



BHS

Belgian Hematology Society

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Classification of small B-cell lymphomas

15 02 2025

BHS course on indolent lymphoma

Prof. dr. Thomas Tousseyn
Dept of Hematopathology, UZ Leuven
Faculty of Medicine, KU Leuven

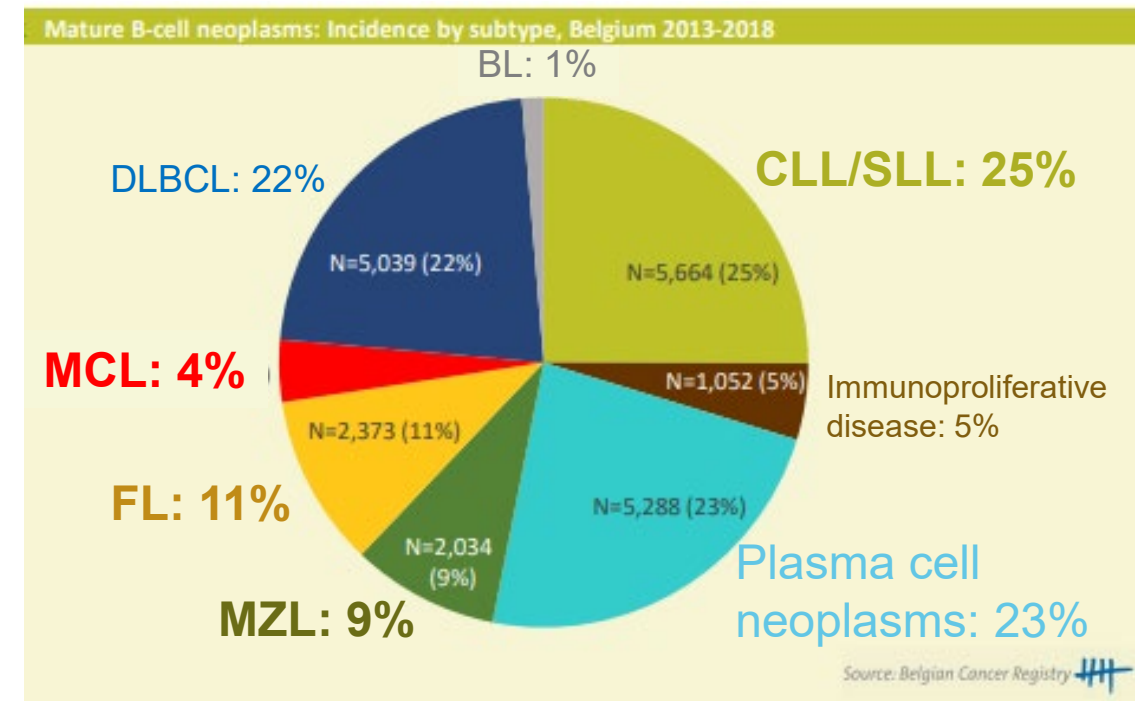
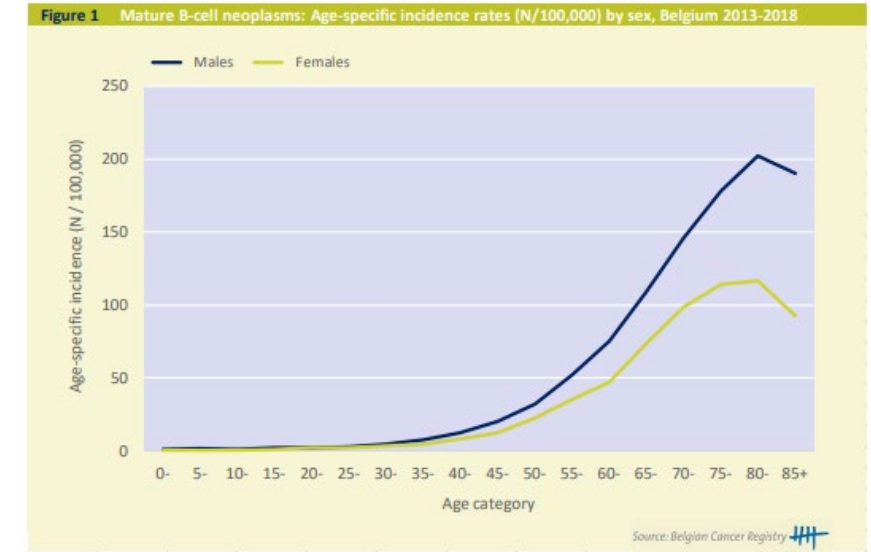


Outline

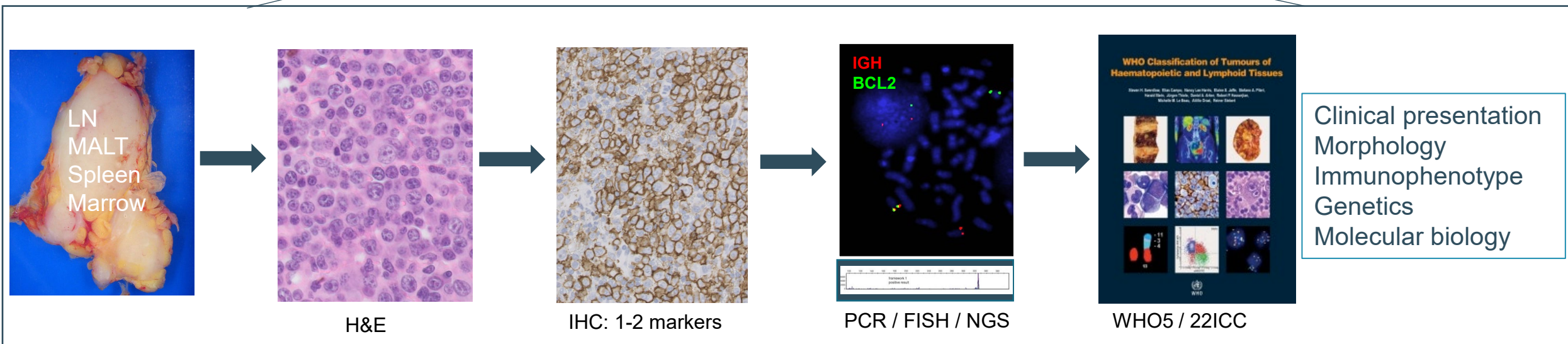
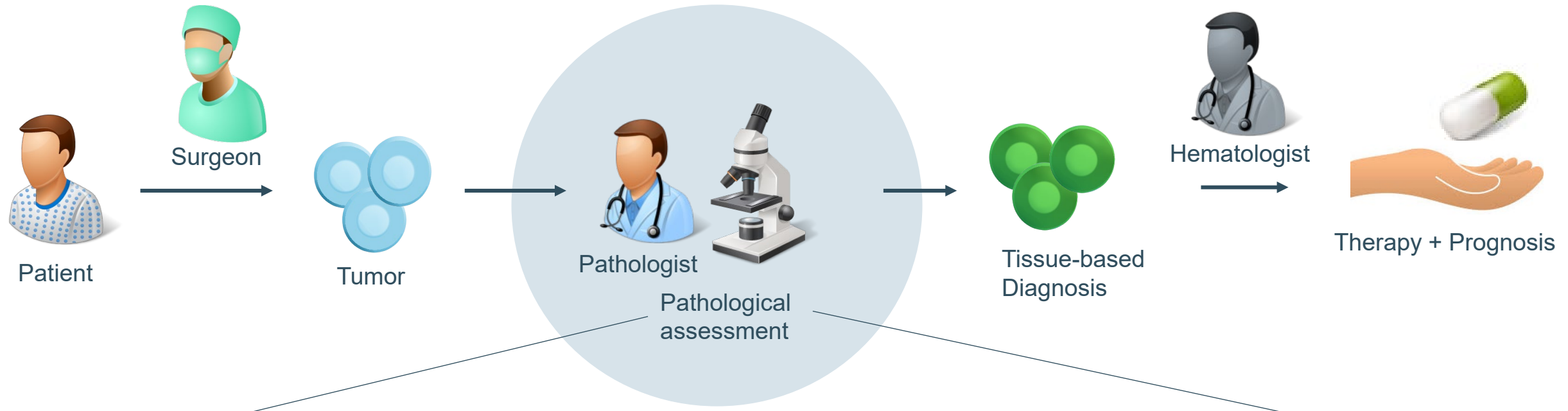
- Intro on the role for the pathologist in diagnosis indolent B-cell lymphoma
- Two running classifications : ICC vs WHO HAEM5
- Changes in the 'small cell' B-cell lymphoma classifications
- Summary

Indolent B-cell lymphoma

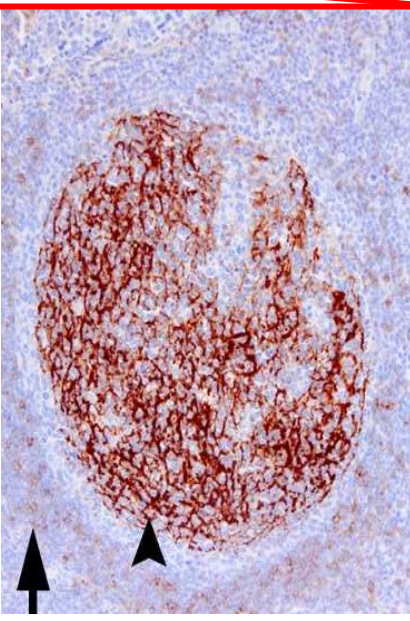
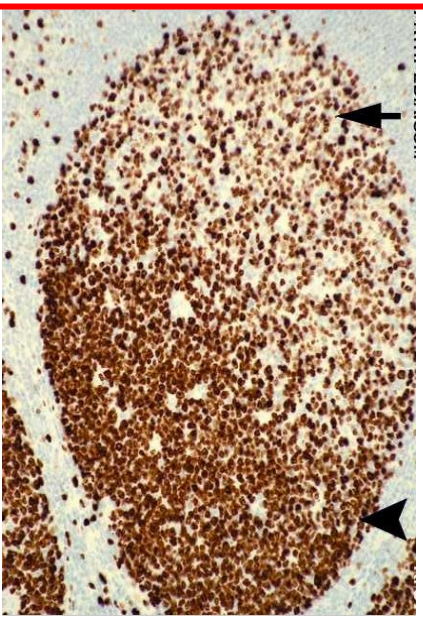
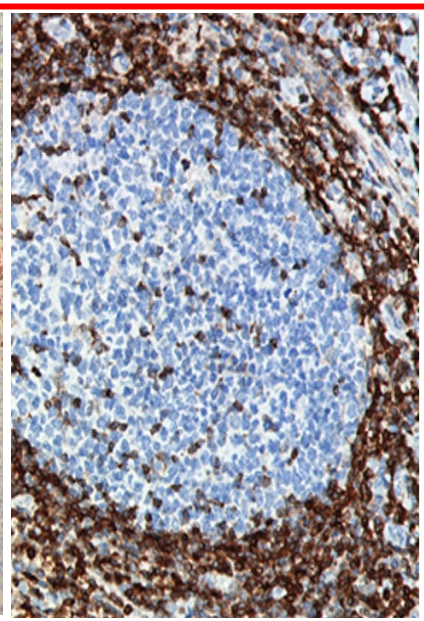
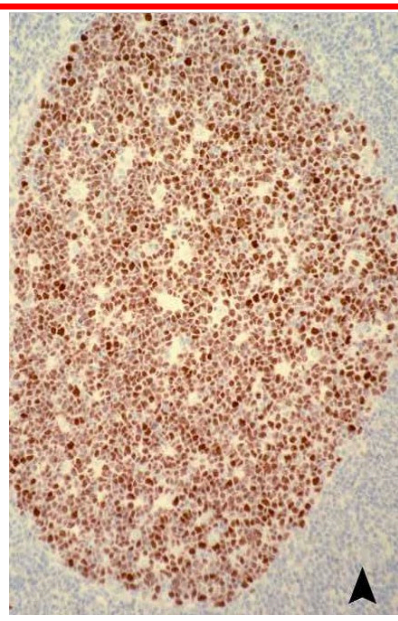
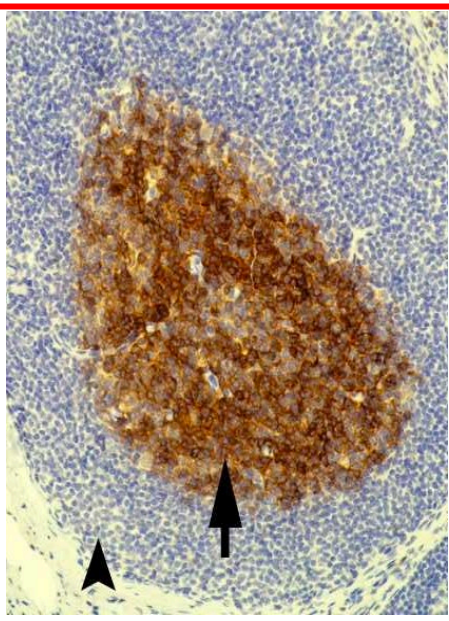
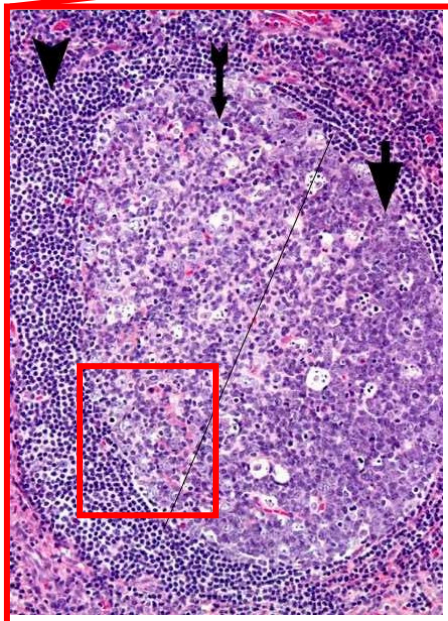
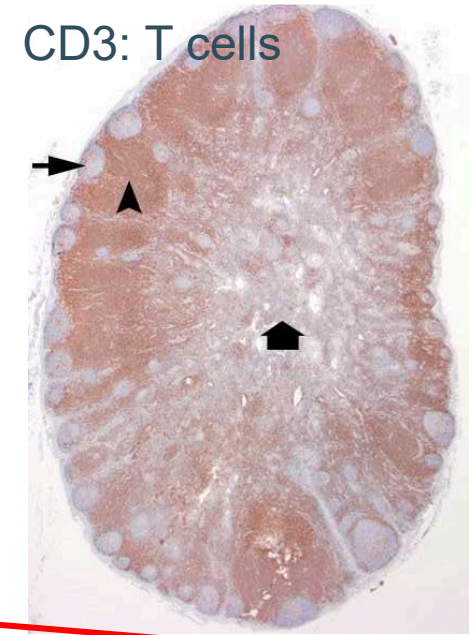
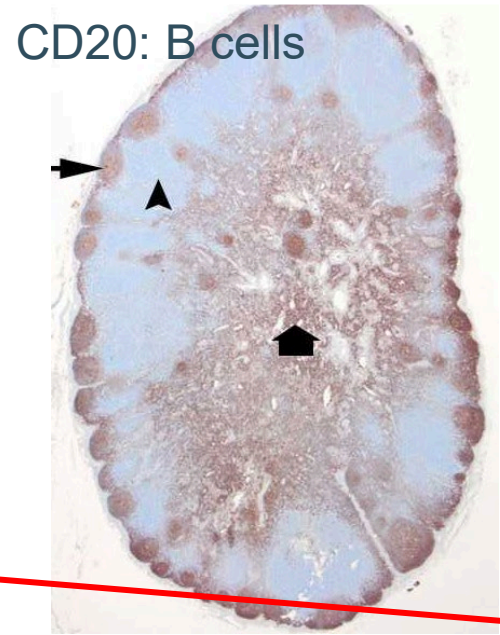
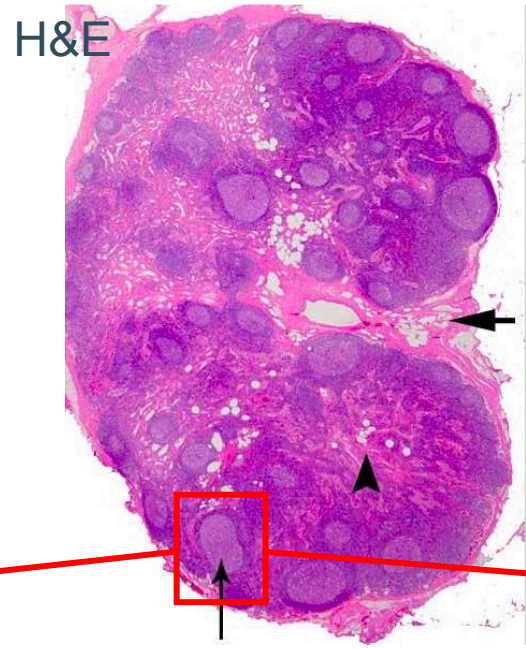
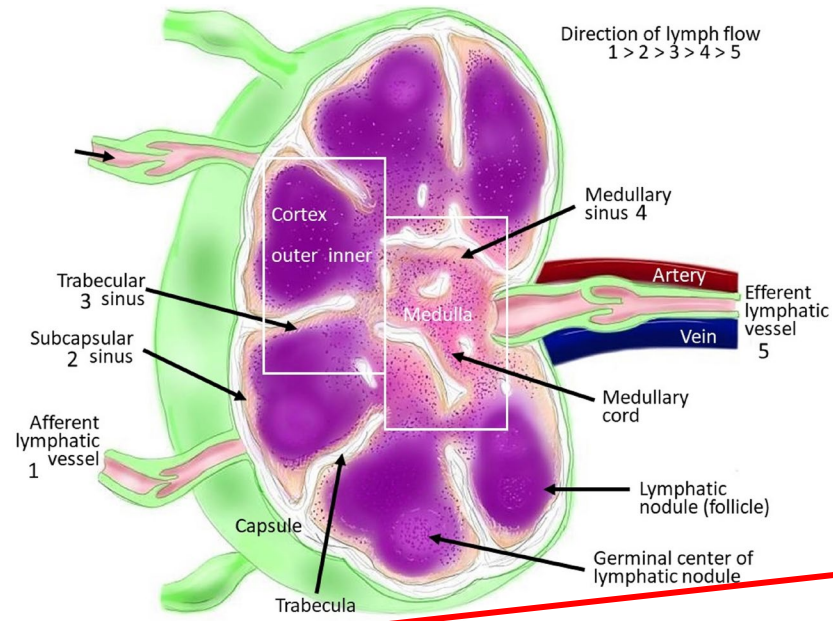
- Mainly in **older** patients; **M>F**
- **Nodal, extranodal, splenic** or **leukemic** involvement
- Follicular or diffuse proliferation of **small B-cells**
- **Low** proliferation **Ki67** index
- Generally **good prognosis**



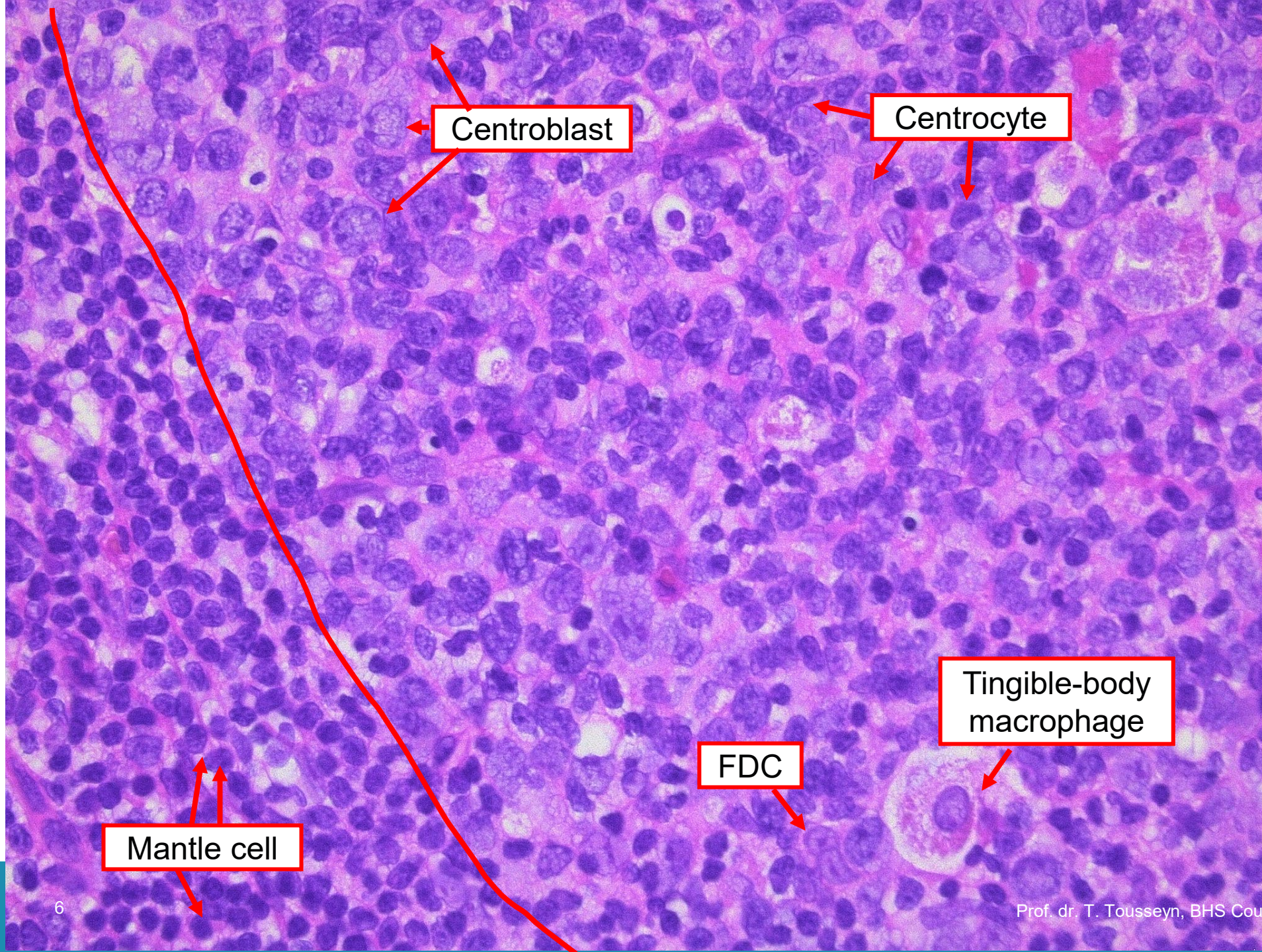
How to make the diagnosis of indolent B-cell lymphomas



Morphology/immunophenotype of normal lymph node



H&E CD10/BCL6: germinal center B-cell BCL2: anti-apoptotic Ki67: proliferation CD23: FDC



Two running classifications since 2022

Clinical Advisory Committee meetings: consensus classification

1997



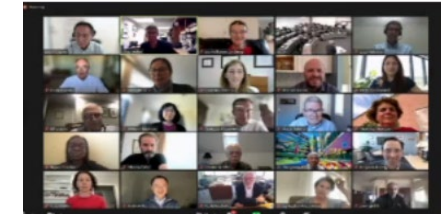
2007



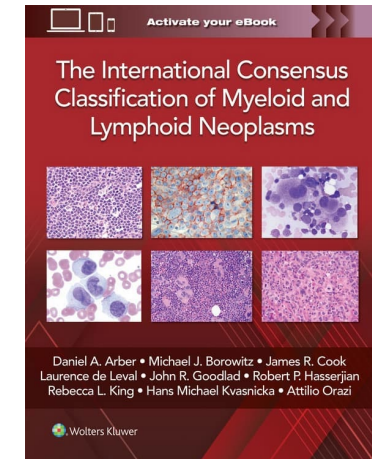
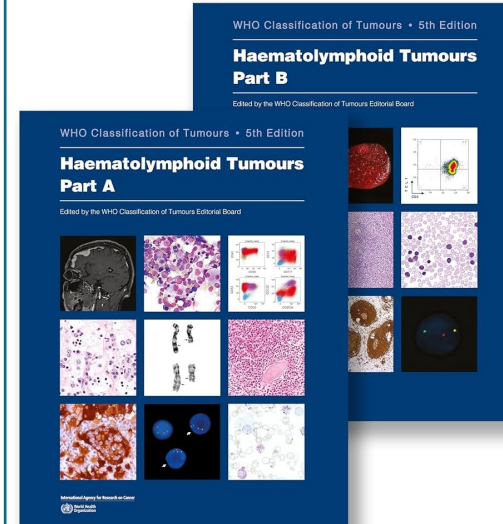
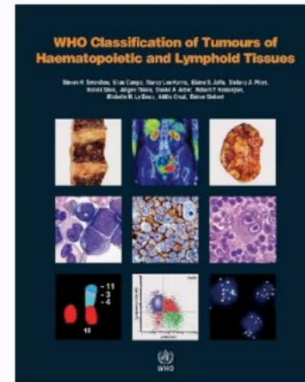
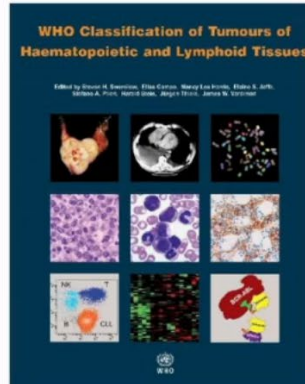
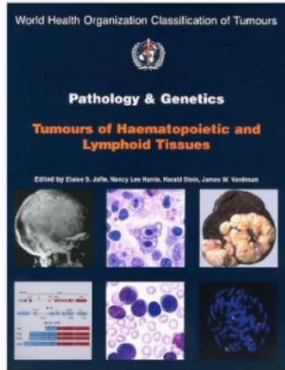
2014



2020:



2026:
HAL6



2001: WHO HAEM3

2008: WHO HAEM4

2017: WHO HAEM4 rev

2022: WHO HAEM5

ICC - International Consensus Classification

'Small cell' B-cell lymphomas in WHO HAEM 2017

WHO 2017	Included entities
(Pre) neoplastic small lymphocytic	Monoclonal B-cell lymphocytosis - CLL-type - MBL, non CLL-type B-CLL/SLL
B-cell prolymphocytic leukemia	
Splenic B-cell lymphomas	Splenic marginal zone lymphoma Hairy cell leukemia <i>Splenic B-cell lymphoma/leukemia, unclassifiable</i> - Splenic diffuse red pulp small cell B-cell lymphoma - HCL-variant
Lymphoplasmacytic lymphoma	- Waldenström macroglobulinemia
Marginal zone lymphoma	Nodal MZL Extranodal MALT
Pediatric nodal MZL	
Follicular lymphoma (1-2;3A;3B)	- In situ follicular neoplasia - Duodenal-type FL
Paediatric-type FL Primary cutaneous follicle center cell lymphoma	
Mantle cell lymphoma	- In situ mantle cell neoplasia - Leukaemic non-nodal mantle cell lymphoma
Transformations of indolent B-cell lymphomas	

Follicular lymphomas

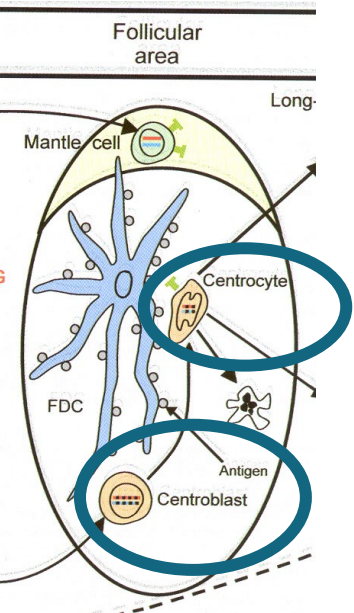
WHO 2017

Follicular lymphoma (1-2, 3A vs 3B)

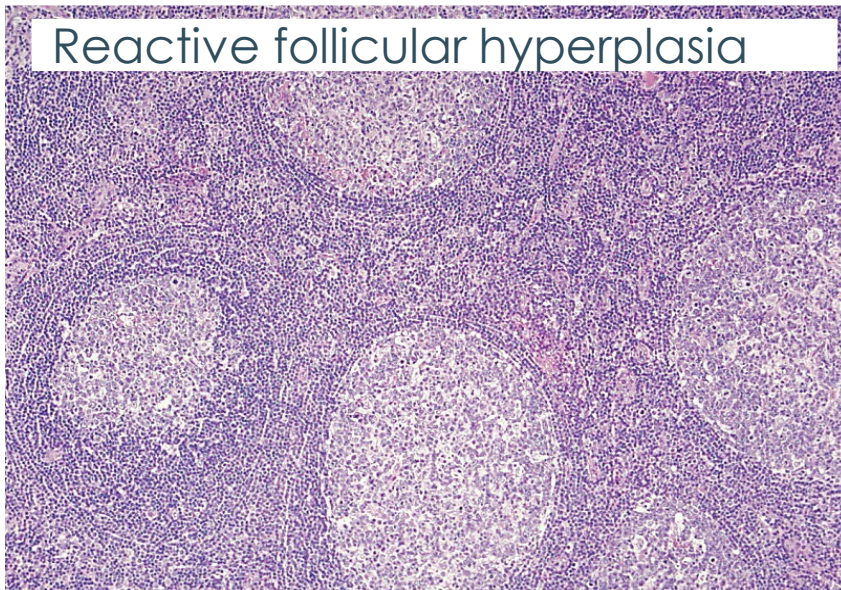
- *In situ* follicular neoplasia
- Duodenal-type FL

Paediatric-type FL

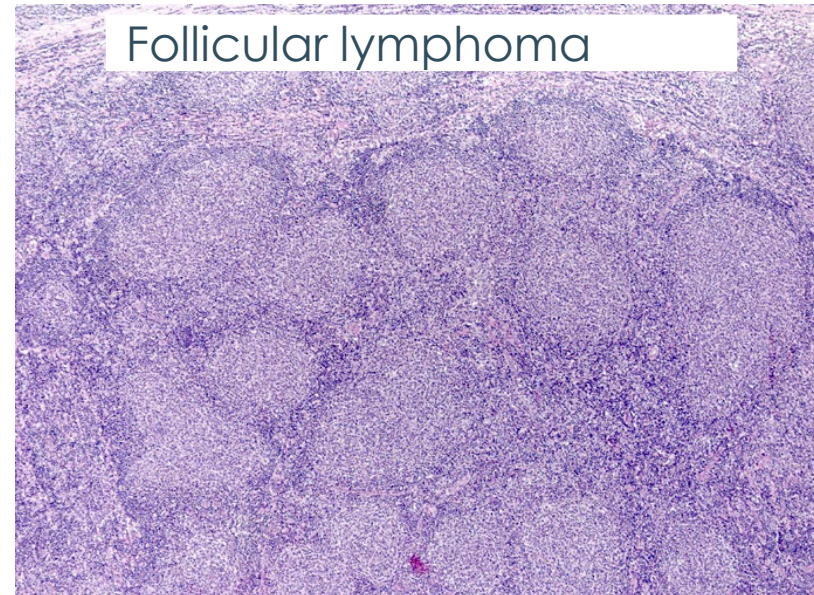
Primary cutaneous follicle center cell lymphoma



Reactive follicular hyperplasia

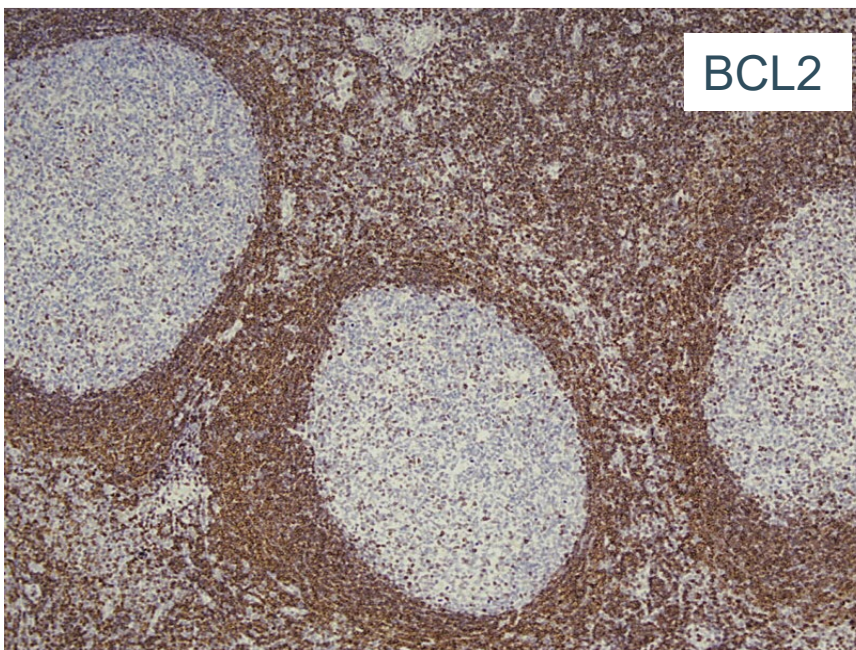


Follicular lymphoma

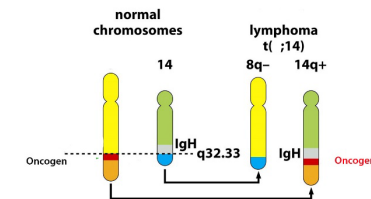
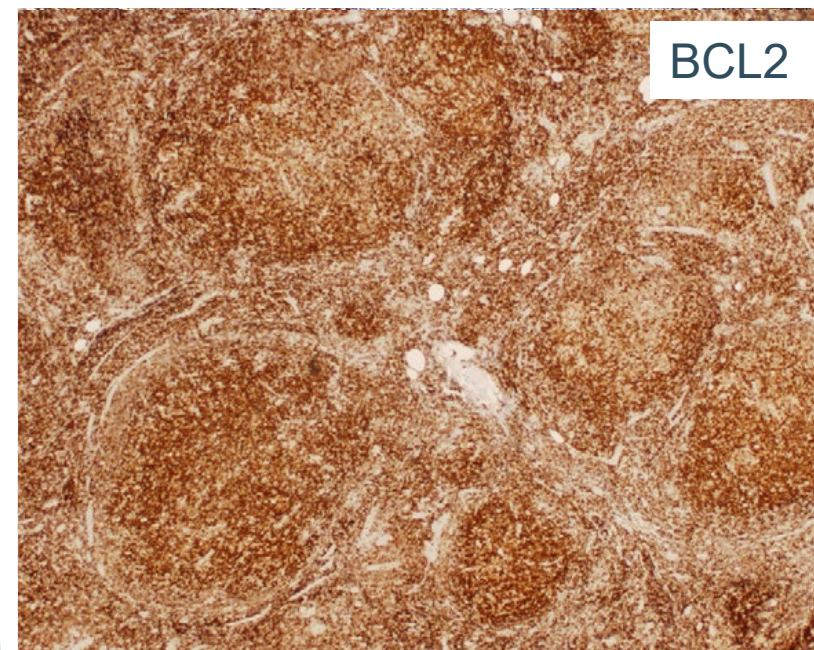


BCL2
Switched off
in germinal
center
B-cells

BCL2

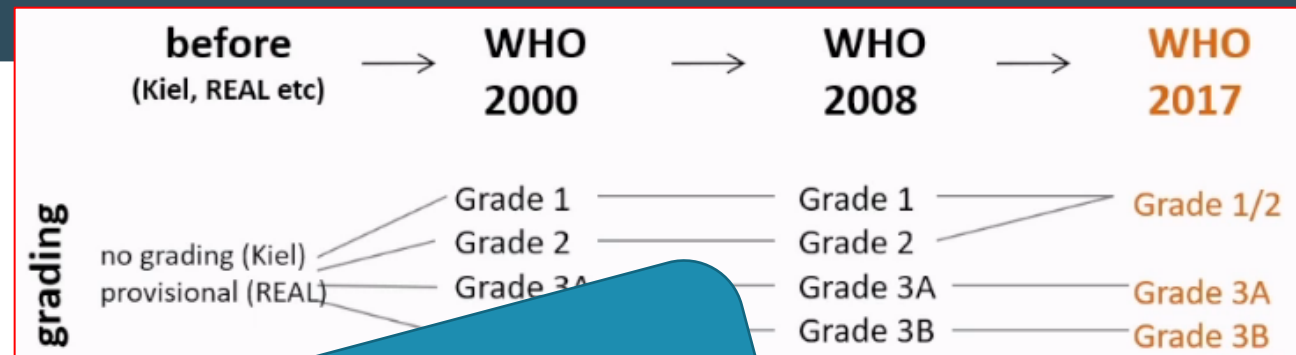


BCL2

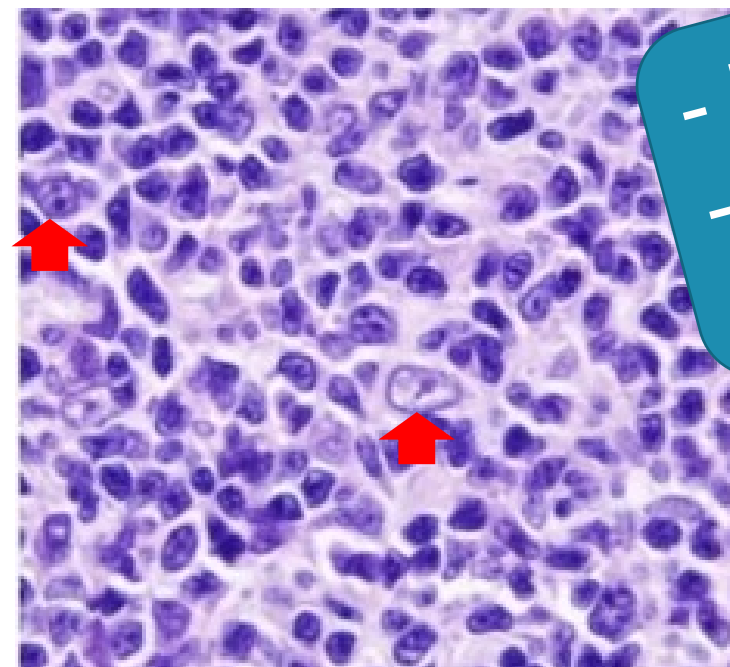


BCL2
overexpression
Related to
t(14;18)(IgH;BCL2)

Problem 1: grading



- Grade 1-2



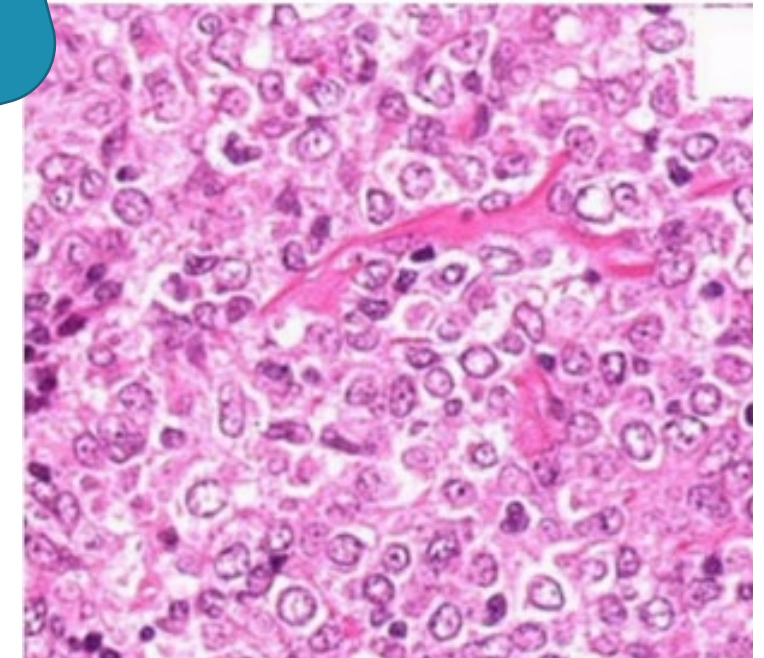
<15 centroblasts/HPF

- Reproducibility?
- Prognostic relevance?
- Cases difficult to grade



>15 centroblasts/HPF

- Grade 3B

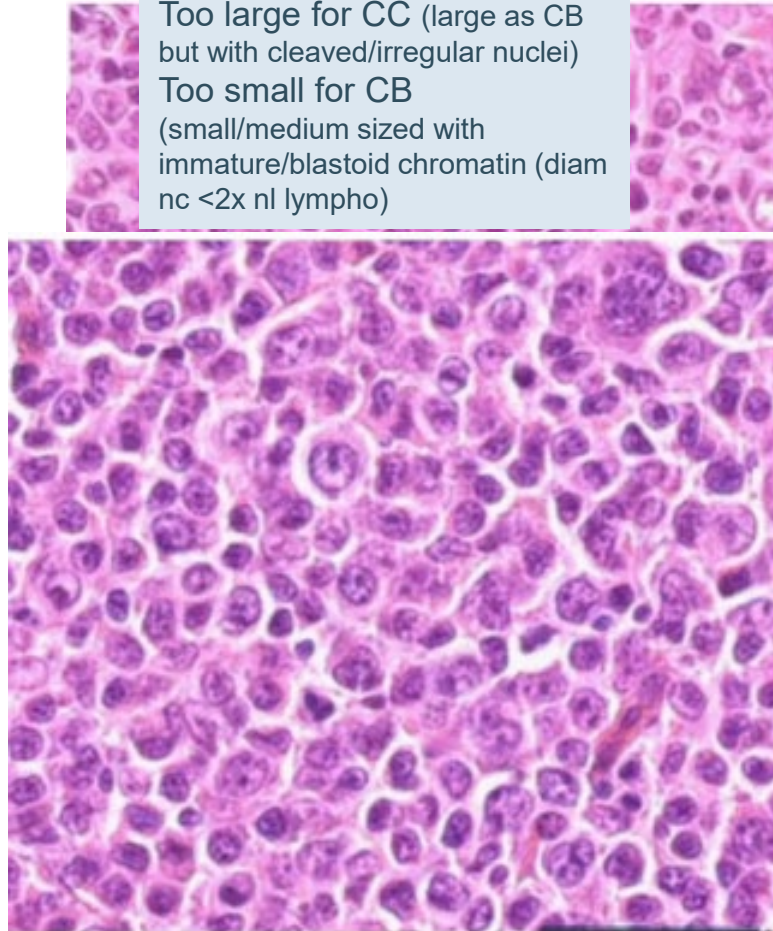


Only centroblasts, no CC

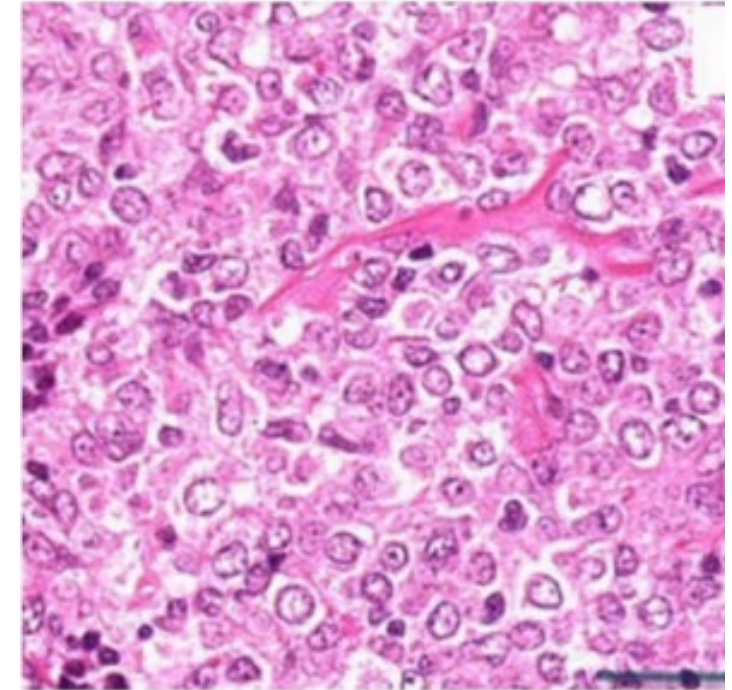
Problem 1: grading: some cases of FL remain difficult to grade

- ?????

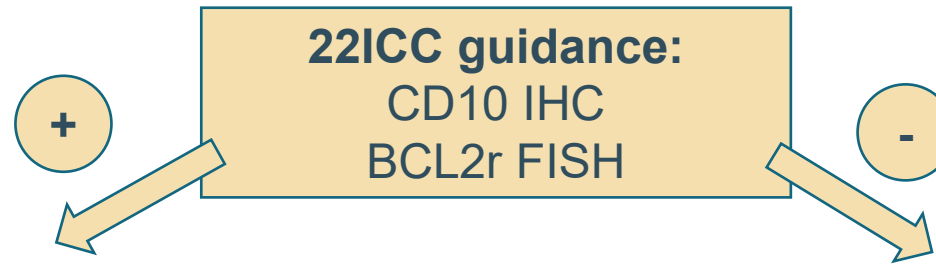
Follicular growth
No conventional CC
Too large for CC (large as CB
but with cleaved/irregular nuclei)
Too small for CB
(small/medium sized with
immature/blastoid chromatin (diam
nc <2x nl lympho)



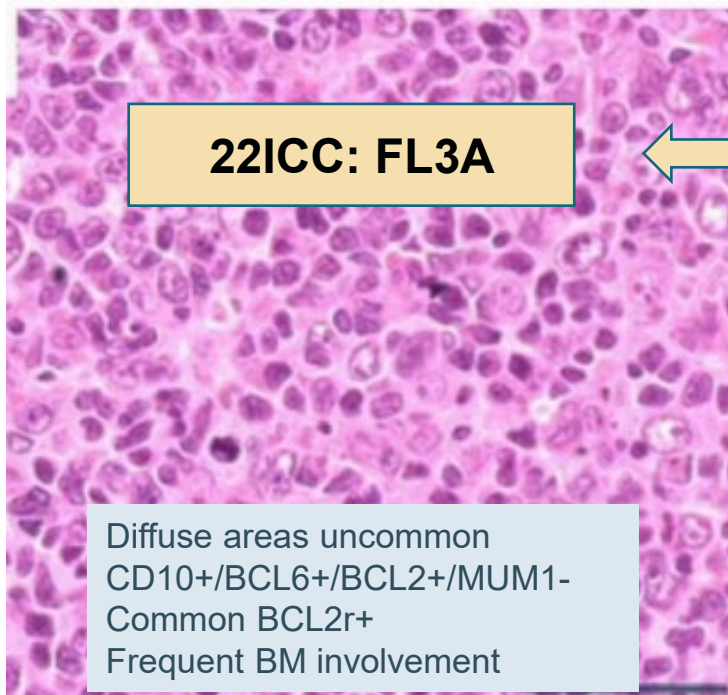
- Grade 3B



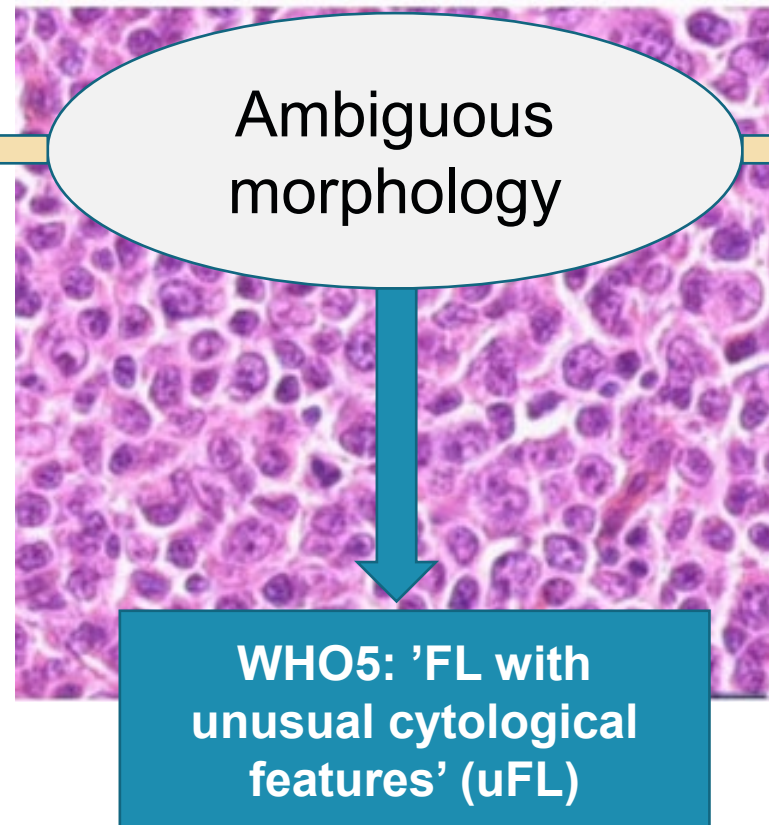
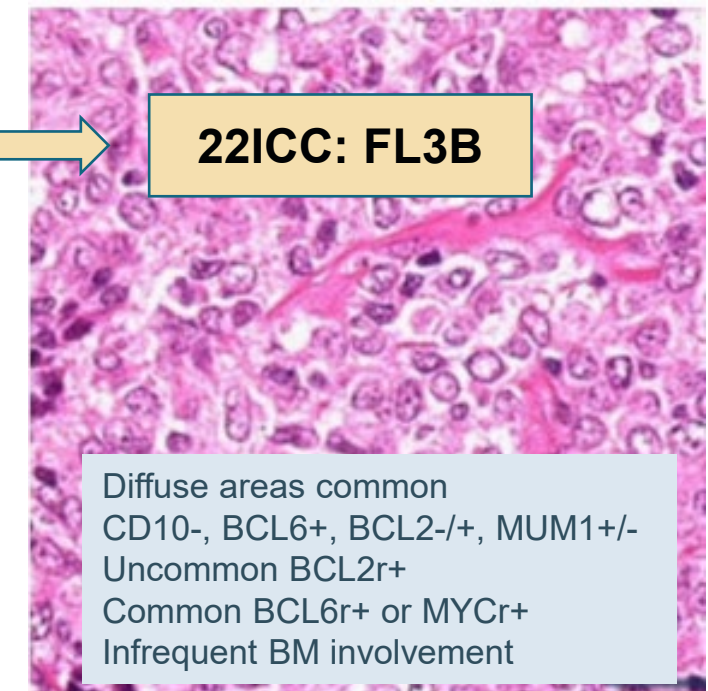
Problem 1: grading: guidance for cases difficult to grade?



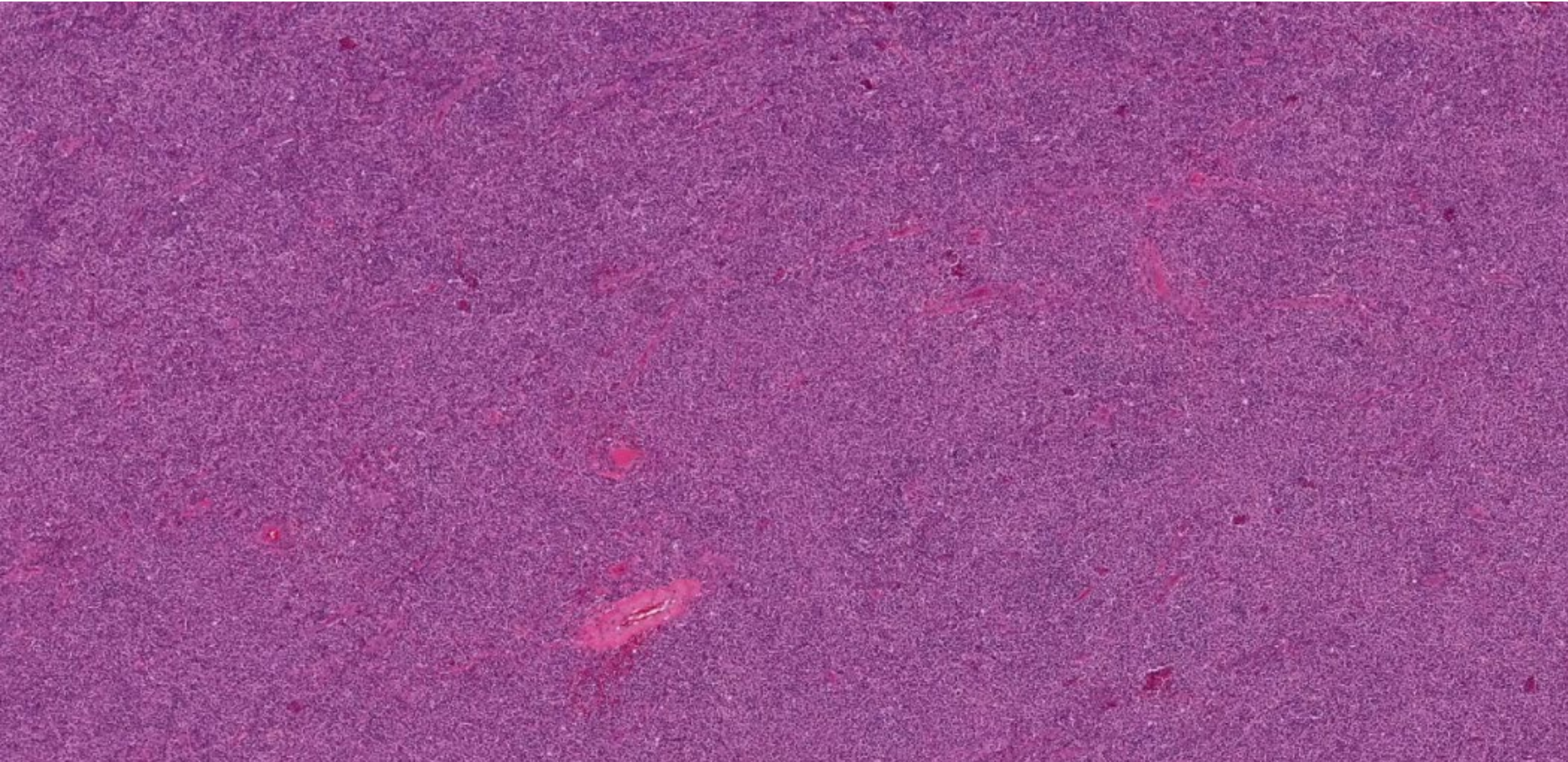
• Grade 3A

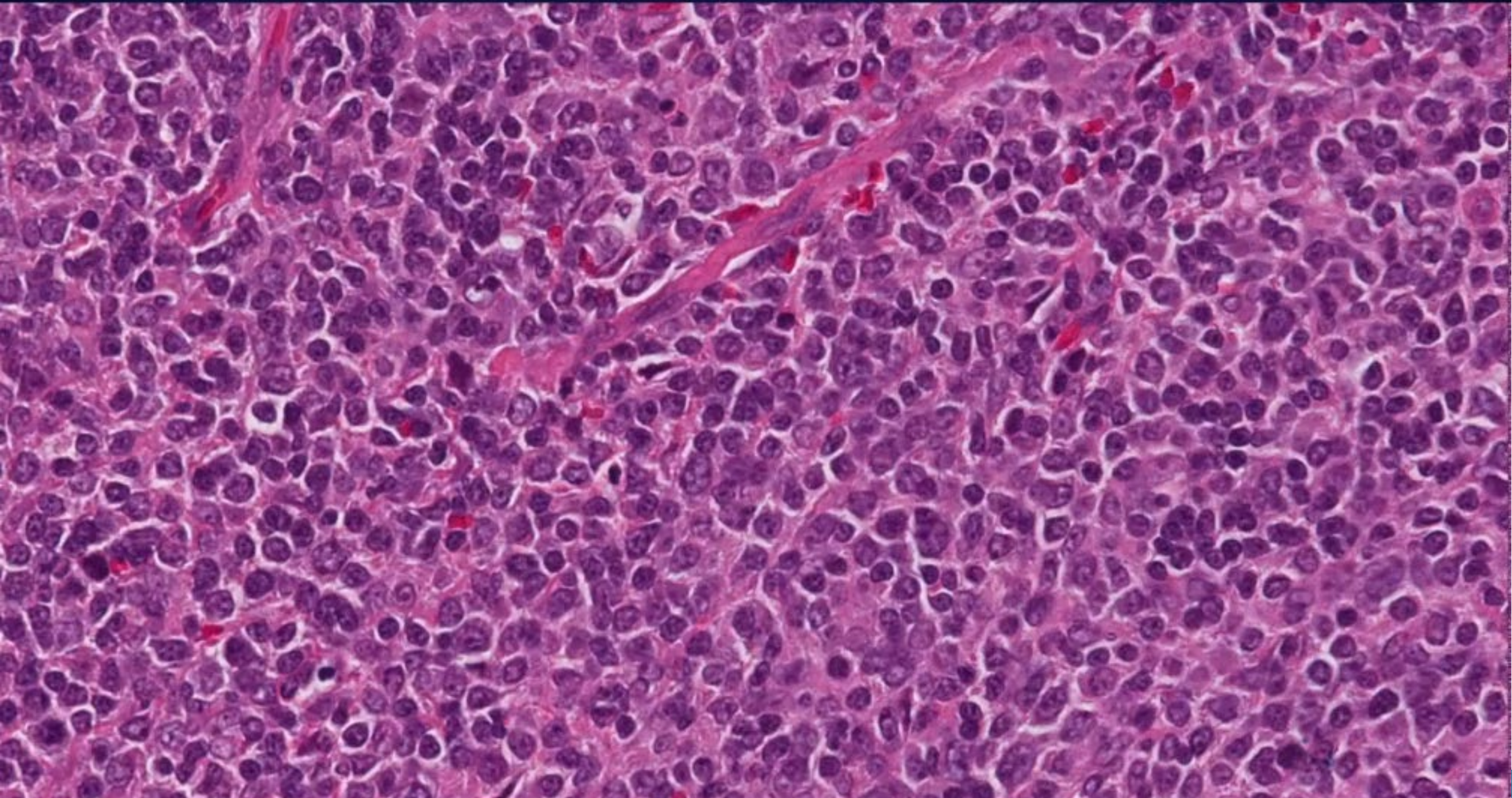


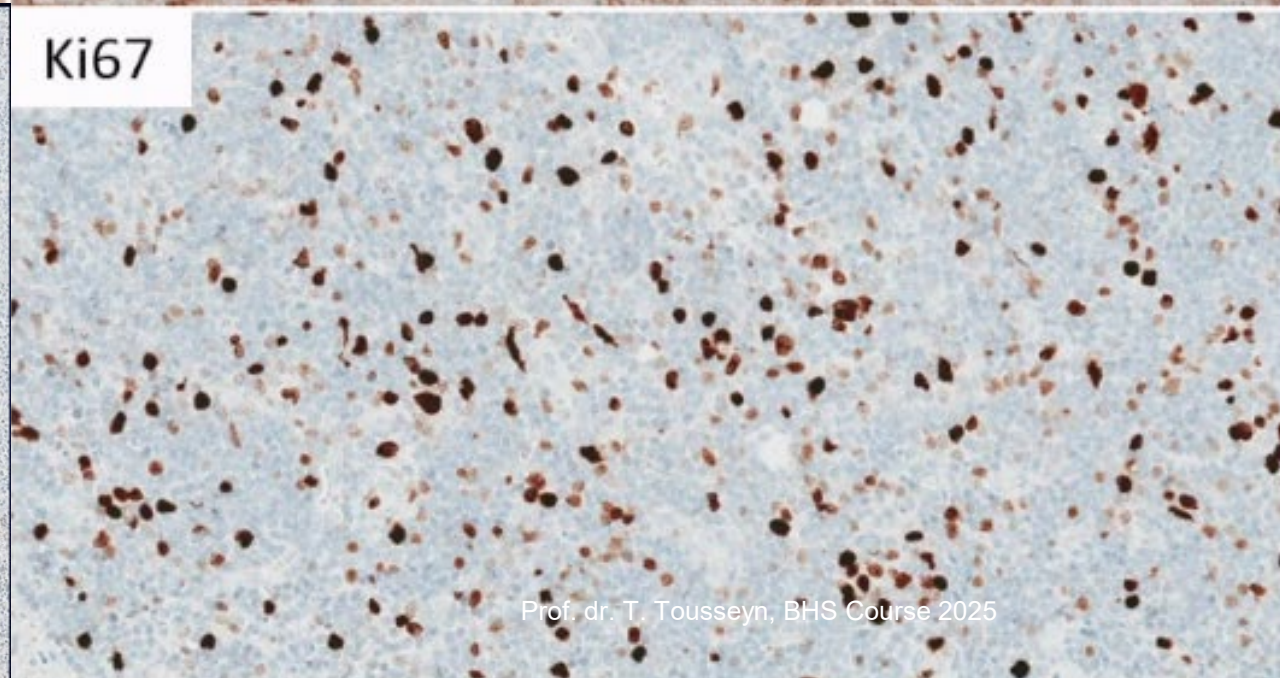
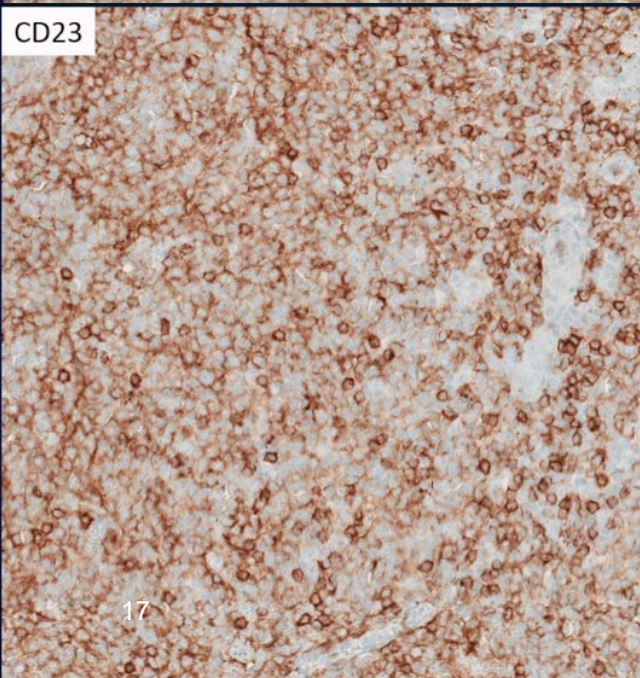
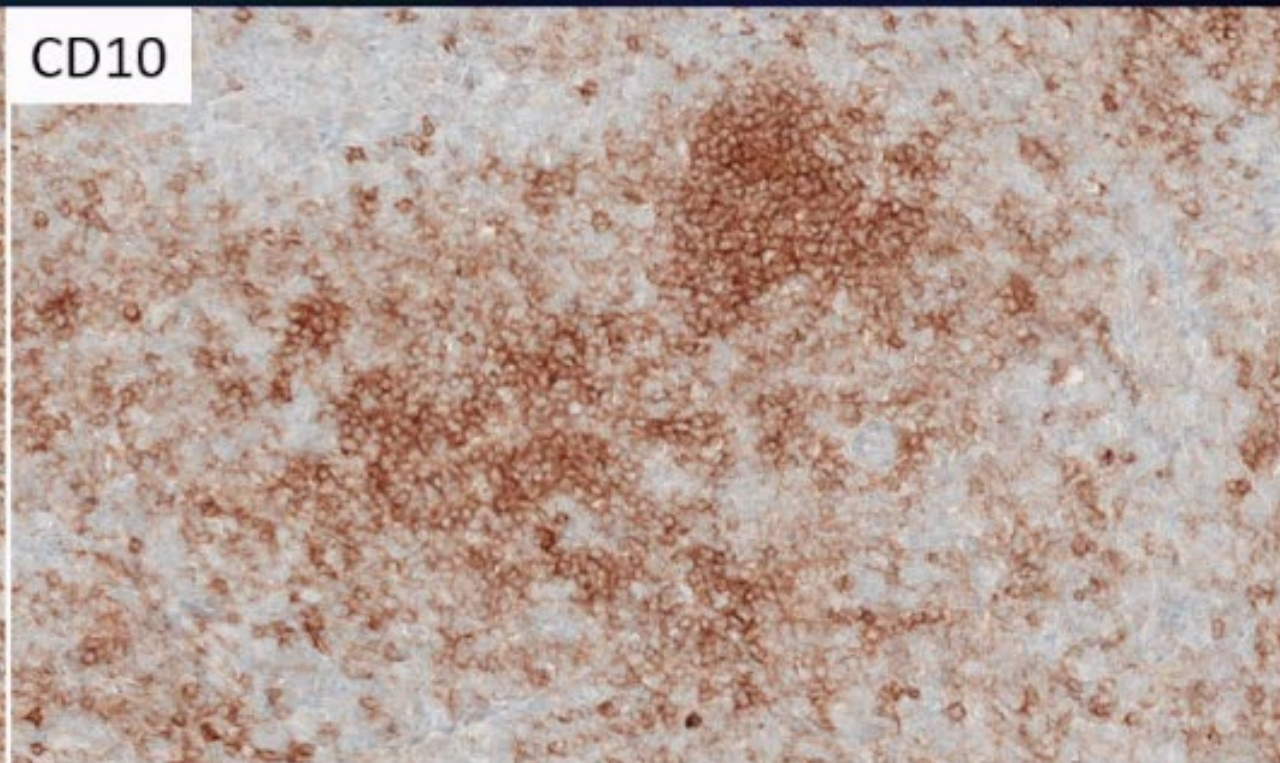
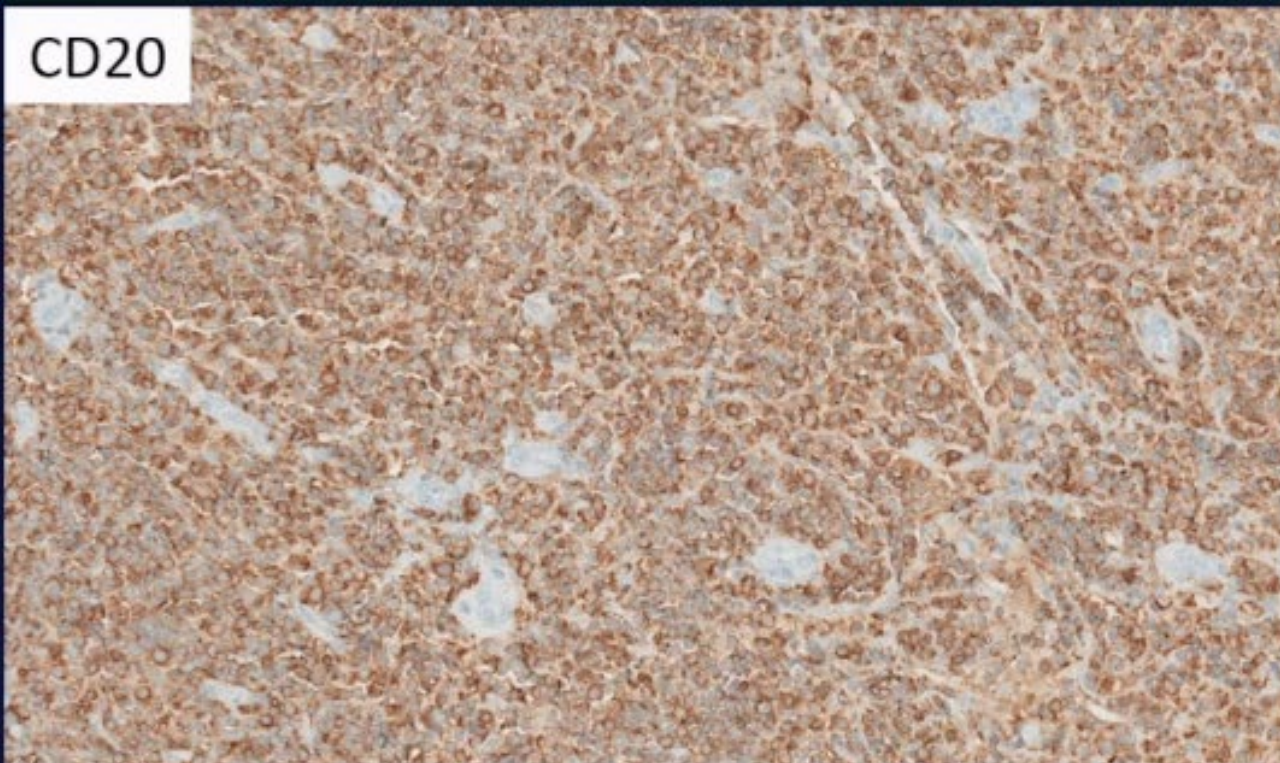
• Grade 3B



Problem 2: some cases of FL lack follicular growth

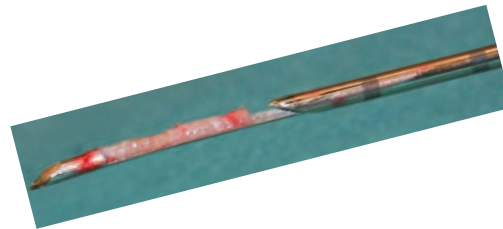




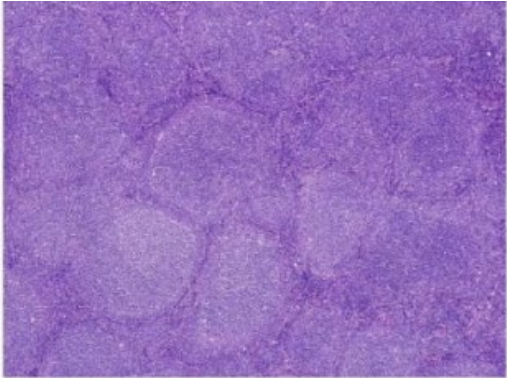
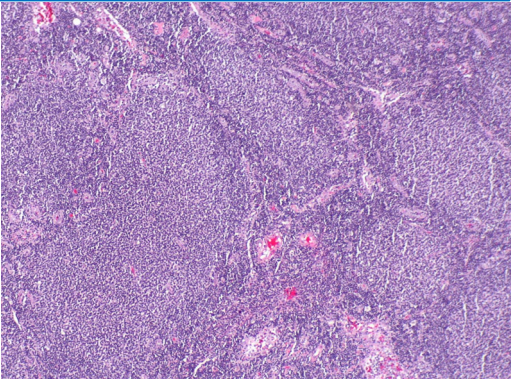
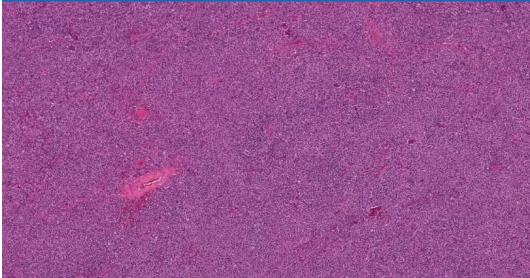
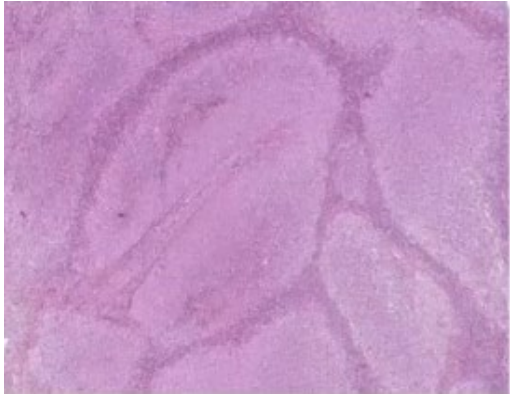
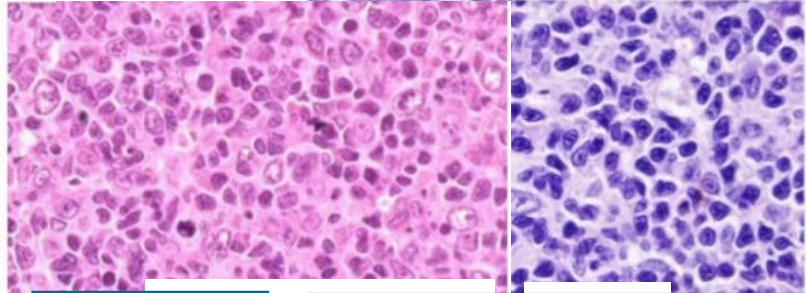
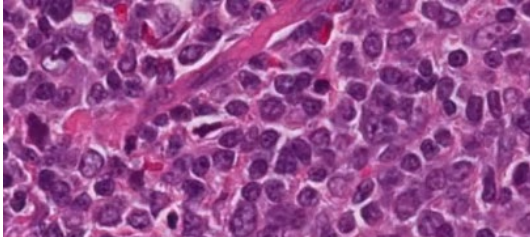
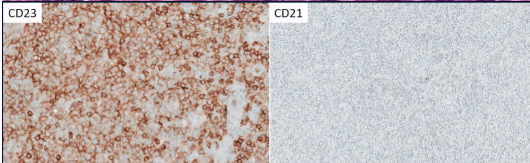
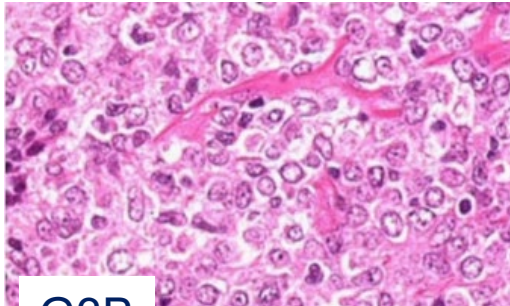
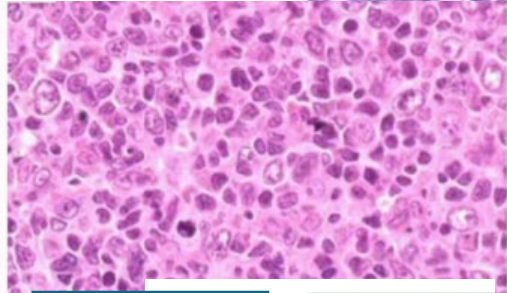
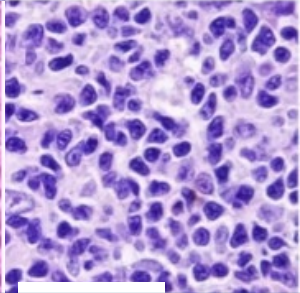
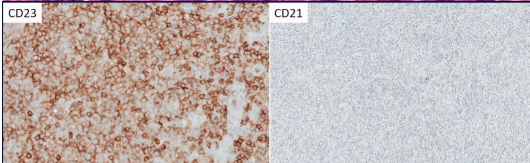
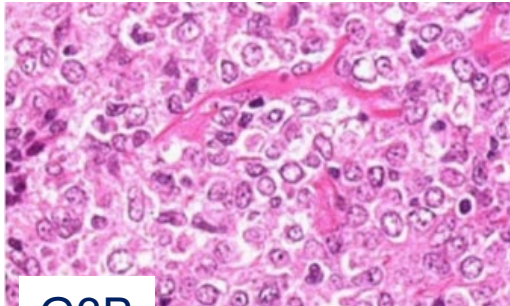


22ICC: *BCL2-R* negative, *CD23*+ follicle center lymphoma

- *New provisional entity in 22ICC* (WHO5: 'FL with predominantly diffuse growth (dFL))
- M:F ratio 1:2
- **Inguinal** LN (also axillary/cervical)
- **Low** stage
- Often **diffuse** pattern (follicular in 35%)
- No *BCL2-R*, but commonly **1p36 loss**
- *CREBBP* and *STAT6* mutations
 - **CD23 expression** serves as surrogate for *STAT6* mutation
- Excisional biopsy preferable

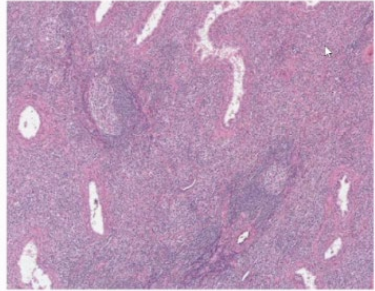


WHO HAEM5 approach on grading and subtyping: 4 subtypes of FL

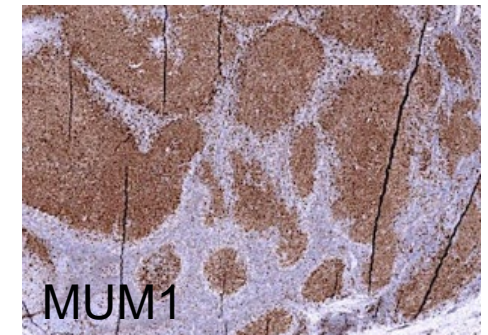
WHO HAEM5:	Classic Follicular Lymphoma (cFL)	FL with unusual cytological features (uFL)	FL with predominantly diffuse growth (dFL)	Follicular Large B-cell lymphoma (FLBCL)
	At least partially follicular pattern Mix of CC and CB (WHO17: FL1-2, 3A)	At least partial follicular No conventional CC Too large for CC (large as CB but with cleaved/irregular nuclei) Too small for CB (small/medium sized with immature/blastoid chromatin (diam nc <2x nl lympho))	Entirely diffuse (can contain pre-existent (micro)follicles) Mix CC + CB, usually CD23+ Mainly inguinal No t(14;18) Frequent del1p36, STAT6	Purely follicular pattern Sheets of CB (WHO17: FL3B)
        	 			
22ICC: 04	22ICC: FL1-2, 3A	FL3A (if CD10+/BCL2r+) FL3B (if CD10-/BCL2r-)	<i>BCL2-R neg, CD23+ FL</i>	FL3B

Some considerations

- If **<40y** of age: consider **paedriatic-type FL** (separate entity)
- If in **small intestine**: consider **duodenal-type FL** (separate entity)
- If in **testis**: classify as **testicular FL** (separate entity in ICC, not in WHO)
 - Predominantly **children/teenagers** (rare in adults)
 - No BCL2 overexpression (IHC), **no *BCL2-r*** (FISH), clonal PCR
 - Can be managed **conservatively** w/o chemo



- If **FL3B** (FLBCL in WHO), or **ambiguous** morphology, exclude **Large B-cell lymphoma with *IRF4* rearrangement** by FISH (*IG:IRF4r*), especially:
 - in **children/young** adults
 - if **strong MUM1** and **BCL6** expression
 - if **CD10-ve** IHC and **no BL2r**
 - Usually **favorable** outcome, good response to chemo



‘Small cell’ B-cell lymphomas of follicle center origin

WHO 2017	22ICC	WHO HAEM5
Follicular lymphoma (1-2, 3A vs 3B) - In situ follicular neoplasia - Duodenal-type FL	Follicular lymphoma (1-2, 3A vs 3B) - In situ follicular neoplasia - Duodenal-type FL	Classic follicular lymphoma (cFL) (replaces FL1-2, 3A) Follicular large B-cell lymphoma (replaces FL3B) Diffuse follicular lymphoma (dFL) FL with uncommon features (uFL) - In situ follicular neoplasm - Duodenal-type FL - Gonadal FL
	Testicular FL	---
	<i>BCL2-R negative CD23+ follicle center lymphoma</i>	
Paediatric-type FL	Paediatric-type FL	Paediatric-type FL
Primary cutaneous follicle center cell lymphoma	Primary cutaneous follicle center cell lymphoma	Primary cutaneous follicle center cell lymphoma
<i>LBCL with IRF4 rearrangement</i>	LBCL with <i>IRF4</i> rearrangement	LBCL with <i>IRF4</i> rearrangement

News on Splenic B-cell lymphomas in WHO5?

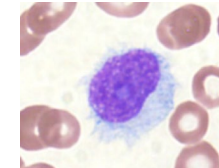
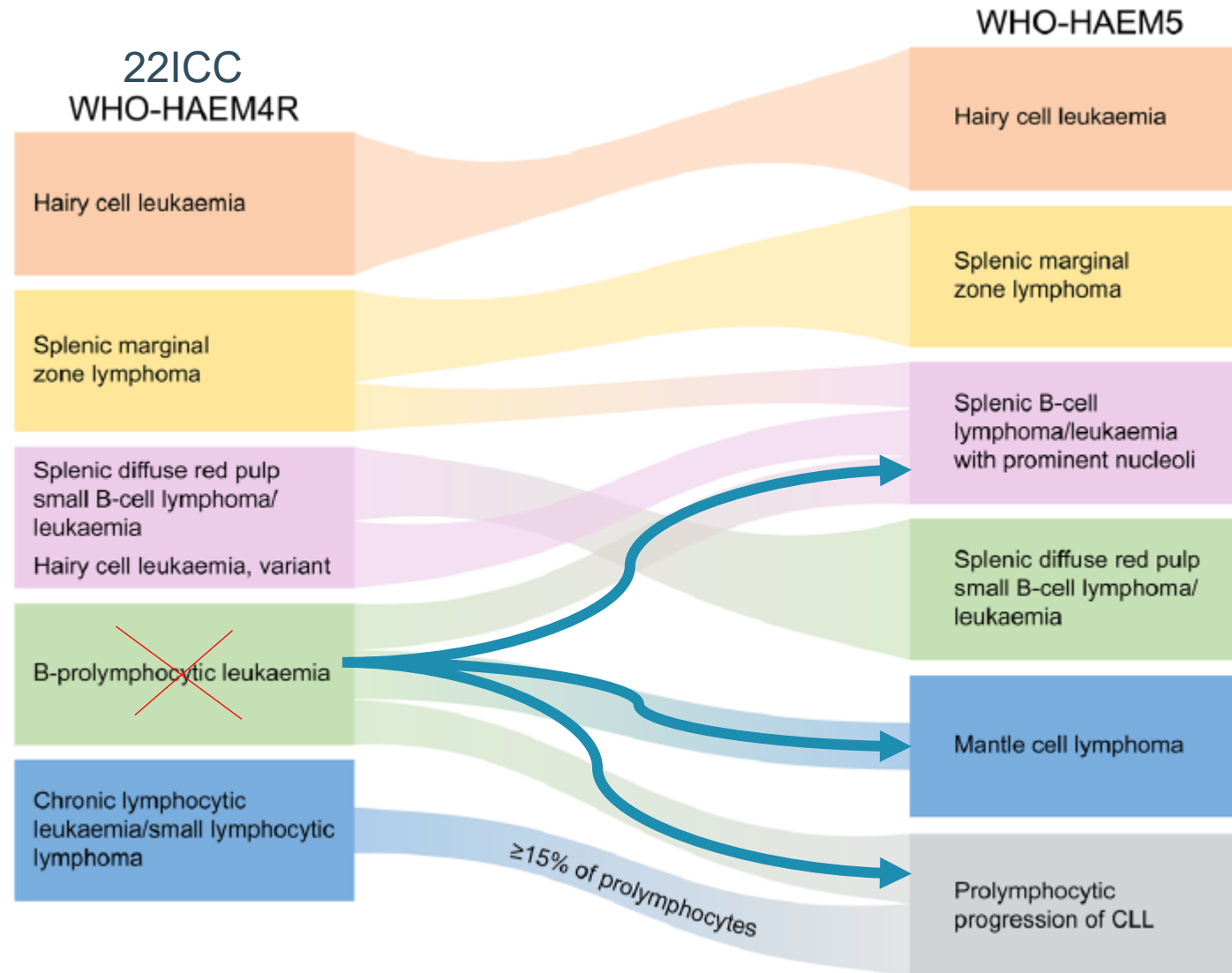
No major changes in 22ICC

But changes in WHO HAEM5

WHO 2017	
B-cell prolymphocytic leukemia	
Splenic marginal zone lymphoma	
Hairy cell leukemia	
<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i>	
<i>- Splenic diffuse red pulp small cell B-cell lymphoma</i>	
<i>- HCL-variant</i>	

- ‘*HCL variant*’ renamed ‘**splenic B-cell lymphoma/leukemia with prominent nucleoli**’
- ~~**B-cell prolymphocytic leukemia (B-PLL)**~~ was abandoned
 - No defining molecular/clinicopathologic features
 - Cytology diagnosis; biopsy often missing (showing low grade B-NHL)
 - Incidence dropped
 - Often transformation to CLL, MCL or other indolent B-NHL
 - Often (2nd) *MYC* and *TP53* aberrations
- **Prolymphocytic progression of CLL**
 - >15% prolymphocytes (vs >55% in WHO4R)

Splenic B-cell lymphoma/leukemia in WHO5



Alaggio R et al. Leukemia 2022 Jul;36(7):1720-1748

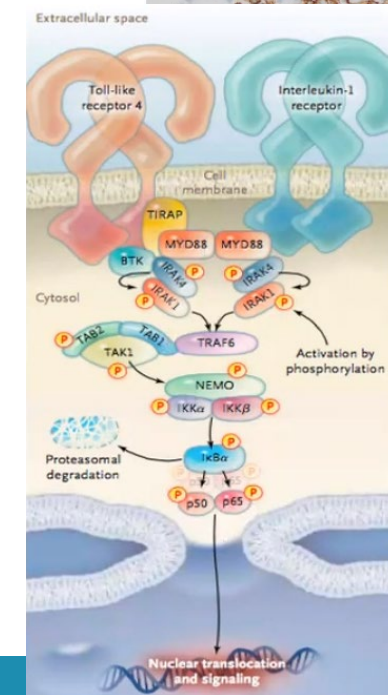
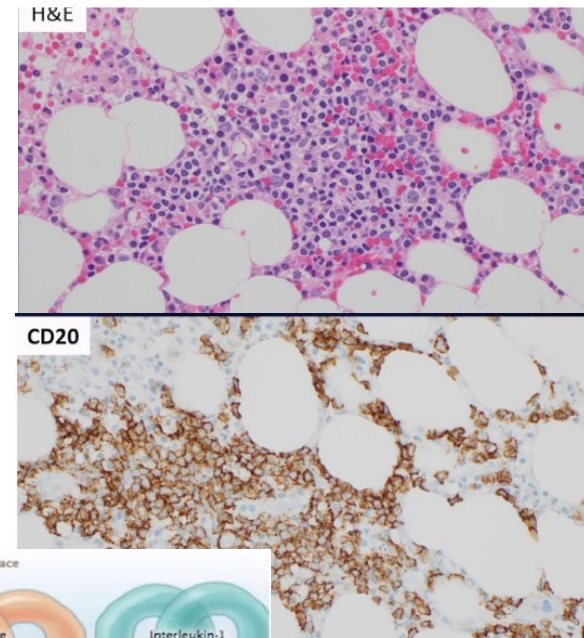
Splenic B-cell lymphomas/leukemias

WHO 2017	22ICC	WHO HAEM5
Mantle cell lymphoma	Mantle cell lymphoma	Mantle cell lymphoma
B-CLL/SLL	B-CLL/SLL	B-CLL/SLL
B-cell prolymphocytic leukemia	B-cell prolymphocytic leukemia	-----
Splenic marginal zone lymphoma	Splenic marginal zone lymphoma	Splenic marginal zone lymphoma
Hairy cell leukemia	Hairy cell leukemia	Hairy cell leukemia
<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i> <i>- Splenic diffuse red pulp small cell B-cell lymphoma</i> <i>- HCL-variant</i>	<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i> <i>- Splenic diffuse red pulp small cell B-cell lymphoma</i> <i>- HCL-variant</i>	<i>Splenic diffuse red pulp small cell B-cell lymphoma</i> <i>Splenic lymphoma with prominent nucleoli</i>

Refined diagnostic criteria for 'Small cell' B-cell lymphomas in 22ICC

Lymphoplasmacytic lymphoma (LPL)

- 2017 WHO-HAEM4r
 - Clonal lymphoplasmacytic infiltrate must be $\geq 10\%$ cellularity
 - If $< 10\%$ considered IgM MGUS
- 2005 Intl Waldenström's Macroglobulinemia workshop
 - IgM paraprotein plus lymphoplasmacytic infiltrate of any extent in trephine
- 22ICC:
 - LPL may be diagnosed when abnl aggregates of clonal B- and plasma cells present, **even if $<10\%$ of cellularity**
 - After exclusion of other small B-cell neoplasms with plasmacytic diff
 - Molecular studies for **MYD88 L265P** and **CXCR4** strongly recommended



Ibrutinib
(BTK-inhibitor)

Novel entities in 22ICC

Testicular FL (WHO5: under cFL)

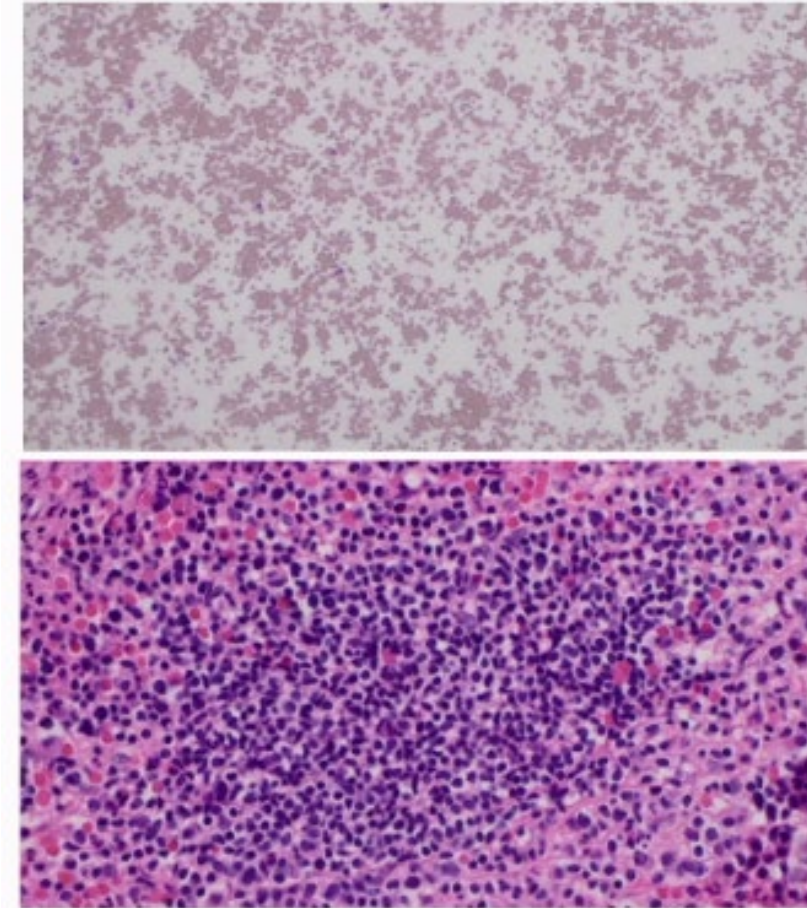
BCL2-R negative CD23+ follicle center lymphoma (WHO5: uFL)

Primary cold agglutinin disease (not in WHO5)

Primary cutaneous marginal zone lymphoproliferative disorder (WHO5: Primary cutaneous marginal zone lymphoma)

Primary cold agglutinin disease

- Distinct entity (*vs secondary AI, inf, malignancy*)
 - Hemolysis due to autoantibodies against RBC Ag
 - Clinical symptoms due to RBC agglutination in cooler parts of the body
- Low-grade clonal B-cell proliferation
 - CD10-, CD5-/+, CD23-
- IGHV4-34 utilisation
- Frequent mutations in **CARD11** and **KMT2D**, but not in **MYD88**
- Trisomies of chr 3, 12 & 18



Primary cutaneous marginal zone lymphoproliferative disorder

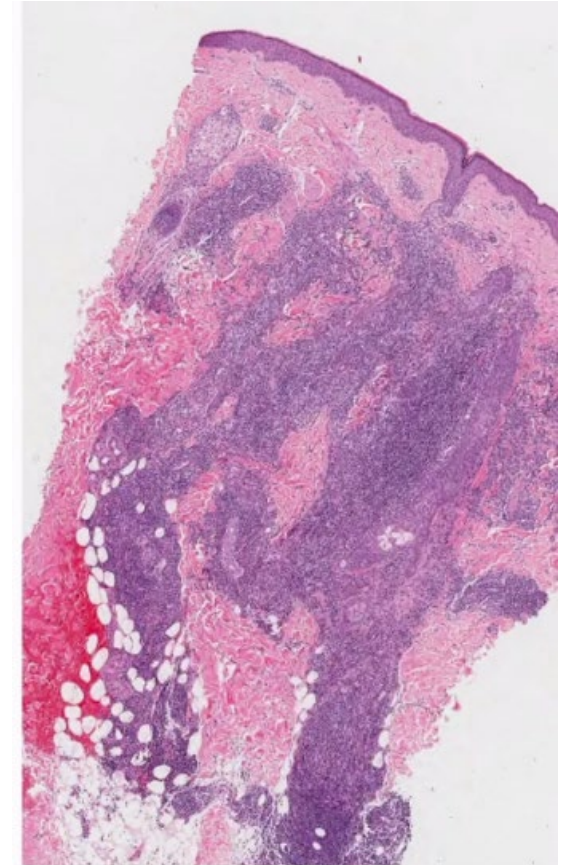
- **LPD** rather than lymphoma (WHO5: lymphoma)
- **2 groups**

Class switched (IgG or IgA)

- >80%
- Cutaneous relapse can occur
- But survival ~100%

Non-class switched (IgM)

- Similar to other MALT lymphomas
- More likely to have involvement at non-cutaneous sites



New terminology in 22ICC, reflecting conceptual changes

MGUS

IgM MGUS, plasma cell type

- T(11;14) IGH::*CCND1* or other myeloma-associated IgH rearrangements

Or

- Clonal plasma cells w/o clonal B-cells and lacking *MYD88* mutation



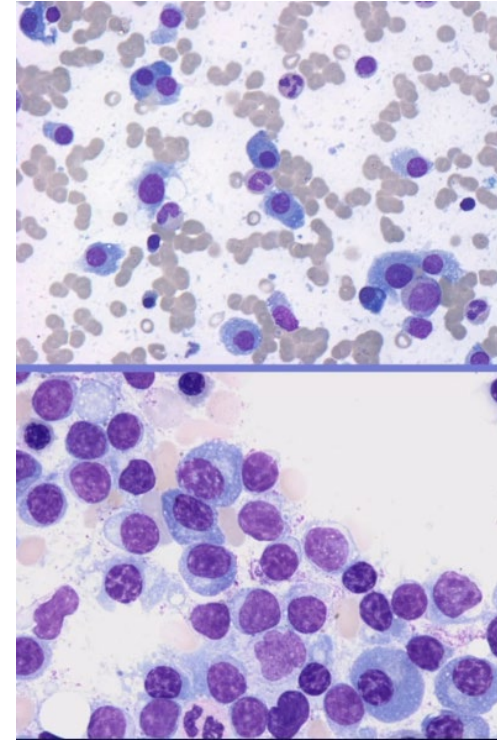
To MM

IgM MGUS, NOS

- Everything else



To LPL



Multiple myeloma (~~plasma cell myeloma~~)

- Clinicians preferred name MM
 - Subcategories
 - Multiple myeloma with recurrent genetic abnormalities
 - MM with *CCND* family translocation
 - MM with *MAF* family translocation
 - MM with *NSD2* translocation
 - MM with hyperdiploidy
 - Multiple myeloma, NOS
- Can be addressed using standard FISH panels

Molecular guidelines for 'small cell' B-cell lymphoma

De Leval *et al.* Genomic profiling for clinical decision making in lymphoid neoplasms. Blood. 2022 Nov 24;140(21):2193-2227

Utility of genomic testing in 'small cell' B-cell lymphoma (de Leval et al. Blood 2022)

Presentation	DDx	FISH	NGS
CD5+ LPD	MCL CLL/SLL CD5+ MZL	CCND1/2/3	ATM,BIRC3,MEF2B NOTCH1,SF3B1,XPO1 KMDT2D,NOTCH2
Cutaneous FL	systemic FL pcFCL	BCL2r+ BCL2r-	BCL2,CREBBP,EP300,EZH2,KMT2D TNFAIP3
CD5-, CD10-, BCL2R- LPD	FL BCL2R-/CD23+ FCL MZL HCL	BCL6r+ del(1p36)	CREBBP, EZH2,TNFRSF14 STAT6 CARD11,IRF8,MAP2K1,MYD88,N2,TNFAIP3 BRAF V600E
Small B-cell LPD w plasmacytic diff	FL MZL Splenic MZL LPL	BCL2r+ +3,+18;MALT1/FOXP1/BCL10 Del7q	CREBBP,EZH2,TNFRSF14 BRAF,KLF2,KMT2D,NOTCH2,TNFAIP3 KLF2,KMDT2,NOTCH2,TNFAIP3 MYD88,CXCR4
IgM disorders in marrow	IgM MGUS _{pc-type} ->MM IgM MGUS _{NOS} -> LPL	CCND1, MAF, NSD2r	BRAF,DIS3,KRAS,NRAS,TENT5C,TRAF3 MYD88,CXCR4
Splenic B-cell lymphoma	Splenic MZL SDRPSBCL HCL HCL-v MCL	Del7q CCND1	KLF2,KMDT2,NOTCH2,TNFAIP3 BCOR, CCND3 BRAF V600E MAP2K1

Summary on major changes on 'small cell' B-cell lymphoma

22ICC

- Novel entities
 - Testicular FL
 - *BCL2-R negative CD23+ follicle center lymphoma*
 - Primary cold agglutinin disease
 - Primary cutaneous marginal zone LPD
- New terms reflecting conceptual changes
 - IgM MGUS, plasma cell type
 - IgM MGUS, NOS
- Refinement in diagnostic criteria
 - Lymphoplasmacytic lymphoma
- Upgraded previous provisional entity
 - Large B-cell lymphoma with IRF4-rearrangement

WHO HAEM5

- B-PLL abandoned as entity
- Novel entity
 - Primary cutaneous marginal zone lymphoma
- New terms reflecting conceptual changes
 - Classic follicular lymphoma (cFL), (incl. testicular)
 - Follicular large B-cell lymphoma
 - Diffuse follicular lymphoma (dFL)
 - FL with uncommon features (uFL)
 - In situ follicular/mantle cell neoplasm
 - *Splenic lymphoma with prominent nucleoli*
- Upgraded previous provisional entity
 - Large B-cell lymphoma with IRF4-rearrangement

Summary on major changes on 'small cell' B-cell lymphoma

WHO 2017	22ICC	WHO HAEM5
B-cell prolymphocytic leukemia	B-cell prolymphocytic leukemia	----
<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i> - Splenic diffuse red pulp small cell B-cell lymphoma - HCL-variant	<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i> - Splenic diffuse red pulp small cell B-cell lymphoma - HCL-variant	<i>Splenic diffuse red pulp small cell B-cell lymphoma</i> <i>Splenic lymphoma with prominent nucleoli</i>
Lymphoplasmacytic lymphoma - Waldenström macroglobulinemia	Lymphoplasmacytic lymphoma - Waldenström macroglobulinemia	Lymphoplasmacytic lymphoma - Waldenström macroglobulinemia
IgM monoclonal gammopathy of undetermined significance/MGUS	IgM MGUS, plasma cell type IgM MGUS, NOS	
	Primary cold agglutinin disease	
	Primary cutaneous marginal zone lymphoproliferative disorder/LPD	Primary cutaneous marginal zone lymphoma
Follicular lymphoma - In situ follicular neoplasia - Duodenal-type FL	Follicular lymphoma (I-IIla vs IIlb) - In situ follicular neoplasia - Duodenal-type FL	Classic follicular lymphoma (cFL), (incl. testicular) Follicular large B-cell lymphoma Diffuse follicular lymphoma (dFL) FL with uncommon features (uFL) - In situ follicular neoplasm - Duodenal-type FL
	Testicular FL	--- (under cFL)
	<i>BCL2-R negative CD23+ follicle center lymphoma</i>	
Mantle cell lymphoma - In situ mantle cell neoplasia - Leukaemic non-nodal mantle cell lymphoma	Mantle cell lymphoma - In situ mantle cell neoplasia - Leukaemic non-nodal mantle cell lymphoma	Mantle cell lymphoma - In situ mantle cell neoplasm - Leukaemic non-nodal mantle cell lymphoma

Recommended literature

- 22ICC
 - Campo *et al.* The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood 2022 Sep 15;140(11):1229-1253
 - De Leval *et al.* Genomic profiling for clinical decision making in lymphoid neoplasms. Blood. 2022 Nov 24;140(21):2193-2227
 - Virchows Archiv. 2023 Vol 482(1): Annual review issue
 - The International Consensus Classification of Myeloid and Lymphoid Neoplasms; ISBN:9781975222598
- WHO HAEM5
 - Alaggio R *et al.* Leukemia 2022 Jul;36(7):1720-1748
 - Online <https://tumourclassification.iarc.who.int>
 - Haematolymphoid Tumours: WHO Classification of Tumours 5th Edition by WHO Classification of Tumours Editorial Board; ISBN: 978-9283245209