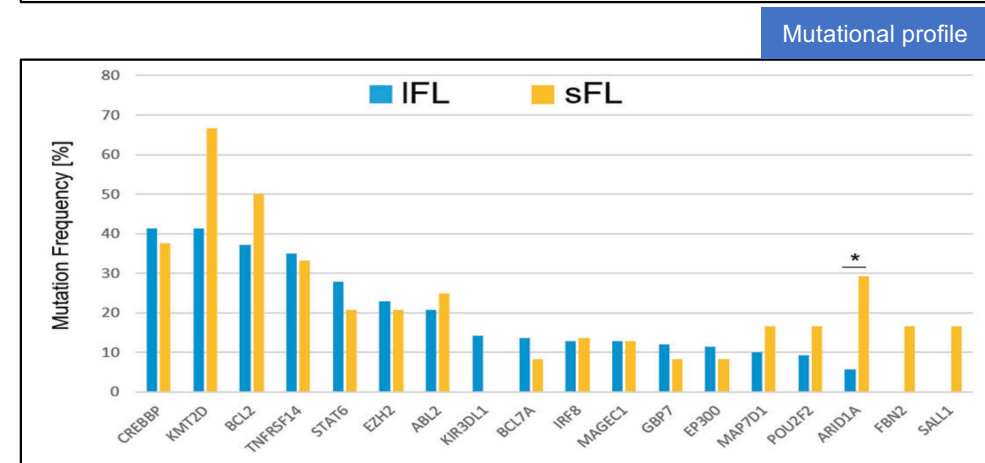
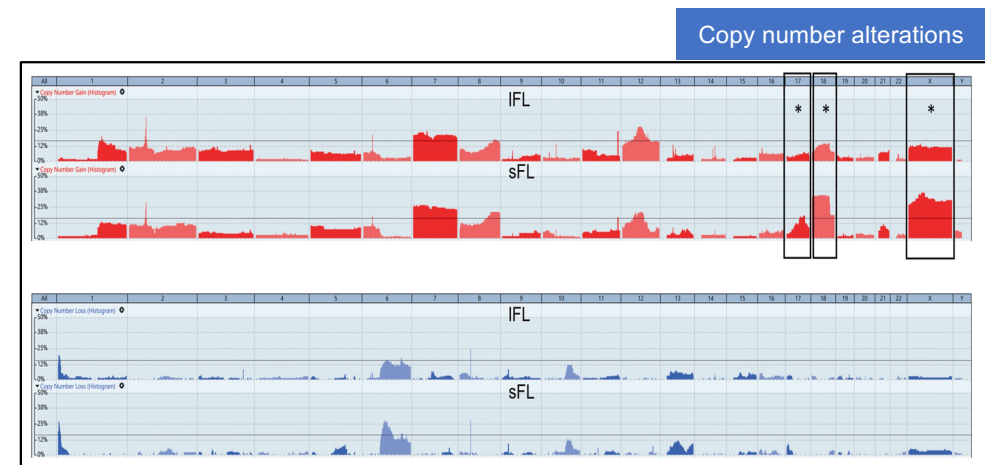
German Low Grade Lymphomas Study Group

- Nodal FLs
- FISH (break-apart probe) and immunohistochemistry

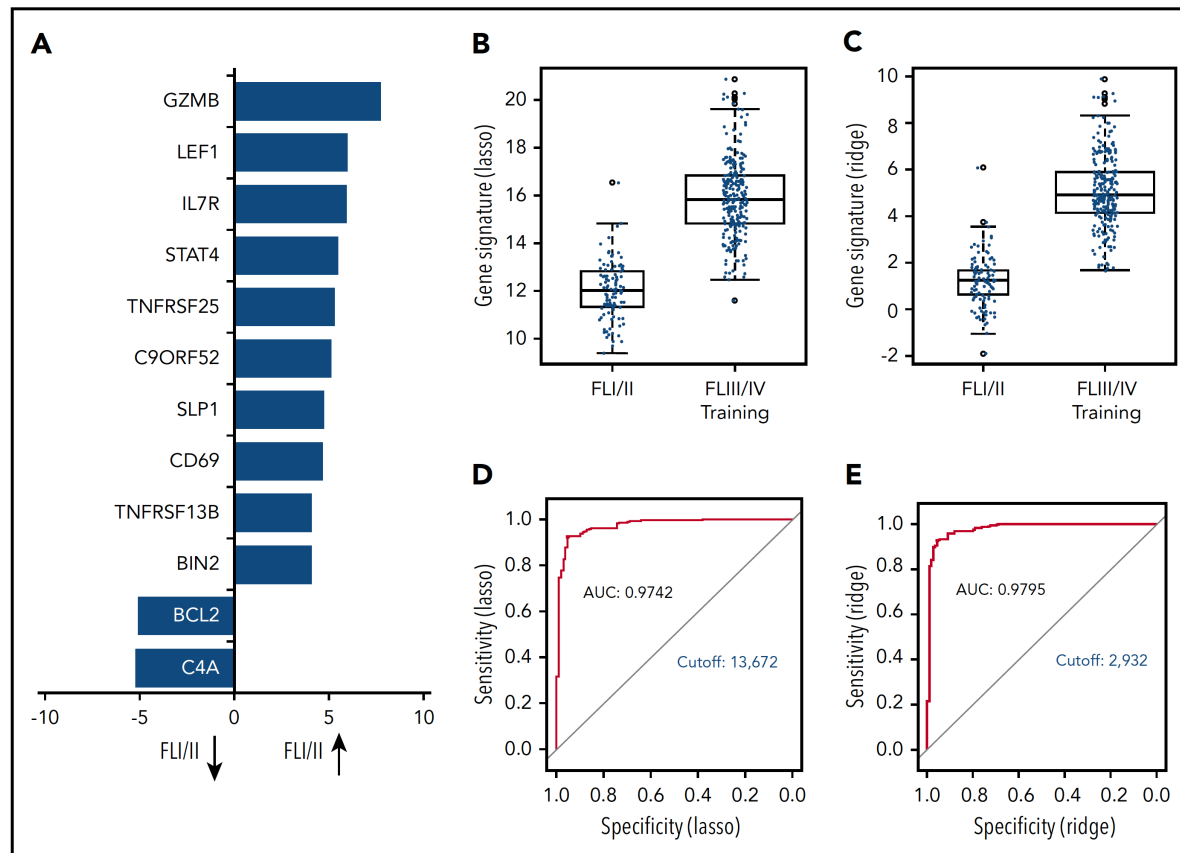


Molecular profiling of localized and systemic FL

- Nodal FL
- 147 localized FL (IFL) and 122 advanced stages FL (sFL)
- Assessment of:
 - Somatic CNA
 - Whole exome sequencing (WES)
- Significant differences
 - 18q21 gains (14% vs. 36%)
 - *ARID1A* mutations (6% vs. 29%)



Localized- and advanced –stage FLs differ in their gene expression profiles (GEP)



Of note:

- 3% of early-stage show advanced-type GEP: ↓ PFS
- 7% of advanced-stage show early-type GEP: ↑ PFS

A real patient from our clinics ...

- 62-year-old gentleman, with no relevant past medical history
- July 2005: small node in left inguinal area (~1.5 cm) – Observation with very slow growth
- August 2006: Hematology clinics
 - Asymptomatic
 - Physical exam: in left inguinal area 3 lymph nodes of 2.5/1/1cm
 - Blood cell counts and biochemistry: N
- Biopsy: grade 2 FL
- Staging

Follicular lymphoma: ESMO guidelines

Recommendations

- Initial staging should be carried out according to the Ann Arbor classification system.
- Initial work-up should include a BM aspirate and biopsy and a CT scan of the neck, thorax and abdomen.
- A PET-CT scan is recommended for routine staging [IV, C] and is mandatory to confirm localised stage I/II disease before ISRT.
- A complete blood count, routine blood chemistry including Ig levels, LDH, B2M and uric acid as well as screening tests for HIV, HBV and HCV are required.
- FLIPI 1/2 and PRIMA prognostic index risk factors can be used for prognostic purposes.

A real patient from our clinics ...

- Biopsy: grade 2 FL
- Staging was performed
 - PET/CT: no other lymph node or extranodal involvement
 - Bone marrow biopsy: N

Diagnosis: grade 2 FL, stage I-"A"

Which approach is the best in this case?

Classic “dogmas” on initial treatment of early-stage FL

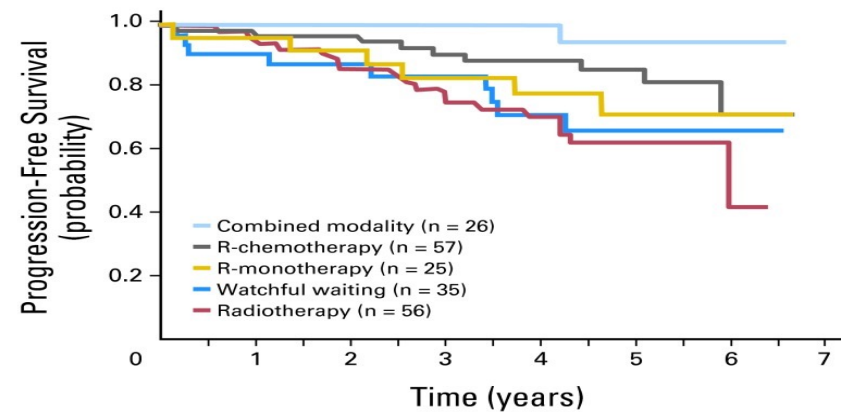
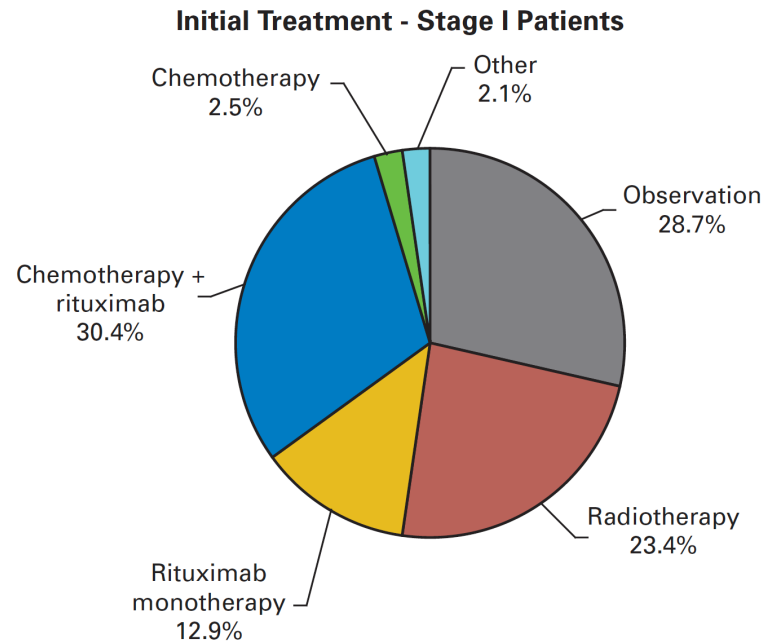
- Staging must be exhaustive, in order to rule out disseminated disease (so, PET/CT + BM assessment)
- The treatment intention is curative
- All patients may be treated irrespective of symptoms
- The gold-standard treatment is local radiotherapy

However, in real life ... many patients are treated differently, even with watchful waiting policy!¹⁻³

Treatment of patients with stage I FL

(National LymphoCare Database)

- 471 patients with stage I FL
- 206 patients with “rigorous staging”



Initial treatment of early-stage FL

- Radiotherapy alone
 - Extension / dosing
- Radiotherapy plus
 - Immunochemotherapy
 - Rituximab

Radiotherapy alone in early-stage FL

Table 1
Outcomes for patients with early stage FL who received RT alone

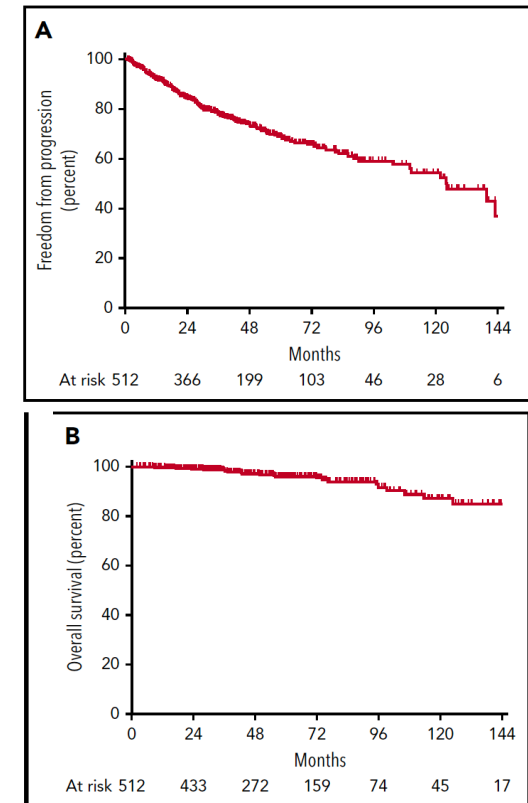
Study	N	PET/CT Staging?	PFS	OS
MacManus et al, ⁹ 2018	75	Some patients	10 y: 41%	10 y: 86%
Manus & Hoppe, ⁸ 1996	177	No	10 y: 40% 20 y: 37%	10 y: 64% 20 y: 35%
Tobin et al, ¹¹ 2019	171	Yes	5 y: 68%	5 y: 93%
Ng et al, ¹² 2019	47	Yes	5 y: 78%	5 y: 97%
Brady et al, ¹³ 2019	512	Yes	5 y FFP: 69%	5 y: 96%
Friedberg et al, ¹⁴ 2012	206	Yes	Median: 72 mo	—
Guckenberger et al, ²³ 2012	86	No	10 y FFP: 58% 15 y FFP: 56%	10 y: 64% 15 y: 50%

LYMPHOID NEOPLASIA

Definitive radiotherapy for localized follicular lymphoma staged by ¹⁸F-FDG PET-CT: a collaborative study by ILROG

Jessica L. Brady,^{1,*} Michael S. Binkley,^{2,3,*} Carla Hajj,⁴ Monica Chelius,⁴ Karen Chau,⁴ Alex Balogh,⁵ Mario Levis,⁶ Andrea Riccardo Filippi,⁶ Michael Jones,⁷ Michael Mac Manus,^{8,9} Andrew Wirth,⁸ Masahiko Oguchi,¹⁰ Anders Krog Vistisen,¹¹ Therese Youssef Andraos,¹² Andrea K. Ng,^{13,14} Berthe M. P. Aleman,¹⁵ Seo Hee Choi,¹⁶ Youlia Kirova,¹⁷ Sara Hardy,¹⁸ Gabriele Reinartz,¹⁹ Hans T. Eich,¹⁹ Scott V. Bratman,^{2,3} Louis S. Constine,¹⁸ Chang-Ok Suh,¹⁶ Bouthaina Dabaja,¹² Tarek C. El-Galaly,¹¹ David C. Hodgson,⁷ Umberto Ricardi,⁶ Joachim Yahalom,⁴ Richard T. Hoppe,^{2,3} and N. George Mikhael¹

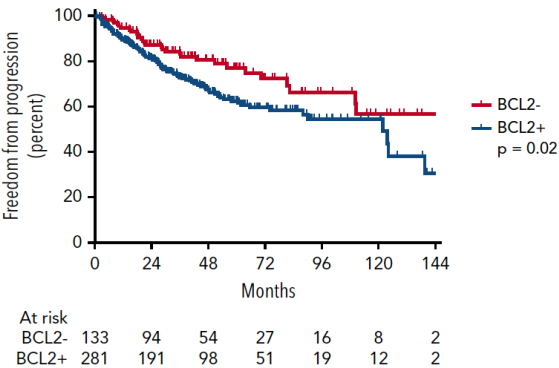
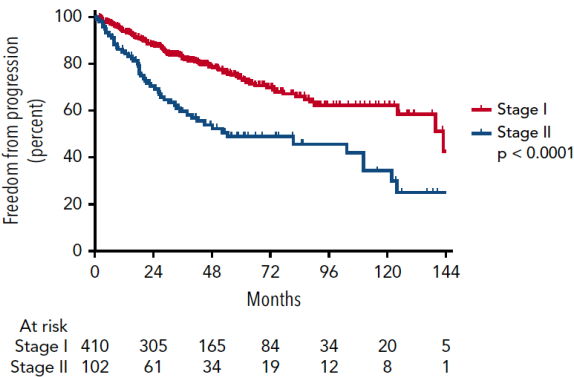
- Multicenter retrospective study of the ILROG
- Main inclusion criteria
 - Untreated grades 1-3A FL in stages I or II
 - Staging with PET/CT
- RT done ≥ 24 Gy
- End-point: Freedom from relapse
- 2000 to 2017; N=512 (stage I, 410; stage II, 102)
- Response assessed by PET/CT or CT scan in 53% of cases at a median of 3 months from RT
- In those assessed by PET/CT: Complete Metabolic Response (Deauville 1-3) in 86%



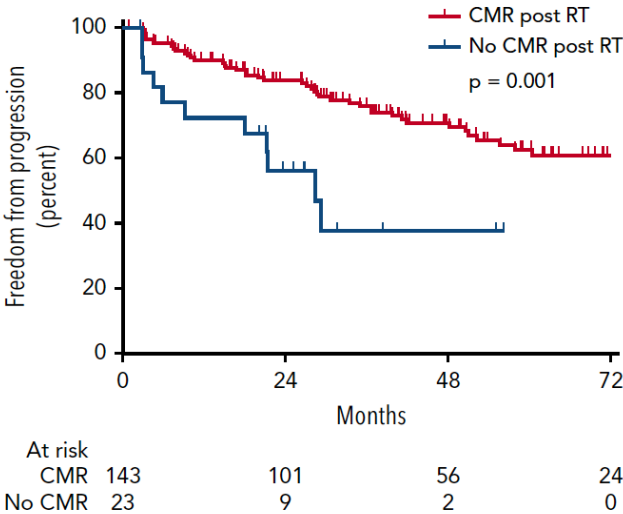
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Factors predicting PFS



Some RT issues ...

- Involved regional RT vs. involved-site RT (ISRT)
- Is possible to reduce the dose?

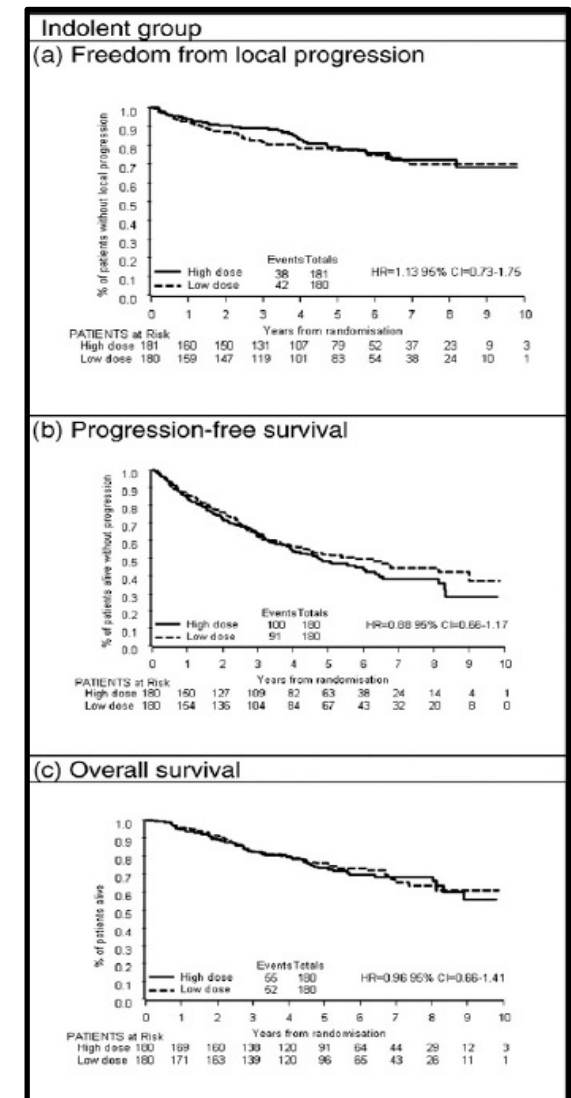


Phase III randomised trial

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,*}

40-45 Gy (20-23 fractions) vs. 24 Gy (12 fractions)
No differences in main parameters



Some RT issues ...

- Involved regional RT vs. involved-site RT (ISRT)
- Is possible to reduce the dose?

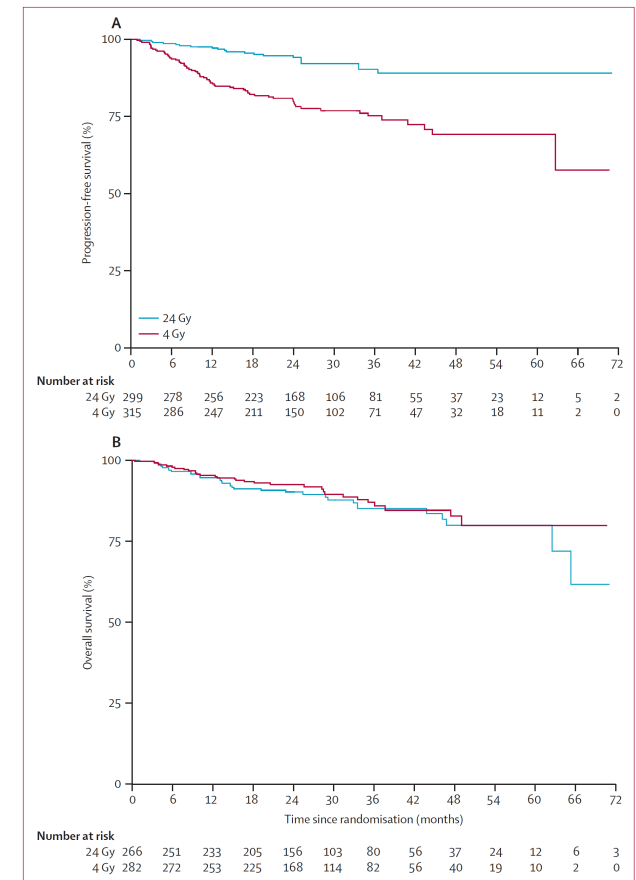
4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial



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

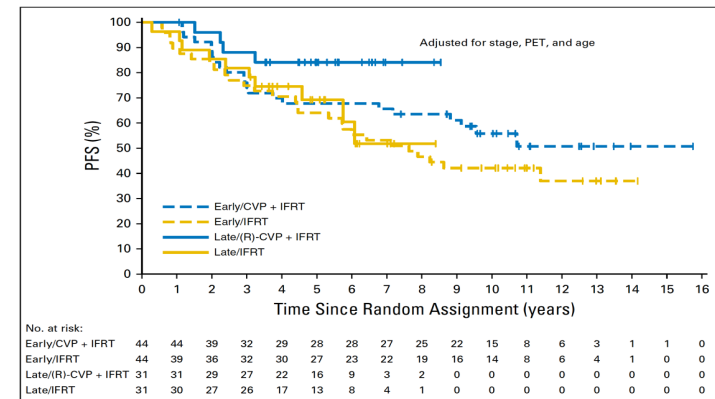
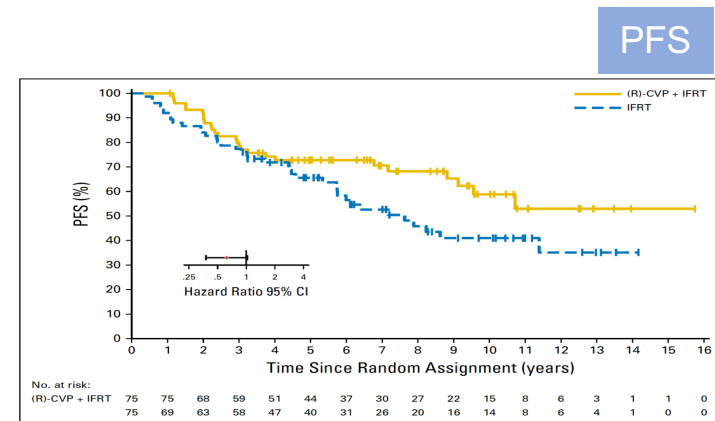
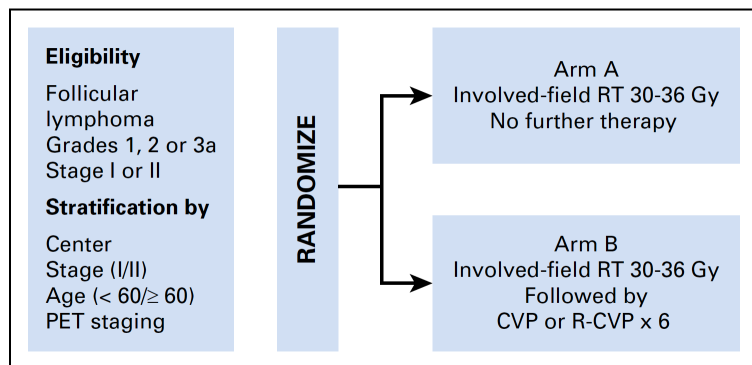
Heterogeneity in the series: FL+MZL / Curative and palliative intent

	24 Gy (12 fractions)	4 Gy (2 fractions)
CR rate	83%	58%
3-yr PFS	~87%	~75%
3-yr OS	~85%	~85%
Toxicity (grade ≥ 3)	3%	1%

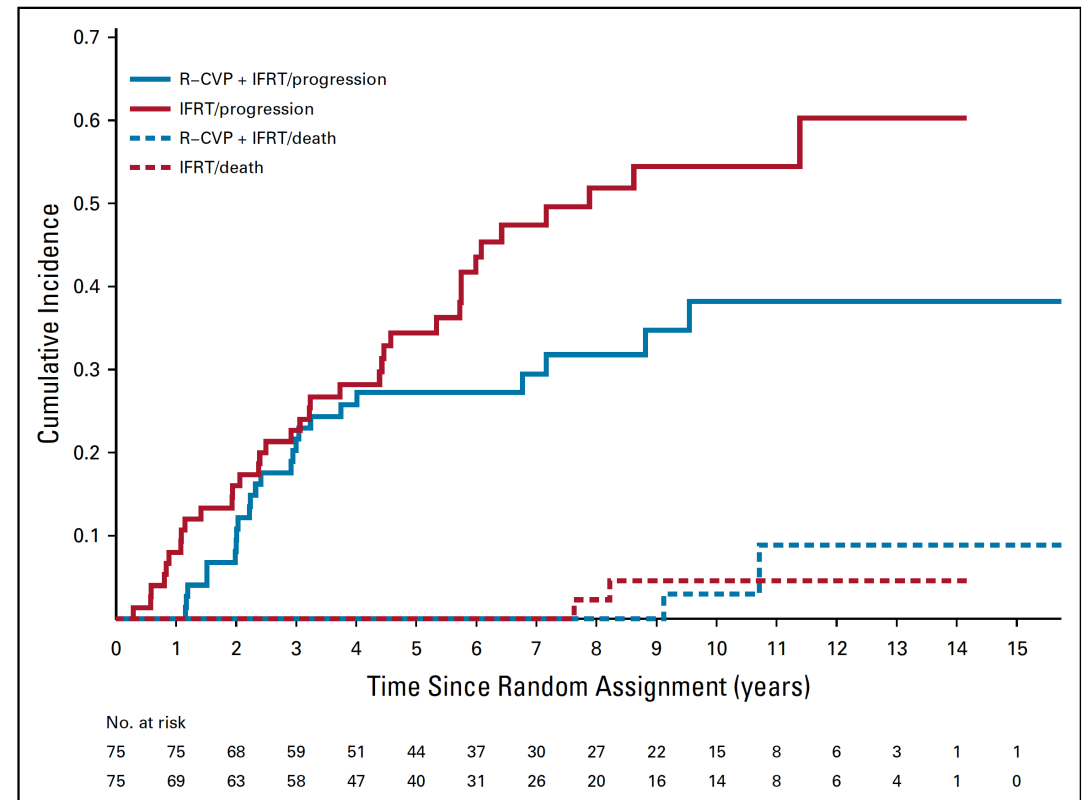
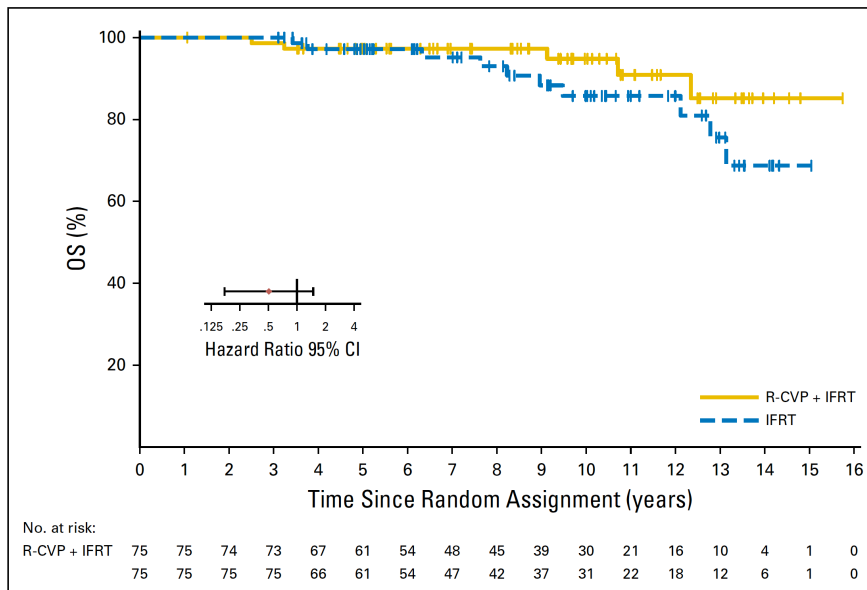


Systemic therapy after IFRT in patients with early-stage FL

- Multicenter, randomized, controlled trial
- Stages I (N=113) or II (N=37) FL
- Staging: CT scan + BM biopsy (PET/CT not mandatory)
- IFRT 30 Gy
- Primary end-point: PFS



Systemic therapy after IFRT in patients with early-stage FL



Rituximab with IFRT in patients with early-stage nodal FL

HemaSphere
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EHA EUROPEAN
HEMATOLOGY
ASSOCIATION
Article
OPEN ACCESS

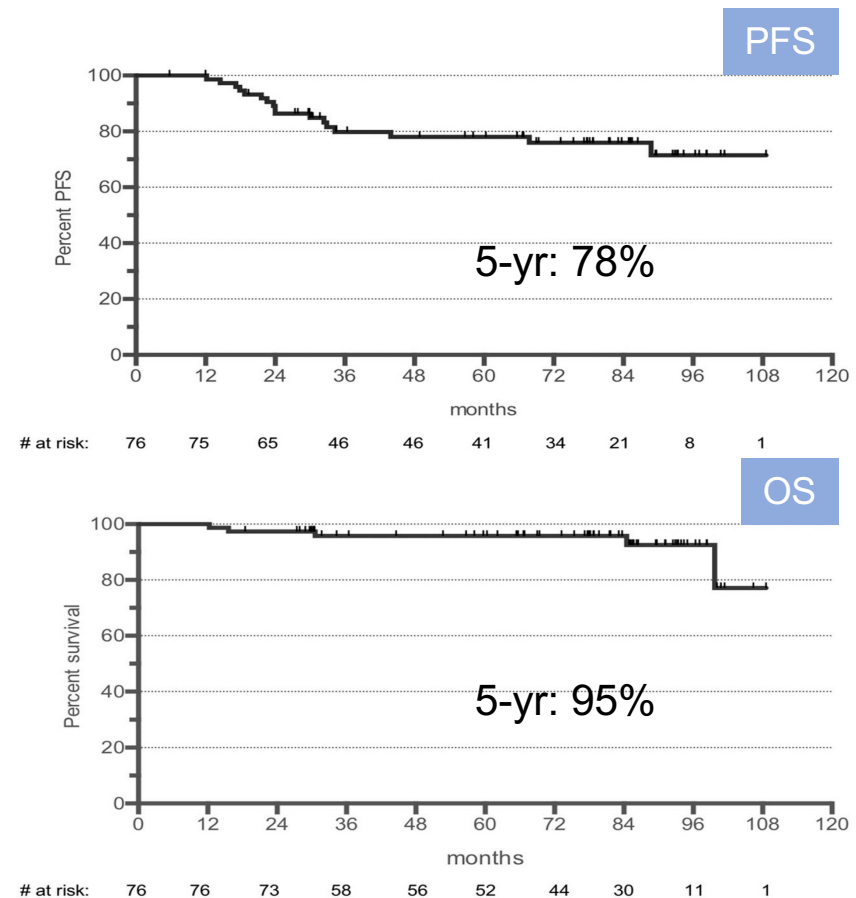
Rituximab With Involved Field Irradiation for Early-stage Nodal Follicular Lymphoma

Results of the MIR Study

Klaus Herfarth¹, Peter Borchmann², Sven Schnaidt³, Karin Hohloch^{4,5}, Volker Budach⁶, Marianne Engelhard⁷, Andreas Viardot⁸, Rita Engenhardt-Cabillic⁹, Ulrich Keller¹⁰, Gabriele Reinartz¹¹, Hans-Theodor Eich^{11,12}, Mathias Witzens-Harig¹³, Clemens F. Hess¹⁴, Bernd Dörken¹⁵, Jan Dürig¹⁶, Thomas Wiegeler¹⁷, Wolfgang Hiddemann¹⁸, Eva Hoster^{18,19}, Christiane Pott²⁰, Martin Dreyling¹⁸

- Prospective, single-arm, multicenter, phase 2 trial
- Stages I or II FL
- Rituximab x8 + IFRT 30/40 Gy
- N=85; Primary end-point: PFS

CR rate (at 6 months): 85%



A real patient from our clinics ...

- Biopsy: grade 2 FL (August 2006)
- Staging was performed
 - PET/CT: no other lymph node or extranodal involvement
 - Bone marrow biopsy: N

Diagnosis: grade 2 FL, stage I-“A”

- IFRT (30Gy) + 4 weekly doses of rituximab
- He reached CMR; almost 18 years after, he maintains the response

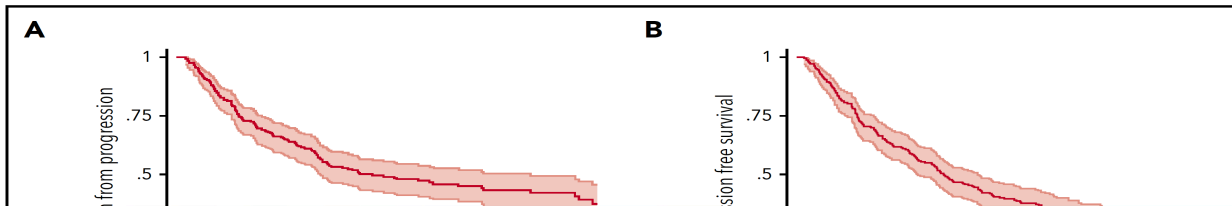
Comment on Brady et al, page 237

Localized FL: how long in response to be cured?

Silvia Montoto | St Bartholomew's Hospital

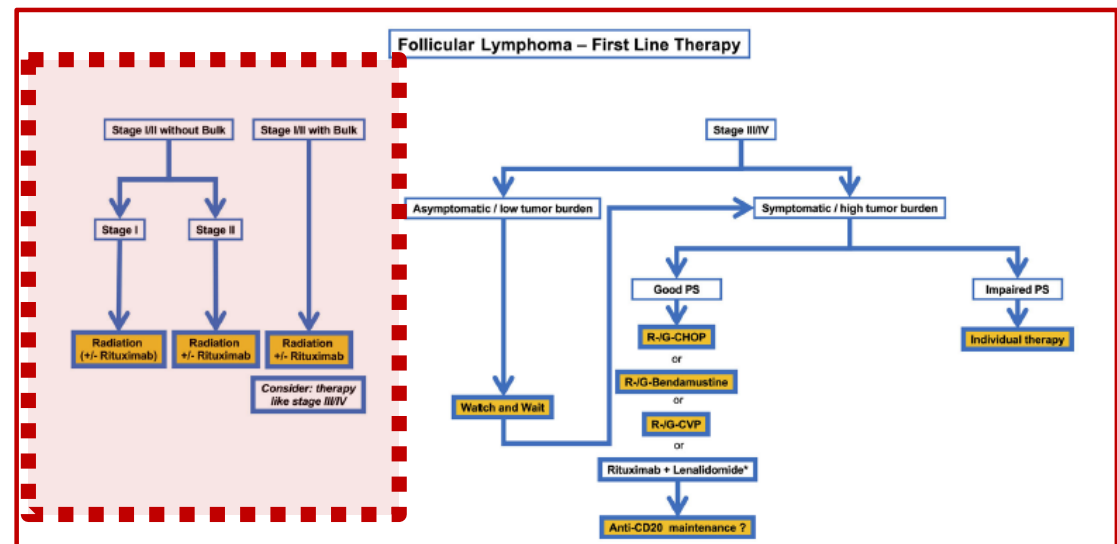
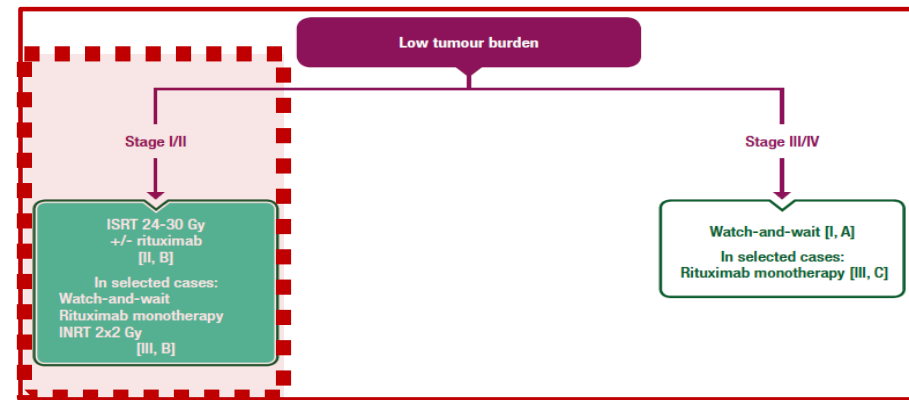
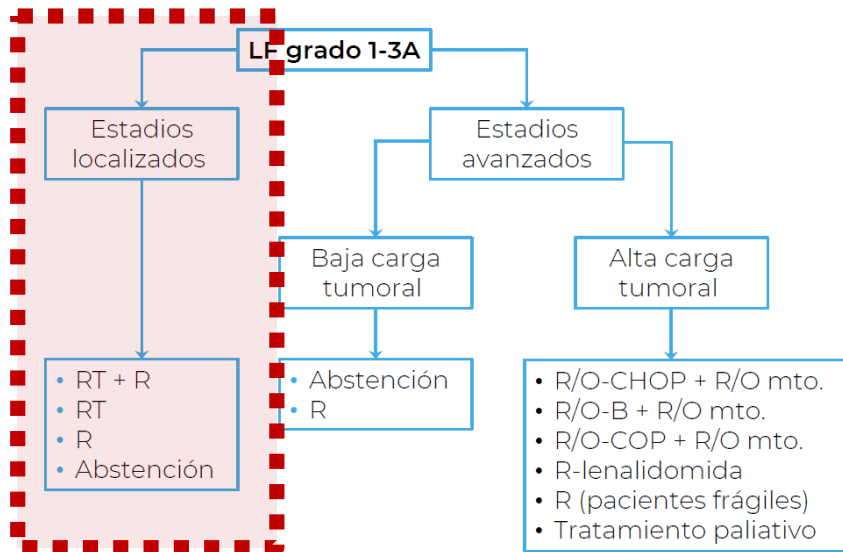
In this issue of *Blood*, Brady and colleagues¹ report the outcome after treatment with definitive radiotherapy (RT) in 512 patients with localized follicular lymphoma (FL) staged with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) with positron emission tomography-computed tomography (PET-CT) to prove the hypothesis that a more accurate staging results in a better outcome, supporting the curative potential of RT.

Long-term follow-up for patients with early-stage FL

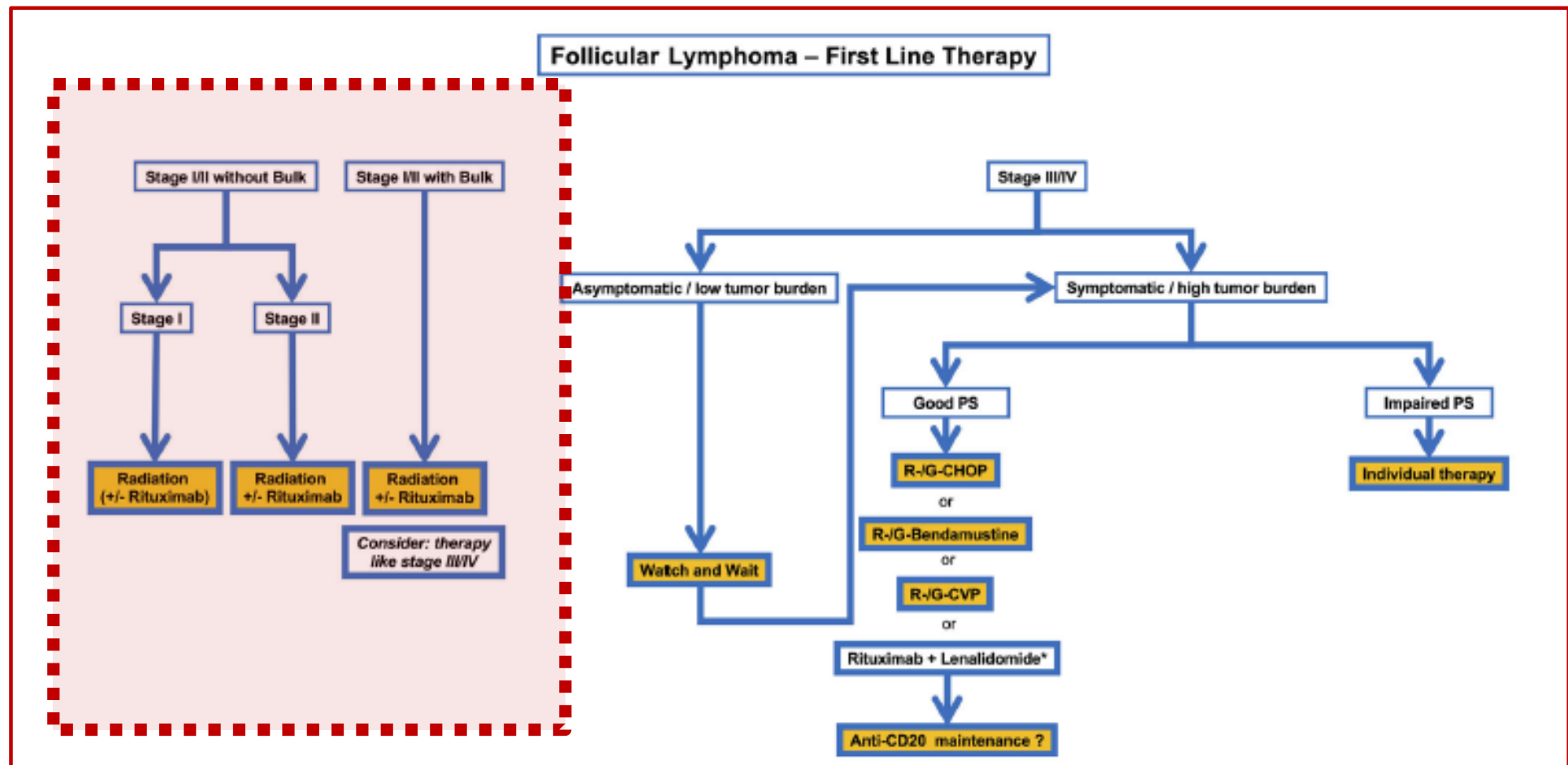


- Population-based study (British Columbia)
- Staging assessed by CT scan
- RT alone (median dose: 20 Gy)
- Median follow-up: 16.1 years

Early stage follicular lymphoma guidelines



Early stage follicular lymphoma guidelines



Other entities and variants related to FL (showing early-stage disease in most cases)

- *In situ* follicular neoplasia
- Duodenal-type FL
- *BCL2*-R-negative, CD23+ follicle center lymphoma*
- Primary cutaneous follicle center lymphoma
- Pediatric-type FL
- Testicular FL
- Large B-cell lymphoma with IRF4 rearrangement

*Provisional entity at the ICC

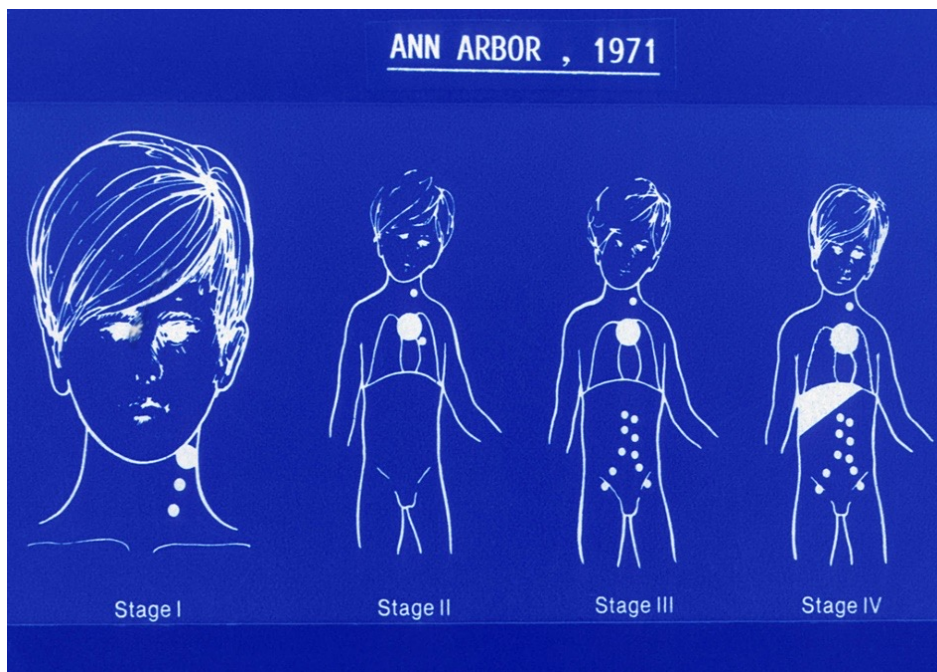
Campo E, Blood 2022;140:1229-53



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BARCELONA



Staging in lymphomas



- Defines disease location and extend
- Suggests prognostic information
- Allows comparisons among studies
- Provides a baseline against which response or disease progression can be compared
- Initial staging criteria were designed for HL and superseded by the Ann Arbor classification
- Staging remains according to Ann Arbor

Resenberg SA, Cancer Res 1971; Carbone PP, Cancer Res 1971;
Rosenberg SA, Cancer Treat Rep 1977; Cheson BD 2014

Revised staging system (Lugano classification)

Revised staging system for primary nodal lymphomas		
Stage	Involvement	Extranodal (E) status
Limited I	One node or a group of adjacent nodes 2 or more nodal groups on the same side of the diaphragm	Single E lesions without nodal involvement
II		Stage I or II nodal extend with limited contiguous E involvement
II bulky	II as above with “bulky” disease	n/a
Advanced III	Nodes on both sides of diaphragm; nodes above diaphragm with spleen involvement Additional noncontiguous extralymphatic involvement	n/a
IV		n/a

GUÍA CLÍNICA para el
**Diagnóstico
y Tratamiento
del Linfoma Folicular**

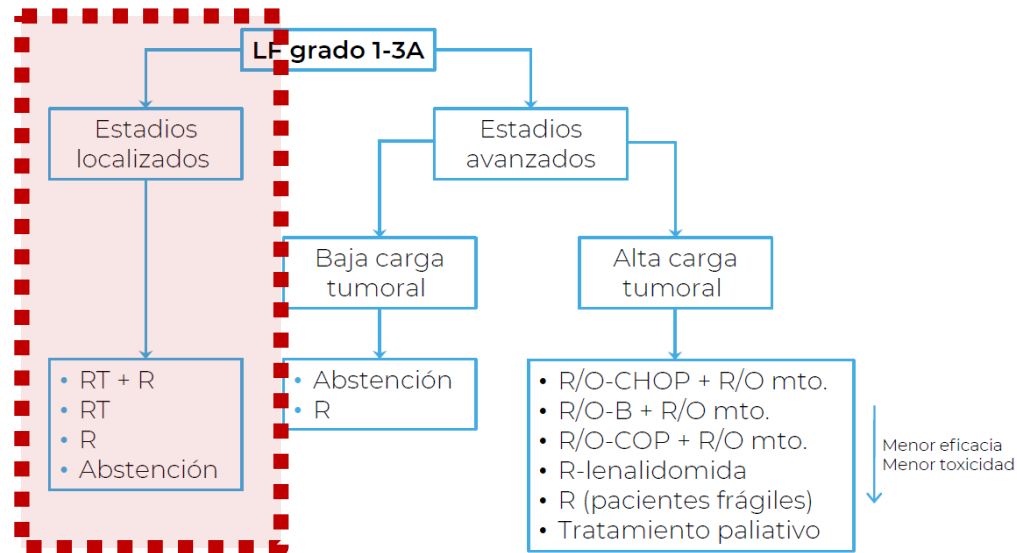


Guía clínica de GELTAMO para pacientes diagnosticados
de linfoma folicular – noviembre de 2022

GELTAMO 2023

www.geltamo.es

Figura 1. Algoritmo terapéutico en primera línea para pacientes con linfoma folicular



El orden de las opciones terapéuticas no pretende reflejar la preferencia de uso: ver las recomendaciones de la guía.

LF: linfoma folicular; **RT:** radioterapia; **R:** rituximab; **O:** obinutuzumab; **C(H)OP:** ciclofosfamida, (doxorrubicina), vincristina y prednisona; **B:** bendamustina; **RP:** respuesta parcial; **RC:** respuesta completa.



Tratamiento estadios localizados → RDT

RDT sola

24Gy limitado a campo afecto
(mejor que dosis más altas)

PFS 60- 80% y OS 80% @ 10 ys



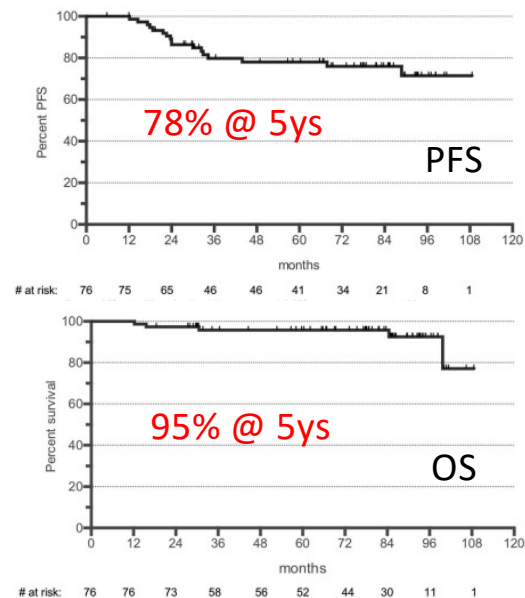
Posible estrategia curativa en algunos pacientes
(40% libres de enfermedad a los 10-20 años)

RDT + iQMT

Aunque mejora la PFS → mas toxicidad por lo
que no parece justificada esta estrategia
No diferencias en OS respecto a RDT sola

RDT + Rituximab

Fase 2, prospectivo GLSG
N= 85



Early stage follicular lymphoma (FL): staging

Localized FL is often neglected from clinical research for two main reasons:

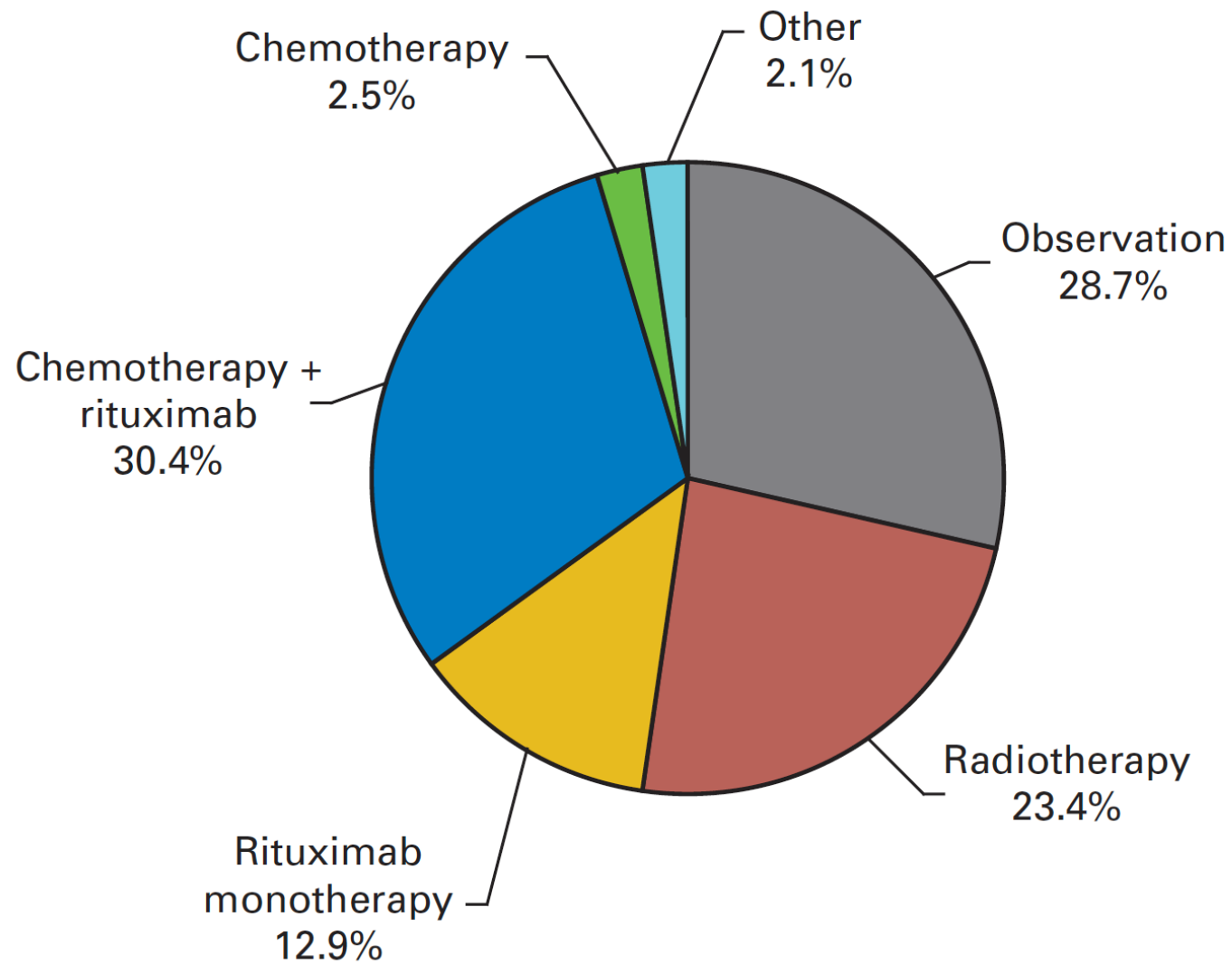
- Small number of patients with excellent prognosis, so prospective trials are time-consuming and expensive.
- Excellent prognosis with standard approaches; most are considered "curable", so less incentive for research.

Conclusions

- Limited stage DLBCLs have good prognosis with current R-CHOP-based +/-IFRT treatment.
- R-CHOPx4 (+Rx2) is adequate for low-risk (smIPI 0) cases.
- PET-based strategy is useful, since it allows to tailor the number of cycles or the use of IFRT in cases with insufficient metabolic response.
- The development of new biomarkers could guide the use of novel targeted therapies.

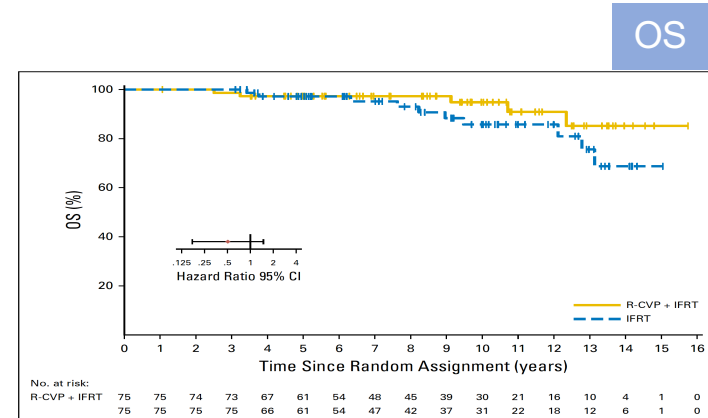
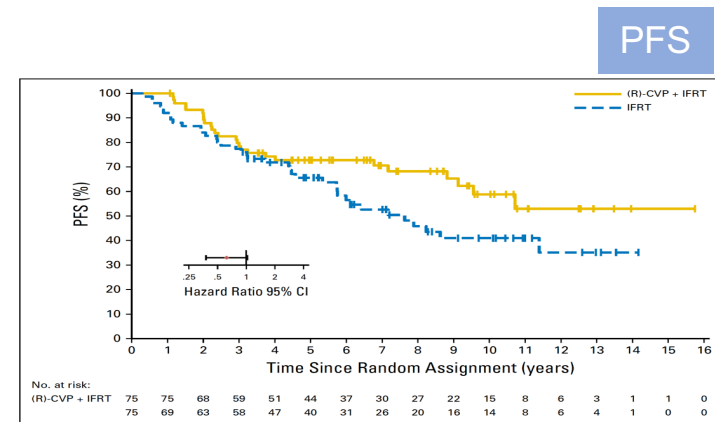
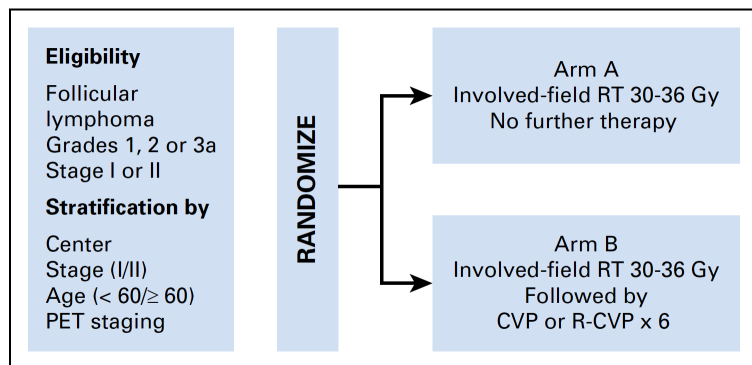
B

Initial Treatment - Stage I Patients



Systemic therapy after IFRT in patients with early-stage FL

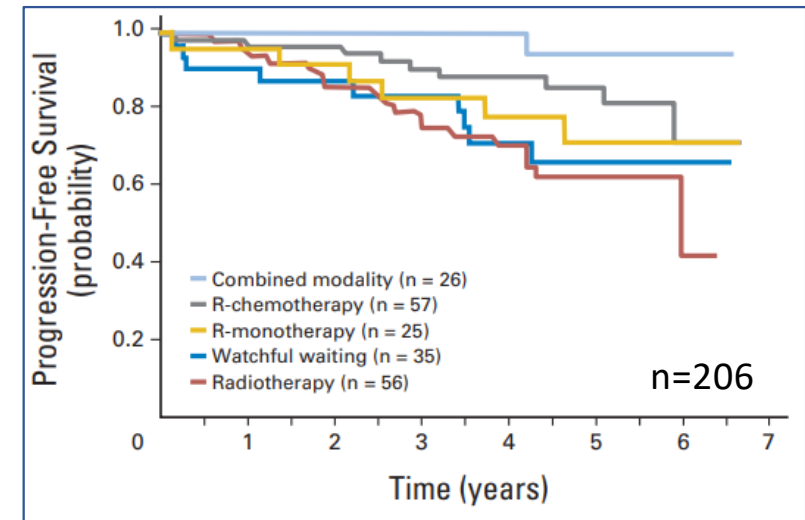
- Multicenter, randomized, controlled trial
- Stages I (N=113) or II (N=37) FL
- Staging: CT scan + BM biopsy (PET/CT not mandatory)
- IFRT 30 Gy
- Primary end-point: PFS



Tratamiento estadios localizados

W&W

- No hay estudios randomizados
- Estrategia poco consolidada dada la potencial curabilidad de este subgrupo
- En algunas series retrospectivas (era pre-Rituximab) → peor SG
- En serie prospectiva de LF estadio I (National LymphoCare Study)
 - N=471
 - Dx entre 2004-2007
 - Pacientes en W&W tenían SLP similar a la RDT sola
 - No diferencias en SG



Rituximab monoterapia

- Alternativa razonable en pacientes que no toleren la RDT (R semanal x 4 dosis)

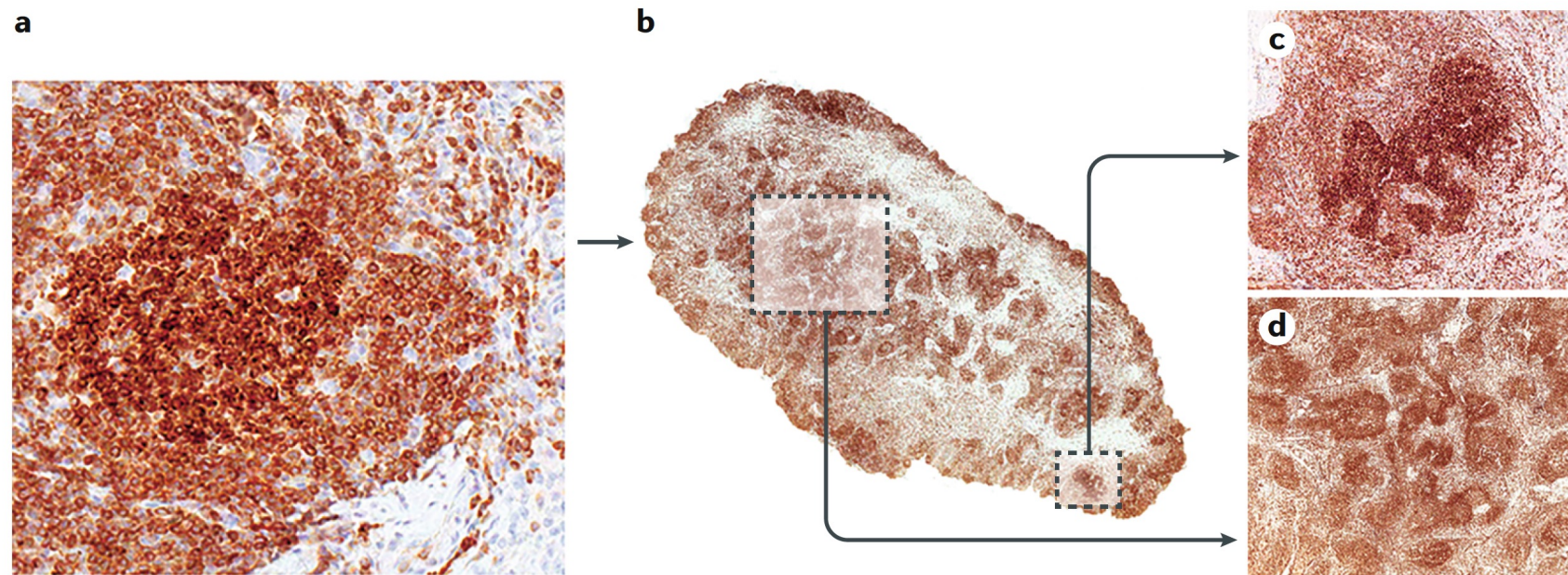


Fig. 6 | **In situ follicular neoplasia.** Tumour progression from in situ follicular neoplasia to early follicular lymphoma (FL) or overt FL. **a** | The strongly immunostained BCL2⁺ B cells are confined to the germinal centre. The BCL2 staining in this population is more intense than that exhibited by the surrounding mantle cells. Magnification $\times 20$. **b** | A lymph node displaying overt FL and early FL. Magnification $\times 0.2$. **c** | Foci of early FL in which BCL2⁺ cells expand outside the follicle without a defined mantle zone. Magnification $\times 2$. **d** | Foci of overt FL showing intense immunostaining of BCL2 within the neoplastic follicle. Magnification $\times 2$. All panels are of formalin-fixed, paraffin-embedded tissue sections.



Early-stage follicular lymphoma

- Importance of ruling out disseminated stage
 - **PET/TC** better than CT scan (44-62% of patients increase stage)¹⁻²
 - **BM biopsy** mandatory

Table 1 Outcomes for patients with early stage FL who received RT alone				
Study	N	PET/CT Staging?	PFS	OS
MacManus et al, ⁹ 2018	75	Some patients	10 y: 41%	10 y: 86%
Manus & Hoppe, ⁸ 1996	177	No	10 y: 40% 20 y: 37%	10 y: 64% 20 y: 35%
Tobin et al, ¹¹ 2019	171	Yes	5 y: 68%	5 y: 93%
Ng et al, ¹² 2019	47	Yes	5 y: 78%	5 y: 97%
Brady et al, ¹³ 2019	512	Yes	5 y FFP: 69%	5 y: 96%
Friedberg et al, ¹⁴ 2012	206	Yes	Median: 72 mo	—
Guckenberger et al, ²³ 2012	86	No	10 y FFP: 58% 15 y FFP: 56%	10 y: 64% 15 y: 50%

1) Luminari S, Ann Oncol. 2013; 2) Metser U, Cancer 2017;123:2860-6; 3) Cohen JB & Kahl BS, Hematol Oncol Clin N Am 2020

Early stage FL

Stage I (<10% of FLs)

- Treatment: XRT (\pm CT/R)
- Long overall survival
- High risk of relapse (>50%)
- Are cured some of the patients?

