



Primary GI lymphoma

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CASE REPORT

**In march 2011, a 45 year-old-man was admitted for
gastric pain**

He is from Egypt

Hepatitis C virus status : negative

**He has no history of smoking or alcohol or drug
abuse**

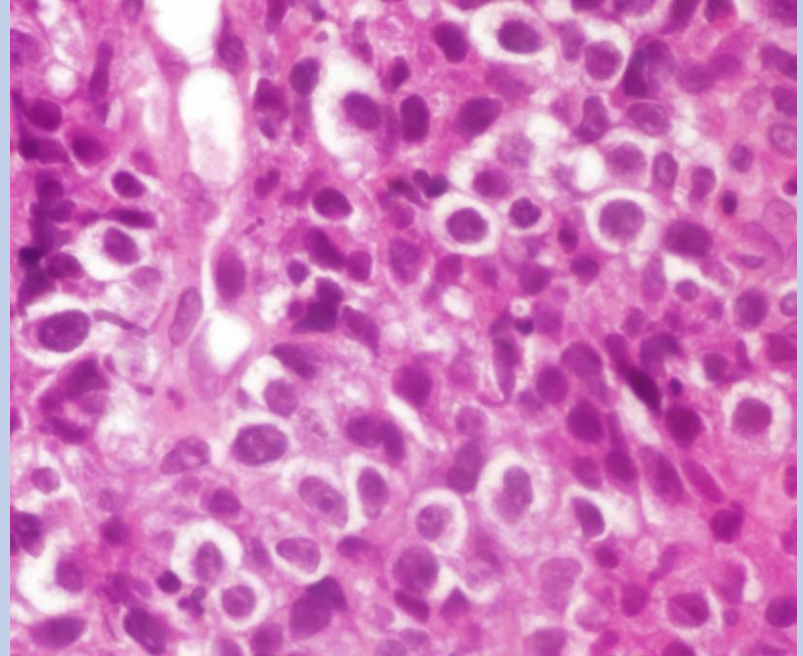
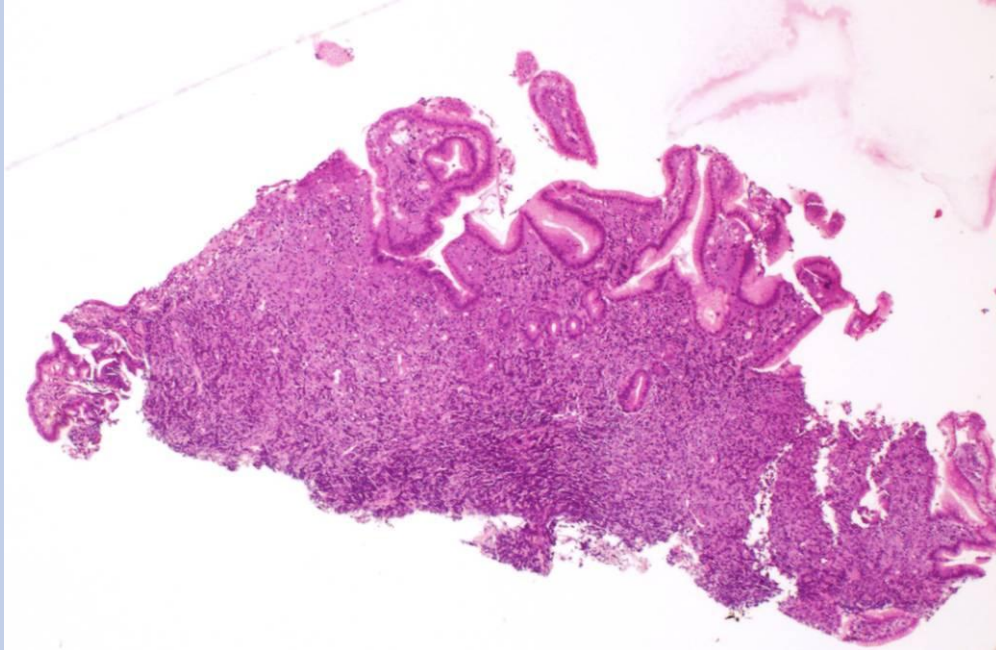
GASTROSCOPY

Massive ulcer in the antral wall (3cm)



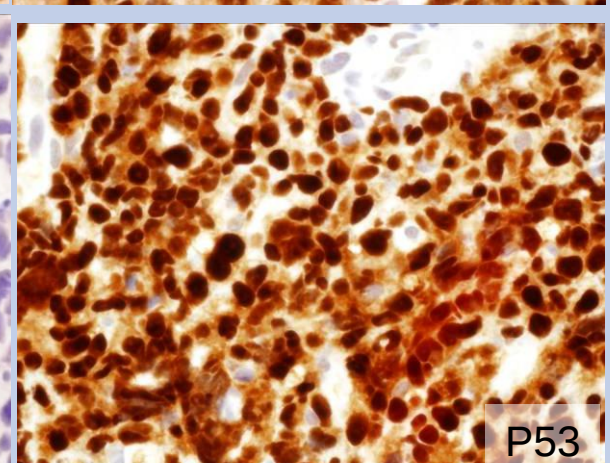
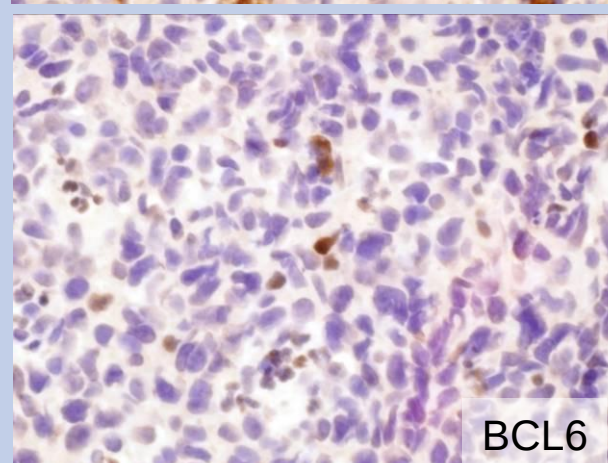
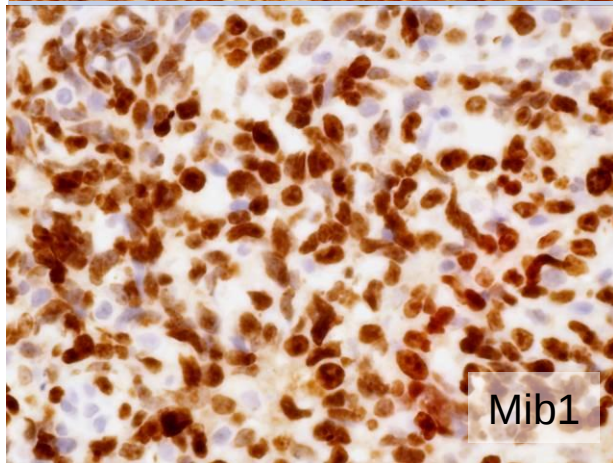
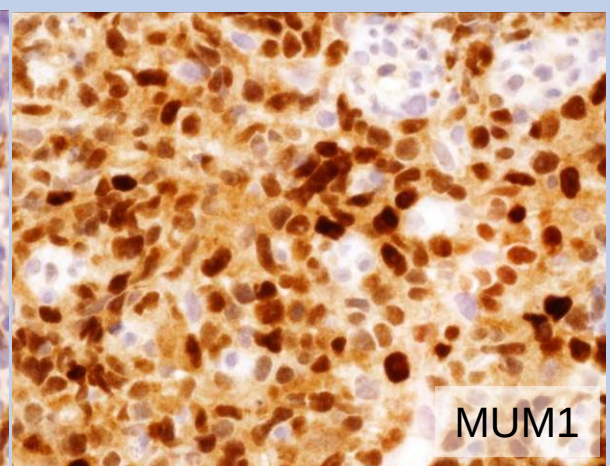
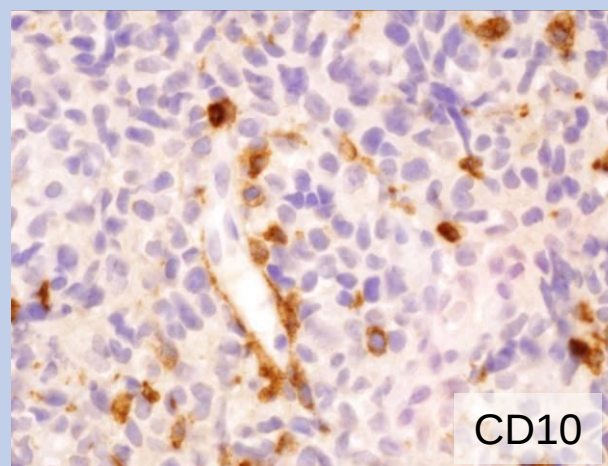
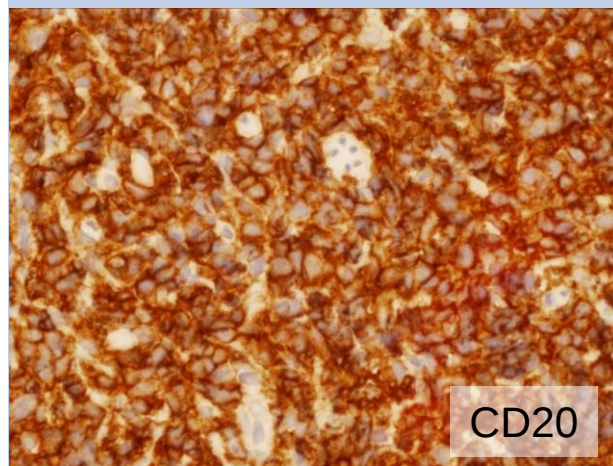
No hemorrhagea

Biopsy



**MALT lymphoma with 30% of large cells
associated to *Helicobacter Pylori***

Biopsy



non-GC DLBCL : CD20+, CD5-, CD10-, BCL2-, BCL6-, MUM1+, Mib1 90%, P53+ 100%

The diagnosis is a Primary GI lymphoma

What has to be done to take a therapeutic decision?

- **Histology** : To decide between a MALT lymphoma or transformed MALT lymphoma considered as a diffuse large B cell lymphoma
- **To stage** the disease

HISTOLOGY

- **non-GC MALT lymphoma with 30% of large cells :
CD20+, CD5-, CD10-, BCL2-, BCL6-, MUM1+, Mib1 90%,
P53+ 100%**
- **No precise guideline for histological transformation**
 - % of large cells
 - Ki67
 - p53 immunostaining
 - LDH level

HISTOLOGY

- non-GC MALT lymphoma with 30% of large cells :
CD20+, CD5-, CD10-, BCL2-, BCL6-, MUM1+, Mib1 90%,
P53+ 100%
- No precise guideline for histological transformation
 - % of large cells = 30%
 - Ki67 = 90%
 - p53 immunostaining = 100%
 - LDH level = Normal

➔ Transformed MALT lymphoma = diffuse large B-cell lymphoma

FINAL DIAGNOSIS

After staging

Primary gastric diffuse large B cell lymphoma

Associated to *Helicobacter Pylori*

Ann Arbor Stage : IE

Performance Status = 1

LDH Level = Normal

aalPI = 0

THERAPEUTIC OPTIONS

- **Surgery**
- **Radiation therapy**
- **Eradication of *H. Pylori***
- **Immunotherapy alone**
- **Immunochemotherapy**

THERAPEUTIC OPTIONS

- Surgery **NO** → **conservative treatment**
except in case of bleeding or perforation
- Radiation therapy **NO**
- Eradication of *H. Pylori* **YES**
- Immunotherapy alone **NO**
- R-CHOP **YES**

TREATMENT

Primary gastric DLBCL dependant to *Hp*?

- **No biomarker to prove it**

✓ **Eradication of *H. Pylori***

Triple therapy : IPP

Clarithromycine	}	10 days
Amoxicilline		

RESULT

After 4 weeks

- Persistence of epigastric pain
- Gastroscopy at 4 weeks : Local **progression**
- Biopsy : Persistence of DLBCL - ki67 = 100%
- CT scan : Stage IE
- LDH level : normal
- aalPI = 0

SECOND LINE TREATMENT : RCHOP

- R-CHOP 21 : 6 cycles**

Response to treatment

- After 3 cycles: CR (cheson 2007)**
- After 6 cycles : CR (cheson 2007)**

Follow- up at 1 year : CR

Primary GI lymphoma

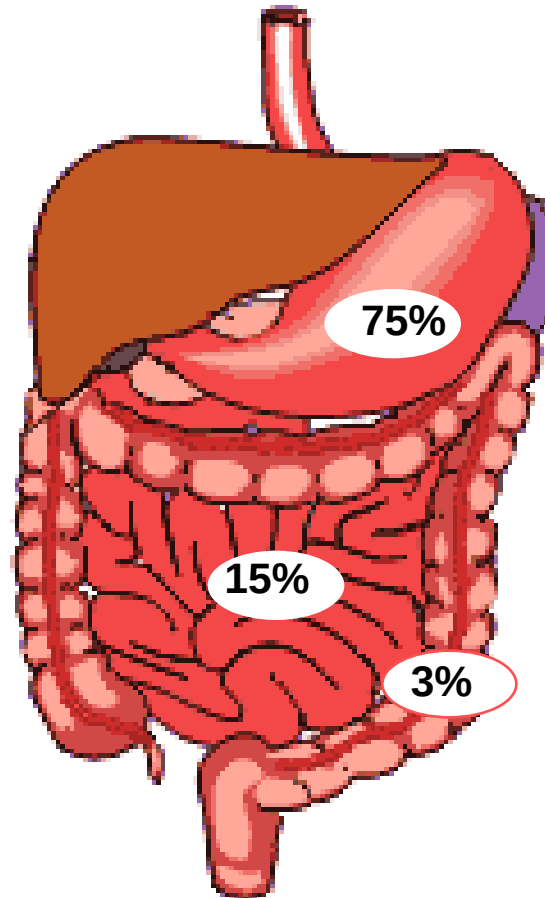
Discussion

Primary GI lymphoma

- Rare : **3%** of all GI cancers
- Most of GI lymphoma are located to the stomach

Table 1. Sites of Origin in Primary GI Lymphoma

Primary Site	No. of Patients	%
Stomach	277	74.7
Small bowel	32	8.6
Ileocecal region	26	7.0
Involvement of more than one GI site	24	6.5
Other sites	12	3.2
Duodenum	3	
Colon, diffuse	3	
Rectum	6	
All	371	100



Large diversity of Lymphoma subtypes in GI

Frequency %

G Gastric

I Intestin

Nodal site

MALT Lymphoma

38%_G - 10%_I

Follicular L.

22%

1.4%_G - 4%_I

others

6%

anaplastic T/null

2%

T-cell lymphoma

7%

0%_G - 25%_I

lymphoblastic

2%

Burkitt. L

1%

0%_G - 20%_I

Diffuse large B cell lymphoma

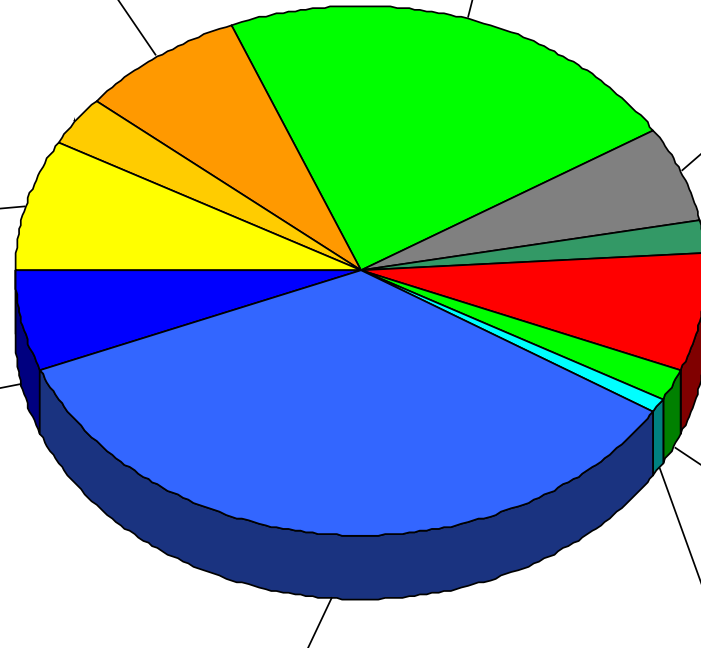
60%

small ly

8%

Mantle cell L.

**1%_G - 20%
(colon)**



STAGING

	Lymphoma	GI lymphoma
Mandatory	• physical exam • complete blood counts • basic biochemical studies (renal and liver function, LDH and β2MG, serum protein immunofixation) • HIV, HCV and HBV serology • CT of the chest, abdomen and pelvis	- GASTRIC : Gastroduodenal endoscopy with multiple biopsies taken from each region of the stomach, duodenum, gastro-esophageal junction and from any abnormal-appearing site; • H. pylori status must be evaluated in gastric L. - SMALL INTESTINE (IPSID – Immuno-Proliferative Small Intestinal Disease): Campylobacter Jejuni search in the tumor biopsy by PCR, immunohistochemistry or in situ hybridization may be performed. - LARGE INTESTINE : colonoscopy
Recommended	• bone marrow aspirate and biopsy	• If clinically indicated, head & neck MRI studies and other imaging are to be realized

Gastric MALT lymphoma

Endoscopic aspects



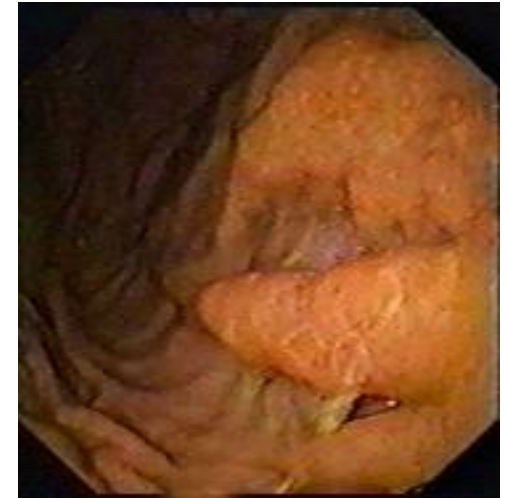
Pseudogastritis

30%



Ulcers

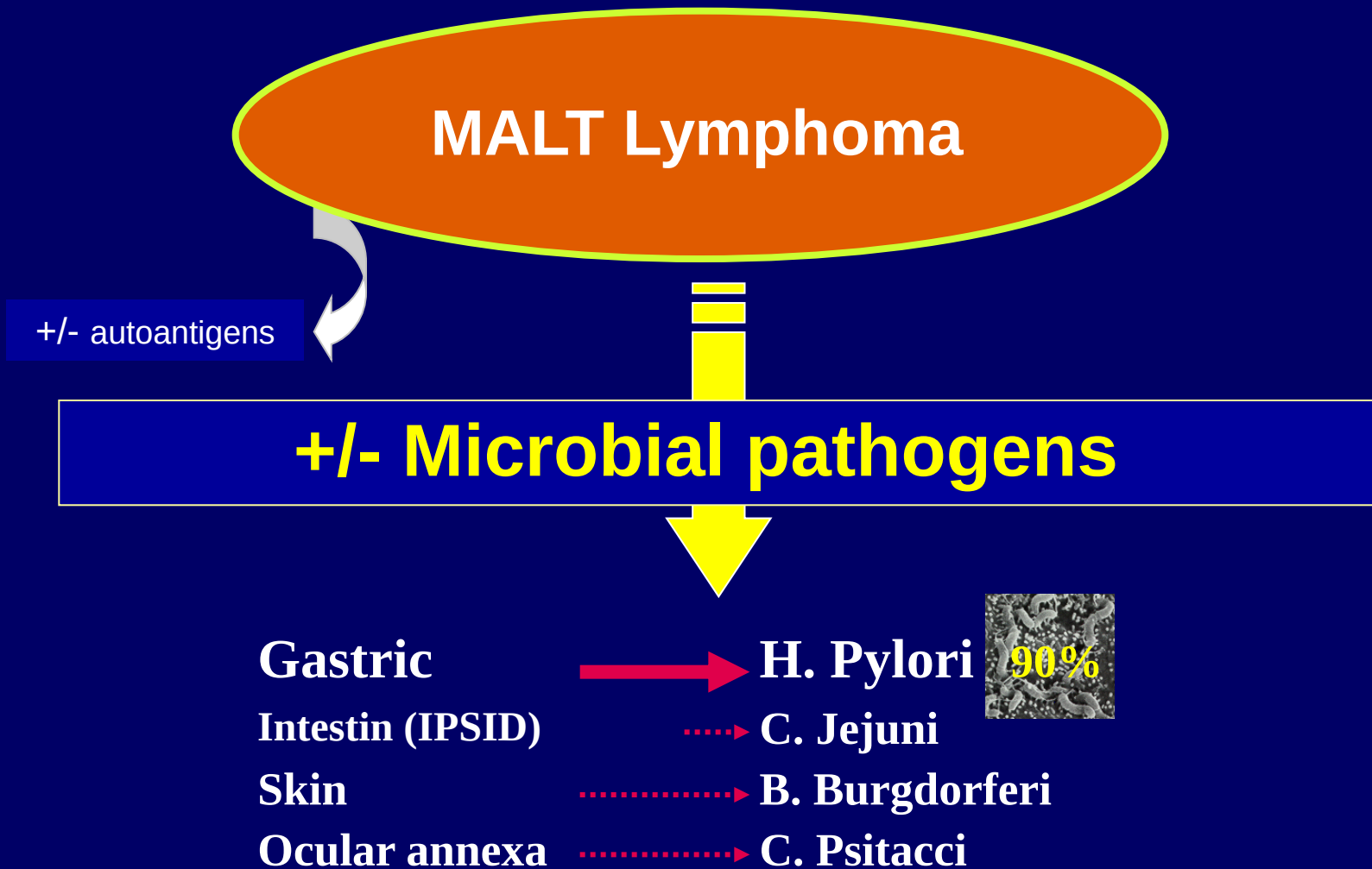
45%

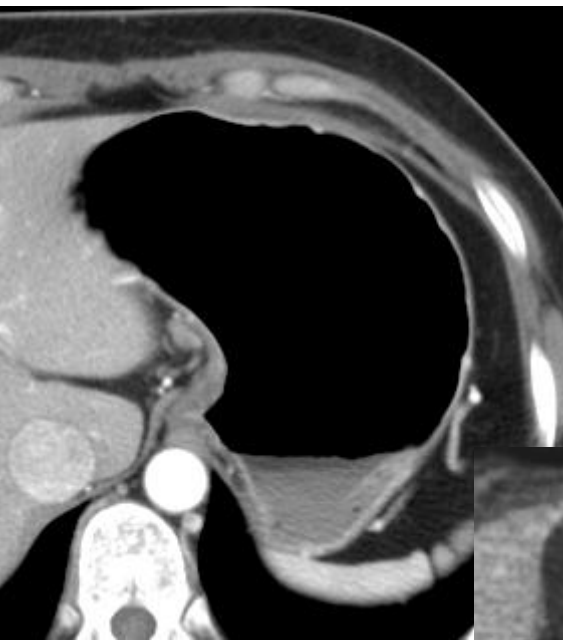


**Nodular
infiltration**

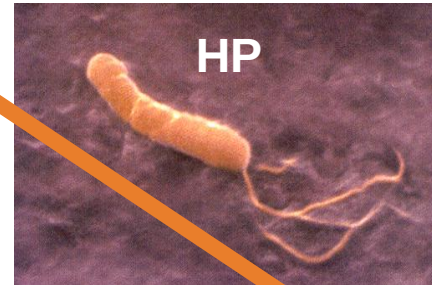
25%

PHYSIOPATHOLOGY : a chronic antigenic stimulation

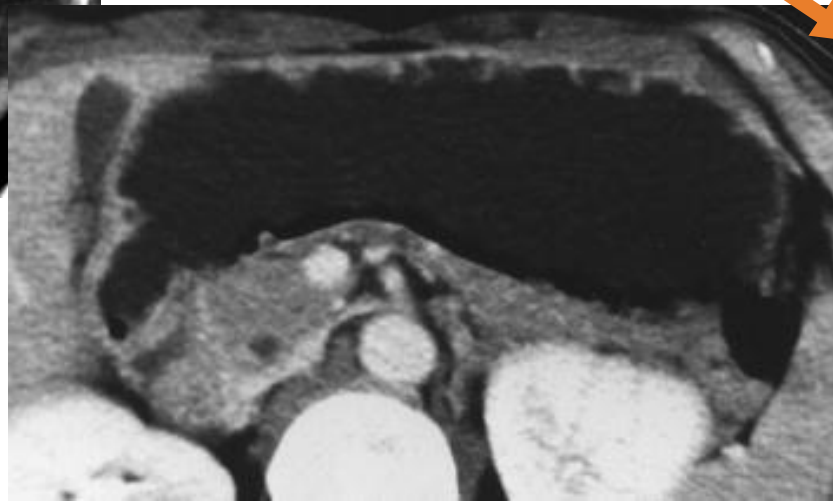




Normal stomach



E. De Kerviler – Saint-Louis Hospital, Paris



Chronic gastritis



MALT Lymphoma

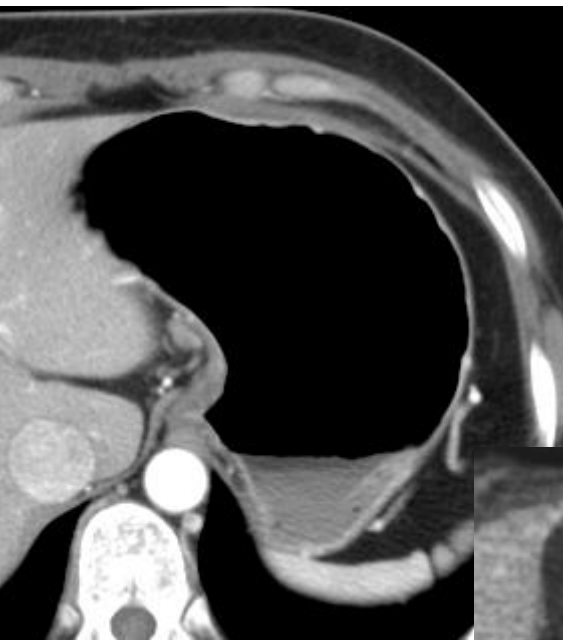
**+ additional factors:
host, environment, genetic**

t(11;18) API2-MALT1

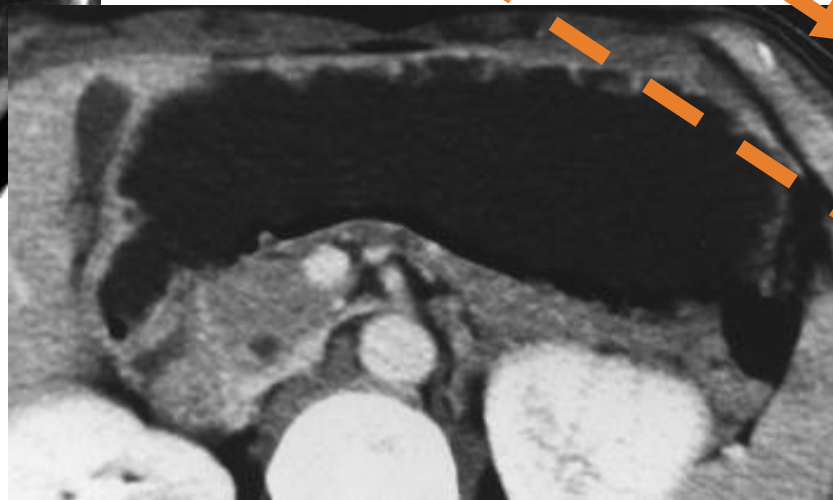
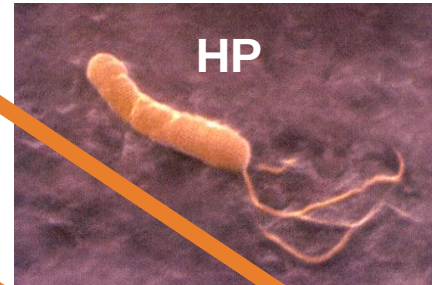
t(1,14) BCL10

t(14;18) Ig-MALT1





Normal stomach



Chronic gastric

MALT Lymphoma

**+ additional factors:
host, environment, genetic**

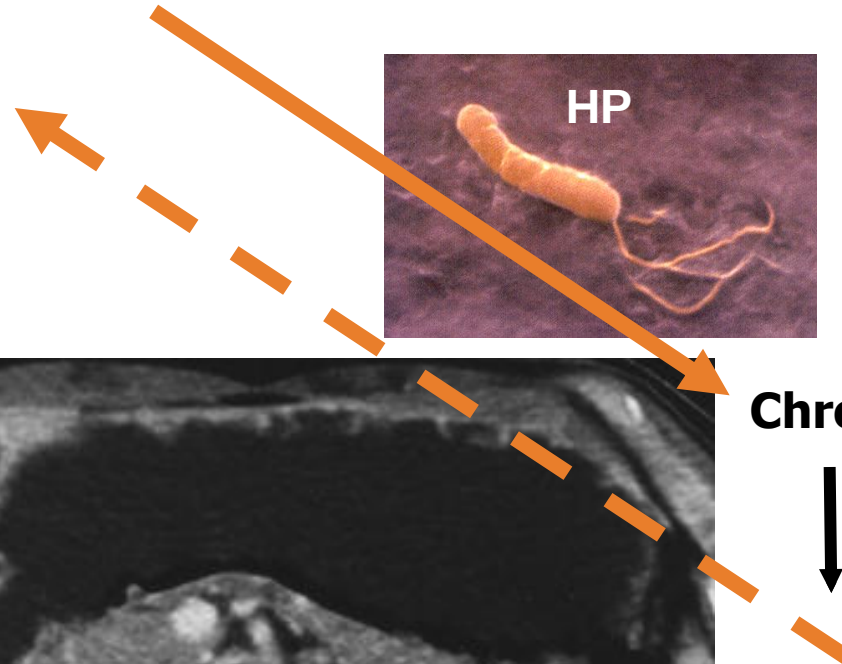
t(11;18) API2-MALT1

t(1,14) BCL10

t(14;18) Ig-MALT1

NFKB

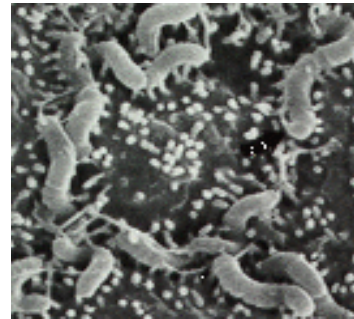
ATB



TREATMENT

Localised gastric MALT lymphoma **dependant** to *H. Pylori*

***Hp.* eradication**



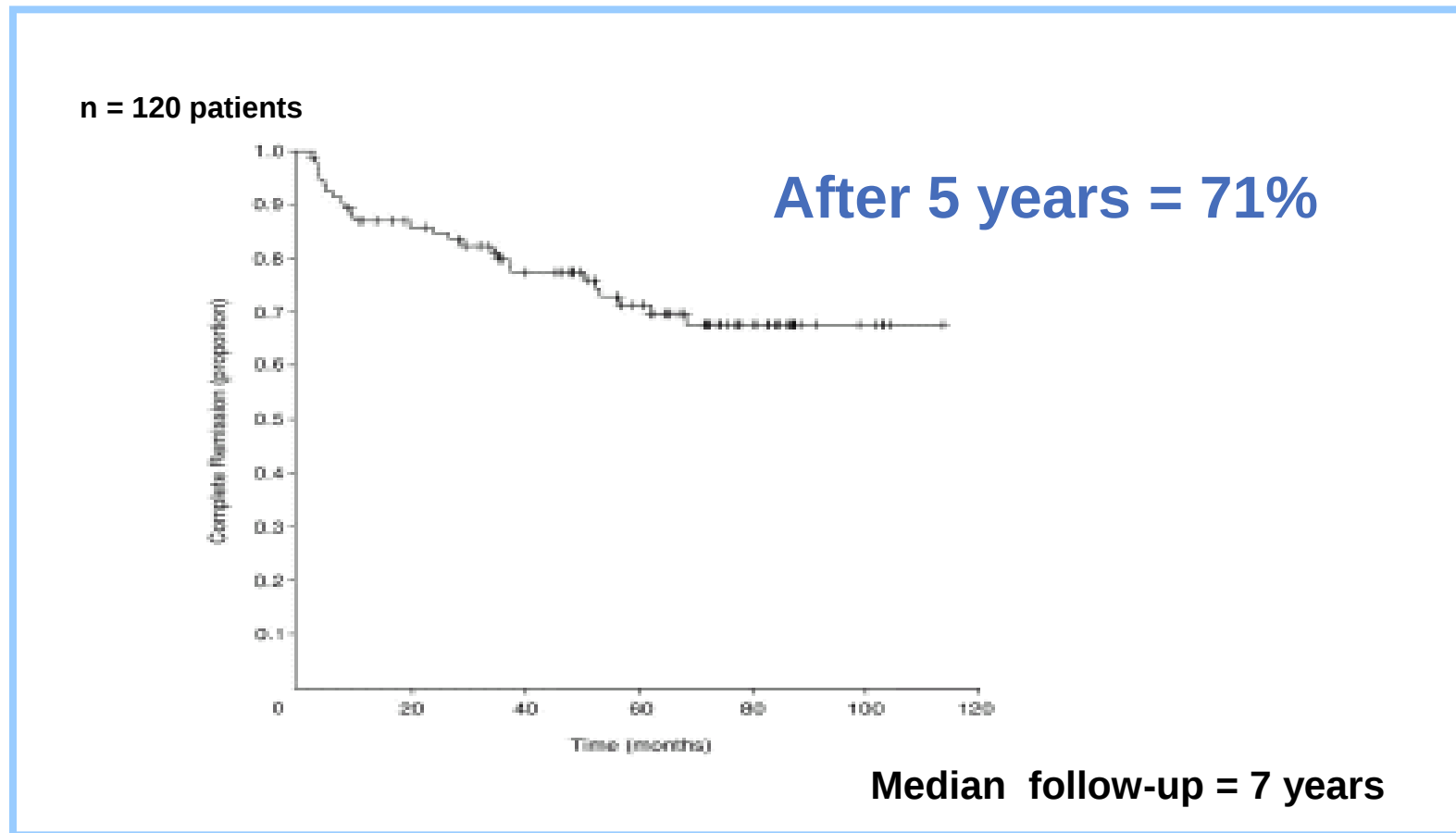
Lymphoma

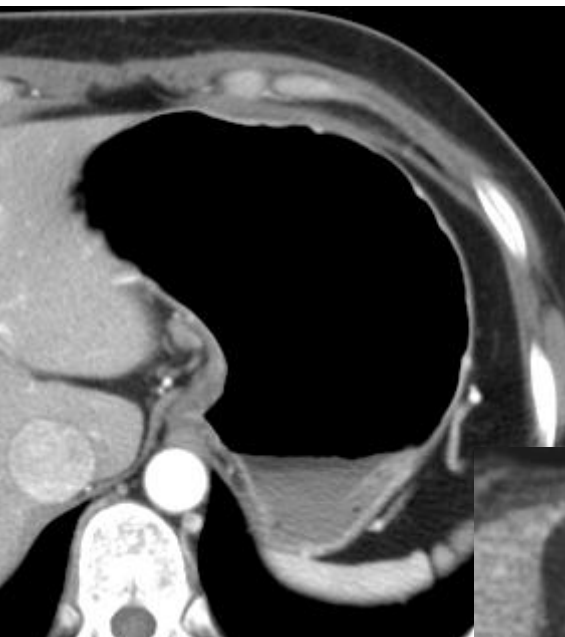
- **Complete response: 60% - 100%**
- **Response: 3 to 28 months !**
- **Resistance associated to t(11;18)**

Response to antibiotics and PPI in stage I gastric MALT lymphoma

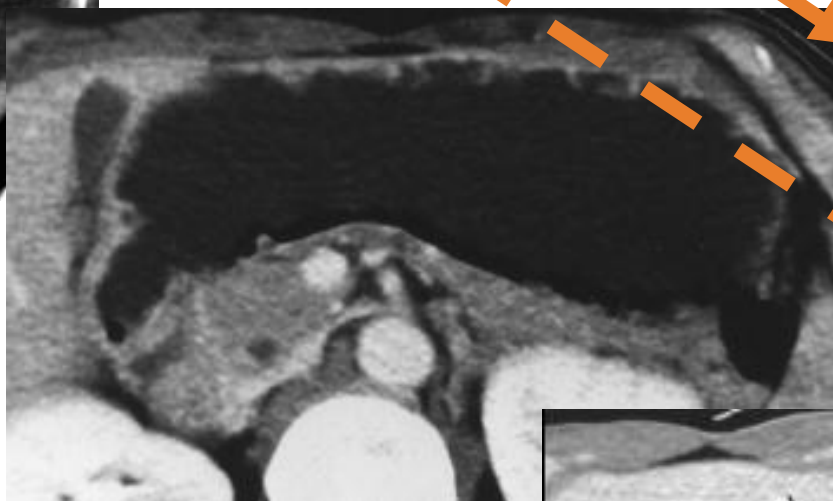
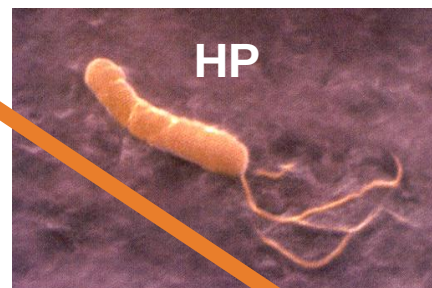
Reference	n	staging procedure	CR rate (%)	time to CR (mos.)	relapses (n)
Savio, 1996	12	CT	84	2-4	0
Pinotti, 1997	45	CT	67	3-18	2
Neubauer, 1997	50	CT±EUS	80	1-9	5
Nobre Leitao, 1998	17	CT+EUS	100	1-12	1
Steinbach, 1999	23	CT±EUS	56	3-45	0
Montalban, 2001	19	CT±EUS	95	2-19	0
Ruskone-Formestaux, 2001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

Duration of response after ATB



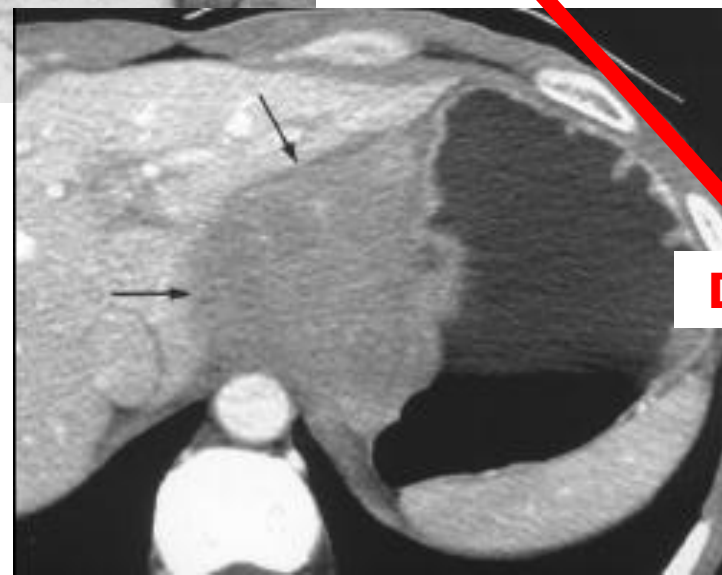


Normal stomach



Chronic gastric

MALT Lymphoma



DLBCL

p53 deletion,
p16 deletion

Gastric DLBCL Dependant to *Hp.* ?

10 pts with Gastric DLBCL - Stage IE or IIE

PPI-amoxicillin-clarithromycin for 7 days

Case N°	Age /sex	Tumor Location	Stage	<i>Hp.</i> Treatment Nber of eradication	Response To lymphoma	Time to CR (mo)
1	67/M	Antrum	IE	2	CR	1
2	65/F	Antrum	IIE2	1	CR	2
3	60/M	Corpus	IE	1	CR	2
4	56/F	Antrum	IE	1	CR	2
5	44/M	Antrum	IE	1	CR	2
6	74/F	Corpus	IIE1	1	Residual MALT	2
7	35/M	Antrum	IE	2	CR	1
8	34/F	Corpus	IIE2	2	CR	4
9	75/M	Antrum	IIE1	1	CR	3
10	73/F	Corpus	IIE1	1	CR	2

Response to antibiotics and PPI in Gastric **DLBCL** dependant to *Hp*.

- After a median follow up of **6 years** (range: 2-11 years) all patients were alive and remained in complete remission
 - Primary gastric DLBCL may regress with *Hp* eradication as the sole therapy
- Consequently, *Hp* eradication could be proposed as the first step of the treatment in patients in good general condition with DLBCL infected by *H pylori* **when these patients can be closely monitored**
- Biomarkers associated with **antigen dependance** are needed to select patients with gastric DLBCL dependant to *Hp*.

H. Pylori eradication in 2012 ?

**Triple therapy :
PPI – Clarithromycine – amoxicilline
7 days**



Resistance in 15-20% of the cases

Guidelines (SFGE 2011)

Antibiogram

Options	Tri-thérapie	Associations	Durée du traitement
1.	Antibiogram clarithomycin - S	IPP – clarithromycin - amoxicilline	14 days
	Antibiogram clarithomycin - R	IPP – Levofloxacin - amoxicilline	14 days
2.	Sequential traitement	IPP-amoxicilline 5j IPP-clarithromycin – amoxcilline 5j	10 days
3.	Nouveau traitement	IPP- PYLERA (sel de bismuth + tetracyclin + Metronidazol)	10 days

Oméprazole	20 mg matin et soir	Clarithromycine	500 mg x 2 /jour
Lanzoprazole	30 mg matin et soir	Amoxicilline	1 g x 2 /jour
Pantoprazole	40 mg matin et soir	Métronidazole ou tinidazole	500 mg x 2 /jour
Esoméprazole	20 mg matin et soir		
Rabéprazole	20 mg matin et soir	Pylera	1 x 4 /jour

Localised gastric MALT lymphoma

non-Dependant to *Hp*

- Multiple therapeutic options
- Proved efficacy with non-randomized trials

- **Stage I and II**

- Radiation
- R-Chemotherapy
- Rituximab

- **Stage III and IV**

- R-Chemotherapy
- Rituximab

RT in localized gastric MALT lymphoma

Author	n	RT dose (Gy)	FFP
Schechter, 1998	17	28-43	100% at 2 yr
Tsang, 2001	9	20-30	100% at 5 yr
Yahalom, 2002	51	30 median	89% at 4 yr
Hitchcock, 2002	9	34 median	78% (100% local)
Goda JS, 2010	25	25-30	79% at 5 yr

Alkylant in monotherapy

(cyclophosphamide or chlorambucil)

- 24 patients, 17 stage I and 7 stage IV
- Cyclophosphamide or Chlorambucil for 8-24 mos.
- 100% ORR (75% CR)
- 5-year EFS: 50%
- 5-year OS: 75%
- 5 relapses at initial sites (1 with transformation)

Rituximab activity in MALT lymphoma

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

<i>response</i>	<i>n</i>	<i>%</i>		
			<i>No prior chemotherapy</i>	<i>Prior chemotherapy</i>
ORR	25	73	ORR 87%	45%
SD	6	18	CR 48%	36%
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.

ORR 77% (95% C.I. 56%-91%)

CR 46% (95% C.I. 27%-66%)

- The t(11; 18) (q21; q21) was not a predictive marker of response

Martinelli et al, JCO 2005

IELSG-19

randomized trial

Control arm

Chlorambucil (6 mg/m² /d) weeks 1-6 // 9-10 // 13-14 // 17-18 // 21-22

Study arms

Chlorambucil (6 mg/m² /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/ m²) ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑

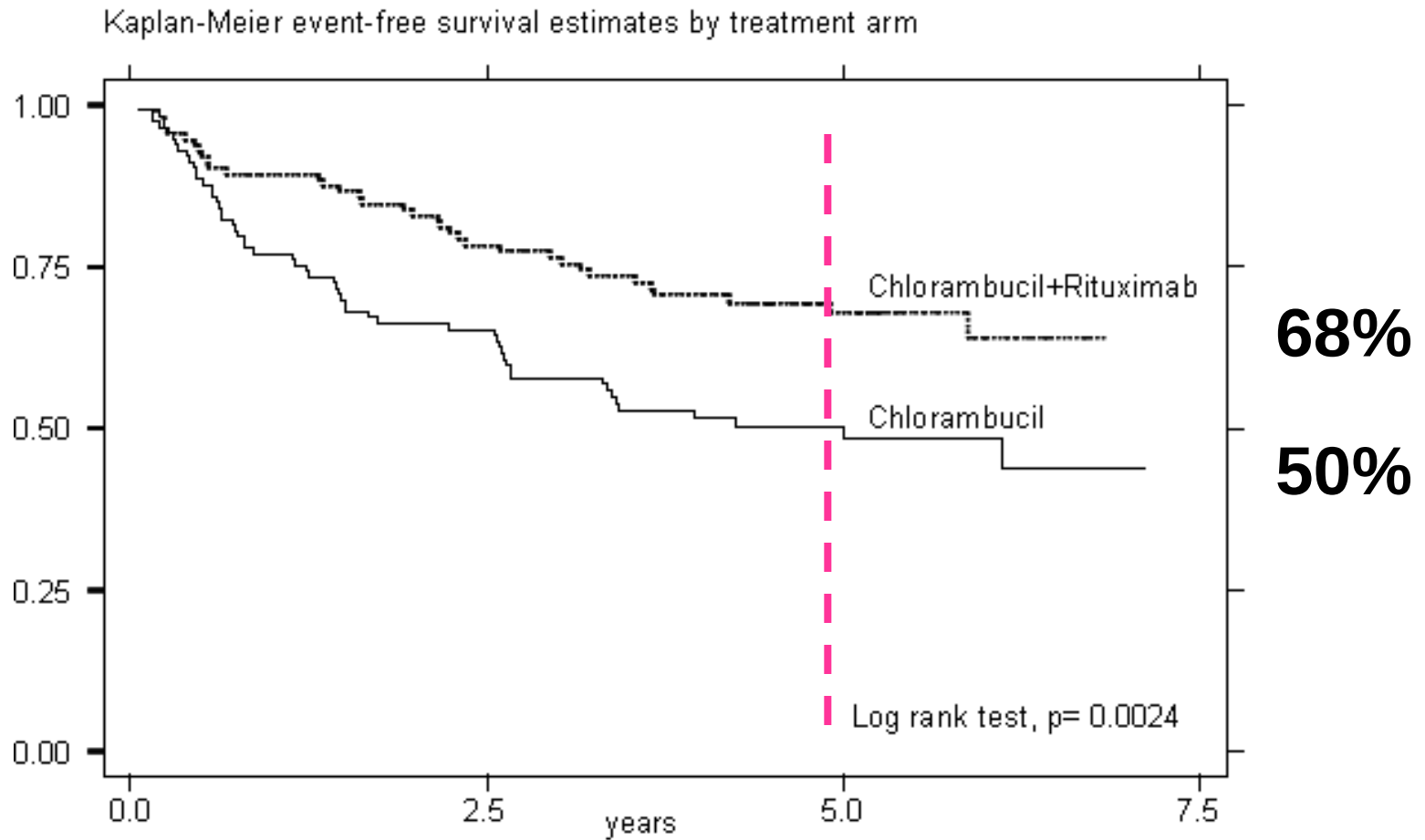
day 1 8 15 22 42 56 70 84 98 112 126 140 154

Rituximab (375 mg/ m²) ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑

Response

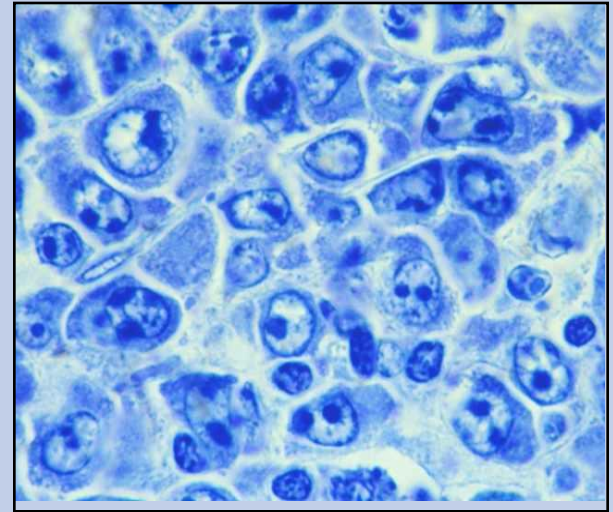
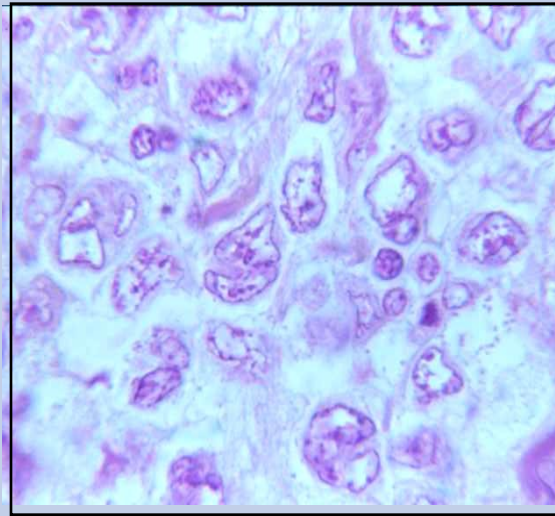
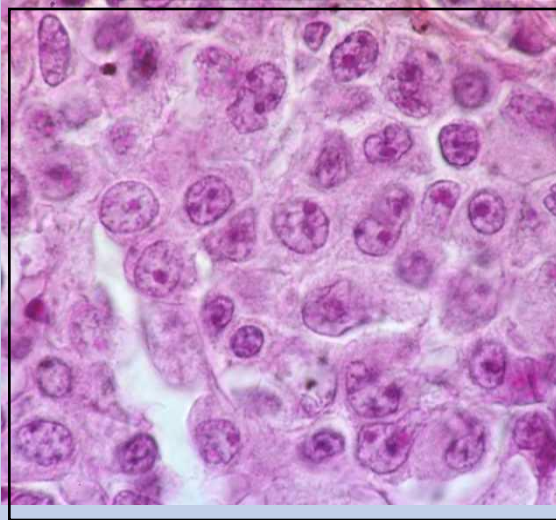
	All	Arm A <i>Chlorambucil</i>	Arm B <i>R-Chlorambucil</i>	p-value
n	227	113	114	
ORR	90%	87 %	94 %	
- CR	71 %	65 %	78 %	0.017
- PR	19 %	22 %	16 %	

Event Free Survival



Diffuse large B cell lymphoma

- 60% of primary GI lymphoma



Clinical presentation

- Aggressive
- B symptoms
- Bulky mass
- Necrosis
- Risk of perforation : **10%!**



Symptom†	Stomach (n = 277)		Small Bowel (n = 32)	
	No. of Patients	%	No. of Patients	%
Pain	216	78.0	24	75.0
Loss of appetite	131	47.3	13	40.6
Loss of weight‡	68	24.5	11	34.4
Bleeding	50	18.8	2	6.3
Vomiting	52	18.1	10	31.3
Night sweats	31	11.2	4	12.5
None	10	3.6	—	—
Diarrhea	10	3.6	4	12.5
Constipation	9	3.2	8	25.0
Fever	6	2.2	2	6.3
Perforation	5	1.8	3	9.4
Ileus	—	—	12	37.5
B symptoms (fever, night sweats)	33	11.9	5	15.6
Median time to diagnosis, days	93		135	

TREATMENT

One Goal

**To cure the patient
with the first line of treatment**

TREATMENT

- **No surgery**
- Biomarkers are needed to detect the *Hp.* - dependant gastric DLBCL

➤ **Standard R-CHOP**

3 weeks

8 cycles

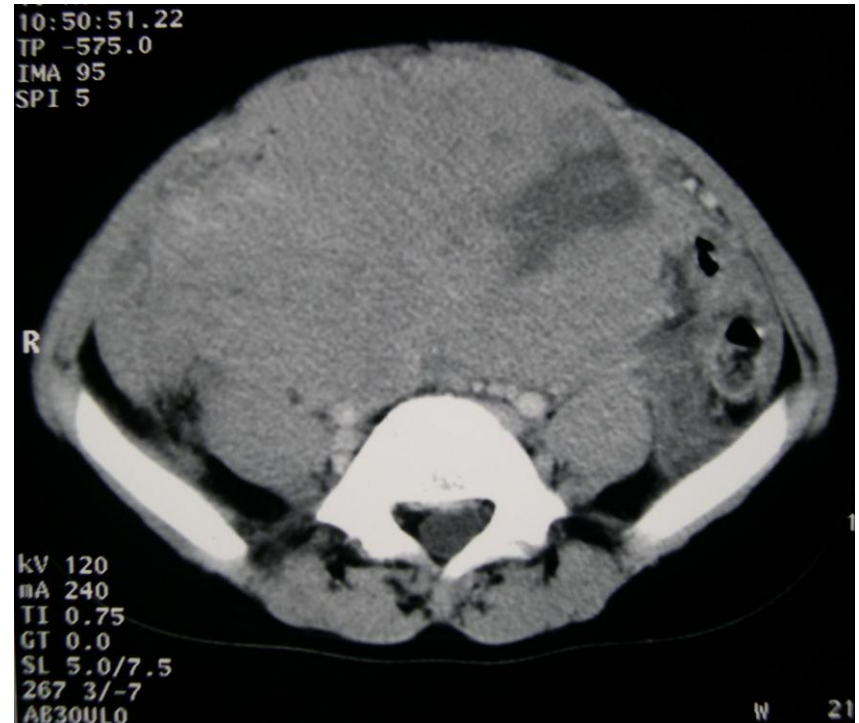
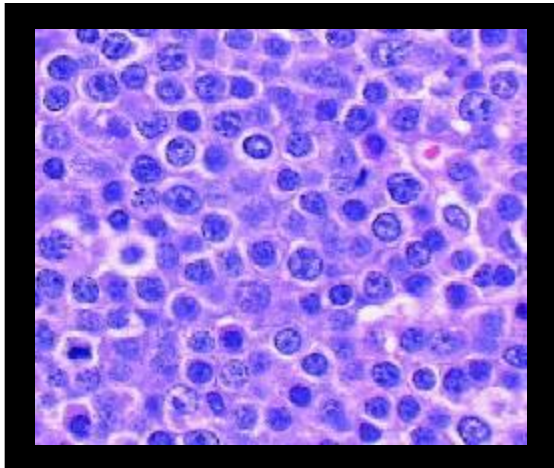
CHOP

Rituximab 375 mg/m²



Burkitt's lymphoma

- 1% of lymphoma
- 20% of (G)I lymphoma

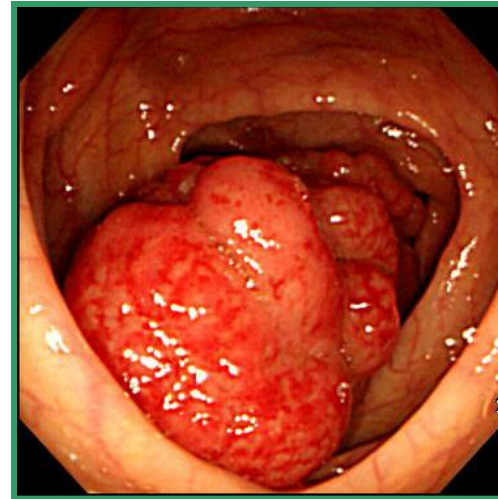
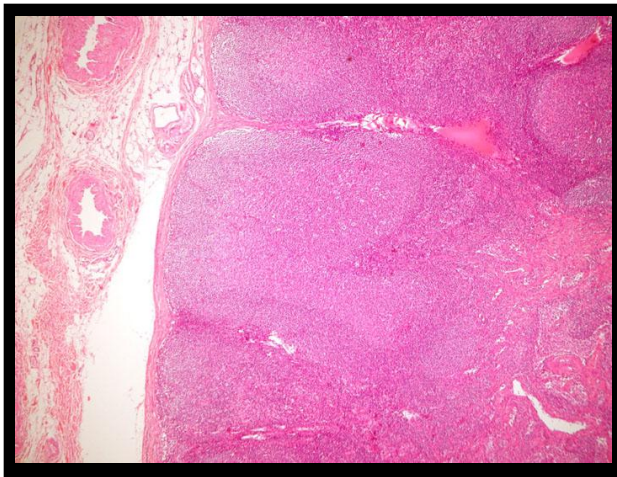


THERAPEUTIC EMERGENCY

➤ **CURE : 90%**

Mantle cell lymphoma

- 6% of lymphoma
- Disseminated disease – Usually not primary GI lymphoma
- Colic involvement



- Treatment :
 - Less than 65 : R- chemo based on Cytarabin + Intensive CT and ASCT
 - More than 65 : RCHOP + Rituximab Maintenance

Enteropathy-type intestinal T-cell lymphoma

- **Usually a prior history of gluten-sensitive enteropathy**
- **Multiple jejunal ulcers**
- **Gluten-free diet**
- **No good chemotherapy**
- **OS 1 and 5 years = 35% and 20% respectively**

Take home messages

- Rare
- Heterogeneous disease
- Histologic diversity
 - Biopsy and expert diagnosis are mandatory
- Clinical diversity
- Therapeutic diversity
 - Dependant or not-dependant to microbial pathogens
- No surgery!!!

MAINTENANCE

Is there a benefit to do more?

- NO benefit of intensification (aaIPI = 0)**
- NO benefit of rituximab maintenance**
- Other : Lenalidomide: in evaluation in patients more than 60 years old with at least 1 pronostic factor (LYSA : clinical trial REMARC)**