

## Gastrointestinal Lymphomas

ESMO Conference: 11th World Congress on Gastrointestinal Cancer

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Groupe d'Étude  
des Lymphomes de l'Adulte

## WHO classification of B-cell neoplasms

**Precursor B-cell neoplasms**

- Precursor B-lymphoblastic leukaemia/lymphoma

**Mature (peripheral) B-cell neoplasms**

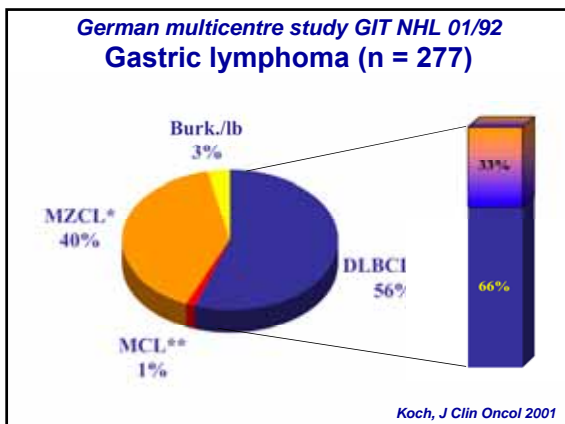
- B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukaemia
- Plasma cell myeloma/plasmacytoma
- **Extranodal marginal zone B-cell lymphoma (MALT)**
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- **Mantle cell lymphoma**
- **Diffuse large B-cell lymphoma**  
Mediastinal large B-cell lymphoma  
Primary effusion lymphoma
- **Burkitt lymphoma/ Burkitt cell leukaemia**

## MATURE T-CELL AND NK-CELL NEOPLASMS

- Indolent large granular NK-cell lymphoproliferative disorder
- Aggressive NK/T cell leukemia/lymphoma
- Adult T-cell leukemia/lymphoma
- **Extranodal NK/T cell lymphoma, nasal type**
- **Enteropathy-type intestinal T-cell lymphoma**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis Fungoides
- Sezary Syndrome
- Primary cutaneous anaplastic large-cell lymphoma
- Primary cutaneous small/medium CD4 positive T-cell lymphoma
- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative


## Subtypes and locations

	Oesophage	Stomach	Duodenum	Intestine	Colon	Rectum
SL				+		+
MALT L		++++		++	+	+
FL			+		+	
MCL		+	++	+++	+++	+
DLBCL	+	+++	+	++	++	+
Burkitt		++			+++	
NK/T nasal				+		
EATCL				+		
Other T		+		+	+	



## MALT lymphomas

- Lymphomas deriving from extranodal organs
- Mucosal organs or non-mucosal organs
- 7-8% of all lymphomas

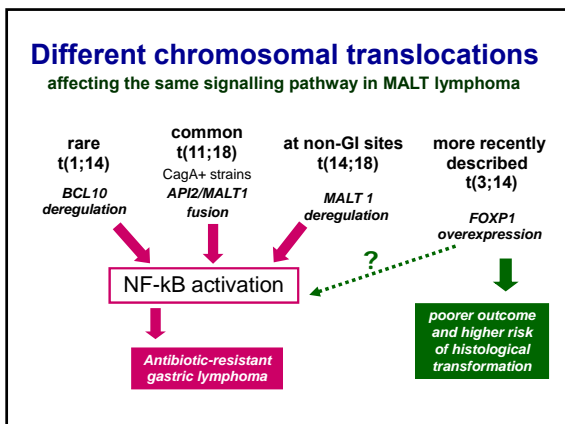
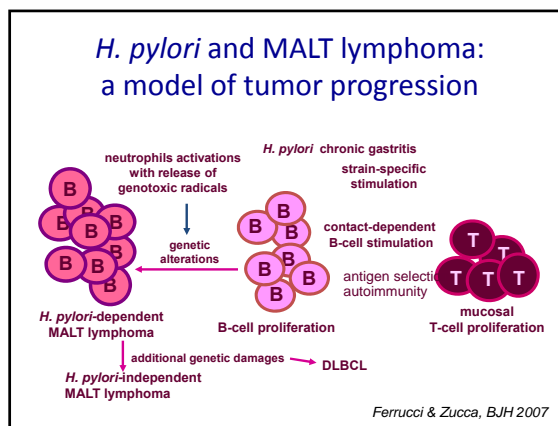
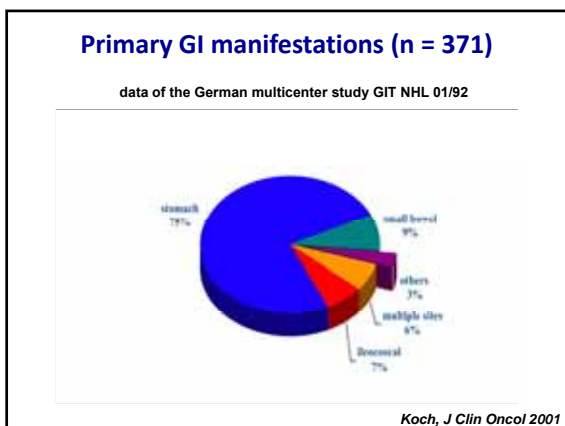
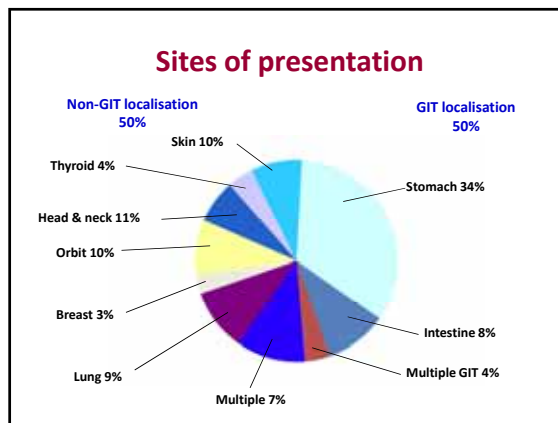


### MALT lymphoma

- Variety of clinical presentations**


Depending on locations

- Indolent disease**
  - B symptoms are uncommon
  - Normal serum LDH and  $\beta 2$  microglobulin
- Disseminated at diagnosis in 1/3 of the patients**
  - multiple involved organs +/- bone marrow (20%)



- ### Staging procedures
- #### *GI MALT lymphoma*
- Endoscopy, multiple biopsies including duodenum
  - Endoscopic ultrasound → depth of infiltration perigastric lymph nodes (better than cat scan)
  - *Helicobacter pylori*: biopsy from normal mucosa
  - "Double balloon enteroscopy" = "push & pull enteroscopy" → biopsies
  - Endoscopy of colon, multiple biopsies
  - *Campylobacter jejuni* (immunoproliferative small intestinal disease = IPSID = sub-type of E-MZCL)

### Gastric MALT Lymphoma: endosonography



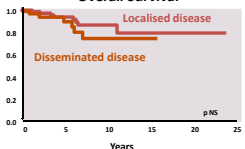
Ultrasound-endoscopy investigation of a MALT patient shows thickening of the wall, with fusion of the normal stratification due to involvement of the mucosa, sub-mucosa and muscularis-mucosa membranes.

*PF Ferrucci et al. Br J Haematol 2006;136:521*

### MALT lymphomas

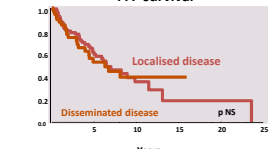
- Recommended staging procedures
  - According to the clinical symptoms
    - Multifocal disease
    - Dissemination does not change the outcome

**Overall Survival**



Years

**FFP survival**



Years

*C Thieblemont. Blood 2000;95:802*

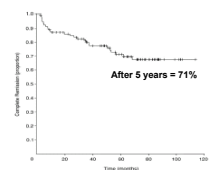
### Gastric MALT lymphomas Treatment- very early stages

Microbial pathogen **DEPENDENT** - MALT lymphoma

↓

#### Treatment of the pathogen

- Eradication of *HP* : 97%
- CR : 60% - 80%
- Response : 3 to 28 months !



Molecular remission is infrequent  
Usefulness of monoclonality determined by PCR?

*Wündisch JCO 2005*

### Response to *H. pylori* eradication

- Complete remission 81% (n = 96)
- Partial remission 10% (n = 12)
- Non-responder 9% (n = 11)

Duration to 1st CR:

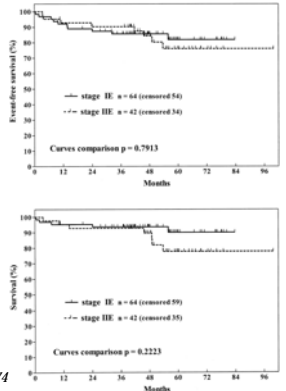
- 59/96 (61%) within 3 months
- 25/96 (26%) within 12 months
- 12/96 (13%) between 12 and 28 months

*M Stolte. Gut 2002;50:19*

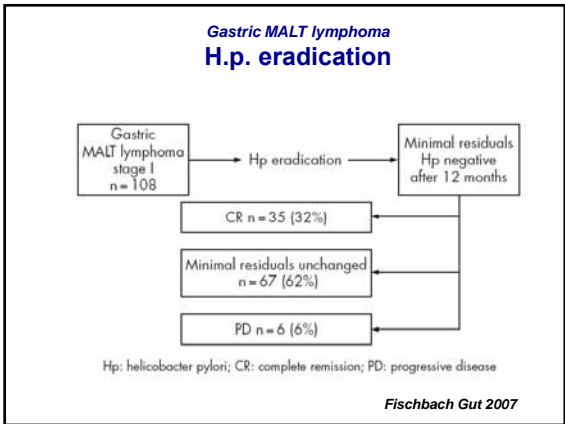
### Response to antibiotics and PPI in stage I gastric MALT lymphoma

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

### Excellent prognosis in non-operated gastric lymphoma



*Koch et al., J Clin Oncol 2001;19:3874*



### Recent data on the long term follow up

**Most patients with minimal histological gastric lymphoma residuals remain stable and can be managed safely by a watch and wait strategy**

- **Fischbach et al.**  
*Gut* 56:1685-7, 2007
  - median follow up 42 months
  - favourable outcome in 94%
  - minimal residual disease in 62%
- **Stathis et al.**  
*Ann Oncol*, 2009 *in press*
  - median follow-up 76 months
  - ~25% had histological score fluctuations and ~13/ had stable residual disease
  - 5-year OS is 92%.

- ### Practical Tips for *H. pylori* eradication
- 2 weeks of triple therapy is the standard regimen
  - The choice of the most effective regimen should be based on the prevalence of antibiotic resistance, especially resistance to clarithromycin and metronidazole
  - Avoid using clarithromycin based regimens in patients who have previously been exposed to a macrolide
  - Strict adherence to current guidelines significantly reduces treatment failure
  - Inform patients that the success of their treatment depends on their adherence to it
  - Eradication should be confirmed by the urea breath test after at least 4 weeks post-treatment
  - Systematic control for recurrence is unnecessary (annual reinfection rate is low in industrialised countries)
- Fuccio et. al BMJ | 27 SEP 2008 | VOL 337**

### How and how long to follow up after antibiotics?

- clear evidence of EUS utility as a staging procedure but less strong evidence in follow-up
- Breath test ±EGD at ~2-3 mos. after antibiotics then EGDS with biopsies q 6 ms x 2 years, then q 12 mos (life-long?)
- are molecular studies needed? (B-cell clonality? allele-specific PCR? PCR for t11:18?)

**Patients with gastric MALT lymphoma have a 6 times higher risk for gastric adenocarcinoma in comparison with the general population and the risk is highest in patients younger than 60**

Capelle et al EJC 2008

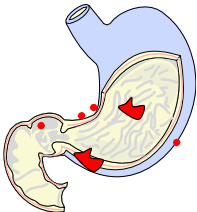
- ### MALT lymphoma Therapy
- Eradication therapy in localized gastric presentation
    - >90% H.Pylori eradication
    - 50-100% histological CR (problems with definition)
  - Recurrence (>20%?)
    - problems with definition
    - increasing recurrences with longer follow-up?
  - How should we treat persistent or recurrent lymphoma after eradication therapy? (and HP-negative cases?)
  - No Consensus on 2nd line Rx

- ### Any role for surgery?
- Several Studies clearly showed that an organ-preserving approach for early gastric lymphoma is not inferior to primary surgery
  - Most contemporary treatment algorithms no longer include surgical resection
  - Reserve surgery for the management of complications

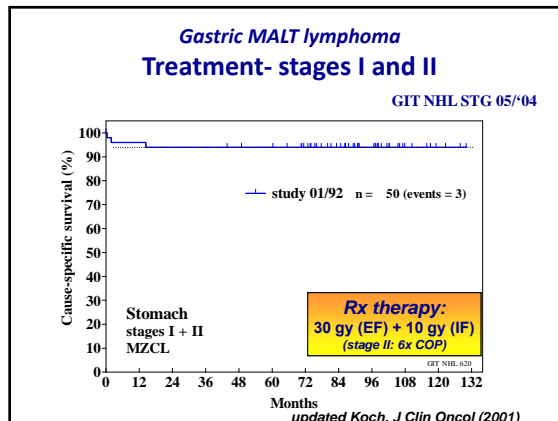
### Gastric MALT lymphoma Treatment-localised stages

⇒ localised disease

⇒ >80% stages I, II



⇒ radiation therapy !



- ### Radiation Therapy
- Radiotherapy is effective and safe
  - It offers the significant advantage of low morbidity compared to surgery
  - It represents a curative treatment option for patients *H. pylori*-negative or unresponsive to eradication therapy
  - It is probably the best therapy for relapsing patients

- ### Chemotherapy
- For patients with disseminated stage
  - For patients with multisite relapses
  - For patients not responding to radiotherapy
  - For multi relapsing patients
  - For patients with transformation

### Rituximab activity in MALT lymphoma

34 pts, 11 with previous CT, 15 gastric, 20 stage IV

response	n	%	No prior chemotherapy		Prior chemotherapy	
			ORR	CR	ORR	CR
ORR	25	73	87%	45%	48%	36%
SD	6	18				
PD	3	9				

*IELSG phase II study, Conconi et al. Blood 2003*

- 26 pts with gastric MALTomas resistant/refractory to antibiotics or with no clinical evidence of *H. pylori* infection.
- CR 46% (95% C.I. 27%-66%)
- ORR 77% (95% C.I. 56%-91%)
- The t(11; 18)(q21; q21) was not a predictive marker of response

*Martinelli et al. JCO 2005*

### INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP IELSG-19 ongoing randomized trial

*Control arm*

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

*Study arms*

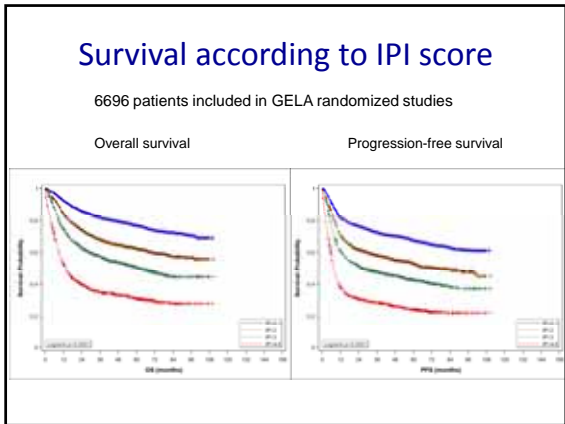
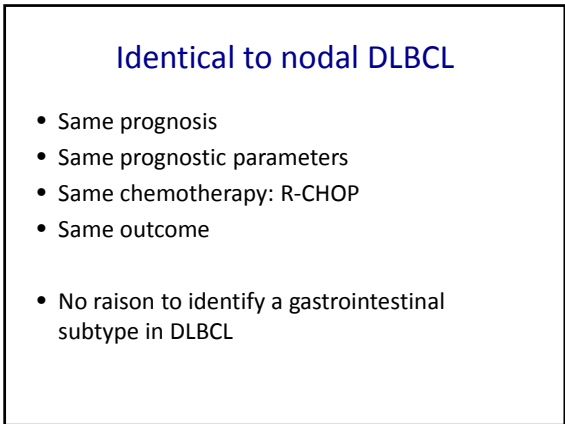
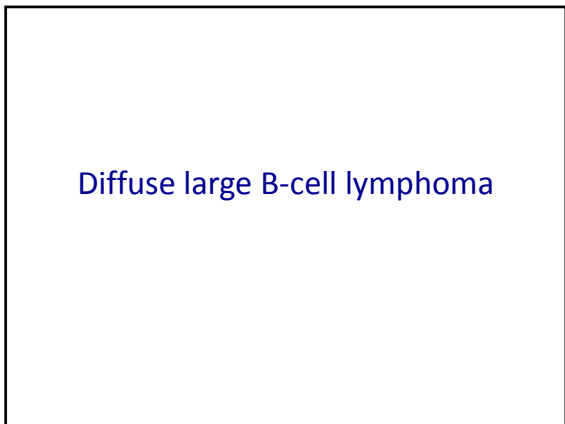
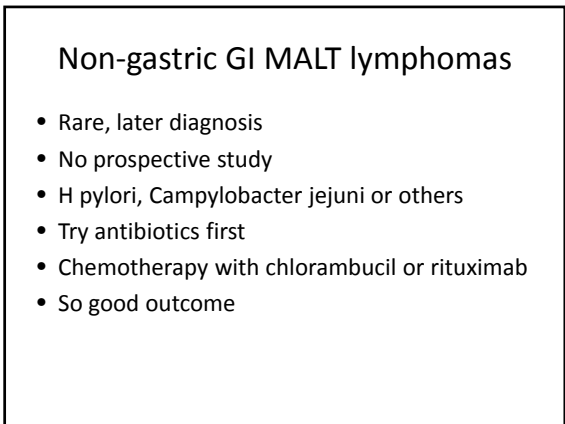
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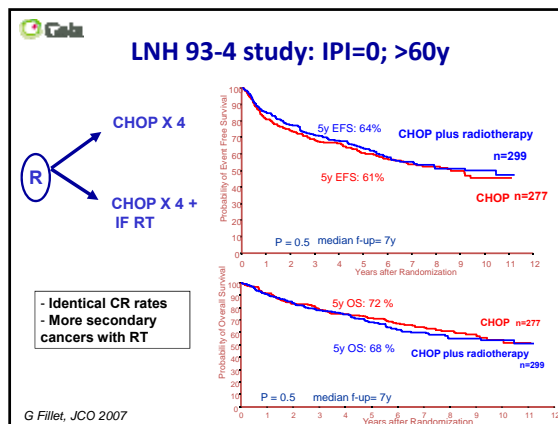
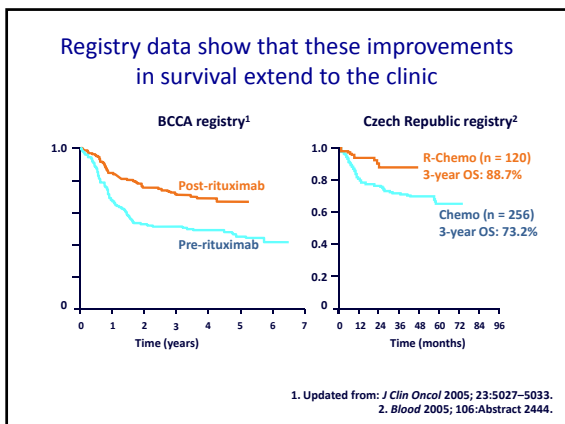
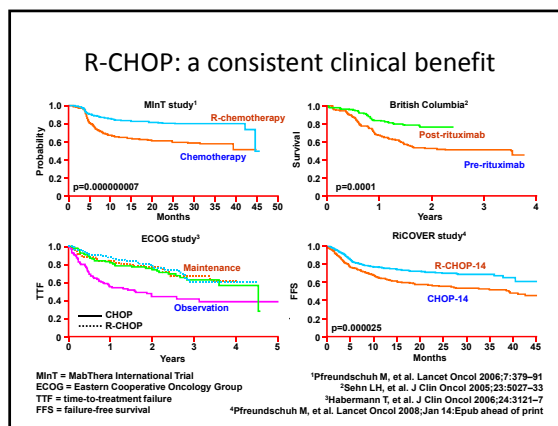
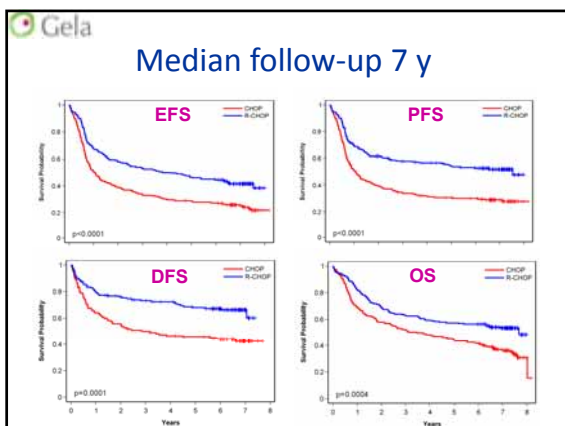
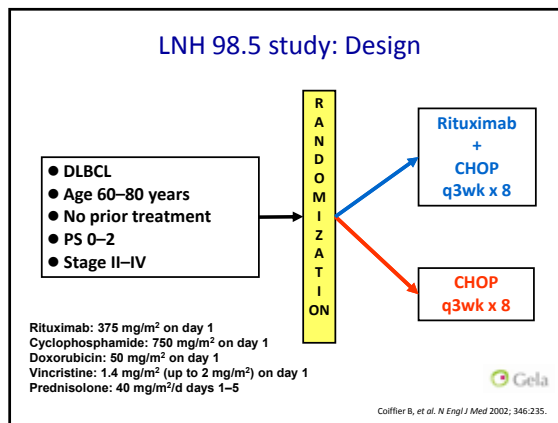
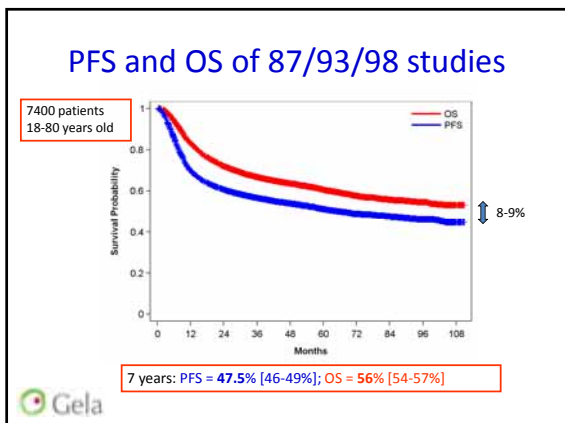
Rituximab (375 mg/m<sup>2</sup>)

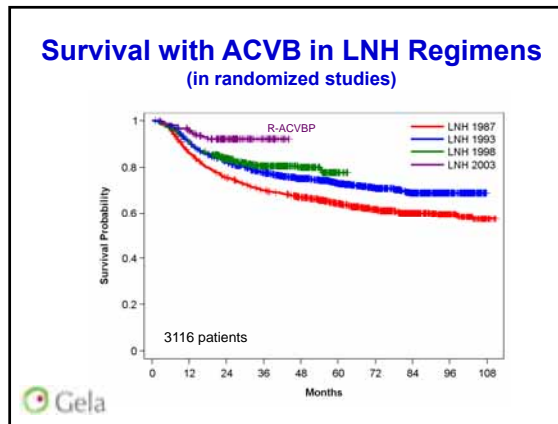
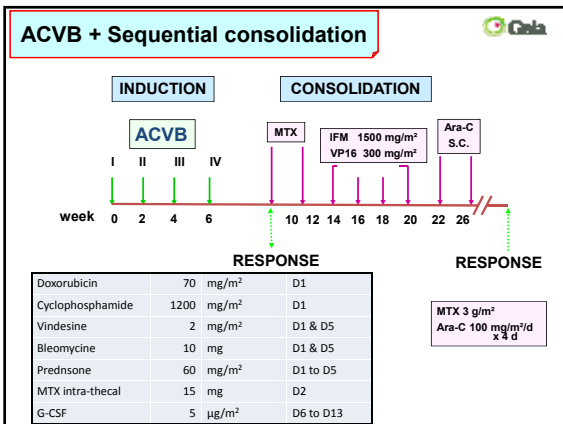
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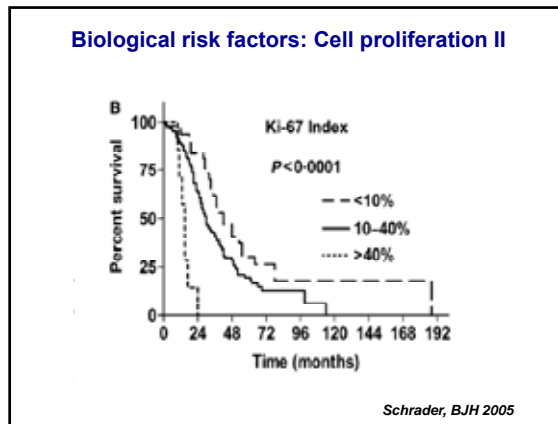
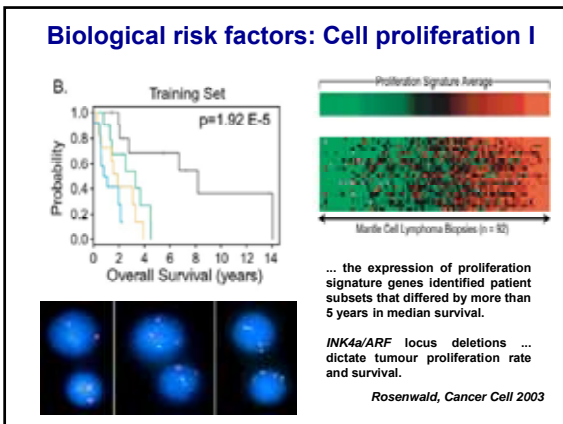


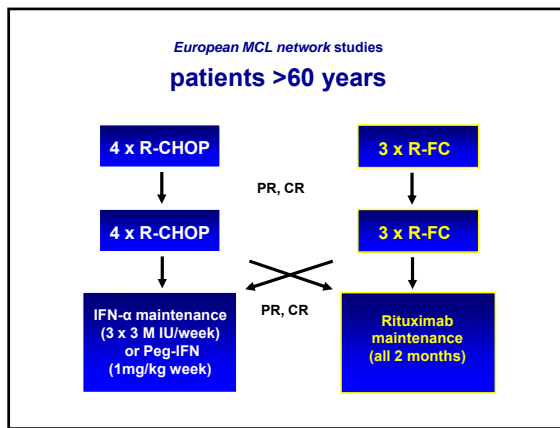
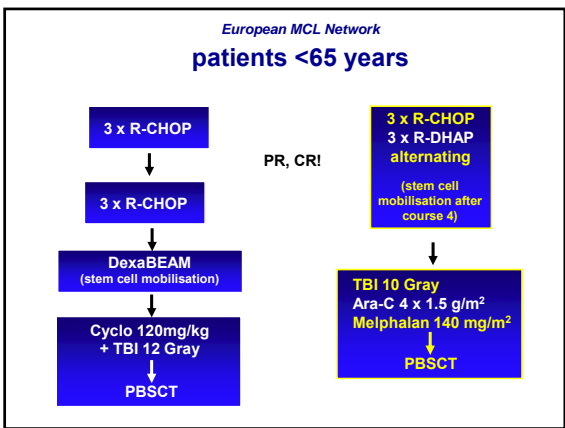
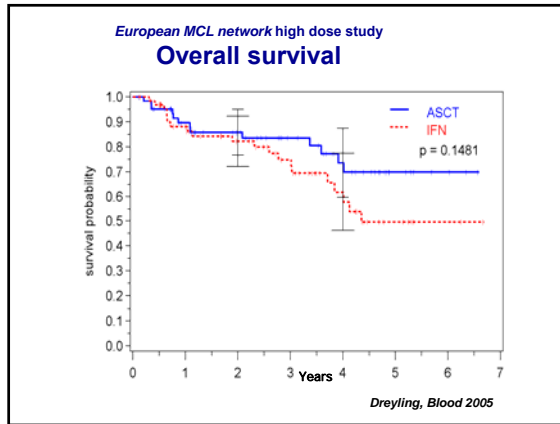
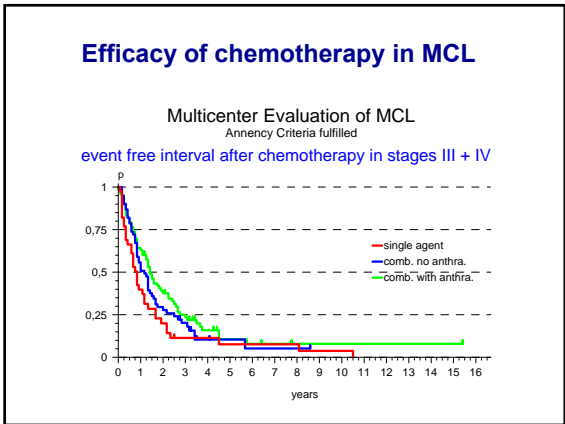


## Mantle cell lymphoma

### Mantle cell lymphoma (MCL)

- Morphology:** small to intermediate size lymphoid cells with irregular, cleaved nuclei, cave: round cell, blastoid and pleomorphic variants
- Immunophenotype:** sig+, I > k, CD19/20/22+, CD5+, CD10-, CD23-, CD11c-, HLA-DR++, CD43+
- Molecular/cytogenetics:** t(11;14)(q13;q32); overexpression of *cyclin D1*
- Clinical outcome:** predominantly elderly, male patients, extranodal involvement, late stage, poor outcome





### Follicular lymphoma. Rare localization

#### Primary gastro-intestinal follicular lymphoma

Rare: < 7% primary GI lymphomas  
Adult median age 56yrs\* F>M  
Small intestine > colon, stomach  
(unifocal lesion) (multifocal)  
lymphomatous polyposis possible  
Histology: FL grade 1, IgH/BCL2 reagent 80%  
IgA+ CD20+ CD10+ Bcl6+ Bcl2+ integrin α4β7+  
clinical course indolent, relapses GI, rarely outside  
origin: local Ag responsive B-cell\*\*

Duodenal FL

MCL

Diff. Dg:  
- mantle cell lymphoma (lymphomatous polyposis)  
CD20+ CD10- CD5+ cyclinD1+ IgH/BCL1 Reagent  
- MALT lymphoma  
CD20+ CD10- BCL6- CD5- cyclin D1- t(11;18) API2/MALT1

\* Damaj G et al Ann Oncol 2003 GELA study: 25 cases  
\*\* Bende R Am J Pathol 2003; 162:105