



# INCIDENCE OF FOLLICULAR LYMPHOMA TRANSFORMATION: MULTICENTRE RETROSPECTIVE ANALYSIS OF THE SPANISH GELTAMO GROUP

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## INTRODUCTION

Follicular lymphoma (FL) may, over time, transform into an aggressive lymphoma, usually diffuse large B-cell lymphoma (DLBCL). Transformed follicular lymphomas (tFL) have a worse prognosis due to poorer response to treatment than primary DLBCL. The incidence of transformation is estimated to be ~3% per year, although this rate varies largely between different studies (24%-70% overall). These differences are mainly due to different criteria to define tFL, lack of evidence of tFL by biopsy, absence of clonality studies discarding secondary *de novo* NHL, studies performed in the pre-Rituximab era, or different follow-up times among studies. With all this pitfalls, the actual incidence of transformation remains an open question

## AIMS

- ✓ To analyse the incidence of transformation in patients with FL in a large retrospective series of the Spanish group of Lymphomas (GELTAMO) in the Rituximab era
- ✓ To investigate the risk factors associated with transformation

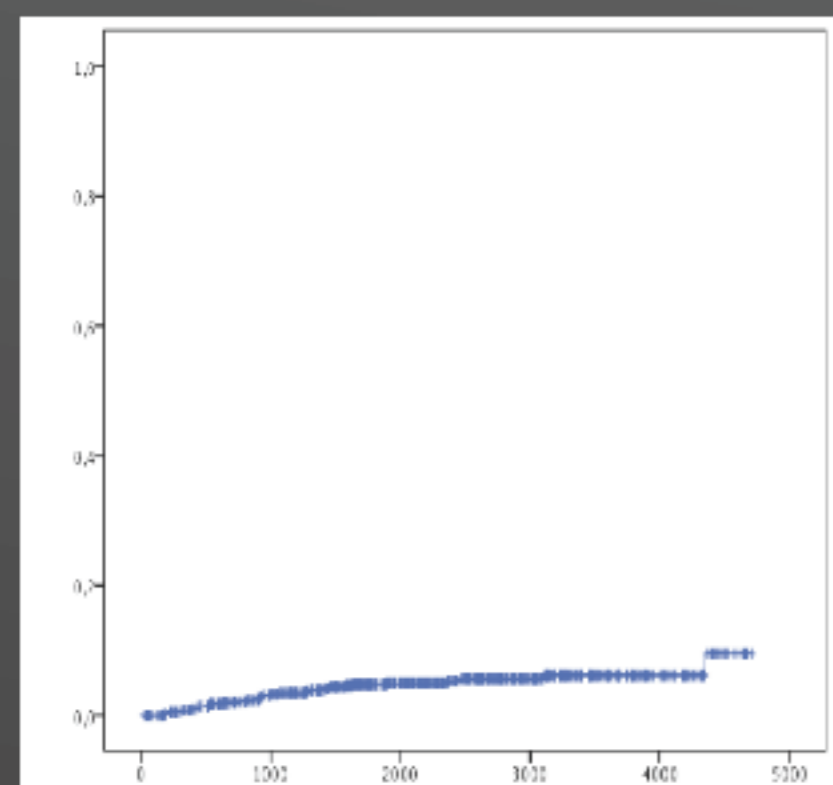
## PATIENTS AND METHODS

A total of 1096 patients (grade I, II, and IIIa) from 8 Spanish centres diagnosed of FL between 2000 and 2010 were included in the study. Data were obtained from the database of centres willing to participate in this study. True tFL (FL to DLBCL) were recorded. Composite FL+DLBCL, discordant tFL (FL in bone marrow and DLBCL in adenopathy or *viceversa*), and downgrading tFL (DLBCL at diagnosis and relapse of FL) were excluded from the preliminary analysis. This study was approved by the Salamanca University Hospital Ethic Committee.

## RESULTS

### PATIENTS CHARACTERISTICS AND INCIDENCE OF TRANSFORMATION

- Median age was 59 (19-92). Ratio female:male was 54:46.
- Follicular lymphoma histologic grades were: I (33%), II (34%), IIIa (14%) and low grade FL ≤IIIa (18%)
- FLIPI prognosis index was 0 (7%), 1 (25%), 2 (31%), 3 (16%), 4 (8%), 5 (3%), undetermined (9%)
- Seventy-one patients (median follow up of 6 years) were transformed to DLBCL (6,5%)



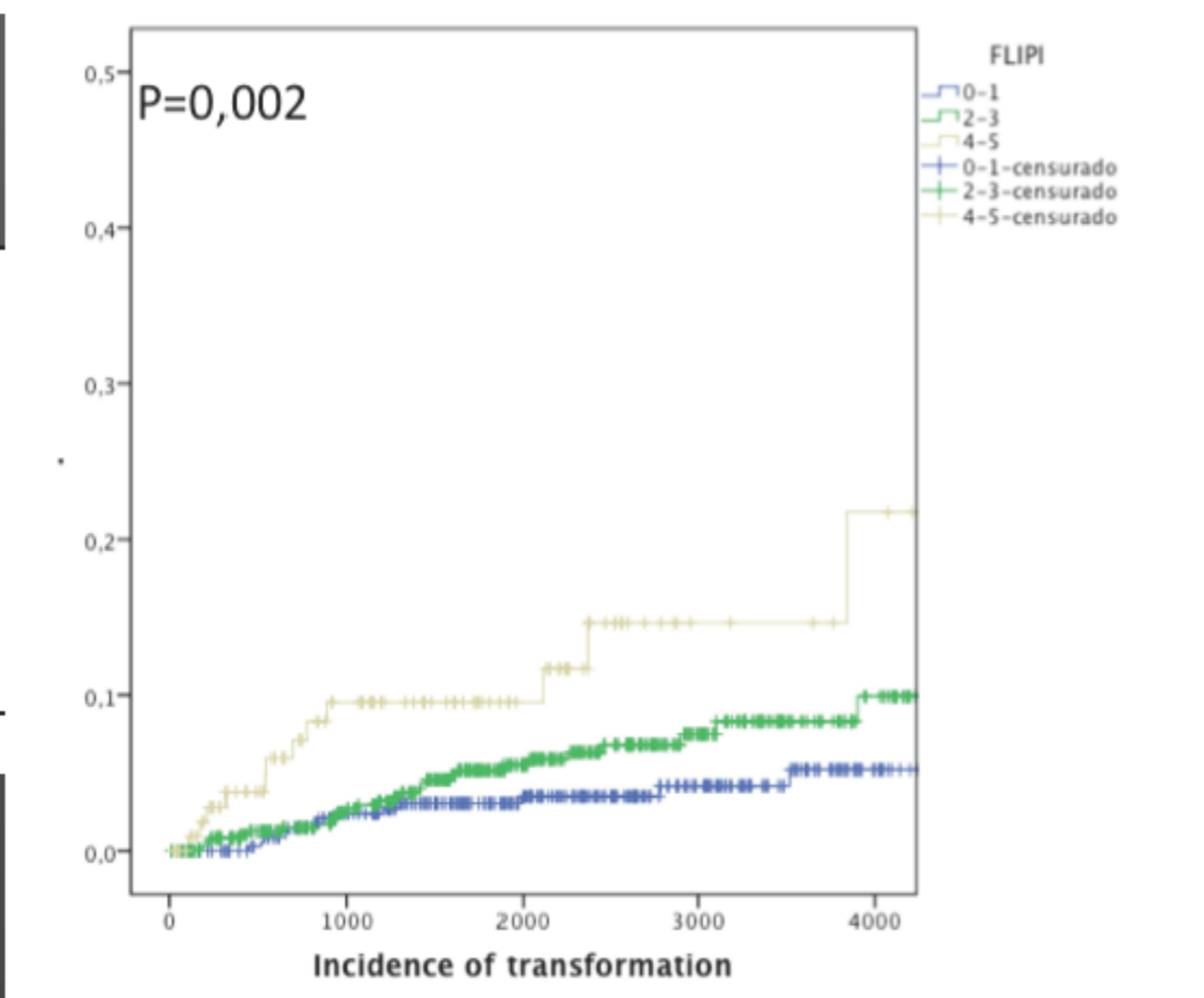
Incidence of transformation in patients treated with Rituximab at 15 years was 10 percent

- Cumulative incidence of transformation at 5, 10, and 15 years was of 5%, 8%, and 14%, respectively.
- Median time to transformation was 30 months (3-150).
- Considering survival from diagnosis of FL, tFL patients had a shorter OS than non-transformed (20% vs. 68%, p<0,0001).
- Most of the tFL patients (92%) had previously received treatment for FL, 56% of them with Rituximab. Median number of treatment lines before transformation was 2 (1-6).

### INCIDENCE OF TRANSFORMATION

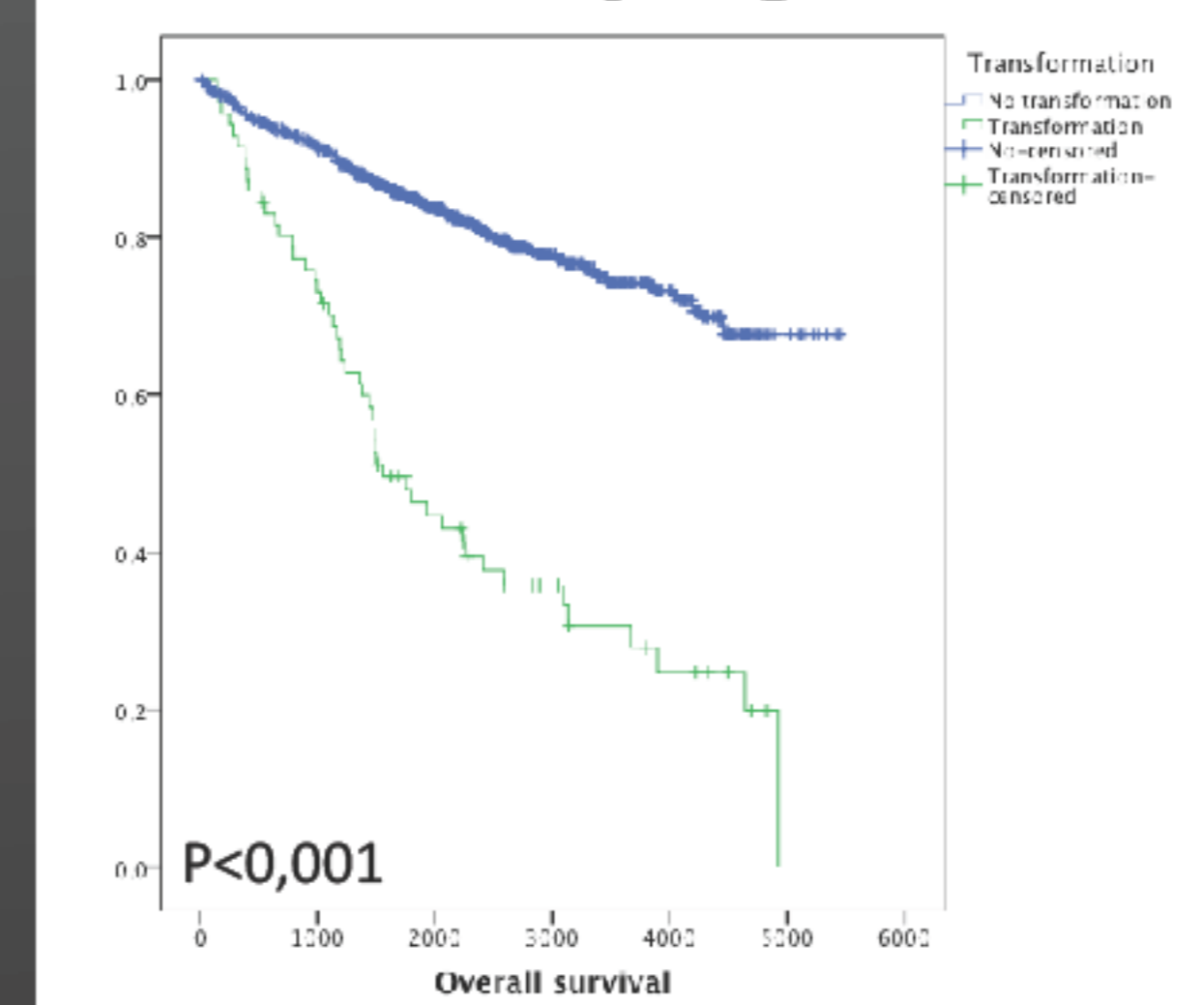
- In the univariate analysis, factors that influenced significantly the risk of transformation included number of treatment lines used for FL >1, age at diagnosis >60 years, FLIPI ≥ 2 and non-having received Rituximab as first line therapy for FL. Patients that received Rituximab based regimens had a longer transformation-free-survival at 15 years than those receiving non-rituximab containing therapies (10% vs 19%, p=0.025). However, no significant difference was observed between patients that underwent watch and wait strategy and those with Rituximab based regimens (p=0,07).
- In the multivariate analysis, FLIPI≥2 and number of lines>1 were the only variables that remained statistically significant.

RISK OF TRANSFORMATION			OVERALL SURVIVAL		
Variable	Hazard ratio (IC 95%)	P	Variable	Hazard ratio (IC 95%)	p
FLIPI (0-5)	5 (1,1-2,1)	0,008	Transformation	3 (1,8-4,5)	<0,001
No. of lines > 1	2 (1,1-4,1)	0,001	Age >60	2 (1,5-3,2)	<0,001
			B2-microglobu.	7 (1,1-2,5)	0,01
			FLIPI	5 (1,2-1,9)	<0,001
			No. of lines >1	2 (1,1-4,1)	<0,001
			Sex (F)	0,6 (0,3-0,9)	0,005



### OVERALL SURVIVAL

- In the univariate analysis, factors that decreased overall survival in the global FL group were: transformation, FLIPI ≥ 2, age > 60, sex (M), histologic grade, B2-microglobulin (elevated), number of lines for FL >1, Ann Arbor stage (>=III).
- In the multivariate analysis, transformation, sex (M), age >60, FLIPI ≥ 2 and B2-microglobulin remained statistically significant.



### ROLE OF STEM CELL TRANSPLANT AFTER TRANSFORMATION

- Consolidation therapy with autologous stem cell transplant (STC) for tFL showed an increase in OS (67% vs. 8%, p=0.001) over allogeneic transplant and non-transplant. 4/5 deaths in those who underwent allogeneic SCT were related to transplant.
- No difference was observed in performance status, sex, number of lines received for FL, or Ann Arbor stage between these groups. However, patients who underwent SCT were significantly younger than those who didn't.
- These results should be confirmed in prospective studies.

## CONCLUSIONS

- ✓ Incidence of transformation of FL in patients treated with Rituximab was 10% at 15 years.
- ✓ High risk FLIPI, response to first line and number of lines for FL treatment have shown to predispose to a higher risk of transformation.
- ✓ Histologic transformation, sex, age, use of Rituximab, FLIPI and B2-microglobulin determined overall survival of FL patients.
- ✓ Autologous transplantation could have a benefit in terms of OS in transformed patients.
- ✓ Effort should be made in order to clarify criteria for transformation. Biological studies on tumoral samples will help to determine tFL pathogenesis in helping to design clinical trials with new molecules.

