

# Extranodal Lymphomas revisited

Franco Cavalli

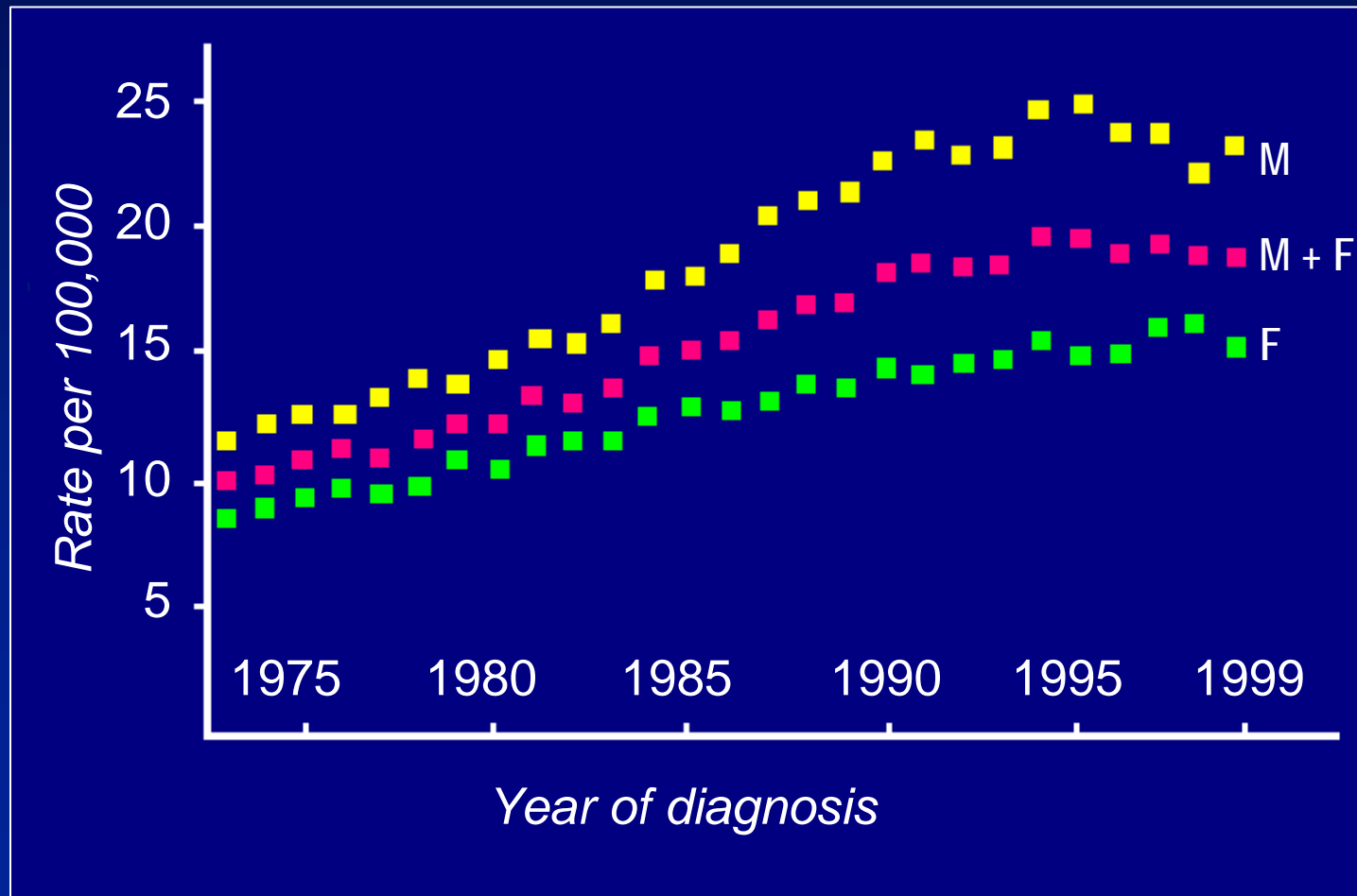
MD, FRCP

*Oncology Institute of Southern Switzerland  
Bellinzona*

# NHL increasing incidence

USA 1973-1999

*SEER age-adjusted incidence rates, by sex*



# Estimates of annual changes in lymphoma incidence in Europe (15-79 yrs olds)


<i>Country</i>	<i>change</i>	<i>95% C.I.</i>
Denmark	2.7%	0.8 to 4.5
Finland	4.5%	1.3 to 7.8
France	2.8%	-3.5 to 9.5
Italy	6.9%	3.3 to 10.5
Netherlands	5.7%	2.1 to 9.4
Spain	8.0%	2.2 to 14.3
UK	3.5%	1.6 to 5.4
<b>total NHL</b>	<b>4.2%</b>	<b>3.1 to 5.3</b>
<b>HODGKIN'S DISEASE, total</b>	<b>0.1%</b>	<b>-1.9 to 2.1</b>

# NHL increasing incidence USA 1974-1988

- nodal cases increase: 1.7 - 2.5% per year
- extranodal cases increase: 3.0 - 6.9% per year

- sites with the greatest increase :
  - skin
  - stomach
  - intestine
  - brain and eye

# Primary Extranodal Lymphomas Frequency in Different Countries

- 
- **Usa and Canada 27% of all NHLs**
  - **Italy 48%**
  - **The Netherlands 41%**
  - **Denmark 37%**
  - **Israel 36%**
  - **Lebanon 44%**
  - **Hong Kong 29%**
  - **Developing countries ?**

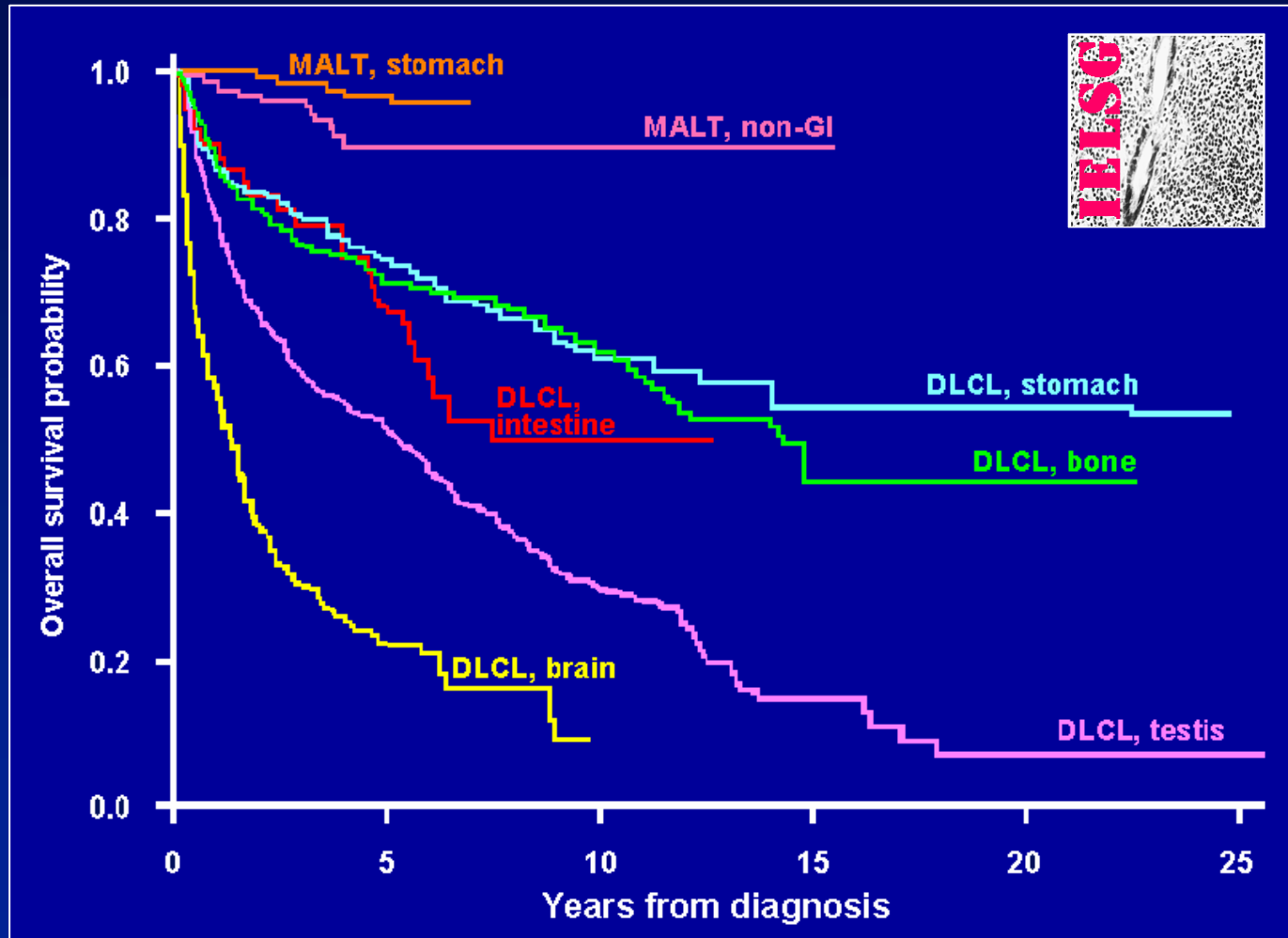
# Primary Extranodal Lymphomas

## A general definition

- “clinically dominant” extranodal component after routine staging procedures
- No or only “minor” ( $\leq 25\%$  of total tumor volume) nodal involvement

*D'Amore et al. 1991*

# Primary Extranodal Lymphomas: Survival by histology and site in the IELSG series



# Primary Extranodal Lymphomas

## Specific staging procedures for specific localizations

- *Gastrointestinal tract:*  
endoscopy with multiple biopsies, endoscopic ultrasound, Waldeyer's ring examination
- *Waldeyer's ring:*  
gastro-duodenal endoscopy with multiple biopsies
- *Central nervous system:*  
cranial (and spinal when appropriate) MRI, stereotaxic biopsy, lumbar puncture with CSF examination, eye examination with slit-lamp
- *Nasal cavity, nasopharynx, paranasal sinus, orbit:*  
CT scan or MRI of the head and neck
- *Testis:*  
clinical and ultrasonographic scrotum examination, lumbar puncture with CSF examination

# Classification of primary gastrointestinal NHL

## B-cell

MALT type

DLCL

IPSID

Mantle cell (Lymphomatous polyposis)

Burkitt's

Other types corresponding to nodal equivalents

## T-cell

Enteropathy associated T-cell lymphoma (EATCL)

Other types not associated with enteropathy

# The MALT concept

- **Native MALT**

normally present in certain extranodal sites  
(e.g., Peyer's patches)

- **Acquired MALT**

where lymphoid tissue is not a natural component  
(e.g., Sjögren, Hashimoto, *H. pylori*-gastritis)

- **MALT Lymphoma**

first described in the stomach by Isaacson and Wright  
in 1983, but can arise from a wide variety of  
extranodal tissues (usually at acquired MALT sites)

# not the same

## WHO CLASSIFICATION 2001

frequency \*

- Extranodal Marginal Zone B-Cell Lymphoma of mucosa-associated lymphoid-tissue (MALT) 7.6%
- Nodal Marginal Zone B-Cell Lymphoma 1.8%
- Splenic Marginal Zone B-Cell Lymphoma 0.8%

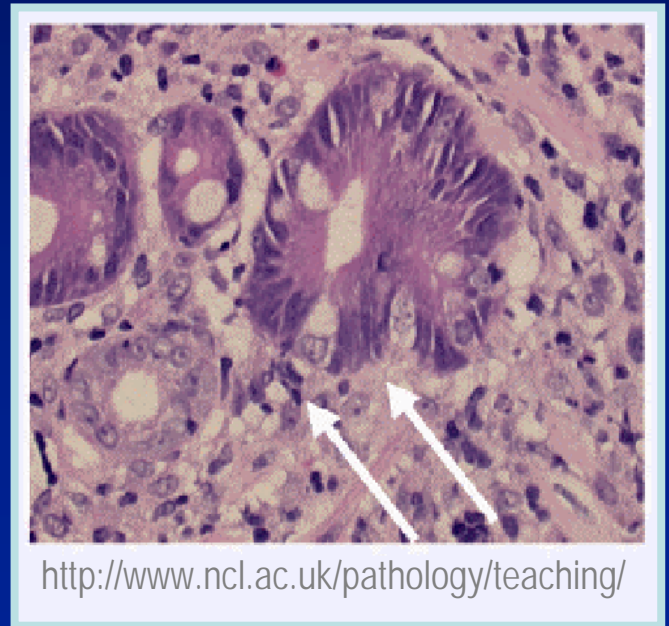
\* *The NHL Classification Project, Blood 1997*

# MALT lymphoma

(Extranodal Marginal Zone B-Cell Lymphoma of MALT)

## HISTOLOGICAL FEATURES AND PHENOTYPE

- centrocyte-like cells (usually)
- lymphoepithelial lesions
- plasma cell differentiation
- scattered transformed blasts
- admixed non-neoplastic T-cell
- follicular colonisation
- slg (usually IgM + and IgD - )
- CD20, CD21, CD35 positive
- CD5, CD10, CD23 negative



# Molecular evidence of an antigen-driven process in MALT lymphoma



- Somatic hypermutation of the immunoglobulin heavy chain gene and intraclonal variation suggest positive antigen selection and derivation from postgerminal center B-cells

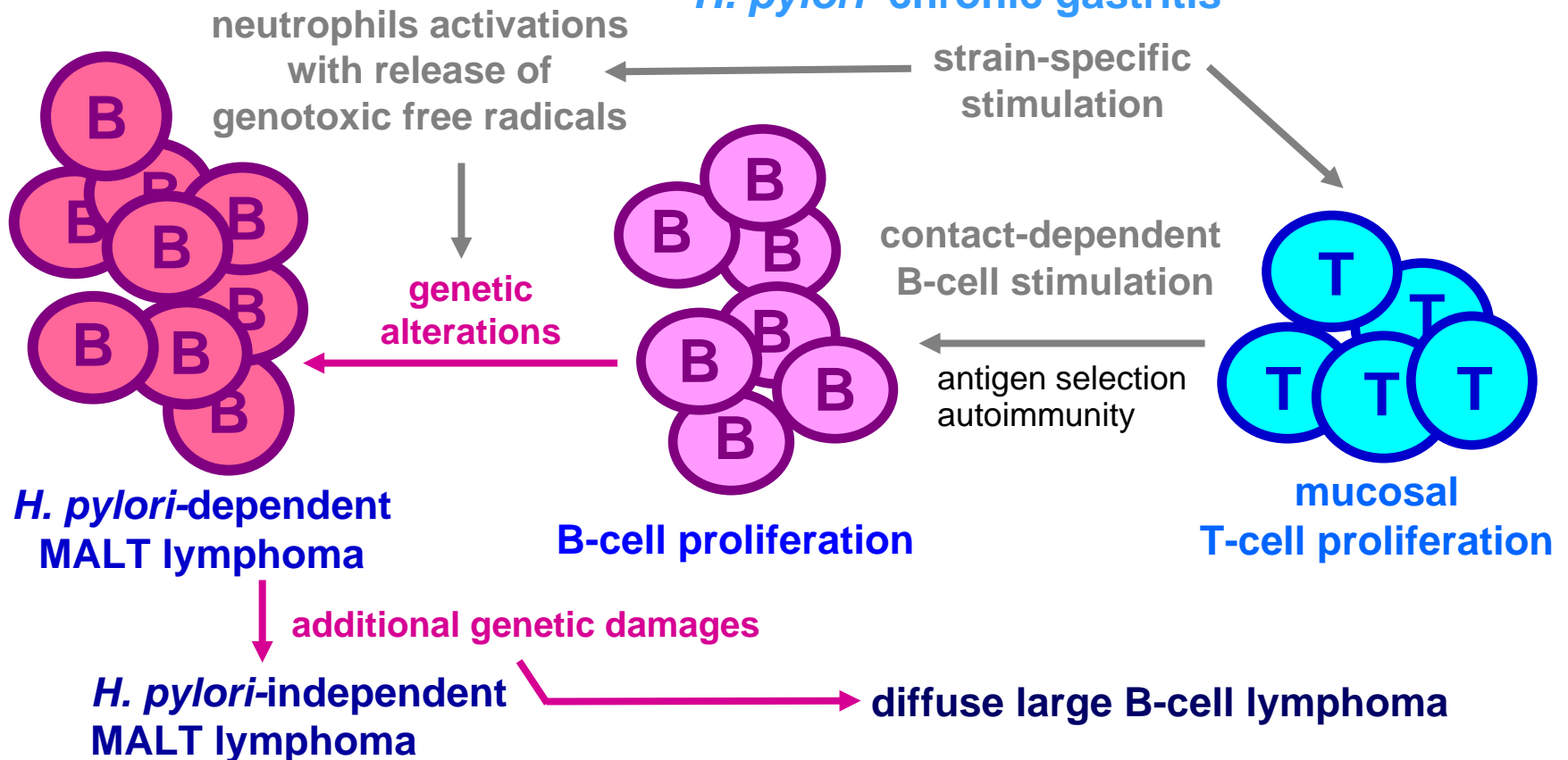
*Bertoni, BJH 1997*

- The tumor Ig does not usually recognize *H pylory* but several autoantigens (it is frequently derived from germline Ig genes that are commonly involved in the production of autoantibodies)

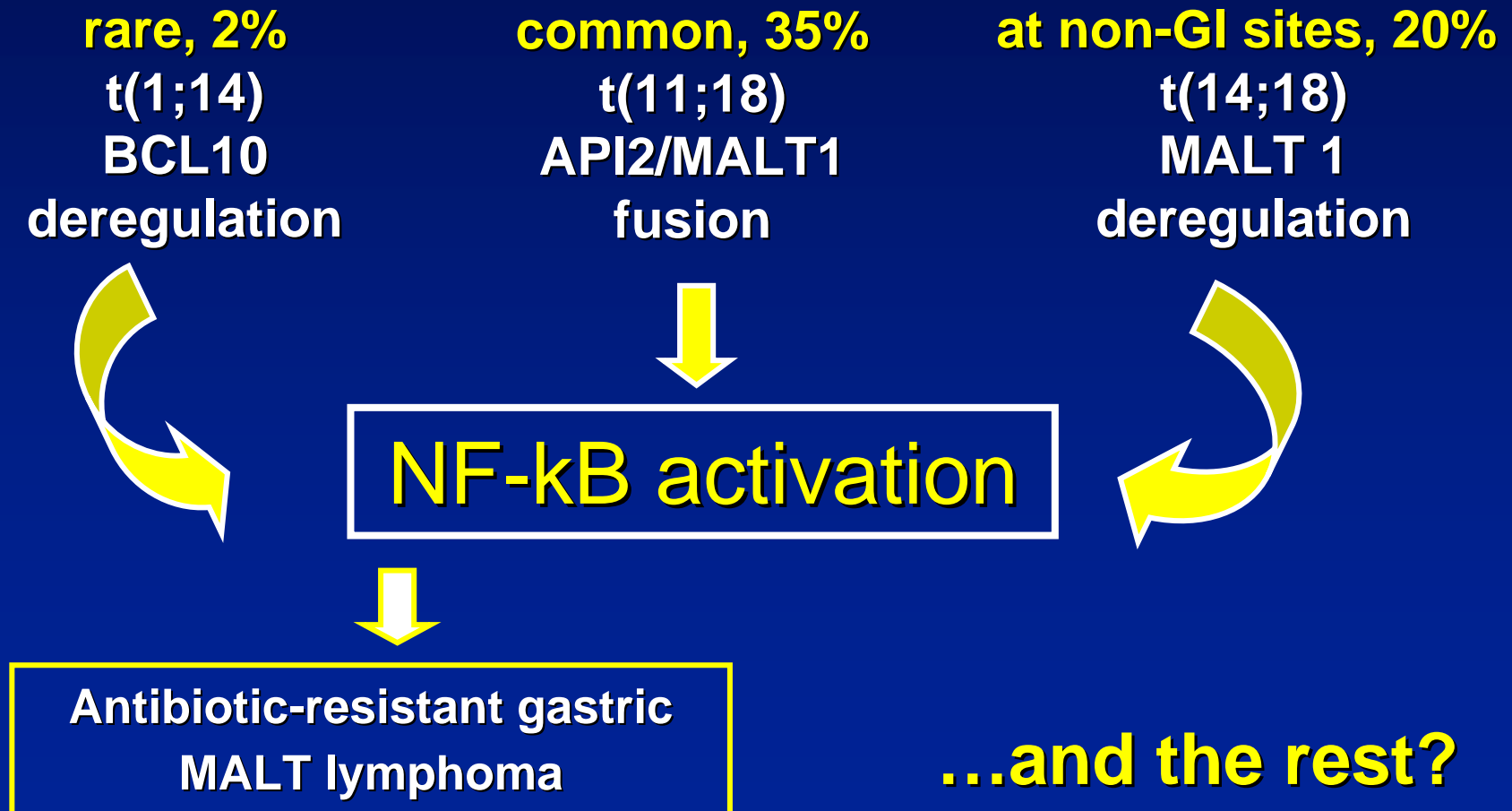
*Zucca, Leukemia 1998*

# *H. pylori* and MALT lymphoma a model of tumor progression

## *H. pylori* chronic gastritis



# Three translocations in one disease affecting the same signalling pathway



# Another translocation in MALT lymphoma

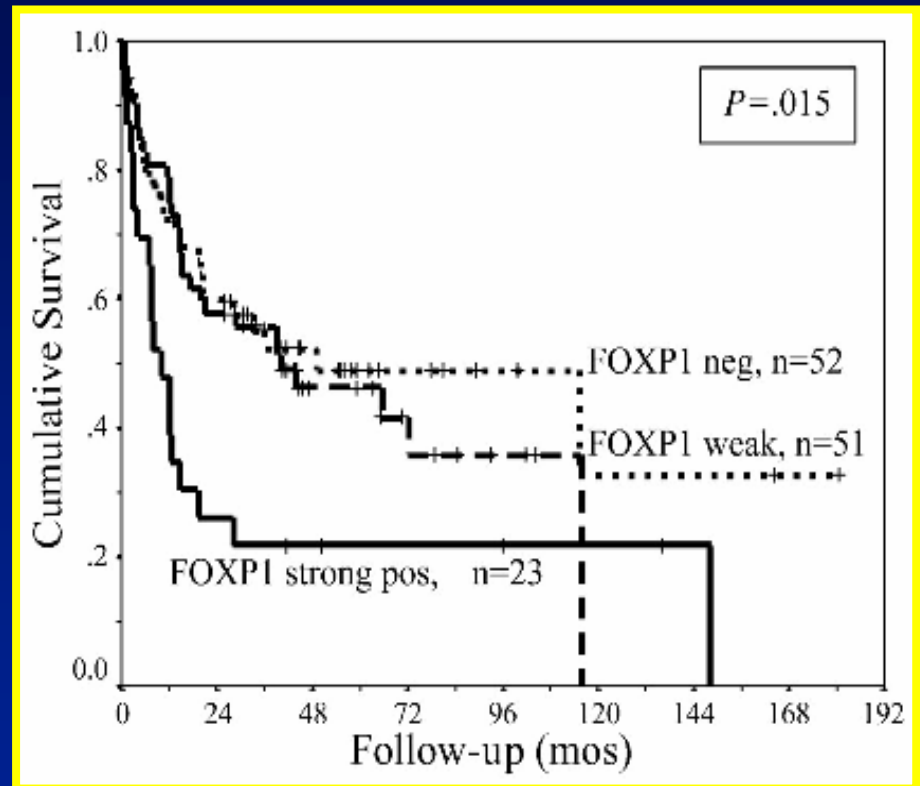
A novel t(3;14)(p13;q32) detected in approx. 9% of cases

- t(3;14) involves the FOXP1 gene and the IgH gene
- t(3;14) found in MALT lymphomas of the ocular adnexa, thyroid skin, seems uncommon in the stomach
- Nearly all t(3;14)+ MALT lymphomas harbored additional genetic abnormalities, such as +3.
- Real-time quantitative RT-PCR showed up-regulation of FOXP1 in cases with t(3;14)(p14.1;q32) or trisomy 3.

*Streubel et al. ASH 2004; Wlodarska et al. ASH 2004*

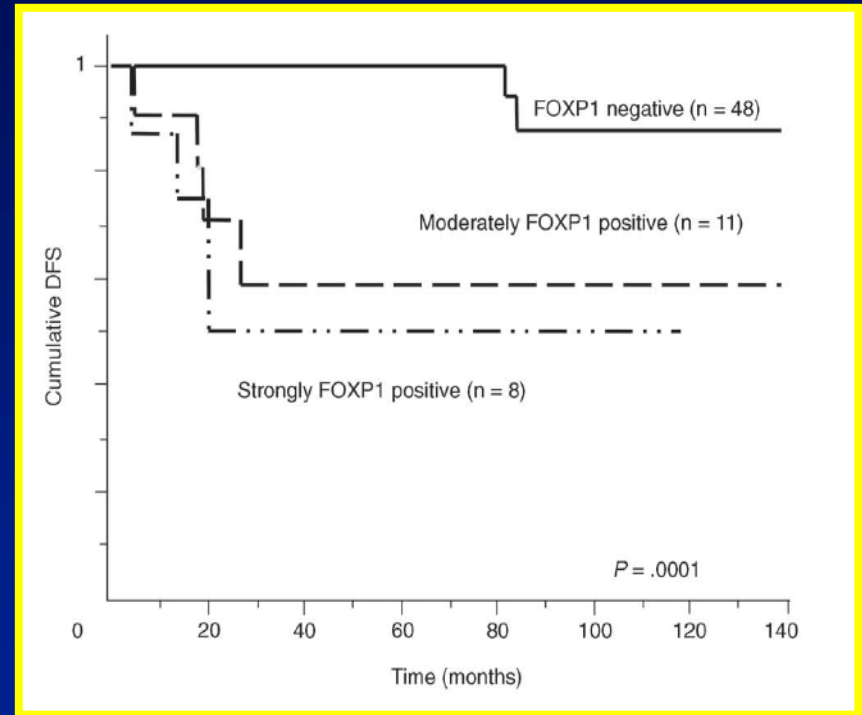
# FOXP1 expression in DLBCL

- FOXP1 a transcriptional repressor differentially expressed in resting and activated B cells
- High FOXP1 expression in 18% of DLBCL, usually with non-GC, activated B-cell phenotype
- High FOXP1 expression associated with MUM-1 and BCL2 expression in the absence of t(14; 18)
- High FOXP1 expression, is an independent poor prognostic factor



# FOXP1 expression in MALT lymphomas predicts poor prognosis and transformation to DLBCL

- Nuclear FOXP1 expression in 30% of MALT lymphomas
- FOXP1 positivity associated with poor outcome
- MALT lymphomas with strong FOXP1 expression are at risk of transforming into an aggressive DLBCL of non-GC phenotype if they carry, in addition, a polymorphic histology and the presence of trisomy 3 and 18.



*Sagaert et al. JCO 2006*

## Clinical and biological features associated with the four main recurrent translocations of MALT lymphomas

Translocation	t(11;18)(q21,q21)	t(1;14)(p22;q23)	t(14;18)(q32,q21)	t(3;14)(p14.1;q32)
<b>Product</b>	cIAP2-MALT1 fusion protein	Overexpression of BCL10	Overexpression of MALT1	Overexpression of FOXP1
<b>% of cases</b>	15–40%	1–2%	20%	10%?
<b>Main lymphoma localizations</b>	Stomach, lung, intestine	Stomach, lung	Salivary glands, skin, orbit, liver	Thyroid, orbit, skin,
<b>MALT1 expression</b>	Cytoplasmic, weak	Cytoplasmic, weak	Cytoplasmic, strong	Unknown
<b>BCL10 expression</b>	Nuclear, strong	Nuclear, strong	Cytoplasmic, strong	Unknown
<b>FOXP1 expression</b>	Unknown	Unknown	Unknown	Nuclear
<b>NFκB activation</b>	Yes	Yes	Yes	Unknown
<b>Additional aberrations</b>	No?	Yes	Yes	Yes
<b>Histologic transformation</b>	No	Yes	Yes	Yes

# Genetic heterogeneity in gastric MALT Lymphoma: is t(11;18) associated with a stable karyotype?

## **CGH study, N=26**

- 9/26 with t(11;18)
- 5/9 with additional aberrations
- all cases without t(11;18) had complex abnormalities

*Du et al, BJH 2006*

## **FISH study, N=42**

- 7/42 with t(11;18)
- 6/7 with additional aberrations

*Tibiletti et al, submitted 2007*

# Genetic Heterogeneity in MALT Lymphoma

- Cytogenetic aberrations in 93%, balanced translocations in 75%
- IGH rearranged in 95% of translocations
- 1 case had novel t(6;7)(q25;q11).
- IGH partner genes involved MALT1, FOXP1, BCL6 and 4 new chromosomal regions on 1p, 1q, 5q, and 9p.
- novel partner genes identified on 1p (CNN3), 5q (ODZ2), and 9p (JMJD2C).
- Immunohistochemistry for MALT1, BCL10, FOXP1, and NF- $\kappa$ B demonstrated that NF- $\kappa$ B and FOXP1 were not activated in the majority of the cases.

## No significant difference in survival between treatment subsets in patients with stage IE gastric MALT lymphoma

Treatment	<i>n</i>	additional tumors ( <i>n</i> of pts)	CR rate	5-years OS (95% CI)
Antibiotics	45	5	67%	94% (65-99)
Local treatment <sup>a</sup>	14	3	100%	92% (57-99)
Chemotherapy	8	3	50%	75% (32-93)
Combined modality <sup>b</sup>	5	1	100%	80% (20-97)
Total	72	12	74%	89% (76-96)

<sup>a</sup> surgery ± RT

<sup>b</sup> surgery+ adjuvant chemotherapy

# Response to antibiotics in stage I gastric MALT lymphoma

Reference	n	staging procedure	CR rate (%)	time to CR (mos.)	relapses (n)
Savio, 1996	12	CT	84	2-4	0
Pinotti, 1997	45	CT	67	3-18	2
Neubauer, 1997	50	CT±EUS	80	1-9	5
Nobre Leitao, 1998	17	CT+EUS	100	1-12	1
Steinbach, 1999	23	CT±EUS	56	3-45	0
Montalban, 2001	19	CT±EUS	95	2-19	0
Ruskone-Formestaux, 2001	24	CT+EUS	79	2-18	2
LY03 interim analysis, 2000	190	CT	62	3-24	15

# Gastric MALT lymphoma: First-Line Therapy

- **Eradication therapy**
  - >90% *H.Pylori* eradication
  - ≈ 50-100% histological CR
  - >10% recurrence ?  
(problems with definition,  
increasing recurrences with longer follow-up?)
- **How should we treat persistent  
or recurrent lymphoma after eradication  
therapy?**

# IELSG Study of Rituximab in MALT lymphoma (375 mg/m<sup>2</sup>/wk x4)

34 pts, 11 with previous CT, 15 gastric, 20 stage IV  
median follow-up 15 months

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<i>response</i>	<i>n</i>	<i>%</i>	<i>95% C.I.</i>
ORR	25	73	55-87
SD	6	18	7-35
PD	3	9	19-24

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4 CR and 4 PR (ORR 73%, 95% C.I. 39-94)  
in 11 patients with localized gastric lymphoma

*Conconi, Blood 2003*

# Initial primary non-GI MALT lymphoma locations

Extranodal site	All patients, N (%)
Total	180 (100)
Skin	22 (12)
Conjunctiva	18 (10)
Orbit	13 (7)
Salivary glands	46 (26)
Thyroid	10 (6)
Upper airways (+Waldeyer ring)	12 (7)
Lung	15 (8)
Breast	3 (2)
Liver	6 (3)
Bowel	9 (5)
Urinary tract	2 (1)
Multiple mucosal sites	24 (13)

Zucca et al. *Blood*. 2003;101:2489

All Patients	n	(%)
Total	158	(100)
One MALT-organ localization	140	(89)
GI tract		
Stomach	52	(33)
Intestinal tract	12	(8.5)
Non-GI tract		
Lung	15	(9.5)
Breast	5	(3)
Orbit	16	(10)
Head and neck	18	(11)
Thyroid	6	(4)
Skin	16	(10)
Multiple MALT-organ localizations	18	(11)

Thieblemont, et al. *Blood*. 2000;95:802

# Bacterial infections and nongastric MALT lymphomas

Analogous to *H. pylori* the in the stomach:

- *Borrelia burgdorferi* infection, may represent the background for the development of cutaneous MZL

*Cerroni 1997, Roggero 2000*

- *Chlamidia psittaci* infection can provide the antigen stimulation, which may contribute to the pathogenesis of ocular adnexa lymphomas

*Ferreri 2004*

- *Campylobacter jejuni* may be associated with IPSID

*Lecuit 2004*

# Lymphoma of ocular adnexa

Location: conjunctiva, lacrimal gland, orbital soft tissues, eyelid

More common than intraocular, which is subset of P-CNS-lymphoma: do not confuse the two sites !

Hystology: 75% MALT  
10-15% follicular  
5-7% DLBCL

# Prospective trial of doxycycline in OAL

- 27 OAL patients treated with a 3-week course of doxycycline
  - 15 newly diagnosed and 12 pretreated
  - 11 *Chlamidia psittaci* -positive and 16 negative
- at a median f-up of 14 mos, 6 CR and 7 PR (ORR = 48%)
  - Lymphoma regression observed in both Cp+ (7 of 11) and Cp- patients (6 of 16)
- Doxycycline was well tolerated.

*Ferreri et al. JNCI 2006*

# Chlamydia or not Chlamydia, that is the question

**Table 1.** Prevalence of *C. psittaci* infection in orbital adnexal extranodal marginal-zone lymphoma of MALT type

Geographical area	No. of patients	Percentage of <i>C. psittaci</i> -positive patients (95% CI)*	Reference
Italy	24	87 (68 to 97)	(5)
South Korea	30	77 (58 to 90)	(12)
Germany	19	47 (24 to 71)	(13)
Italy and Hungary†	27	41 (22 to 61)	(7)
United States (east coast region)	17	35 (14 to 62)	(13)
The Netherlands	21	29 (11 to 52)	(13)
Italy	15	13 (2 to 40)	(13)
United Kingdom	33	12 (3 to 28)	(13)
Southern China	37	11 (3 to 25)	(13)
Cuba	19	10 (1 to 33)	(14)
United States (northeast)	7	0 (0 to 41)	(15)
The Netherlands	19	0 (0 to 18)	(16)
Japan	18	0 (0 to 19)	(17)
Japan	12	0 (0 to 26)	(18)
United States (Florida)	46	0 (0 to 8)	(19)
France	6	0 (0 to 46)	(20)

**Zucca & Bertoni**  
**JNCI 2006**

# Lymphoma of ocular adnexa

## Treatment:

1. avoid extensive surgery
2. in most cases Radiotherapy treatment of choice

After CR, risk of locoregional relapse very low.

Most common site of relapse: contralateral orbit

Distant failure rate: 20-40%

Overall survival at 10 years: > 90%

Role of Doxocycllin?

# IELSG Study of non-gastric MALT lymphoma: Outcome according to the primary site

<i>Extranodal site</i>	<i>5-years OS (95% CI)</i>	<i>5-years PFC (95% CI)</i>
Skin	100%	53% (22-77)
Orbit	80% (40-95)	23% (1-62)
Conjunctiva	100%	100%
Salivary gland	97% (81-100)	67% (48-81)
Upper airways	46% (7-80)	0
Lung	100%	75% (41-91)
Thyroid	100%	100%
Multiple MALT sites, only	100%	0

# INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP

## IELSG-19 Study

Randomized trial of chlorambucil *versus* chlorambucil plus rituximab in MALT lymphoma

*Control arm*

Chlorambucil (6 mg/m<sup>2</sup> /d) weeks 1-6 // 9-10 // 13-14 // 17-18 // 21-22

*Study arm*

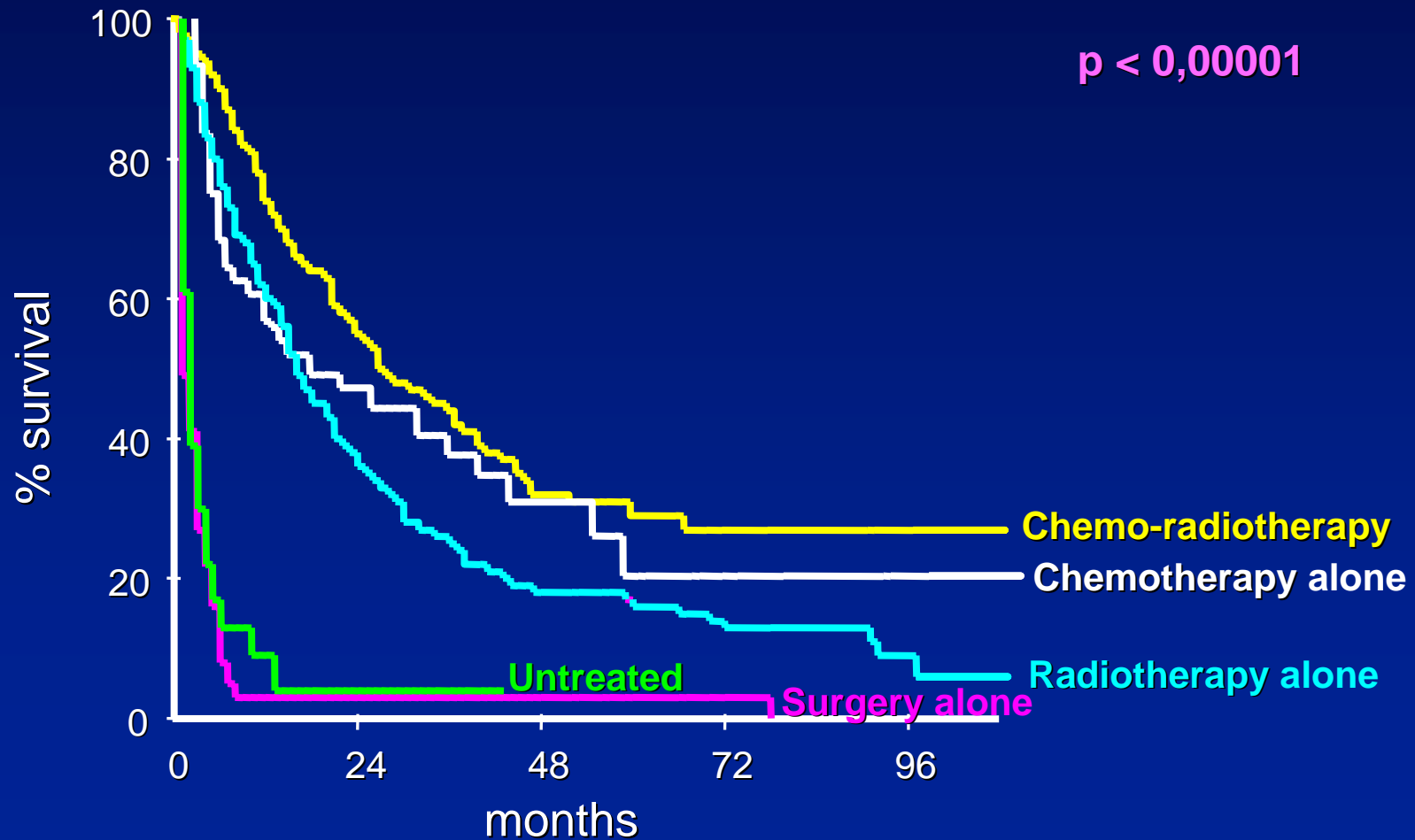
Chlorambucil (6 mg/m<sup>2</sup> /d) weeks 1-6 // 9-10 // 13-14 // 17-18 // 21-22

day	1	8	15	22	42	56	70	84	98	112	126	140	154
Rituximab (375 mg/ m <sup>2</sup> )	↑	↑	↑	↑		↑		↑		↑		↑	

# PCNSL: An Exciting Challenge

- Progressively increasing incidence.
- Peculiar clinical behavior
- Poorly known molecular profile
- It arises from a cell type not normally present in CNS
- It arises in an anatomical site with certain structural, biological and immunological characteristics
- Even if it exhibits one of the worst prognoses among NHL, it is a curable brain tumor.

# Standard Practice Therapeutic Strategy

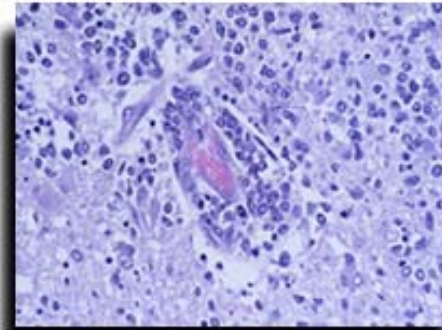


# Relevant Question

*... the question is not whether chemotherapy should be administered, but what is the best regimen? HD-MTX is the single most active agent in PCNSL, but what is the optimal dose and can it be given as a single agent or is combination therapy necessary?*

*De Angelis LM. J Clin Oncol (Dec 15) 2003*

# The International PCNSL Collaborative Group



Report of an International Workshop to define consensus guidelines on standard baseline evaluation and response criteria for primary CNS lymphoma

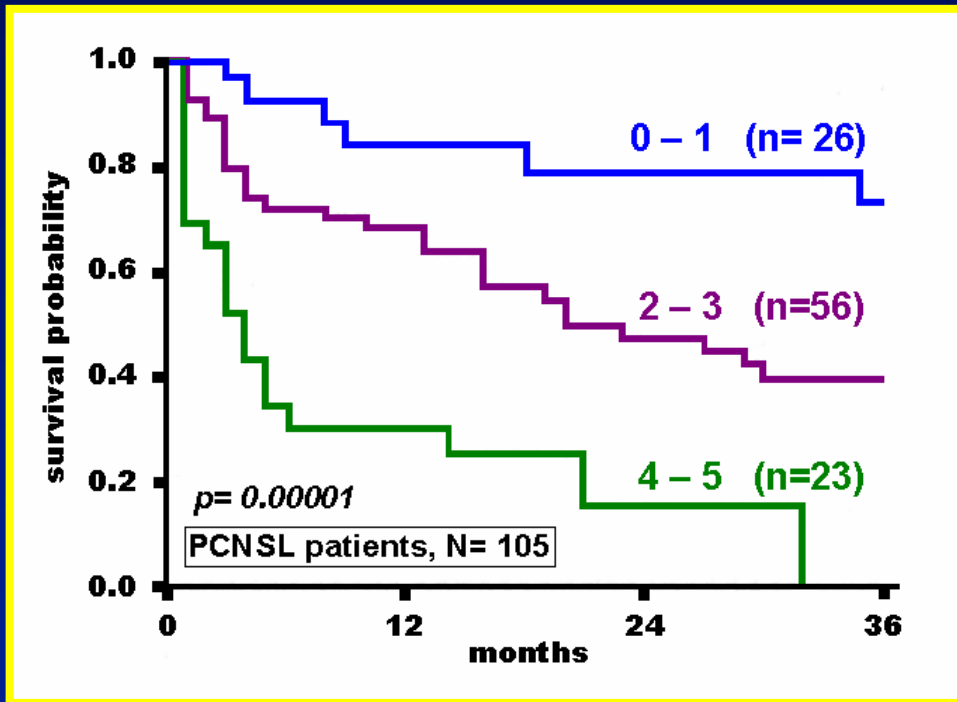
*Lauren E. Abrey, and others or for the IPCG*

***JCO, 23:5034;2005***

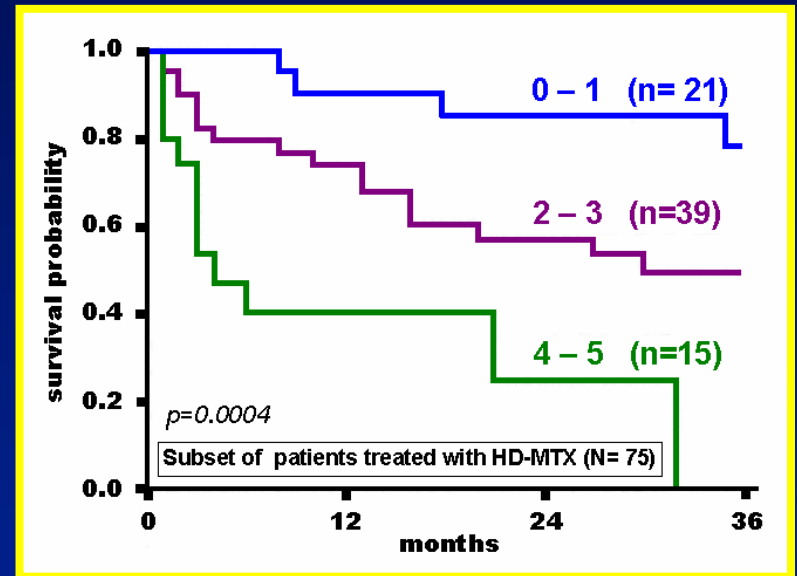
# IELSG prognostic score for PCNSL

- Significant predictors of poor outcome:
  - Age >60 ys
  - PS >1
  - elevated LDH
  - high CSF protein concentration,
  - involvement of deep regions of the brain
- These 5 variables were used to design a prognostic score

# PCNSL survival according to the IELSG prognostic score



105 cases with complete data about all the 5 prognostic variables



Subset of 75 cases treated with HD-MTX +/- WBRT

*Ferreri et al. J Clin Oncol 2003*

# Randomization

IELSG score: 0 - 1 / 2 - 3 / 4 - 5

Intention to irradiate pts > 60 ys. in CR after CHT



MTX 3.5 g/m<sup>2</sup>, d1  
(every 3 weeks)



MTX 3.5 g/m<sup>2</sup>, d1  
Ara-C 2 g/m<sup>2</sup> x 2, d2-3  
(every 3 weeks)

# Intrathecal Chemotherapy

- Meninges are involved only in 5% of failures.
- Meningeal failure is associated with brain relapse in >90%.
- Brain failure is the cardinal prognostic event, obscuring the effect of concurrent meningeal relapse on survival, and the potential benefit of intrathecal chemotherapy.
  
- No defined role for intrathecal chemotherapy in PCNSL.
- Intrathecal chemotherapy only for CSF +ve patients.
- HD-MTX ( $\geq 3 \text{ g/m}^2$ ) treats adequately meninges.
- Improvements in CHT and RT should be considered as priorities.

# Lymphoma of the testis

## *Epidemiology*

- First report in 1877 (*M. Malassez, Bull.Soc.Anta Paris*)
- 5% of all testicular malignancies
- <2% of all non-Hodgkin's lymphoma
- Incidence: 0.26/100,000 per year
- 85% of case in men older than 60 yr
- the commonest testis neoplasm after 60 yr

# Lymphoma of the testis

## *Peculiar features*

- Somatic hypermutation of IgH genes and plasmacytoid differentiation in ~50%  
→ **antigen-driven stimulation?**

*Hyland et al. 1998*

- Altered expression of adhesion molecules  
→ **early dissemination?**

*Horstmann & Timens 1996*

- Alterations of HLA class I and II regions  
→ **immune escape?**

*Riemersma et al. 2000; Jordanova et al. 2003*

# IELSG Testis Lymphoma Study

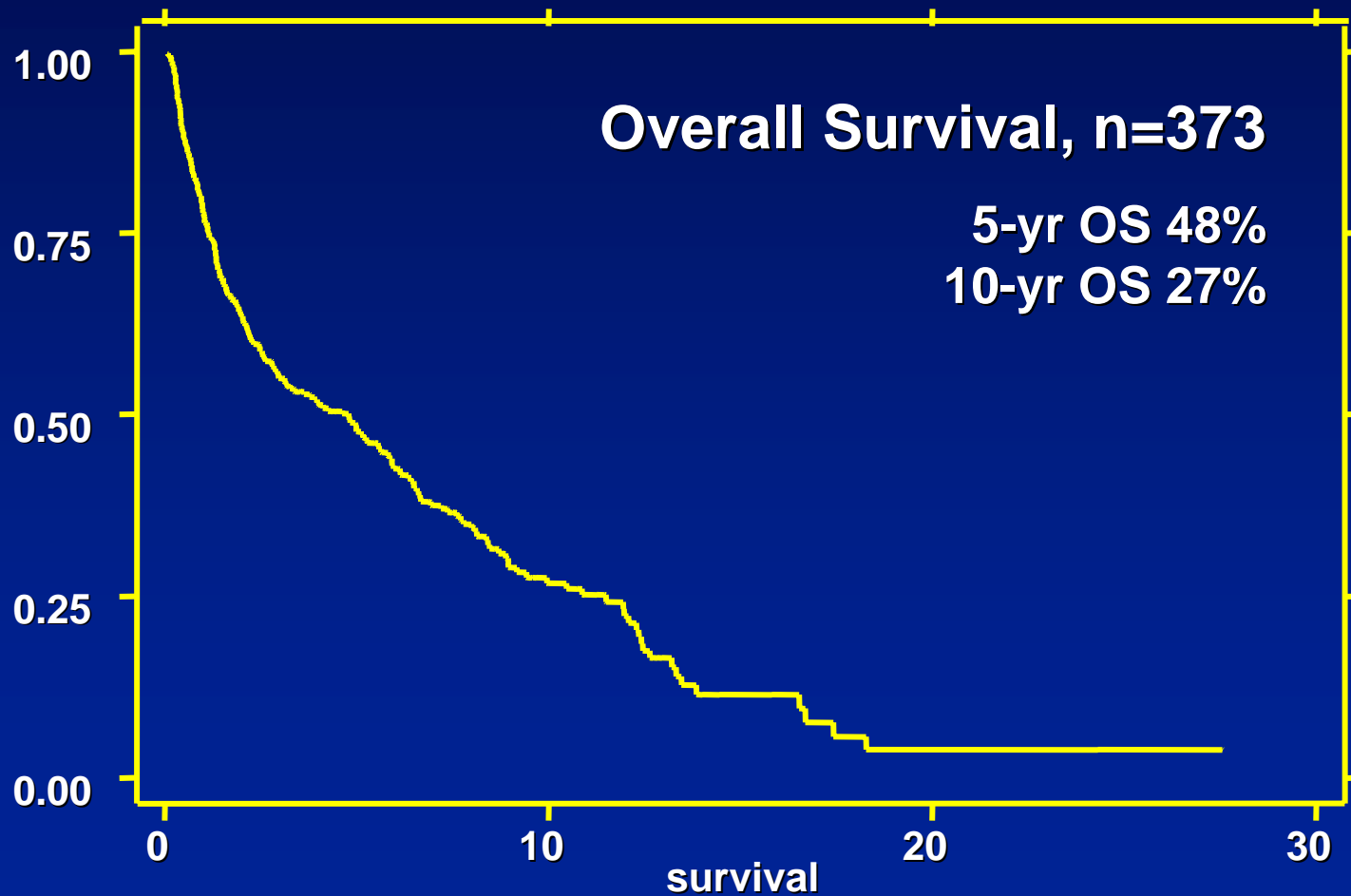
(Zucca et al. JCO 2003)

## Patients characteristics

- 373 patients, median age 66 years (range:19-91)
- Data provided by 23 centers
- Stage (n=373)
  - I 214 pts
  - II 81 pts
  - III 7 pts
  - IV 71 pts } 79%
- IPI (n=302)
  - Low 82 pts
  - Low-Int 25 pts
  - Int-High 26 pts
  - High 19 pts } 81%
- B symptoms 33 pts → 9%
- PS (ECOG) >1 50 pts → 13%
- Additional extranodal sites 69 pts → 18%

# IELSG Testis Lymphoma Study

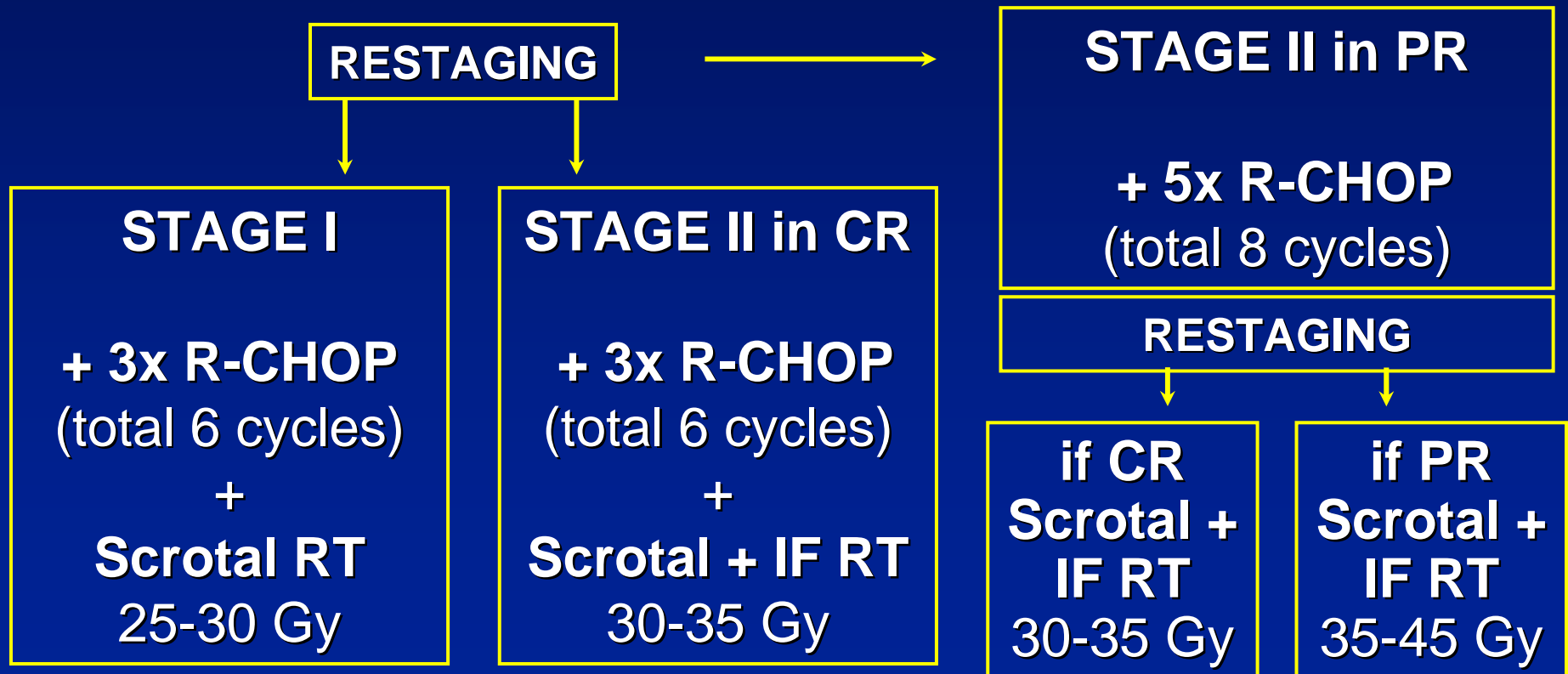
*(Zucca et al. JCO 2003)*



# IELSG-10 Study Design

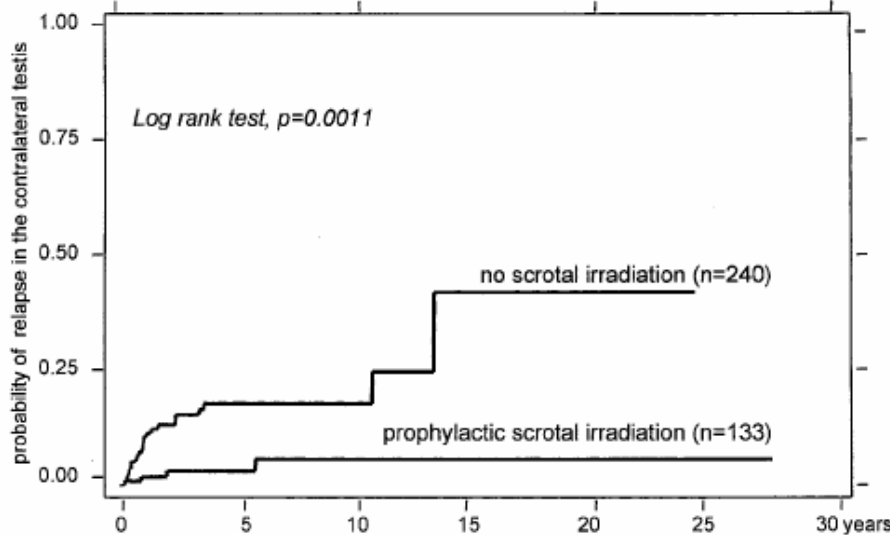
*Prospective therapeutic study of testis lymphoma*

**3x R-CHOP + intrathecal MTX (12 mg/wk on weeks 1 to 4)**

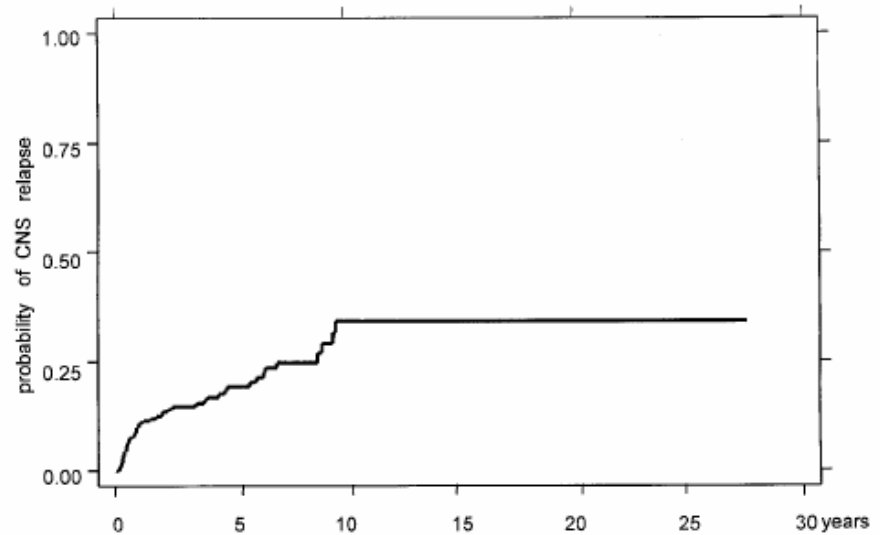


# Challenges in the treatment of primary testicular lymphoma

- high risk of extranodal relapses
- high risk of contralateral failure (42% at 15 years)
- high risk of CNS recurrence (34% at 10 years)



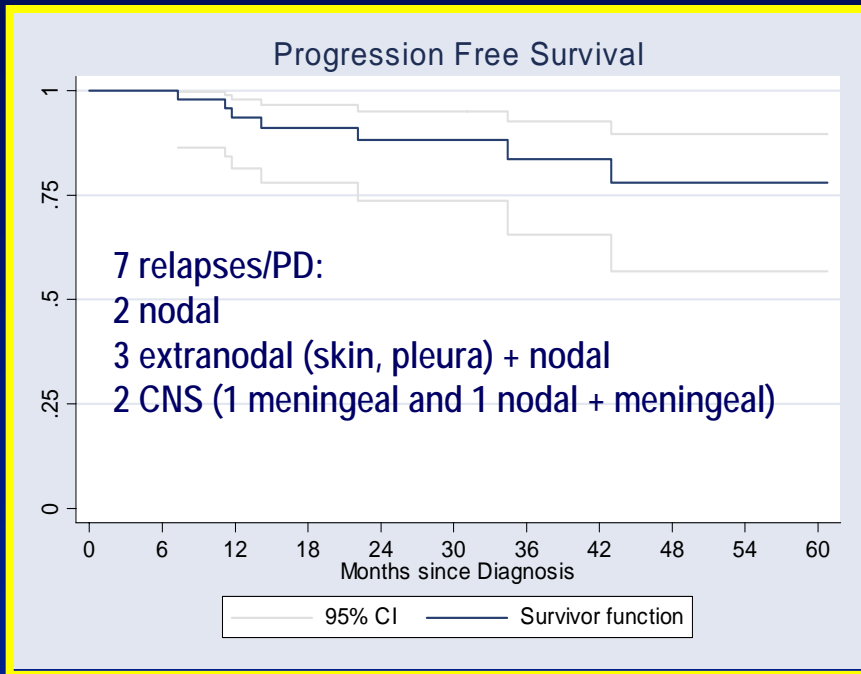
Risk of contralateral testis relapse with and without RT



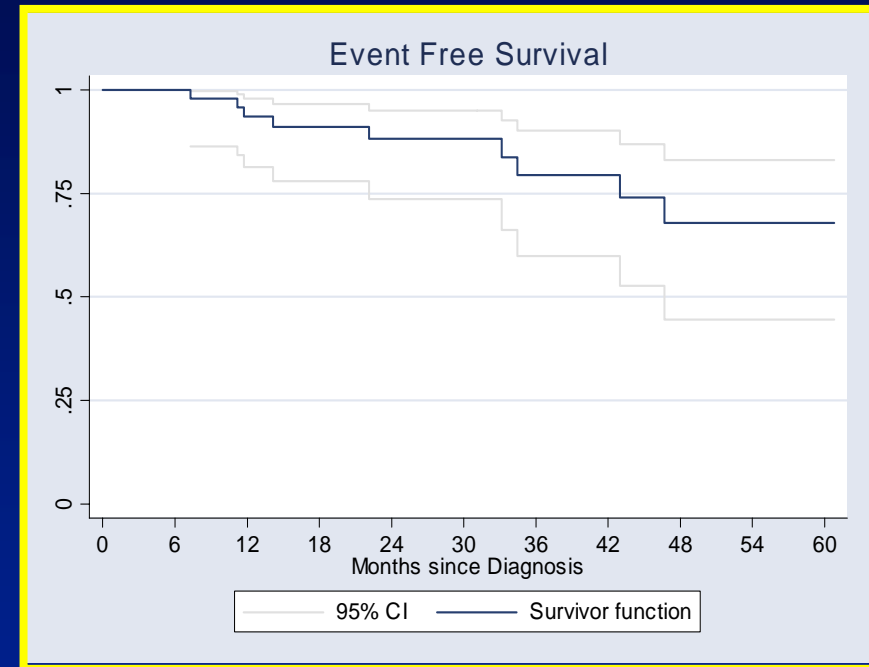
Risk of CNS failure

# IELSG 10- Outcomes

**3-year PFS 84% (95% CI 65-93%)**



**3-year EFS 79% (95% CI 60-90%)**



**Median Follow-up 30 months, Overall Survival 87%**

**9 Failures (6 relapses and 1 PD, 1 AML, 1 heart failure)**

**5 Deaths (3 due to NHL, 1 AML, 1 heart failure)**

**No early toxic deaths**

**Late events: 1 AML, 1 Heart failure, 1 MDS)**

**(Vitolo et al ASH 2006)**

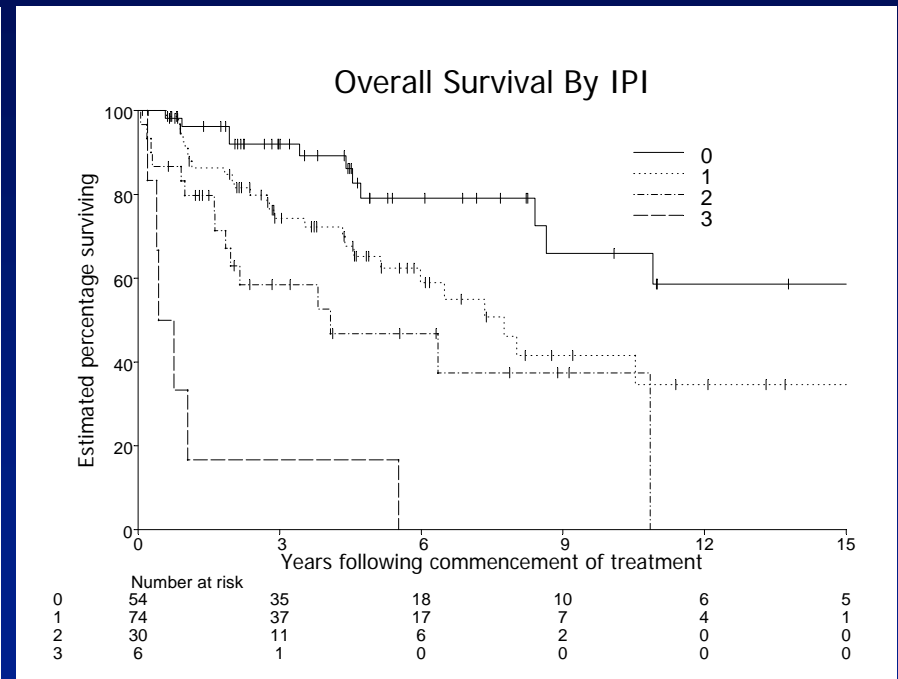
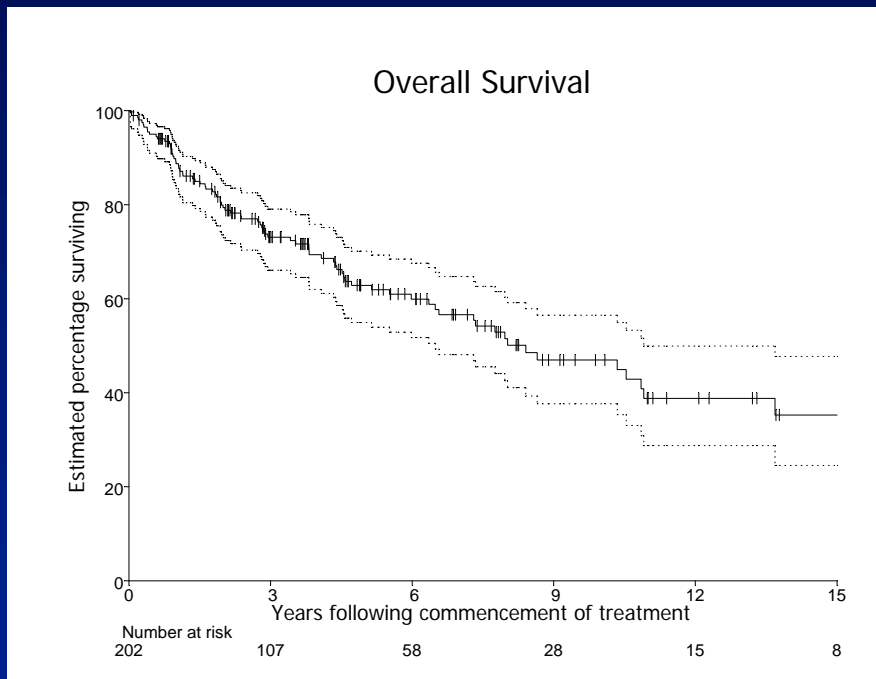
# IELSG 10- preliminary analysis

- ➔ R-CHOP + IT MTX + Scrotal RT is a feasible program with acceptable toxicity also in elderly patients
- ➔ With a median FU of 30 mos, 3-yrs PFS is 84%.
- ➔ The results suggest an improvement in comparison with our retrospective series
- ➔ Contralateral testis relapses have been eliminated
- ➔ CNS recurrence seems to be reduced

*(Vitolo et al ASH 2006)*

# A retrospective international study of Primary Lymphoma of the Breast (IELSG-15)

## Overall Survival



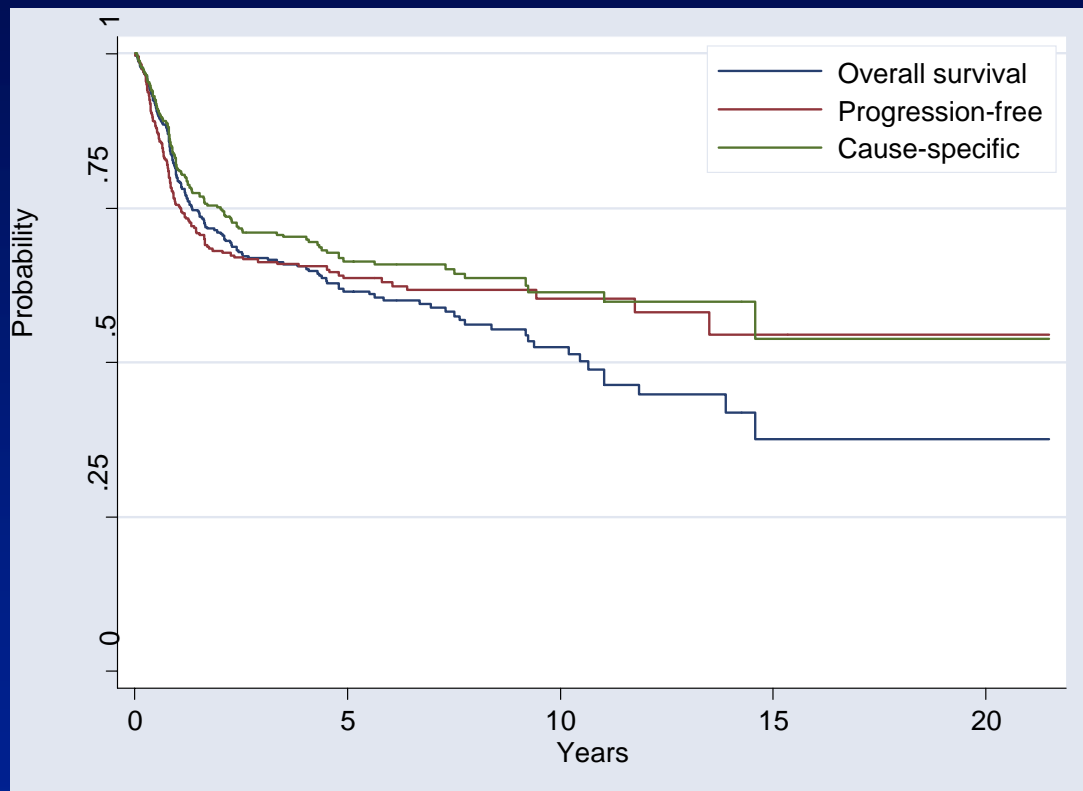
The median overall survival was **8.4 years** (95% CI: 6.5, 10.9)

The median follow-up duration was 5.5 years

IPI was the only prognostic factor that retained statistical significance at multifactor analysis for overall survival

# Patterns of outcome and prognostic factors in Primary Bone Lymphoma (IELSG 14)

## Overall survival



**The median overall survival (OS) was estimated at 10.7 years.**

**Median progression free survival (PFS) and cause-specific survival (CSS) had not yet been reached.**

# Primary mediastinal (thymic) large B-cell lymphoma (PMBCL)

- First described in adults in 1980 (Lichtenstein et al. Am J Med 68:509)
- Uncommon but not rare (2-5% of NHLs)
- Proposed as a possibly separate entity since the second half of the 1980s
- Still considered a subtype of DLBCL in the WHO classification (as opposed to a distinct disease)

# PMBCCL: a clinical entity or a subset of DLCL?

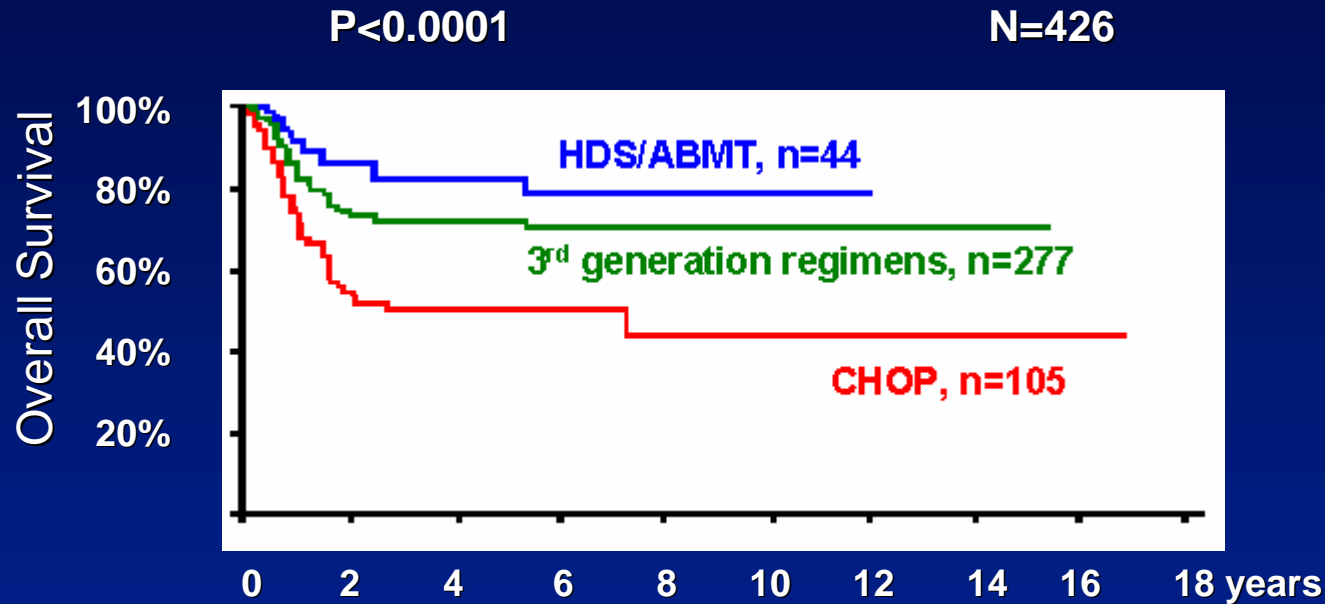
Statistically significant differences found in a large retrospective study of the GELA :

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	<b>PMLCL (n=141)</b>	<b>vs.</b>	<b>DLCL (n=916)</b>
Median age	37 yrs		54 yrs
Young women	59%		42 %
Bulky	77%		7%
High LDH	76%		51%
BM+	2%		17%
CR rate	79%		68%
3-yr OS	66%		61%

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# INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP IELSG-9 study of primary mediastinal DLBCL



	<b>CHOP</b>	<b>3<sup>rd</sup> generation</b>	<b>HDS / ABMT</b>
CR after CT	49%	51%	53%
CR after CT+RT	61%	79%	75%
10-year OS	44%	71%	77%
Follow-up	52 mos	55 mos	36 mos



# PMBCL: the key questions

- Can the initial response rate be improved by relatively dose-intense chemotherapy in combination with rituximab?
- PET a valuable means of measuring response and determining prognosis following chemoimmunotherapy?
- Can RT be reduced or eliminated in a population of patients destined to be cured by chemoimmunotherapy?

# Primary cutaneous lymphomas: EORTC vs. WHO classifications

- Differences in the classification of cutaneous T-cell lymphomas other than mycosis fungoides, Sezary syndrome and the group of primary cutaneous CD30-positive lymphoproliferative disorders and the classification and terminology of different types of cutaneous B-cell lymphomas have resulted in considerable debate and confusion.
- **Recent agreement on a new classification, which is now called the WHO-EORTC classification**  
*(Willemze et al. Blood 2005)*
- Both systems have shortcomings

# B-cell lymphoma biology

- Normal B cells depend on B-cell receptor (BCR) expression for survival
- Although there is strong evidence that most B-cell lymphomas depend on BCR expression, there are a few exceptions — namely classical Hodgkin's lymphoma, primary mediastinal B-cell lymphoma, some post-transplant lymphomas, and the rare primary effusion lymphomas.
- In several lymphomas, there is a strong indication that stimulation by antigen binding contributes to the survival and proliferation of lymphoma cells.

# B-cell lymphoma biology (2)

- In many lymphomas, such as follicular lymphoma, mucosa-associated lymphoid tissue lymphomas and classical Hodgkin's lymphoma, the tumor micro-environment seems to be important for the survival and/or proliferation of the lymphoma cell
- The recognition that the survival and/or proliferation of many B-cell lymphomas depends on their interaction with other cells in the microenvironment, as well as on expression of the B-cell-receptor and, sometimes, antigen activation, might lead to novel treatment options for B-cell lymphomas