Gastrointestinal Lymphoma
MALT-lymphom

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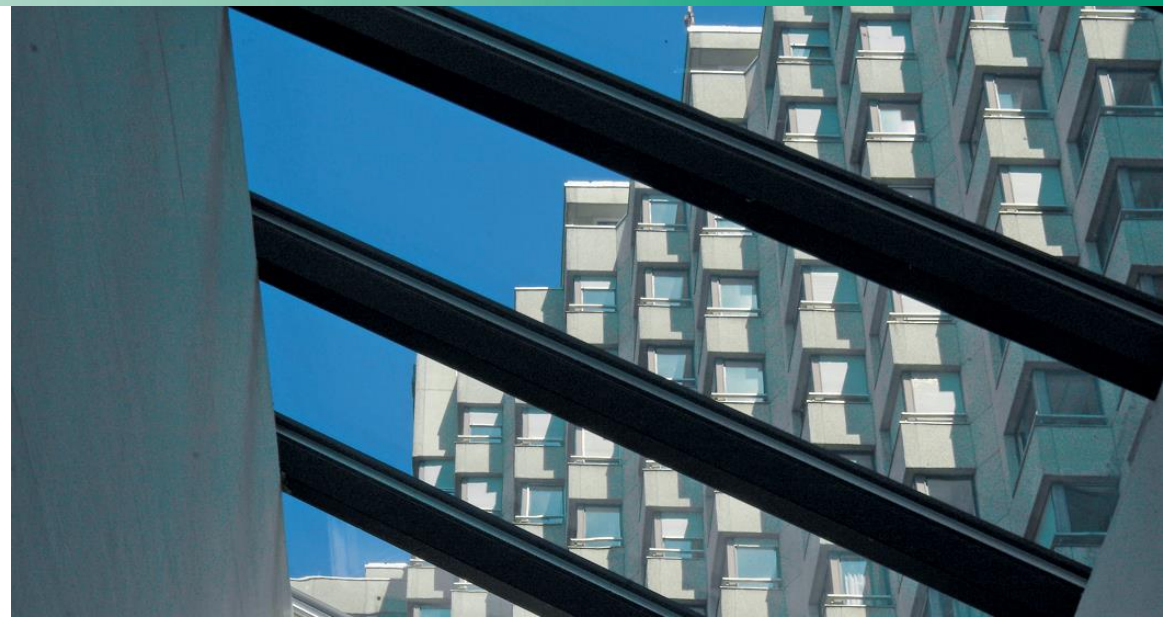

BC 07.04.2021
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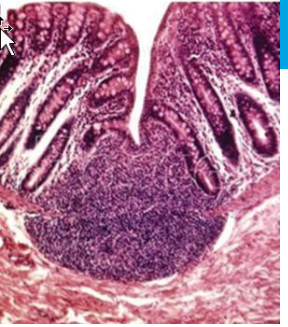
Universitätsklinik für Viszerale Chirurgie und Medizin

GENERAL ASPECTS LYMPHOMA
and
MALT



What means or is MALT ?

Mucosa-associated lymphoid tissue is:

Scattered along the mucosal linings in the human body

- ✓ Constitutes the most extensive component of human lymphoid tissue
- ✓ Protects the body from an enormous quantity and variety of antigens

MALT is understood to include:

- ✓ Gut-associated lymphatic tissue (GALT)
- ✓ Bronchial-associated lymphoid tissue (BALT)
- ✓ Nose-associated lymphoid tissue (NALT)
- ✓ Vulvovaginal-associated lymphoid tissue (VALT)

Examples in GI/digestive tract are

Tonsils, parotid glands, Peyer Patches, vermiform appendix …..

Does the stomach have MALT ?

Unlike the rest of intestinal tract

Stomach lacks MALT since

Low pH under physiological conditions

Prevents survival of lymphocytes

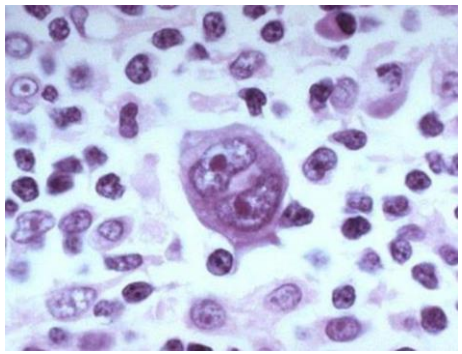
Lymphoma Classification (WHO 2001)

B-cell neoplasms
- **precursor**
- **mature**

T-cell and NK-cell neoplasms
- **precursor**
- **mature**

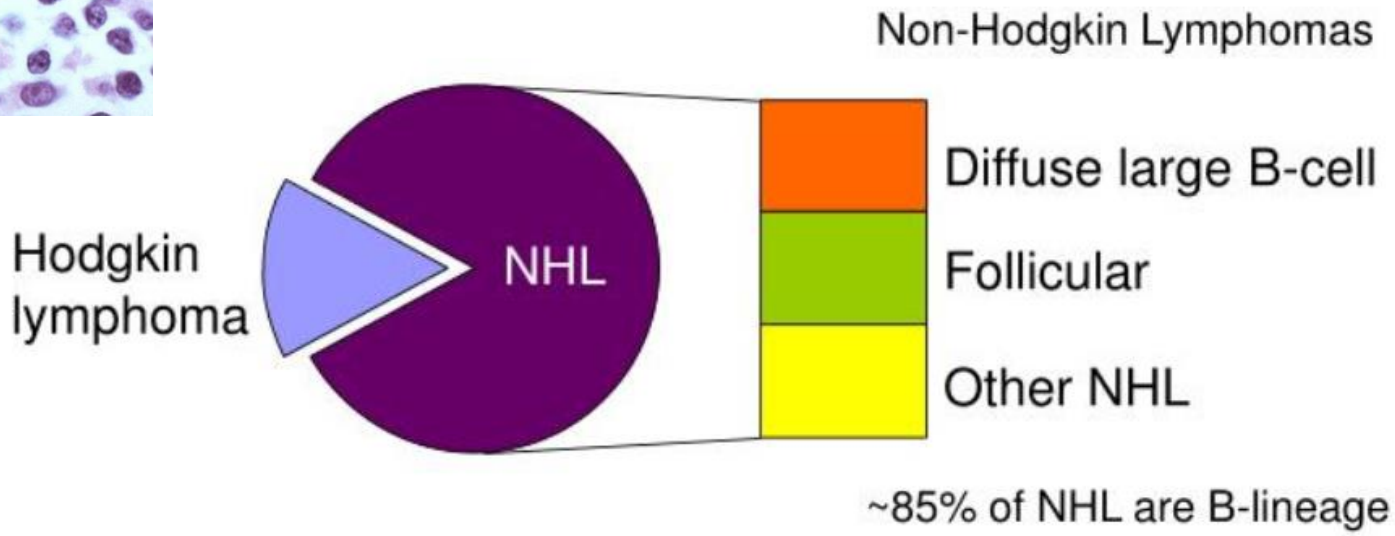
Hodgkin-Lymphoma

Non-Hodgkin-Lymphoma



This is a ?

Reed-Sternberg-Cell



Gastrointestinal lymphomas are classified into ?

➢ **B-cell**

Extranodal NHL of MALT

Immunoproliferative Small Intestinal Disease (IPSID)

Others: Diffuse Large B-Cell lymphoma (DLCBL)

Mantle-Cell-lymphoma

Burkitt-lymphoma

Follikular lymphoma

➢ **T-cell**

associated or not with enteropathy and/or atrophy

Epidemiology of primary gastrointestinal lymphoma (PGIL) – incidence, age, location ..?

➢**PGIL:**

very rare: <1% of all GI-tumors

0.5 – 1.3/100.000

age 50-70 at diagnosis

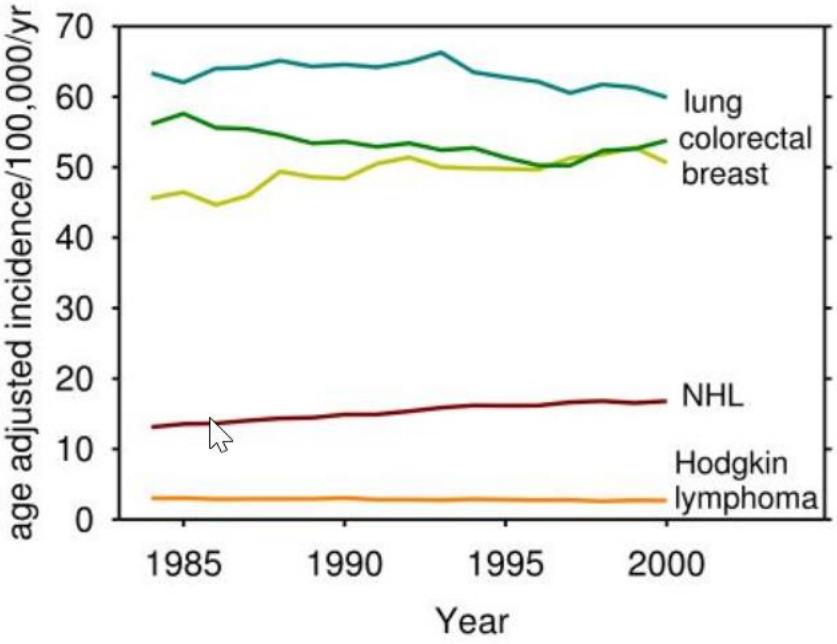
stomach > small intestine > colon in frequency

90% B-cell-derived

➢**MALT:**

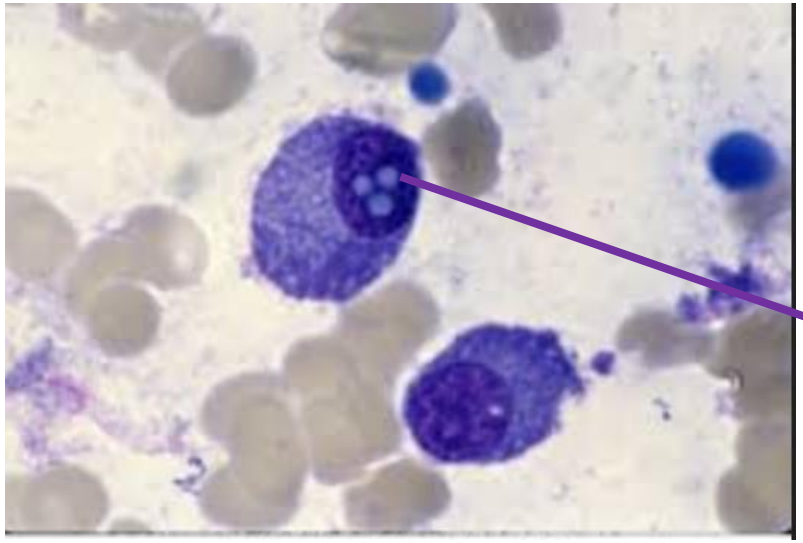
1:30.000 to 1:100.000 (USA)

Incidence Lymphomas in comparison with other cancers in US/Canada



Overall lymphoma 5th most frequently diagnosed cancer in both sexes
NHL rather increasing (Hodgkin Lymphoma stable)

Most difficult question of BC
For the expert: What are dutcher bodies ?

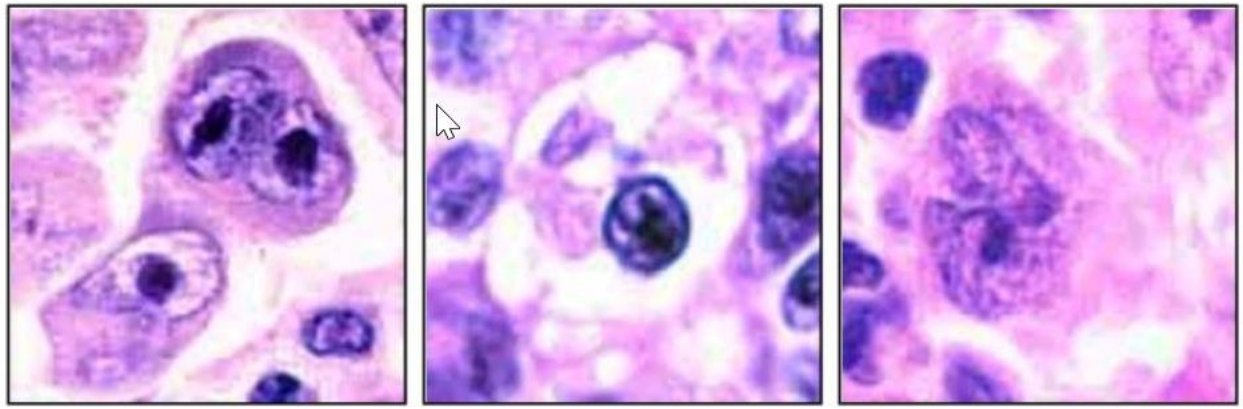


„intranuclear“ Immunoglobulins

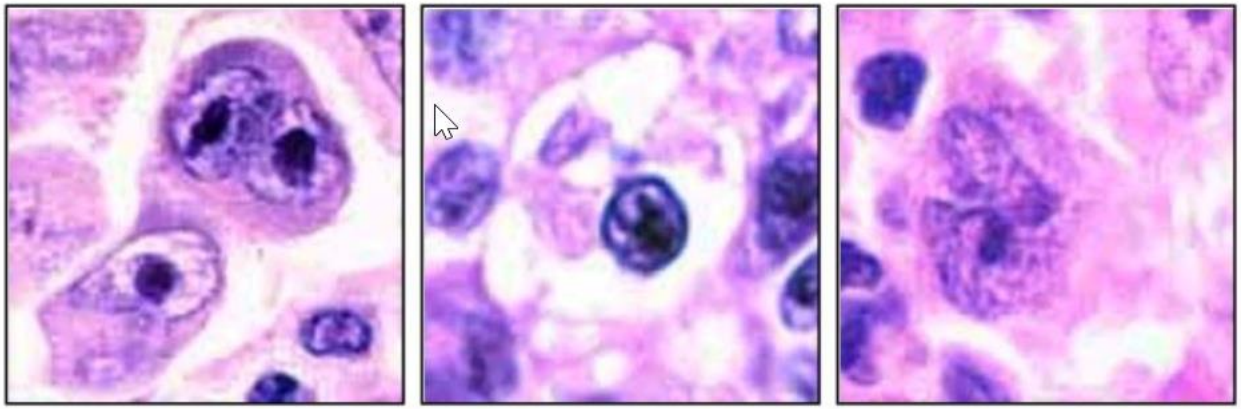
(in EM rather invaginating Into the nucleus but being Cytoplasmic)

Non-specific, non-pathognomonic
In/from plasma-cells – and high-volume production of antibodies.....

Out of league: Which is - what is a popcorn-cell ?



Out of league: Which is - what is a popcorn-cell ?



classic RS cell

(mixed cellularity)

lacunar cell

(nodular sclerosis)

popcorn cell

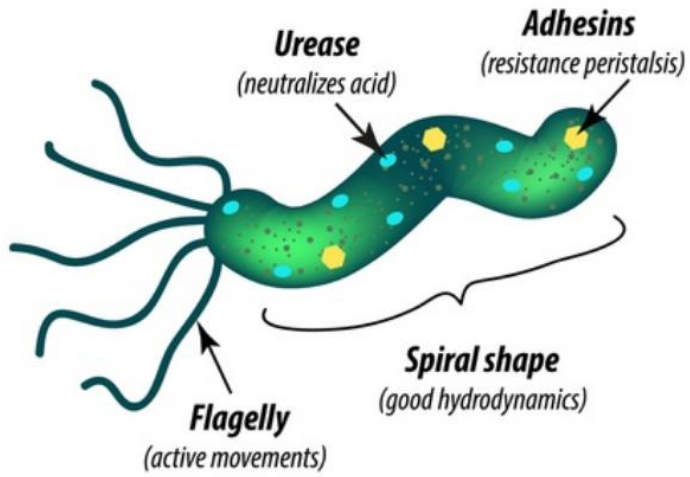
(lymphocyte predominance)

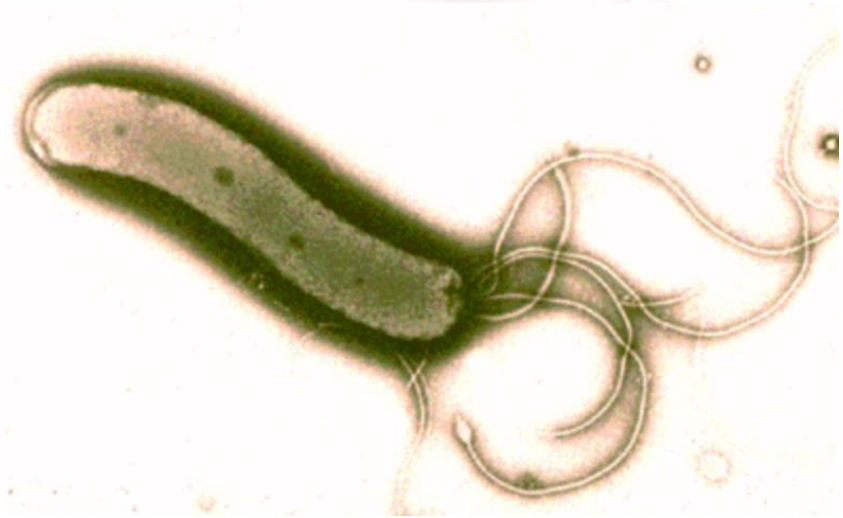
SPECIFIC PART
GASTRIC B-LYMPHOMA

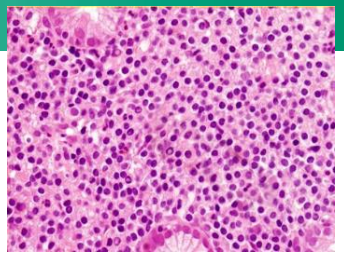
Extranodale NHL/PGIL -> marginal zone MALT (small B-cells, low malignancy)

Most easy question of BC:
What is the mainstay in treatment of gastric MALT ?

Failure to answer →







Marginal-zone-Lymphomas: WHO classification according to anatomic location

Splenic zone

Nodal marginal zone

Extranodal marginal zone

- **arises in organs normally lacking lymphoid tissue**
- **but have accumulated B-cells**
- **in response to either chronic infection or autoimmune process**

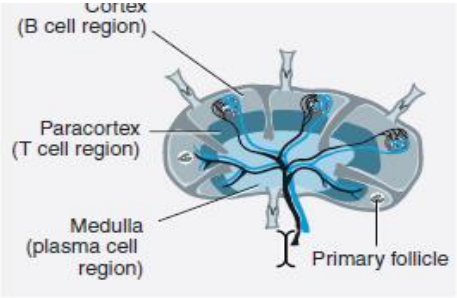
Gastric MALT =

most frequent primary lymphoma of GI-tract (about 50%)

85% of all gastrointestinal MALT lymphomas are located in stomach

Cook et al. 2017

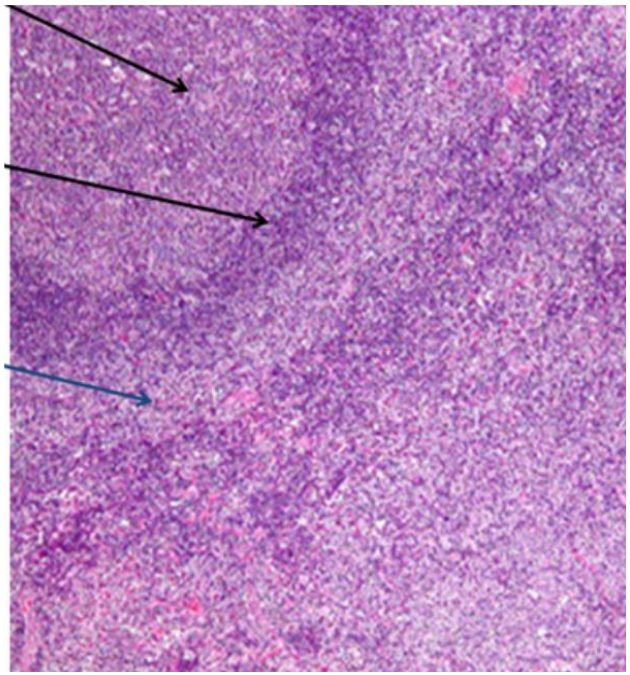
Lymph Follicle:
sort accordingly to nomenclature

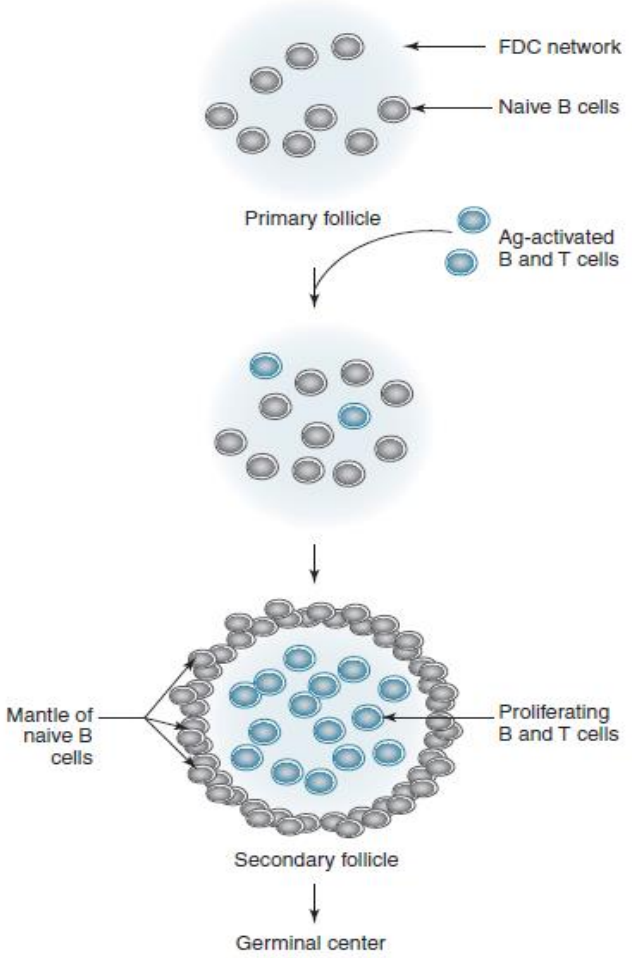


Germinal Centre

Benign Mantle Cells

Marginal Zone





Lymph Follicle: sort accordingly to nomenclature

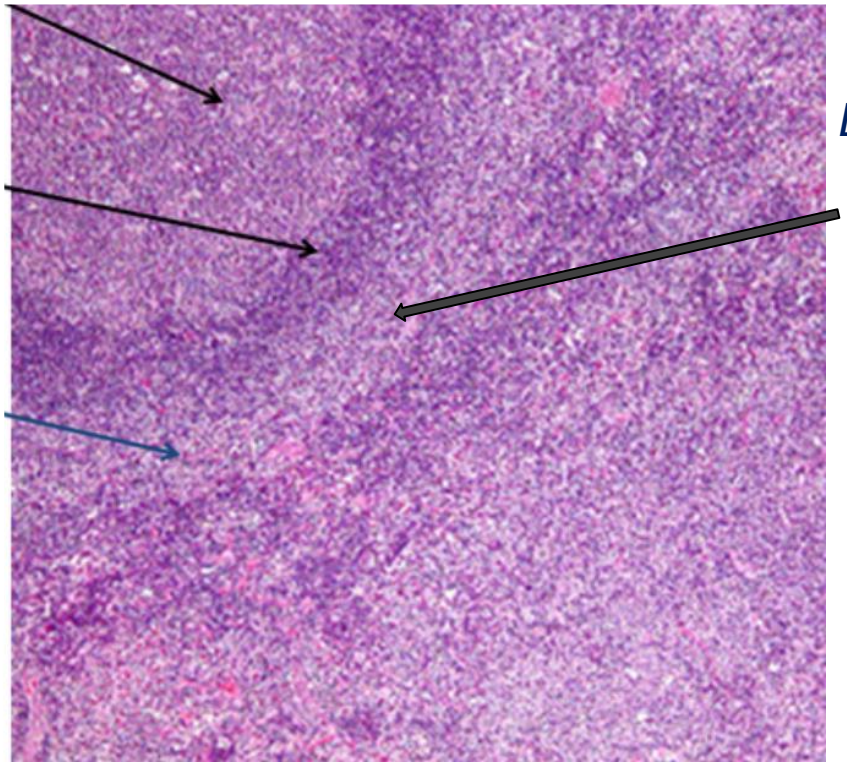
Germinal Centre

mature B cells proliferate, differentiate, and mutate their antibody genes

Benign Mantle Cells

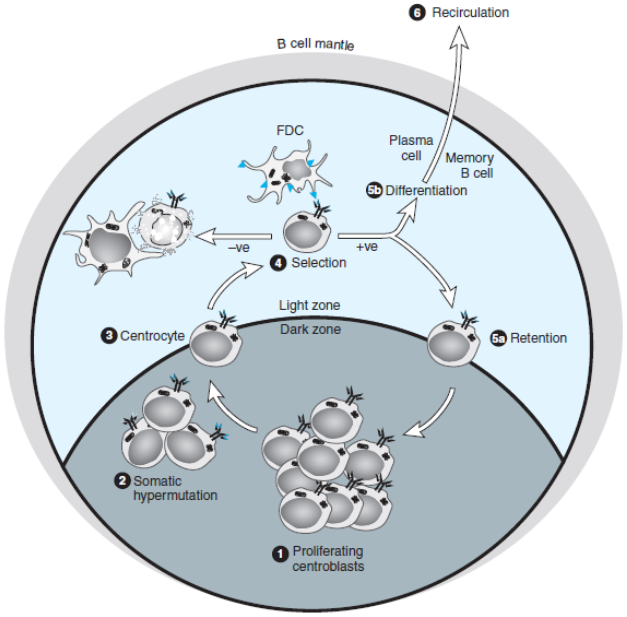
outer ring of small lymphocytes

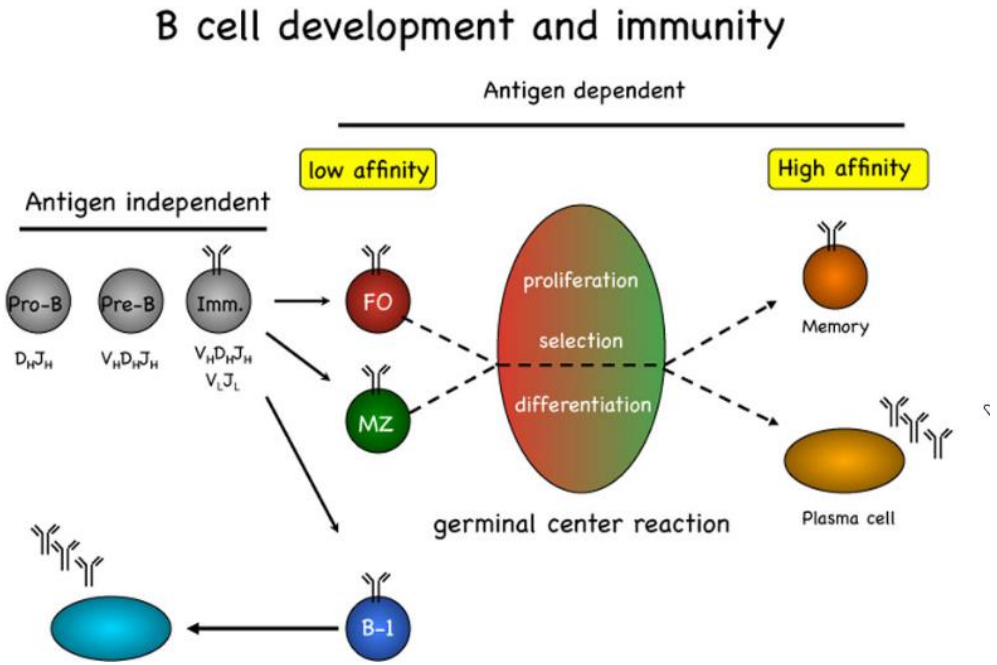
Marginal Zone Lymphoma



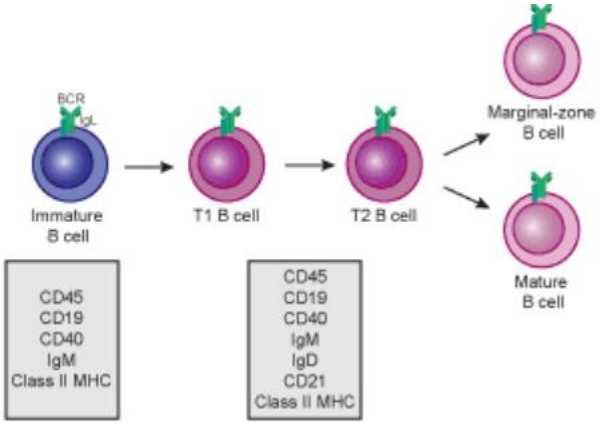
MZ-B-cells Express polyreactive B-cell-receptors Binding microbial molecular patterns

In MALT Derived from Memory B-cells Within the germinal centre





	Small pre-B cell	Immature B cell	Mature B cell
		IgM	IgD IgM
H-chain genes	VDJ rearranged	VDJ rearranged	VDJ rearranged
L-chain genes	V–J rearranging	VJ rearranged	VJ rearranged
Surface Ig	Intracellular μ chain	IgM expressed on cell surface	IgD and IgM made from alternatively spliced H-chain transcripts



Definition of MALT-lymphoma ?

WHO classification under designation of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT)

- Stomach and – small intestine (IPSID)

It is defined as lymphoma that recapitulates the histology of MALT (Peyer Patches), normal cell counterpart in marginal zone B cell

It typically arise in areas devoid of constitutive organised lymphoid tissue

It consists of morphologically **heterogenous small B cells** including the marginal **zone (centrocytes) cells**, cells resembling monocytoid cells, small lymphocytes and scattered **Immunoblast and centroblast like cells**

Etiology of gastric MALT-lymphoma ?

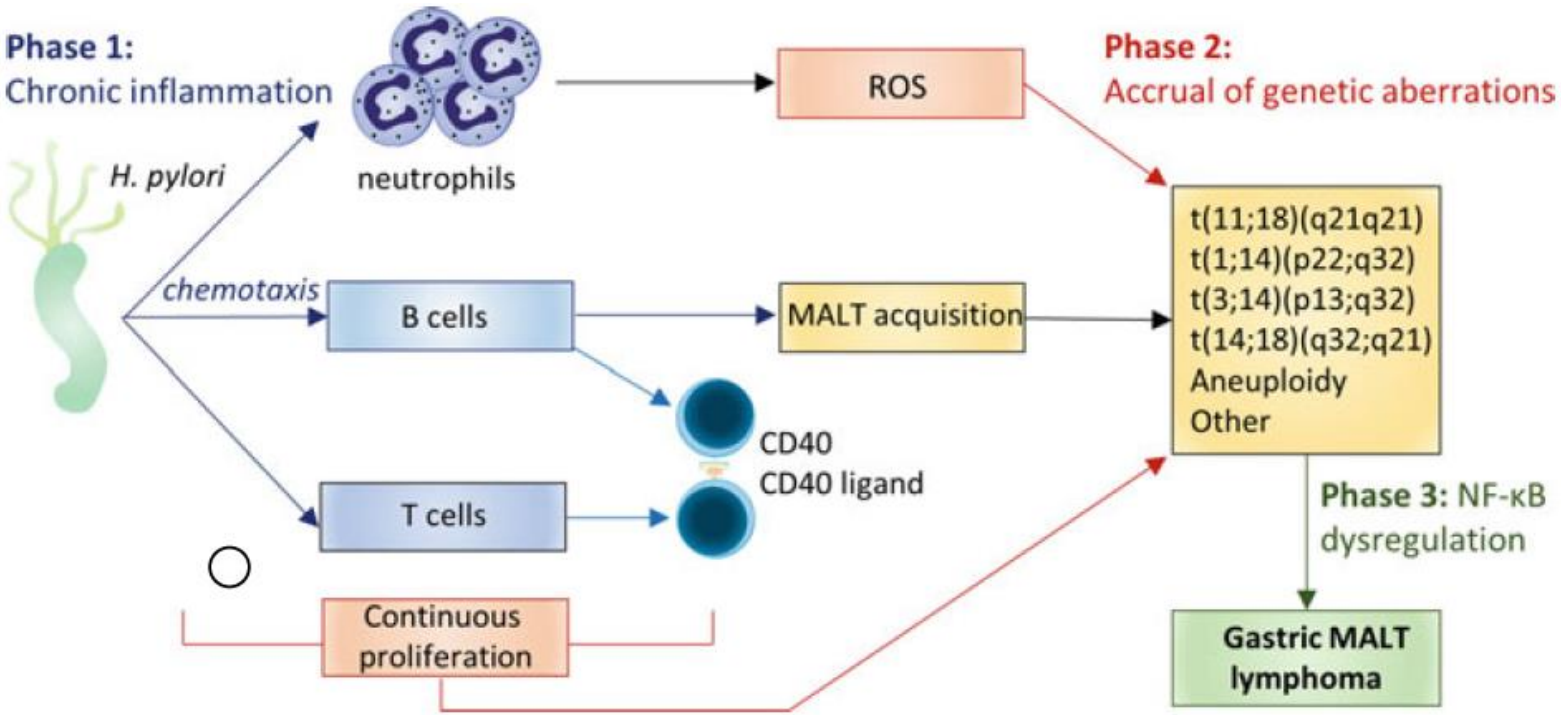
- ✓ **Rarely arise from native lymphoma**
- ✓ **Usually arise from MALT that is acquired as a result of chronic inflammatory disorder at sites normally devoid of MALT, e.g. stomach**

- ✓ **Most commonly: result of infection with**

  Helicobacter pylori, preceding most cases of MALT-lymphoma

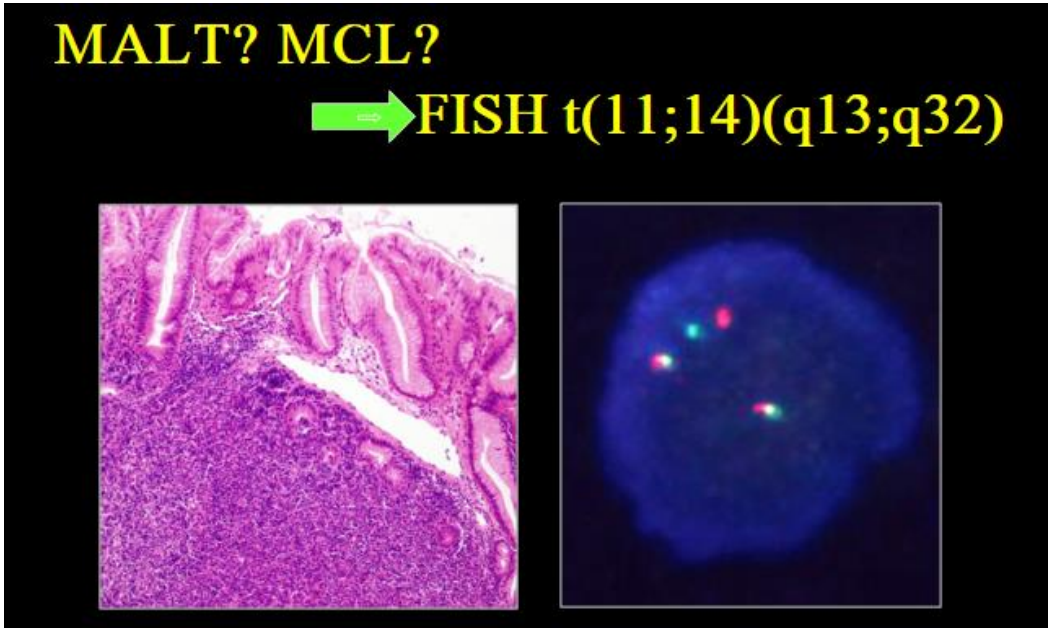
  also seen Helicobacter heilmannii or in Sjoegrens Syndrome

Hypothetical model of gastric MALT-lymphoma pathogenesis



Genetic abnormalities in MALT-lymphom commonly affect ?

Signalling pathways that regulate NFkB activities namely

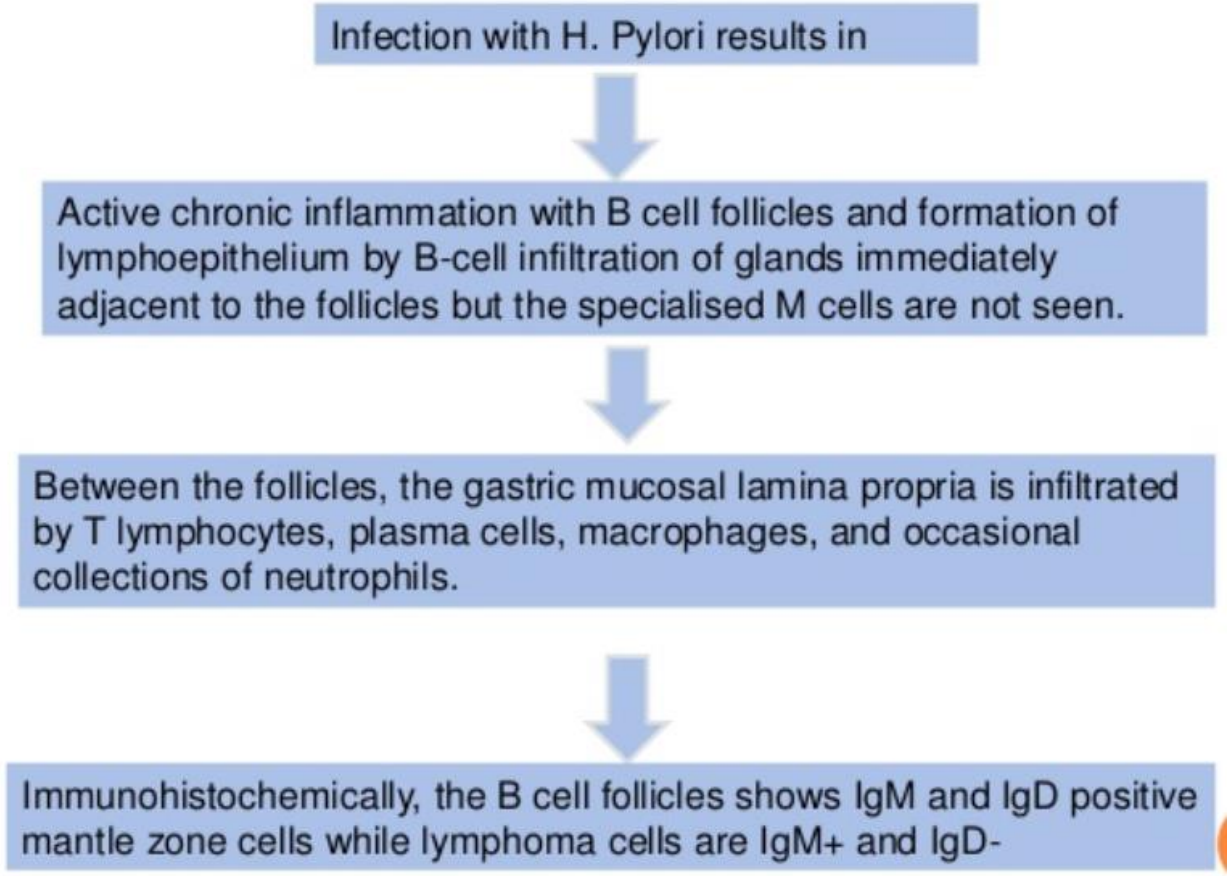


- t(11;18)/API2-MALT1
- t(1;14)/IGH-BCL10
- t(14;18)/IGH-MALT1
- A20 inactivation
- MYD88 mutation

Genetic abnormalities in gastric MALT ?

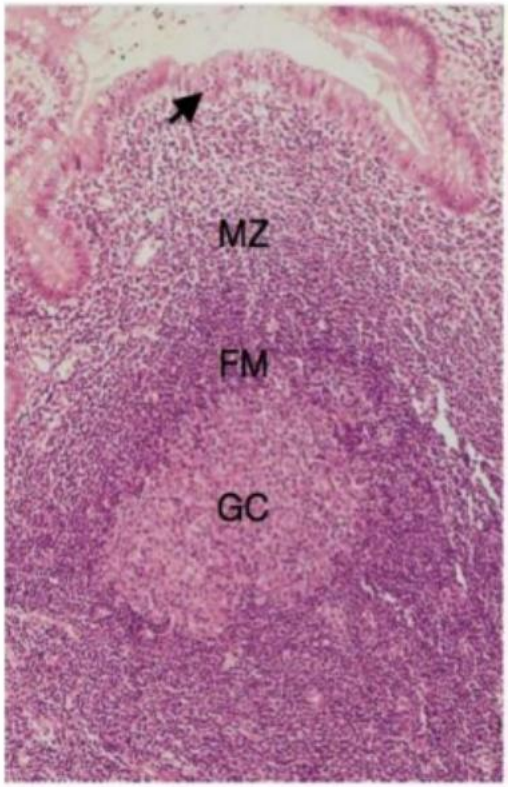
- **t(11;18)(q21;q21)- *API2-MALT1-*** present in about 25%.
  - *This creates a novel functioning fusion product by translocating the terminus region of apoptosis inhibitor 1 (API1) gene to the carboxy terminus of MALT1.—this activate the NF-kB pathways.*
- **t(1;14)(p22;q32) *-BCL10-IGH-***
  - *present in about 5% of gastric MALT lymphomas, translocation of the BCL-10 gene into to come under influence of immunoglobulin heavy chain(IGH) gene*
- trisomies 3, 12, and 18

Pathophysiology of gastric MALT-lymphoma: Sequence events

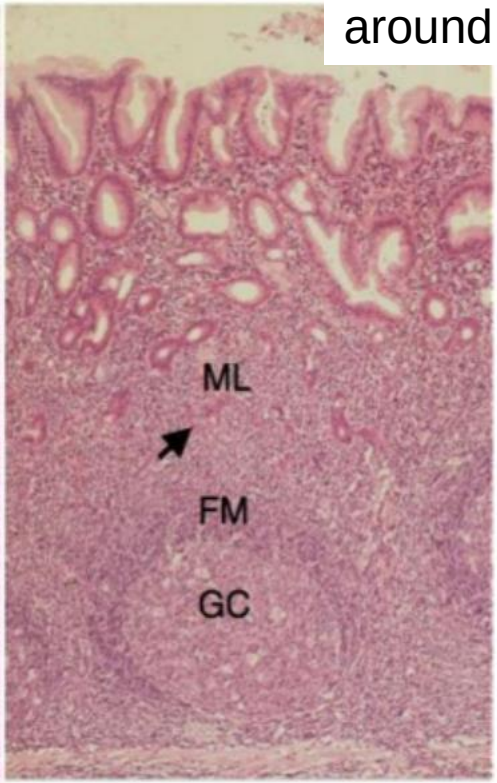


First steps on the way….s

Closely resembles normal MALT
Expansion of marginal zone (MZ) around follicles



Normal (PP)



Early stage lesion MALT-lymphoma

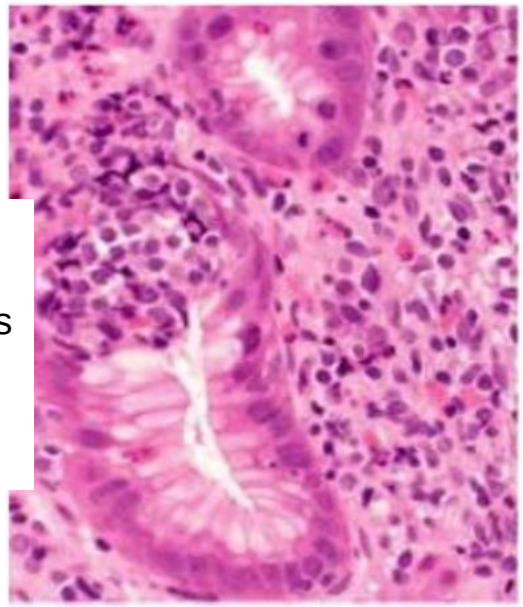
MZ composed:
centrocyte-type cells resembling small lymphocytes with abundant pale cytoplasm, clear cell borders

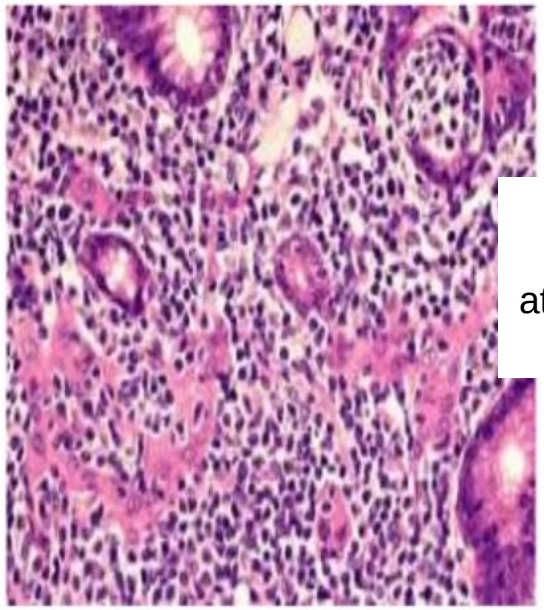
Variable:
plasma cell infiltrate (1/3rd of MALT lymphomas)
Dutcher bodies possible

Followed by

Infiltration of neoplastic cells into the gland/crypt epithelium with destruction of architecture resulting in LELs

Intact follicle are overrun by lymphoma cells (presence demonstrated by Immunostaining)





Most early LEL
Cluster of 3 or more atypical neoplastic cells in epithelium

Gastric MALT-lymphoma
Characteristic LEL
Lymphoepithelial lesion

+ distorted glands
Eosinophilic change of gastric epithelium

WHO Histological GRADING

0	Normal mucosa	Plasma cells in LP No lymphoid follicles
1	Chronic active gastritis	Lymphocyte clusters in LP No follicles
2	Chronic active gastritis with lymphoid follicles	Prominent follicles with surrounding mantle zone and **plasma cells**, No LELs
3	Suspicious lymphoid infiltrate, probably reactive	Lymphocytes **infiltrate diffusely** in LP
4	Suspicious ……, probably lymphoma	Lymphocytes **infiltrate diffusely** in LP and ***epithelium***
5	Marginal zone MALT lymphoma	Dense diffuse infiltrate of CCL in LP with **prominente LELs**

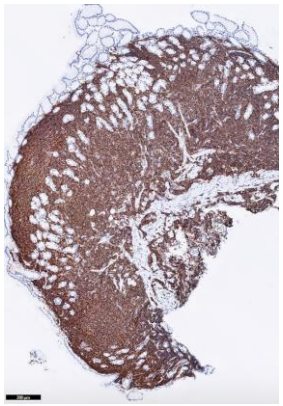
CCL: centrocyte-like-cells; LELs: lympho-epithelial-lesions; LP: lamina propria

Which stains/antibodies to use in diagnosis ?

Differential diagnosis mainly depends on **Immunohistochemistry:** for MALT-lymphoma would be..

- **B-cell marker:**

  typically CD20 (+ CD19, CD22, PAX5)



- **Neoplastic nature** suggested by:

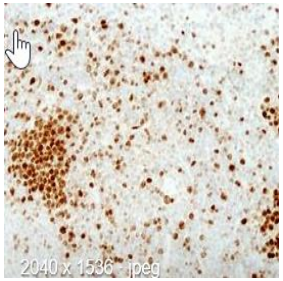
  aberrant CD 43 (normal B-cells negative)

  bcl2-protein (reactive germinal centre cells negative)

  Ki67 (proliferation-associated)

  Staining for cytokeratin-highlight the Lymphoepithelial-Lesions

  Light chain restriction (kappa more than lambda)



Differential diagnosis mainly depends on Immunohistochemistry for other MZ-lymphoma

Molecule	Type of test	Expected result	Level of recommendation
CD20	IHC	Positive	Mandatory
CD5	IHC	Negative[a]	Mandatory
CD23	IHC	Negative/positive	Suggested[b]
CD10	IHC	Negative	Mandatory
IgD	IHC	Negative[c]	Suggested
Cyclin D1	IHC	Negative	Mandatory[d]
MYD88 mutation	PCR	Negative	Suggested[e]

IgD, immunoglobulin D; IHC, immunohistochemistry; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; PCR, polymerase chain reaction; SMZL, splenic marginal zone lymphoma.

[a] Few exceptions may occur.

[b] In cases with small cell morphology, irrespectively of CD5-concurrent positivity.

[c] In cases with splenomegaly, as it is usually positive in SMZL.

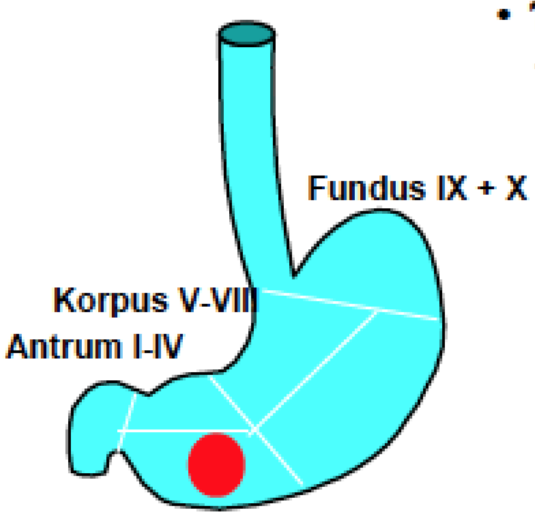
[d] In cases positive for CD5.

[e] When present, a differential diagnostic problem with LPL arises (cases of MZL with *MYD88* mutation may represent rare exceptions).

ESMO-guidelines
MZ-Lymphoma
Annals Oncology 2020

CD5+, Cyclin D1+ in Mantel-cell-lymphoma; CD10+, bcl-6 and-2 +: follicular lymphom

Endoscopic diagnosis / Gastric mapping – how ?



- 1 biopsy from corpus and antrum, resp. for urease test
- 4 biopsies from normal mucosa in antrum and corpus, resp., and 2 biopsies from the fundus

≥ 10 biopsies from macroscopic visible lesions

If no HP in IHC
It must be ruled out
(C13-breath, feces-Ag, serology)

No H.pylori eradication
before results of reference pathologist is available

How to stage gastric MALT-lymphoma – What to examine, test, seek ?

- **Physical exam: Lymph nodes, Waldeyer ring/HNO, liver, spleen...**
- **Lab work+:** CBC, LDH, b2-microglobulin, Immunofix (S+U), HIV, HCV, HBV
- **CT-Tx,Abd, pelvis for LN`s and spreading assessment**
- **Bone marrow biopsy**

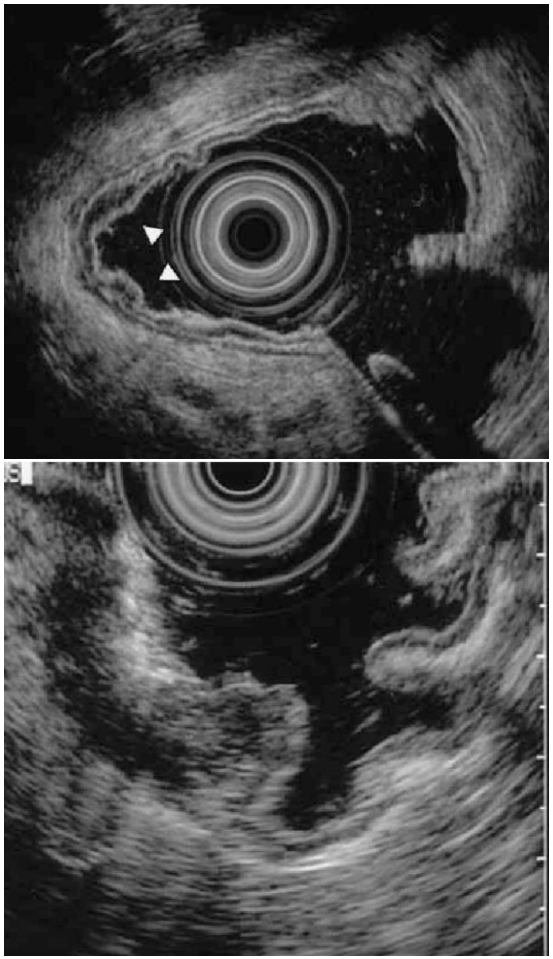
  if no regression after HP-eradication and before oncological treatment
- **Ileocolonoscopy should be considered- mapping endoscopically**

  always independent of macroscopic suspicious lesions

+: liver (ASAT/ALAT, Bili/AP), kidney (Crea)-function

Is EUS absolutely needed for staging ?

- Only reliable method to stage
  - Depth of invasion and
- Seperate T1 from T2 and thus
  - I1E from I2E



What staging system to use for gastric MALT-lymphoma ?

Infiltration into subserosa +

regional lymph node compartment 2 = ?

T2N1M0 = II1E

	Ann Arbor system, modified*	Paris staging system†	
local	I1E	TI N0M0	
	I2E	T2N0M0	Muscularis propria, subserosa
	I2E	T3N0M0	Serosa penetration
	I2E	T4N0M0	Per continuitatem infiltration of neighbouring organs
	II1E	T1—4N1M0	Regional lymph nodes (compartment I+II)
	II2E	T1—4N2M0	Intra-abdominal distant lymph nodes
advanced	IIIE	T1—4N3M0	Extra-abdominal lymph nodes
	IV	T1—4 N0—3M1	Diffuse or disseminated infiltration of distant or extra-gastrointestinal organs
		B1	Bone marrow

Clinical symptoms of gastric MALT –lymphoma ?

Indolent behaviour = asymptomatic

Slow progression with vast majority being I1E

- ✓ **90% lower than II1E (= no lymph nodes)**
- ✓ **many many years localized, but prospective longterm 15-30% N+**
- ✓ **< 10 % bone marrow/ or extra-gastric-involvment**

H.pylori-eradication – how you do it ?

Success dependend on rate/risk of resistence

- History of antibiotic exposure ?
- Geographic/local rate of resistance low to clarithromycin, metronidazole then conventional triple possible
- Dual resistance to clarithromycin+metronidazole > 15%
  hampers also success of non-bismuth quadruple regimen

Highest Cure Rate else with either

- Bismuth Quadruple with > 90% eradication rate

Malfertheiner et al. Maastricht Gut 2017

What is Bismuth-Quadruple -H.pylori-eradication ?

• **PPI**	Standard dose, bid
• **Bismuth subcitrate**	420 mg, qid
• **Metronidazole/Tinidazole**	500 mg, tid
• **Tetracycline**	500 mg, qid
For 10 – 14 days	

3-3-3-3

Highly effective: Eradication rate 92%

Cost effective: 14d course < 87 CHF

Why H.pylori-treatment in H.pylori-negative MALT ?

Eradication in all cases, stages of disease since

- ***also other Helicobacter species can cause MALT***
- ***diagnostic test has missed H.pylori***

Success-rate reported to be about 19%

When is no good response to H.pylori-eradiation to be expected ?

- **translocation t(11,18) and t(1,14) ***
- **H.pylori-negative Lymphoma**
- **Lymphnode positive stage of disease**

***: but still up to 20% of cases respond to H.pylori eradication**

Prognosis of gastric MALT ?

10 year

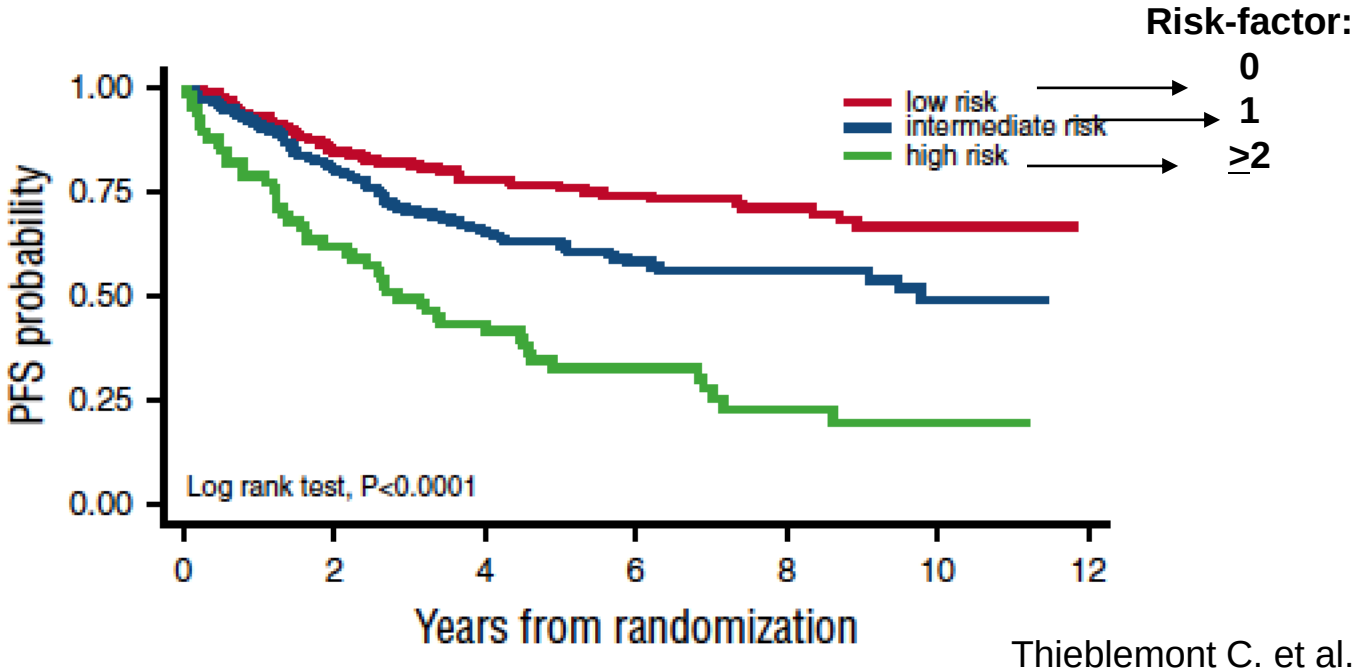
survival rate of ≈ 90%

Disease-free survival rate ≈ 70%

Thieblemont et al. 2000

Prognostic Index for gastric MALT and CTx

N = 400	HR	Standard Error	95% CI	*P*
Stage III-IV	1.79	0.26	1.35-2.38	<.001
Age >70 y	1.72	0.27	1.26-2.33	.001
LDH >UNL	1.87	0.37	1.27-2.77	.002



Thieblemont C. et al. Blood 2017

Grading-system for post-treatment follow-up ?

GELA: Group dÈtude des Lymphomes de LÀdulte

CR Complete Histological Response
=total disappearance of tumorous infiltrates

pMRD Probable Minimal Residual Disease
persistence of some lymphocytic aggreg ELs

Partial Response

rRD Responding residual disease
at least reduction visible- with persistence of diffuse
or nodular lymphocytic infiltration + some stromal changes
focal LELs possible

NC No Change
no macroscopic change, histolog. ide

Stable Disease/ Progression

Complete Remission is defined as ?

2 sequential gastroscopies with mapping Bx

and no lymphoma - histomorphologically

Rate of Complete Remission in

IE1 mucosa:	**> 82%**
IE1 submucosa:	**78%**
IE2: = deeper infiltration:	**54%**

Follow-up after H.pylori-eradication: Frequency of endoscopy/biopsies/EUS ?

- **6 weeks after HP-eradication endoscopy:**

to rule out progression + to test HP in histology + C13 Breath-test

- **3-6 months after completion of eradication endoscopy:**

then every 4-6 months for first 2 years/ until CR or pMRD

- **at each endoscopy mapping biopsies**

HP-persistence -> Re-biopsy with culture + susceptability test

- **EUS not generaly recommended BUT**

Surveillance after complete remission ?
How long and Why ?

Annually endoscopy for up to 10 years

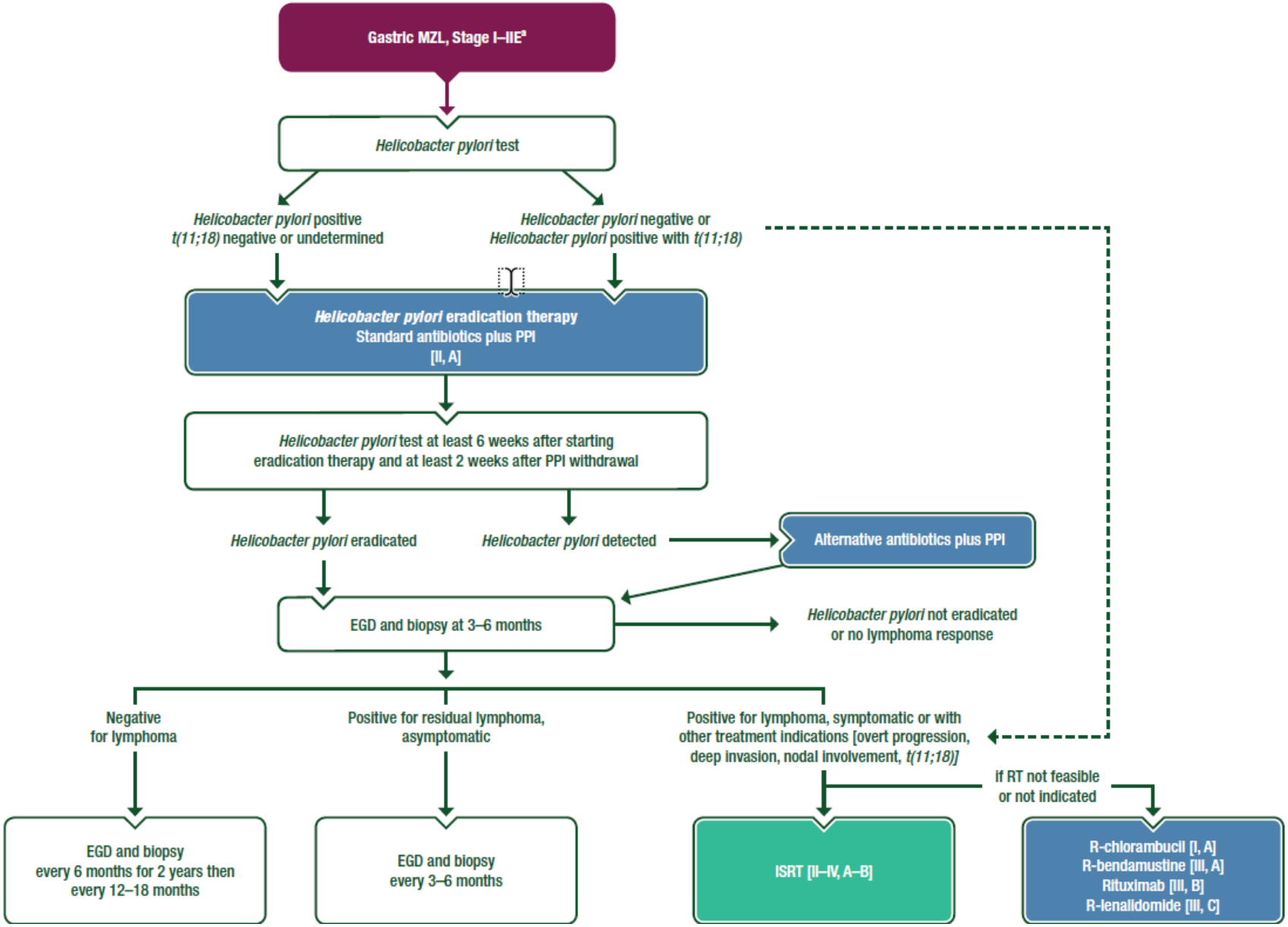
(after 5 years rather arbitrary) due to

Risk of AdenoCarcinom up to 6-fold increased

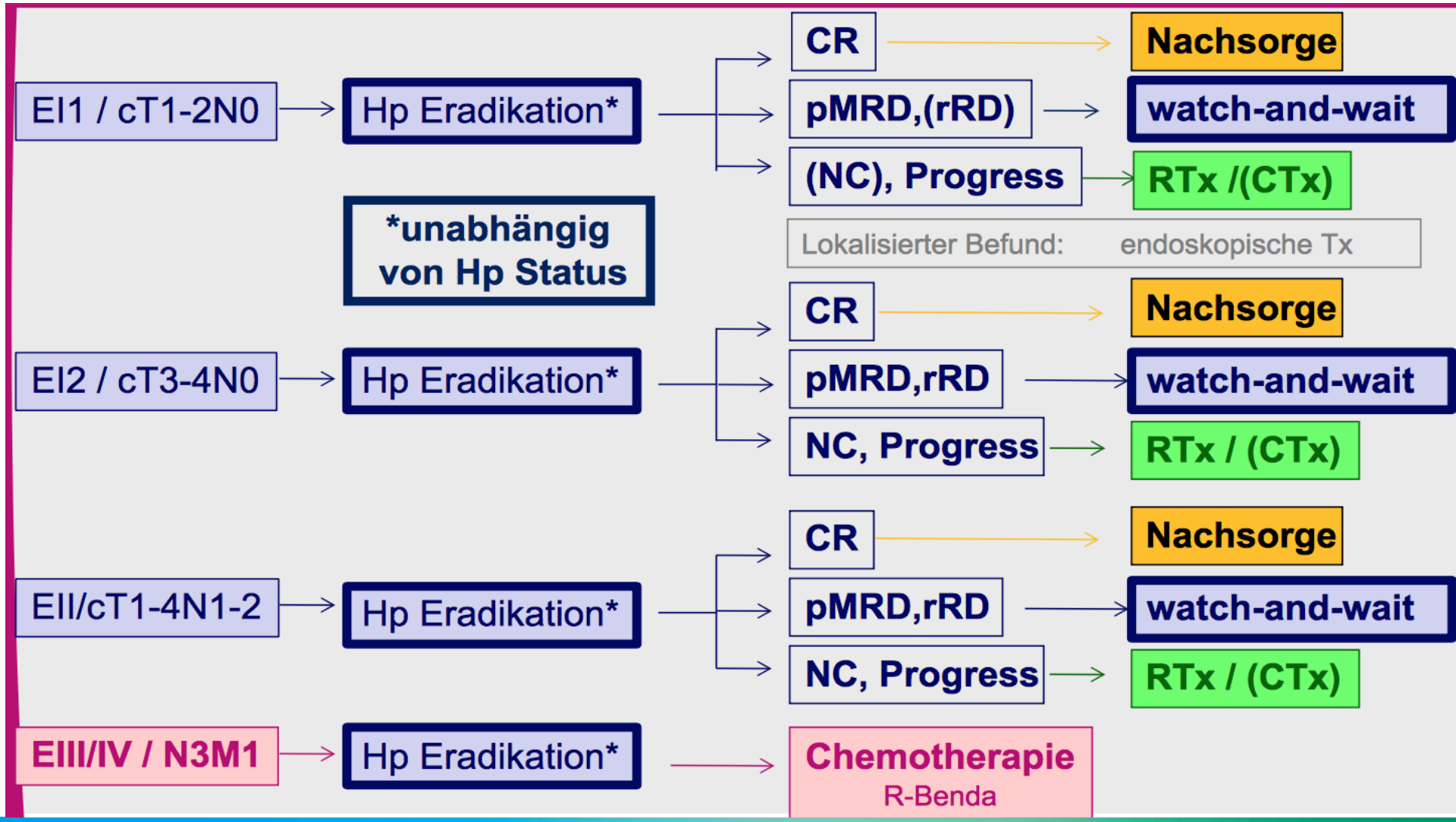
particularly if intestinal metaplasia, dysplasia present, develops

7.2% suffer relapse (or rather incomplete regression)

Yearly 2.2% relapse rate


Gastric MZL, Stage I–IIE[a]
Helicobacter pylori test
Helicobacter pylori positive
t(11;18) negative or undetermined
Helicobacter pylori negative or
Helicobacter pylori positive with t(11;18)
Helicobacter pylori eradication therapy
Standard antibiotics plus PPI
[II, A]
Helicobacter pylori test at least 6 weeks after starting
eradication therapy and at least 2 weeks after PPI withdrawal
Helicobacter pylori eradicated
Helicobacter pylori detected
Alternative antibiotics plus PPI
EGD and biopsy at 3–6 months
Helicobacter pylori not eradicated
or no lymphoma response
Negative
for lymphoma
Positive for residual lymphoma,
asymptomatic
Positive for lymphoma, symptomatic or with
other treatment indications [overt progression,
deep invasion, nodal involvement, t(11;18)]
if RT not feasible
or not indicated
EGD and biopsy
every 6 months for 2 years then
every 12–18 months
EGD and biopsy
every 3–6 months
ISRT [II–IV, A–B]
R-chlorambucil [I, A]
R-bendamustine [III, A]
Rituximab [III, B]
R-lenalidomide [III, C]

When and what further local/systemic treatment after H.pylori-eradication ?



Radiation in gastric MALT – when – why - how ?

Localized gastric MALT

I1E- II1E (T1-4, N0/1 M0B0)

MALT radiation sensitive

Cure Rates up to 100%

30 (-40) Gy mostly sufficient (15-20 sessions in fasted state)

Chemo-Tx in gastric MALT – when – why - how ?

Rather reserved for disseminated MALT:

For symptomatic disease or other treatment indications:
- overt progression or Bulky disease
- Impending organ damage or patient preference

active irrespective of translocations:
2CdA (Cladribine/prodrug)
Rituximab + Chlorambucil/CHOP
(or R-Bendamustin)

Cave: Secondary Carcinomas

Progression-free Survival 72%

Alkylating agents: 75% CR (except in t(11,18))
Others: Bortezomib, Oxaliplatin, MTx

Indications for surgery in gastric MALT ?

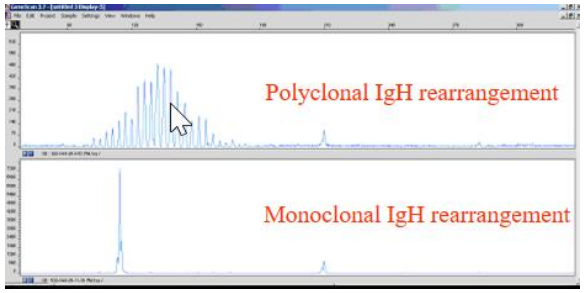
Usually NO

Only complications such as

Perforation, Bleeding

....

What is the relevance of clonality in MALT-lymphoma?



Monoclonality by PCR is not a prerequisite for diagnosis

- **BIOMED-2-PCR-protocol: in 50% during follow-up still positive despite lack of macroscopic/immunohistochemical lymphoma**
  - **With clonality: only slightly higher relapse risk = ergo not of major clinical and/or diagnostic relevance**

OTHER
Intestinal B-Cell Lymphoma

Intestinal B-cell lymphoma: types and treatment

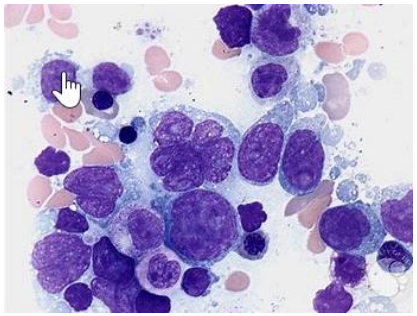
Diffuse Large-B-cell-Lymphoma (DLBCL):
CTx plus Rituximab (R-CHOP), 6-8 cycles every 3 weeks

Mantelcell-lymphoma:
most frequent intestinal lymphoma, often multifocal intestinal sites+LN, blood...
< 65 R-DHAX plus autologous-Stemcell-Tx
> 65 R-CHOP plus maintenance Rituximab

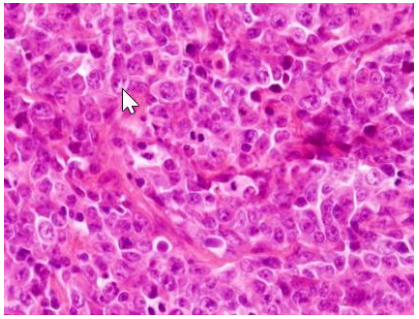
Follicular lymphoma: endoscopic aspect of lymphomatous polyposis
If asymptomatic then no treatment – if symptomatic or high tumor mass: R-CHOP

Burkitt-Lymphom

Immunoproliferative small intestinal disease (IPSID)

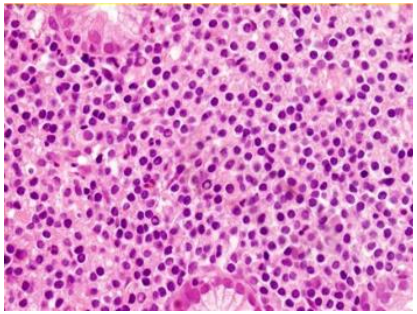


Diffuse Large-B-cell-Lymphoma
DLBCL



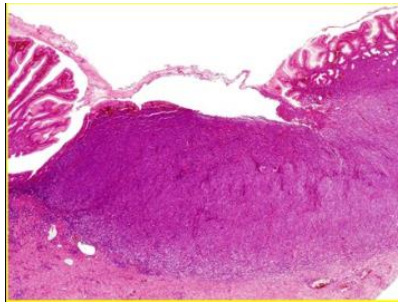
Gastric MALT-lymphom
can evolve into DLBCLymphoma

e.g. when clearly separate sheets of large cells comprising > 20% of the neoplastic population

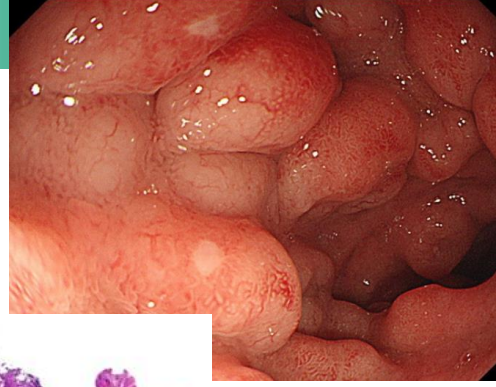


Usually symptomatic
Extranodal involvement is common
Cell of origin: germinal center B-cell

Curable in about 40%

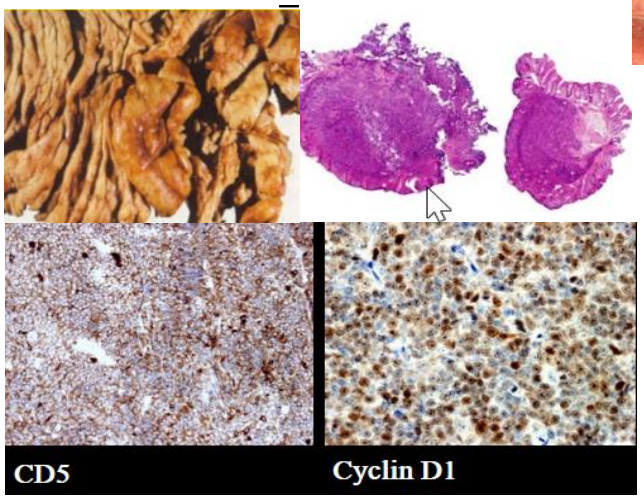


Multiple lymphomatous polyposis…… can be



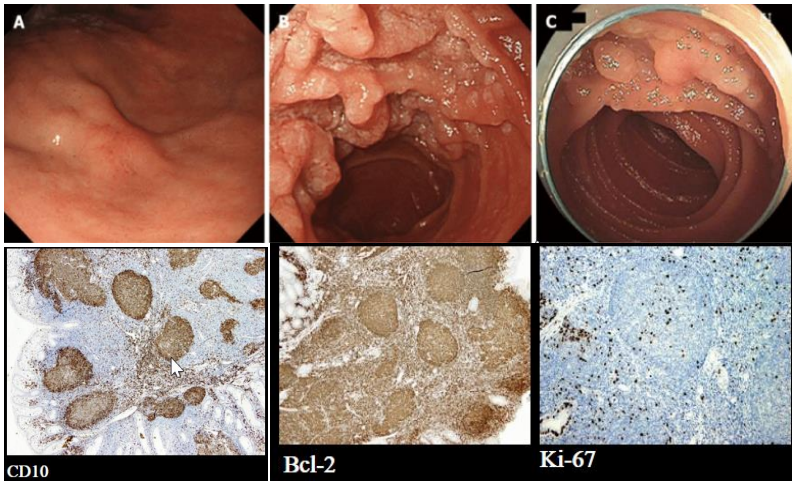
➢ Mantle-cell-lymphoma

Often male, > 60 y
Rather bad prognosis
IHC : CD5, Cyclin D1



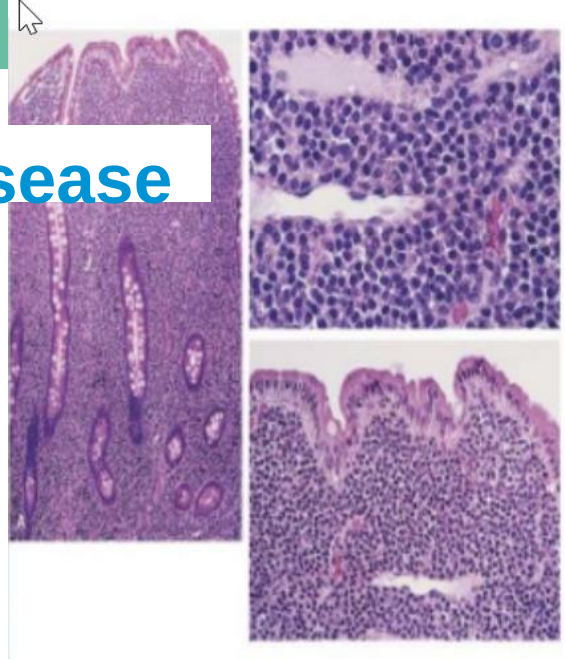
➢ Follicular lymphoma

Often asymptomatic, «indolent»
Not curable (some exceptions)
Associated BCL2-gene rearrangement t (14;18)



➢ MALT-lymphoma

Immunoproliferative Small intestinal disease (IPSID) is .....



- Subtype of MALT lymphoma
- Frequently in Middle East, Mediterranean
- At any age, mainly young adults 25-30y
- Associated synthesis of IgA1 chain (Alpha-Chain Disease)

  Duodenal juice shows raised levels of IgA

- May transform to large cell lymphoma
- Pathogenic role of Campylobacter jejuni
- Stages: Plasmocyte – Intermediate - Immunoblastic

Immunoproliferative Small intestinal disease: TP...

depends on age, general/nutritional status: due to malabsorptive /enteropathy->

substitution of deficiencies (iron, folate, magnesium, calcium....)

> enteral/parenteral nutrition

treatment according to Tumor stage:

A/Plasmocyte/localized intestinal +/- LN-> macrolide and/or tetracycline

B/Intermediate/ Immunoblastic stage C: R-CHOP

(evtl. autologous stem-cell-transplantation)

Who is Who in mucosa-associated .....

Isaacson PG

seen and described histomorphology of MALT first time...

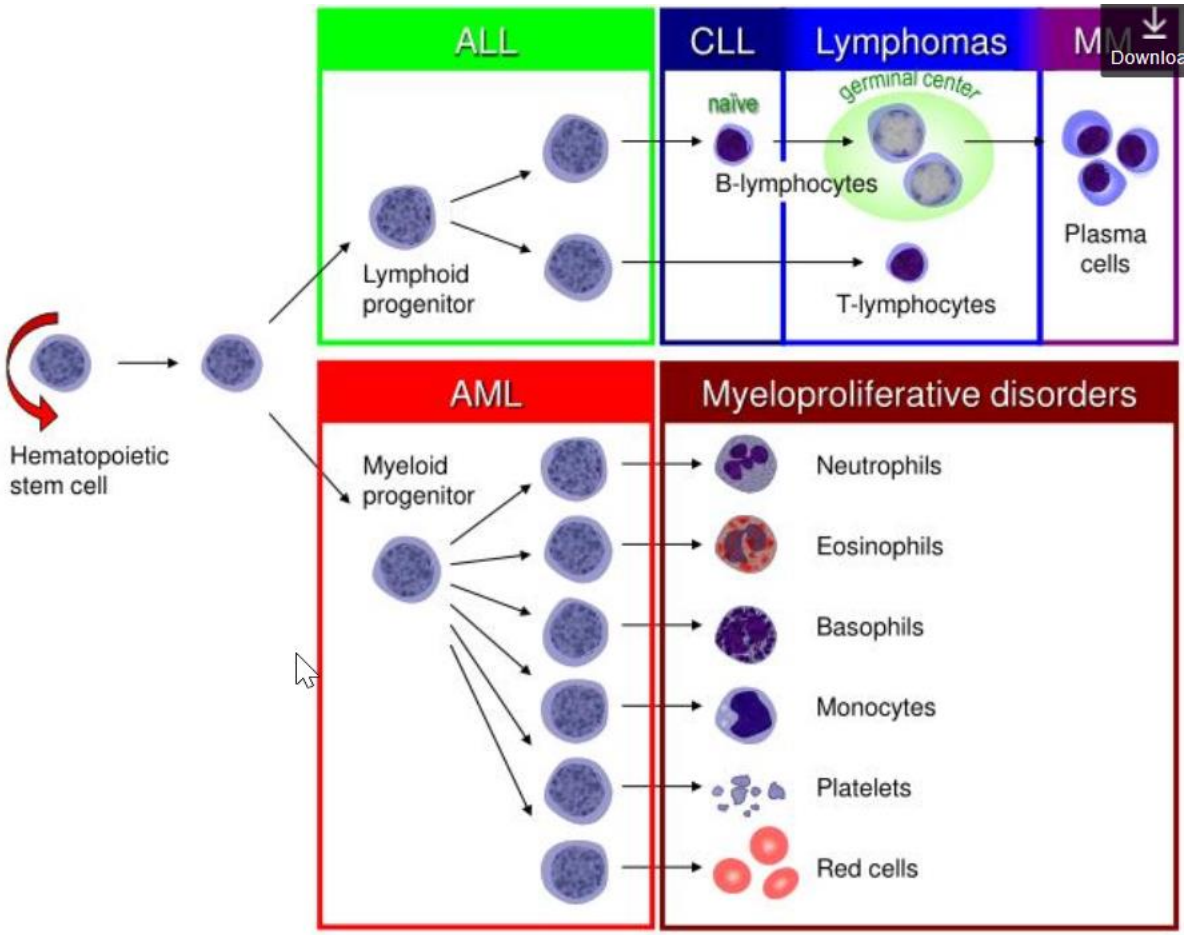
Fischbach W

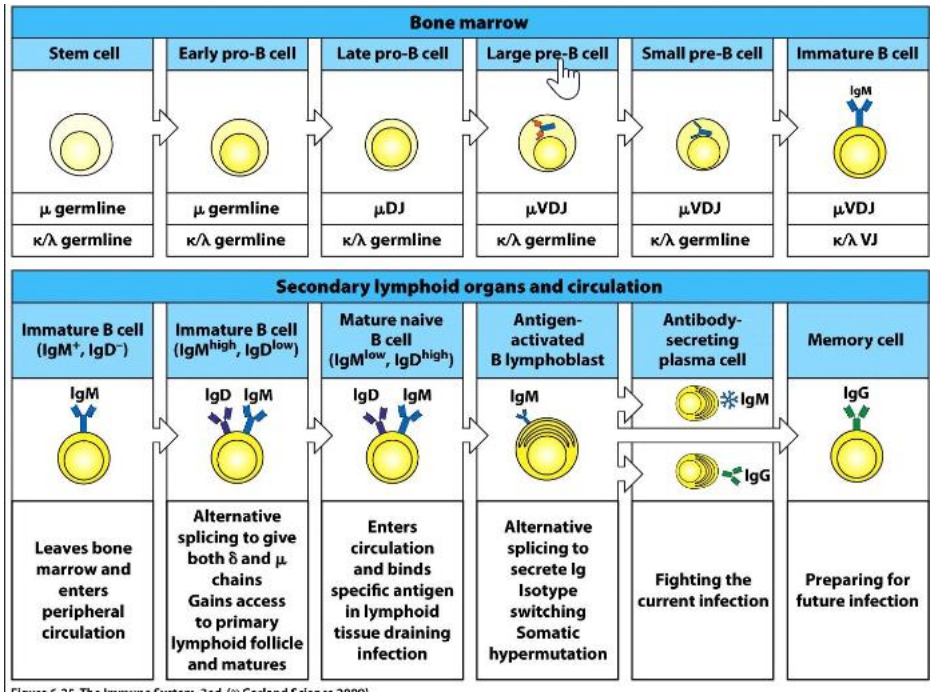
Meta-Analysis GastroUpdate-„Expert“

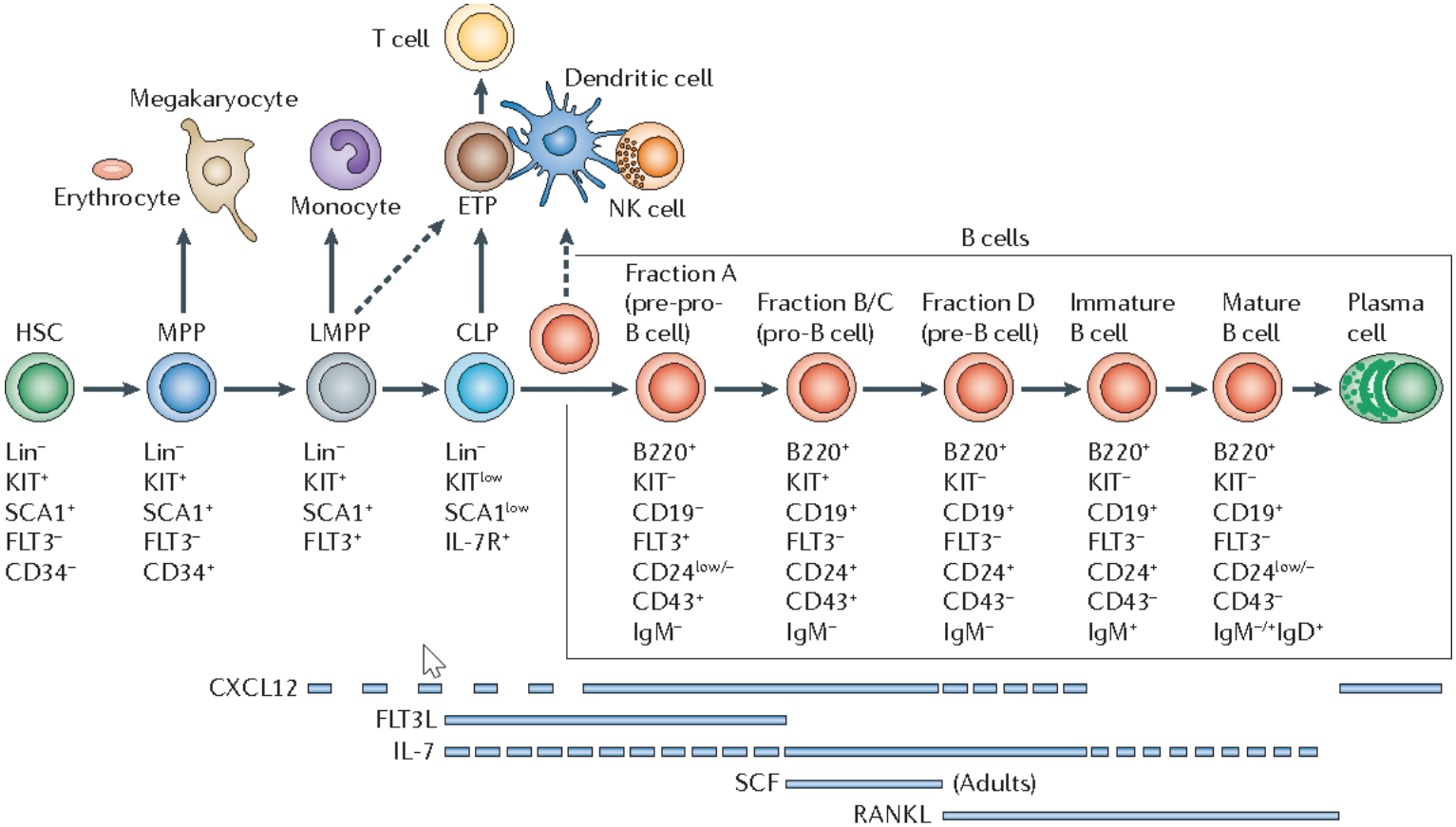
MacPherson A

Truely understands B/T-cells and....

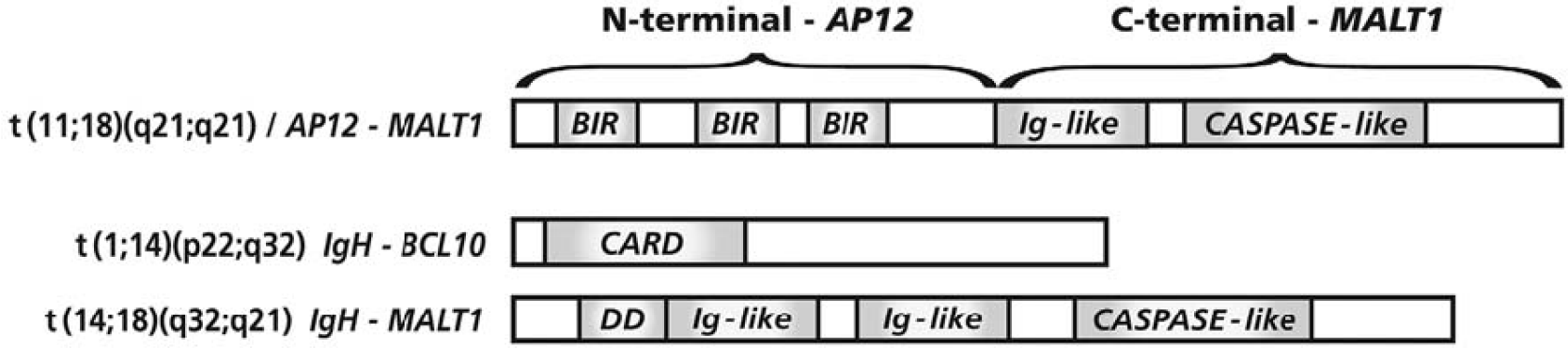

Backspace
Thank You
Page Up
Home
Page Down
Insert
Shift

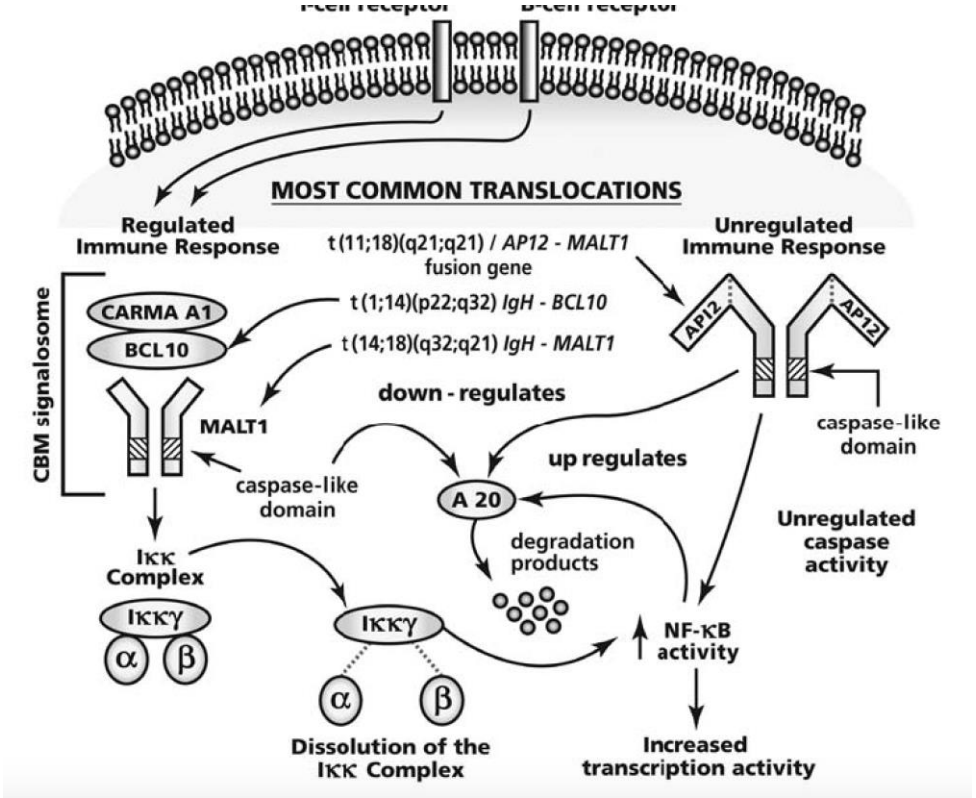

ALL
CLL
Lymphomas
MM
naïve
germinal center
B-lymphocytes
Plasma cells
Lymphoid progenitor
T-lymphocytes
Hematopoietic stem cell
AML
Myeloproliferative disorders
Myeloid progenitor
Neutrophils
Eosinophils
Basophils
Monocytes
Platelets
Red cells

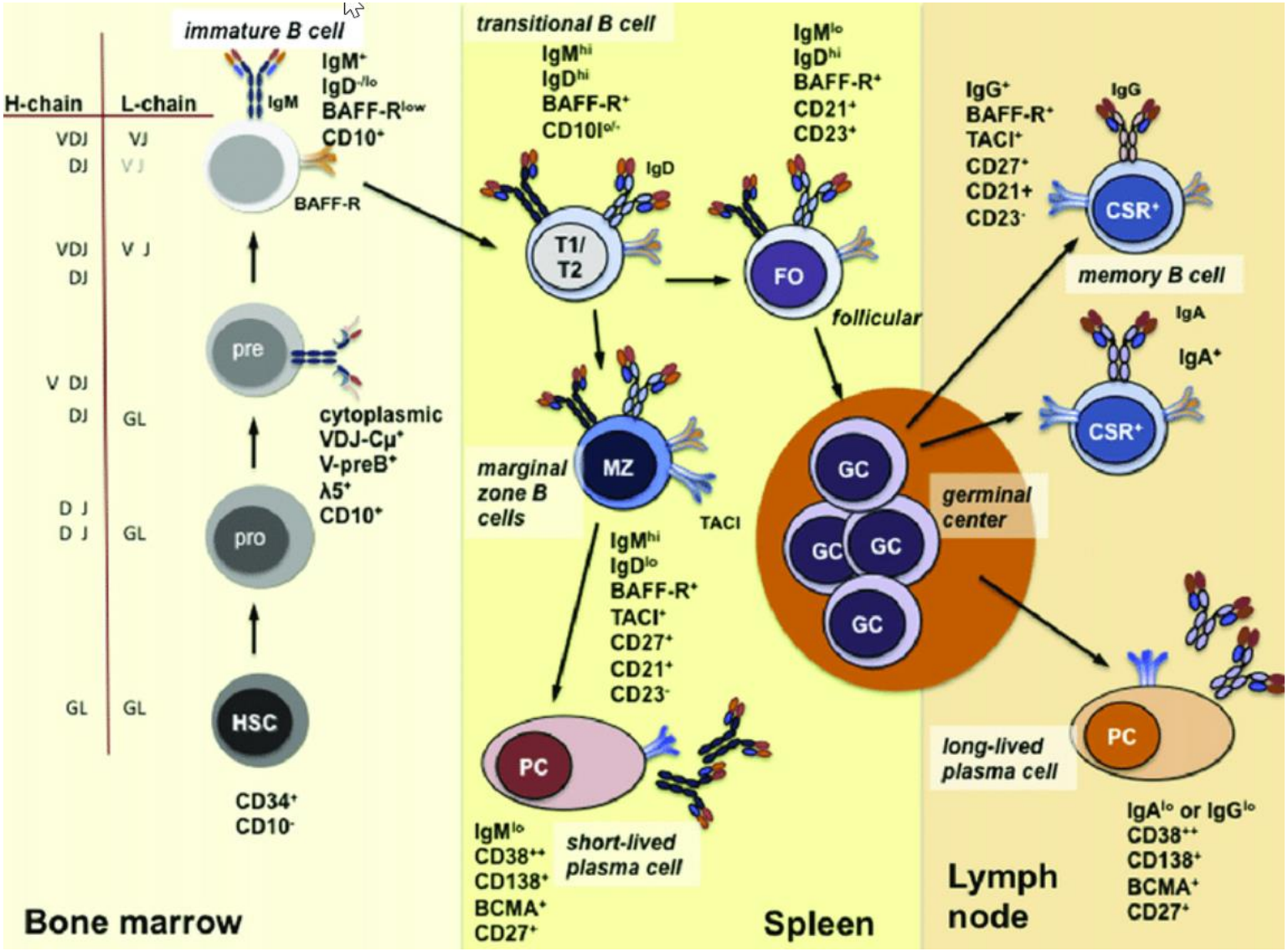

Bone marrow
Stem cell
Early pro-B cell
Late pro-B cell
Large pre-B cell
Small pre-B cell
Immature B cell
IgM
μ germline
κ/λ germline
μ germline
κ/λ germline
μDJ
κ/λ germline
μVDJ
κ/λ germline
μVDJ
κ/λ germline
μVDJ
κ/λ VJ
Secondary lymphoid organs and circulation
Immature B cell (IgM+, IgD−)
Immature B cell (IgMhigh, IgDlow)
Mature naive B cell (IgMlow, IgDhigh)
Antigen-activated B lymphoblast
Antibody-secreting plasma cell
Memory cell
IgM
IgD IgM
IgD IgM
IgM
IgM
IgG
IgG
Leaves bone marrow and enters peripheral circulation
Alternative splicing to give both δ and μ chains
Gains access to primary lymphoid follicle and matures
Enters circulation and binds specific antigen in lymphoid tissue draining infection
Alternative splicing to secrete Ig
Isotype switching
Somatic hypermutation
Fighting the current infection
Preparing for future infection

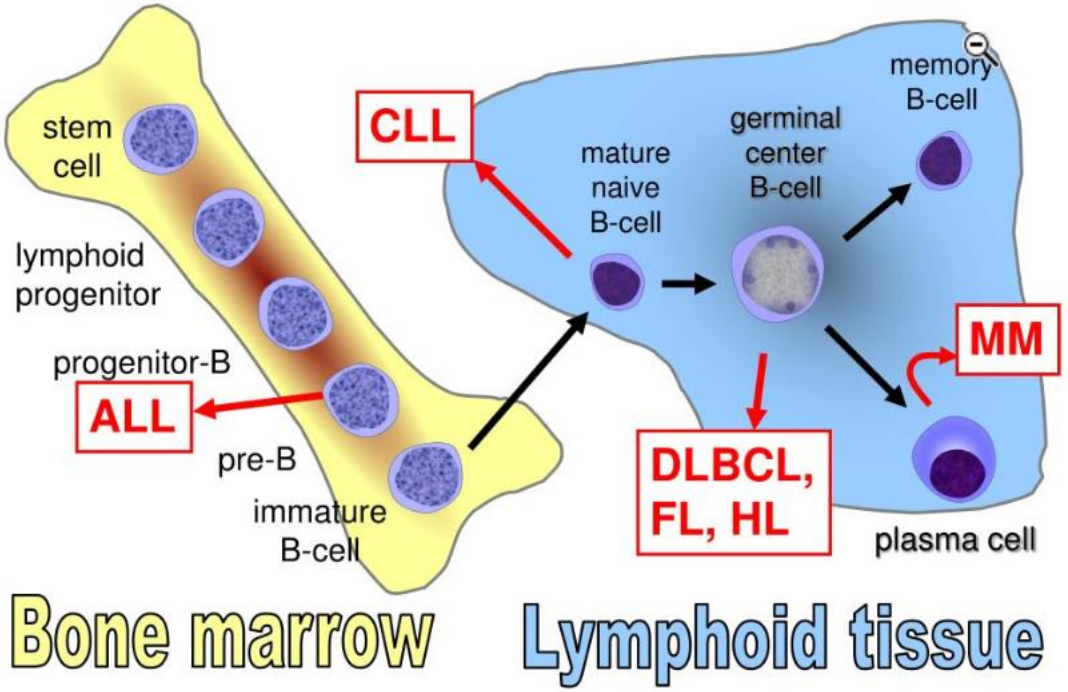

T cell
Dendritic cell
Megakaryocyte
Erythrocyte
Monocyte
ETP
NK cell
B cells
HSC
MPP
LMPP
CLP
Fraction A (pre-pro-B cell)
Fraction B/C (pro-B cell)
Fraction D (pre-B cell)
Immature B cell
Mature B cell
Plasma cell
Lin⁻ KIT⁺ SCA1⁺ FLT3⁻ CD34⁻
Lin⁻ KIT⁺ SCA1⁺ FLT3⁻ CD34⁺
Lin⁻ KIT⁺ SCA1⁺ FLT3⁺
Lin⁻ KIT^low SCA1^low IL-7R⁺
B220⁺ KIT⁻ CD19⁻ FLT3⁺ CD24^low/– CD43⁺ IgM⁻
B220⁺ KIT⁺ CD19⁺ FLT3⁻ CD24⁺ CD43⁺ IgM⁻
B220⁺ KIT⁻ CD19⁺ FLT3⁻ CD24⁺ CD43⁻ IgM⁻
B220⁺ KIT⁻ CD19⁺ FLT3⁻ CD24⁺ CD43⁻ IgM⁺
B220⁺ KIT⁻ CD19⁺ FLT3⁻ CD24^low/– CD43⁻ IgM^–/+IgD⁺
CXCL12
FLT3L
IL-7
SCF
(Adults)
RANKL

Lymphom	Therapie
Gastrales MALT Lymphom	Hp Eradikation (RTx, CTx)
Diffuses großzelliges B-Zell-Lymphom (DGBZL)	CTx: R-CHOP (± Radiatio)
Follikuläres Lymphom I/II	Watch-and-Wait
Mantelzelllymphom	CTx: R-Bendamustin
Intestinale B-Zell-Lymph	CTx: R-CHOP
Intestinales T-Zell-Lymph	Hochdosis-CTx + autologe/allogene SZTx


N-terminal - AP12
C-terminal - MALT1
t(11;18)(q21;q21) / AP12 - MALT1
BIR
BIR
BIR
Ig-like
CASPASE-like
t(1;14)(p22;q32) IgH - BCL10
CARD
t(14;18)(q32;q21) IgH - MALT1
DD
Ig-like
Ig-like
CASPASE-like


MOST COMMON TRANSLOCATIONS
Regulated Immune Response
t(11;18)(q21;q21) / AP12 - MALT1 fusion gene
Unregulated Immune Response
t(1;14)(p22;q32) IgH - BCL10
t(14;18)(q32;q21) IgH - MALT1
CBM signalosome
CARMA A1
BCL10
MALT1
API2
API2
down - regulates
caspase-like domain
caspase-like domain
up regulates
A 20
degradation products
Unregulated caspase activity
IKK Complex
IKKγ
α
β
IKKγ
α
β
NF-κB activity
Dissolution of the IKK Complex
Increased transcription activity


immature B cell
IgM+
IgD-/lo
BAFF-Rlow
CD10+
IgM
BAFF-R
H-chain
L-chain
VDJ
DJ
VJ
V J
VDJ
DJ
V J
V DJ
DJ
GL
pre
cytoplasmic
VDJ-Cμ+
V-preB+
λ5+
CD10+
D J
D J
GL
pro
GL
GL
HSC
CD34+
CD10-
Bone marrow
transitional B cell
IgMhi
IgDhi
BAFF-R+
CD10lo/-
IgD
T1/
T2
IgMlo
IgDhi
BAFF-R+
CD21+
CD23+
FO
follicular
marginal
zone B
cells
MZ
TACI
IgMhi
IgDlo
BAFF-R+
TACI+
CD27+
CD21+
CD23-
PC
IgMlo
CD38++
CD138+
BCMA+
CD27+
short-lived
plasma cell
Spleen
GC
GC
GC
GC
germinal
center
IgG+
BAFF-R+
TACI+
CD27+
CD21+
CD23-
IgG
CSR+
memory B cell
IgA
IgA+
CSR+
PC
long-lived
plasma cell
IgAlo or IgGlo
CD38++
CD138+
BCMA+
CD27+
Lymph
node


stem cell
lymphoid progenitor
progenitor-B
ALL
pre-B
immature B-cell
CLL
mature naive B-cell
germinal center B-cell
memory B-cell
MM
DLBCL, FL, HL
plasma cell
Bone marrow
Lymphoid tissue