Diagnostikk av maligne lymfomer

OnkoLis februar 2019

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Avdeling for patologi
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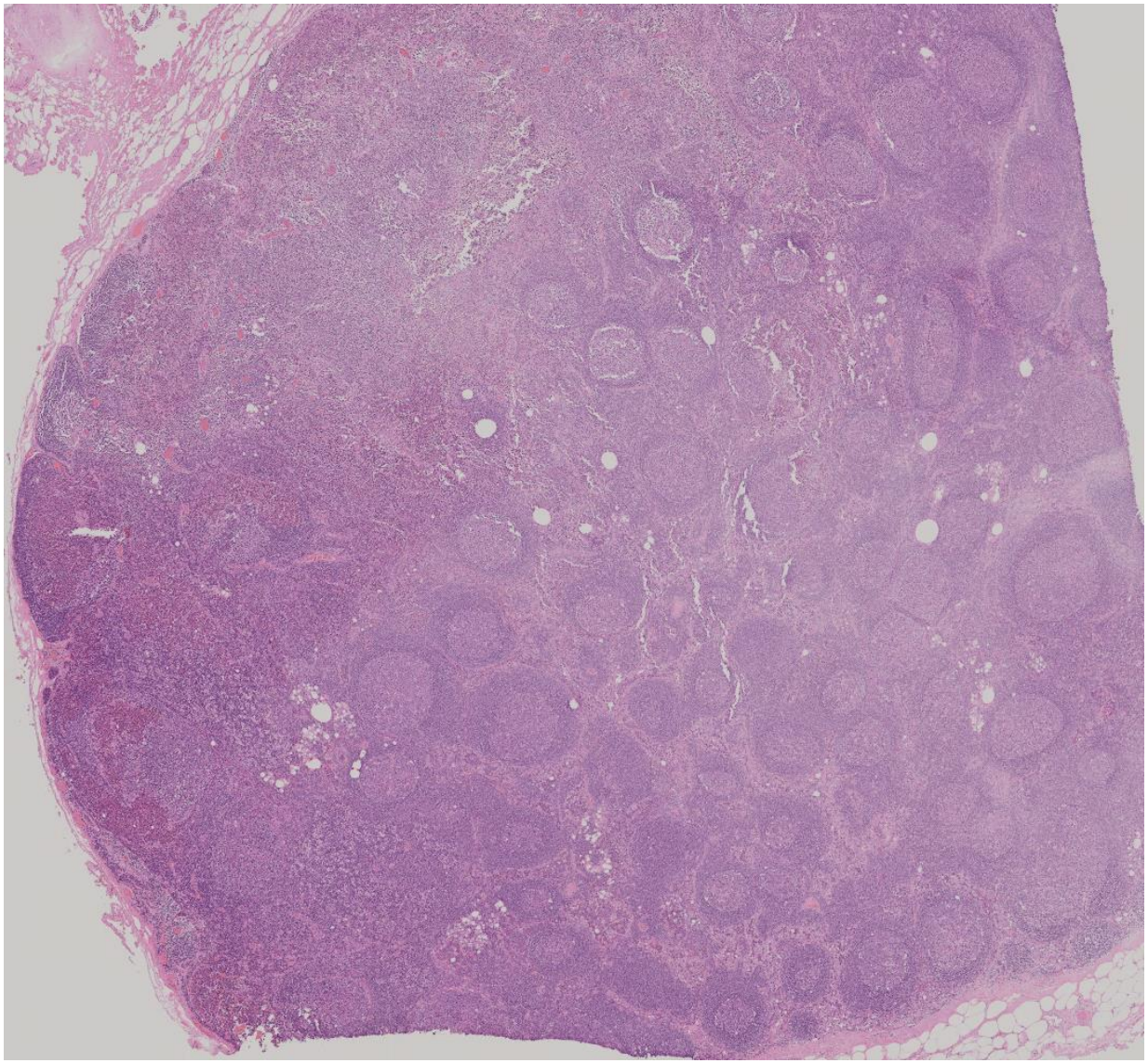
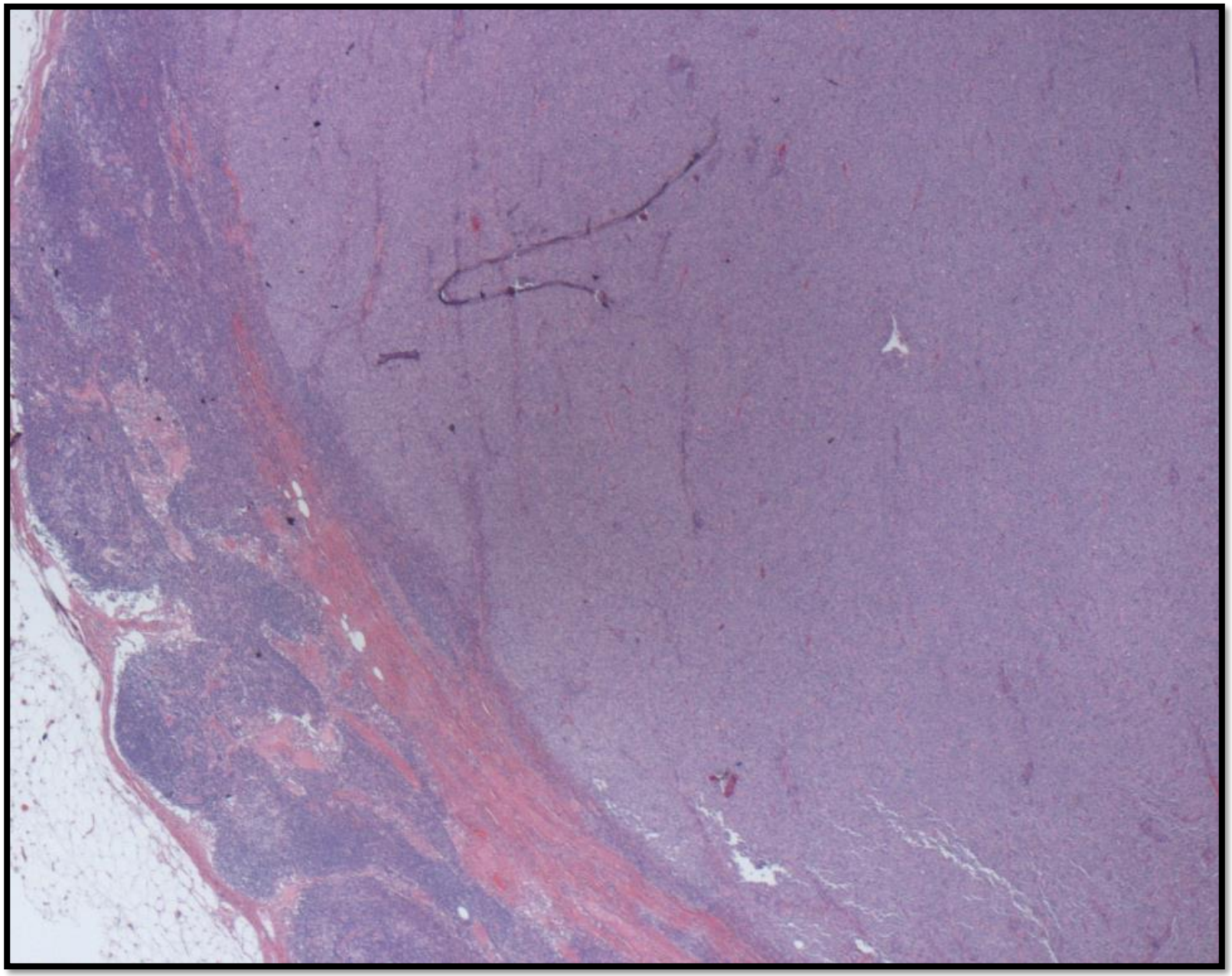




Maligne lymfomer

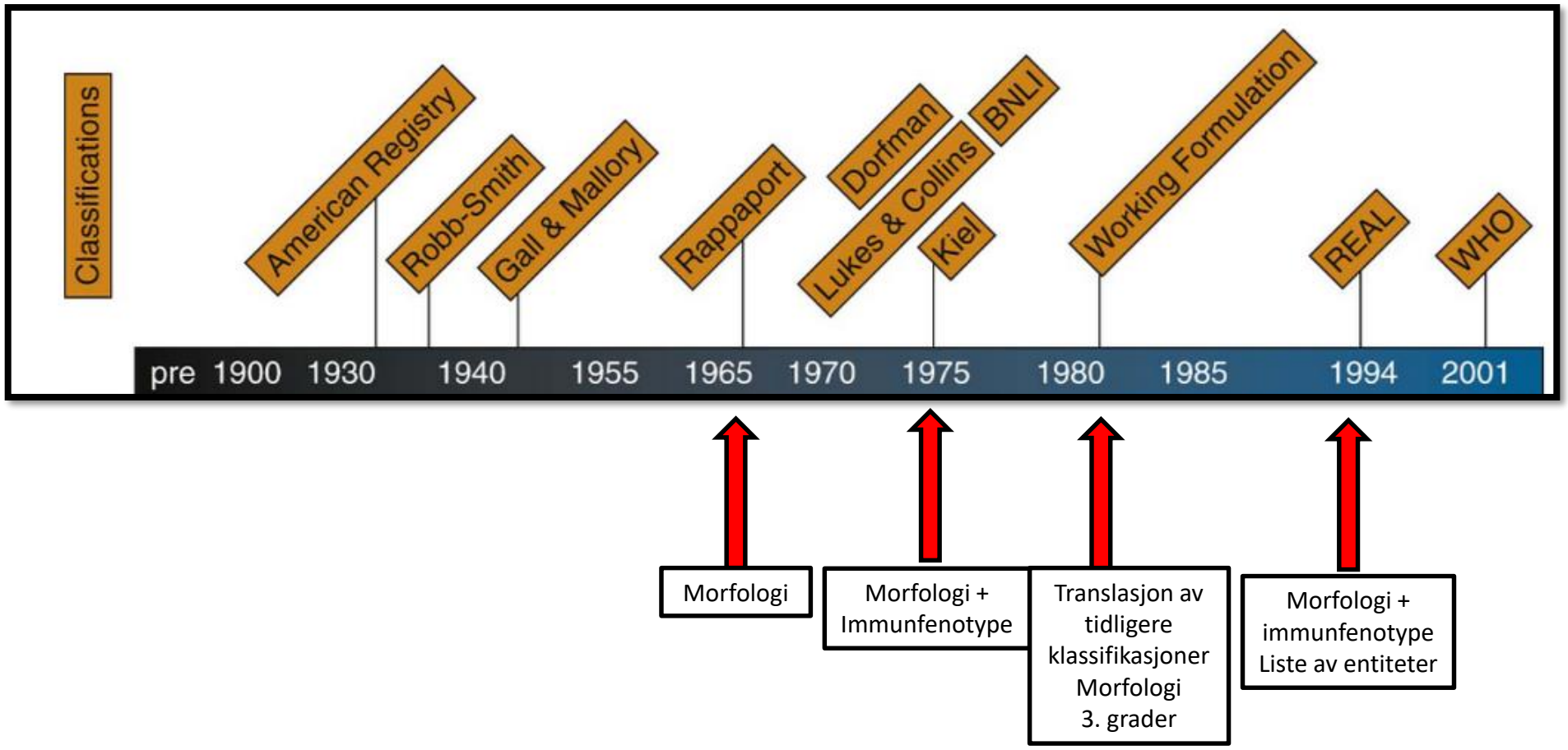
- Ca 4% av alle nye krefttilfeller. (Ca 1000 per år)
- Av disse er ca 80-85 % modne B-cellelymfomer (Non-Hodgkin).
- Hodgkin lymfom i overkant av 10%.

- Overvekt av T-cellelymfomer i hud

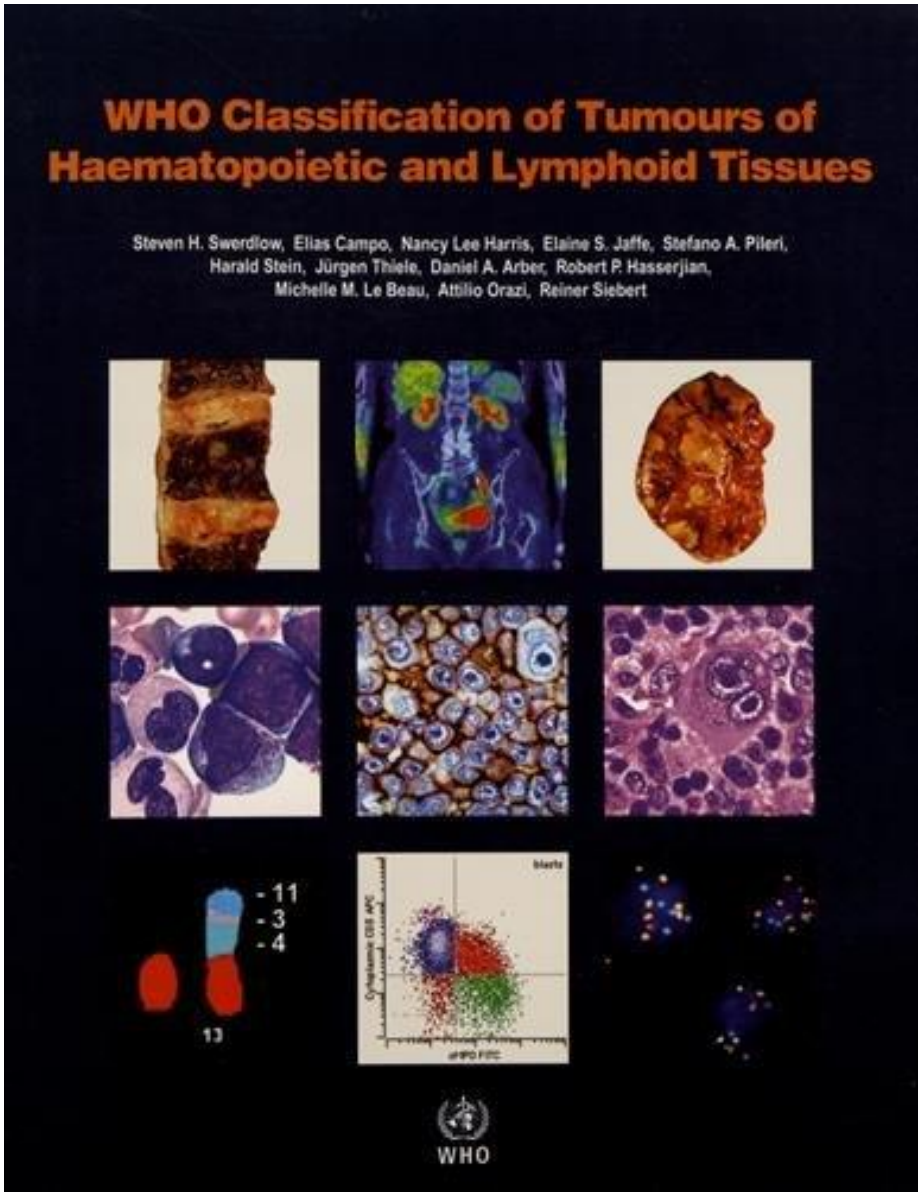
Etiologi

- Ukjent (?) for de fleste
- Helicobacter pylori – Marginalsonelymfom i ventrikkel
- Øker risiko:
  - Immunsvikt: Behandling, HIV, organtransplantasjon, medfødt, alder
  - Kronisk betennelse
  - Fremmedlegeme/proteser (brystimplantatassosiert-ALCL)
  - Autoimmune sykdommer
- Medvirkende
  - EBV – spesielt ved samtidig immunsvikt

Historikk
Klassifikasjonssystemer



«Blå boka»
WHO 2017



Mature B-cell neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic B-cell lymphoma/leukemia, unclassifiable*
  - *Splenic diffuse red pulp small B-cell lymphoma*
  - *Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- μ heavy-chain disease
- γ heavy-chain disease
- α heavy-chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - In situ follicular neoplasia*
  - Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- *Large B-cell lymphoma with IRF4 rearrangement**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type*
  - Activated B-cell type*
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV$^+$ DLBCL, NOS*
- *EBV$^+$ mucocutaneous ulcer**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK$^+$ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8$^+$ DLBCL, NOS**
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration**
- High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
- High-grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV$^+$ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8$^+$ T-cell lymphoma**
- *Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK$^+$
- Anaplastic large-cell lymphoma, ALK$^-$*
- *Breast implant–associated anaplastic large-cell lymphoma**

Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)
- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis PTLD
- Florid follicular hyperplasia PTLD*
- Polymorphic PTLD
- Monomorphic PTLD (B- and T-/NK-cell types)
- Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms
- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease*

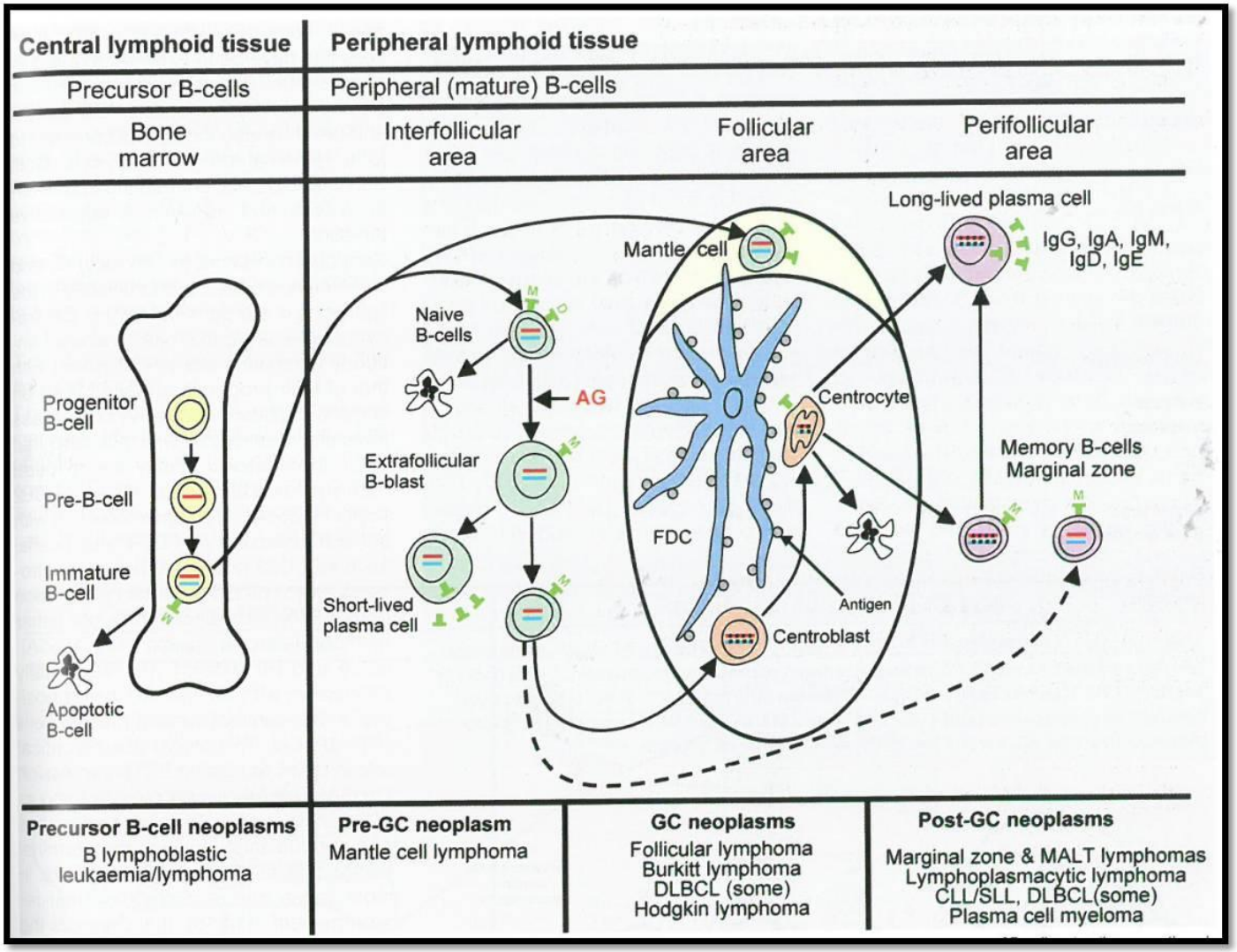
Hovedinndeling

- Hodgkin lymfom: ca 10%
  - Nodulær lymfocyttrikt Hodgkin lymfom
  - Klassisk Hodgkin lymfom
- Non-Hodgkin lymfom: Ca 90%
  - B-NHL: ca 90% av NHL
    - B-lymfoblastlymfom/leukemi
    - B-NHL av moden/perifer type
  - T-NHL: ca 10% av NHL
    - T-lymfoblastlymfom/leukemi
    - T-NHL av moden/perifer type

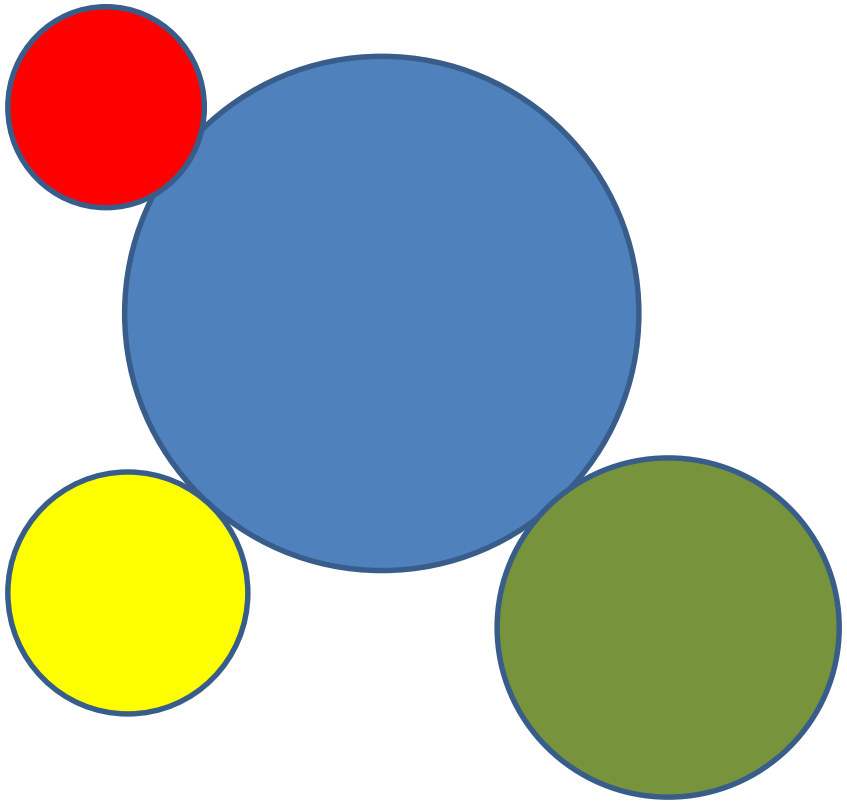
Klassifikasjonsprinsipp

- Lymfomene klassifiseres ut i fra det modningsstadium cellene er i når tumor oppstår.
- ”Frozen stage model”
- En teori/modell, men en ganske god en

B-cellemodning



Entitetene er ikke alle like klart definert



Hva bygger WHO-klassifikasjonen på

- Morfologi/histologi
- Immunfenotype (immunhistokjemi/flowcytometri)
- Molekylærpatologi/genetiske avvik

Patolog

- Klinikk

Onkolog
Radiolog

- Diagnostikk = teamarbeid

Hva bygger WHO-klassifikasjonen på

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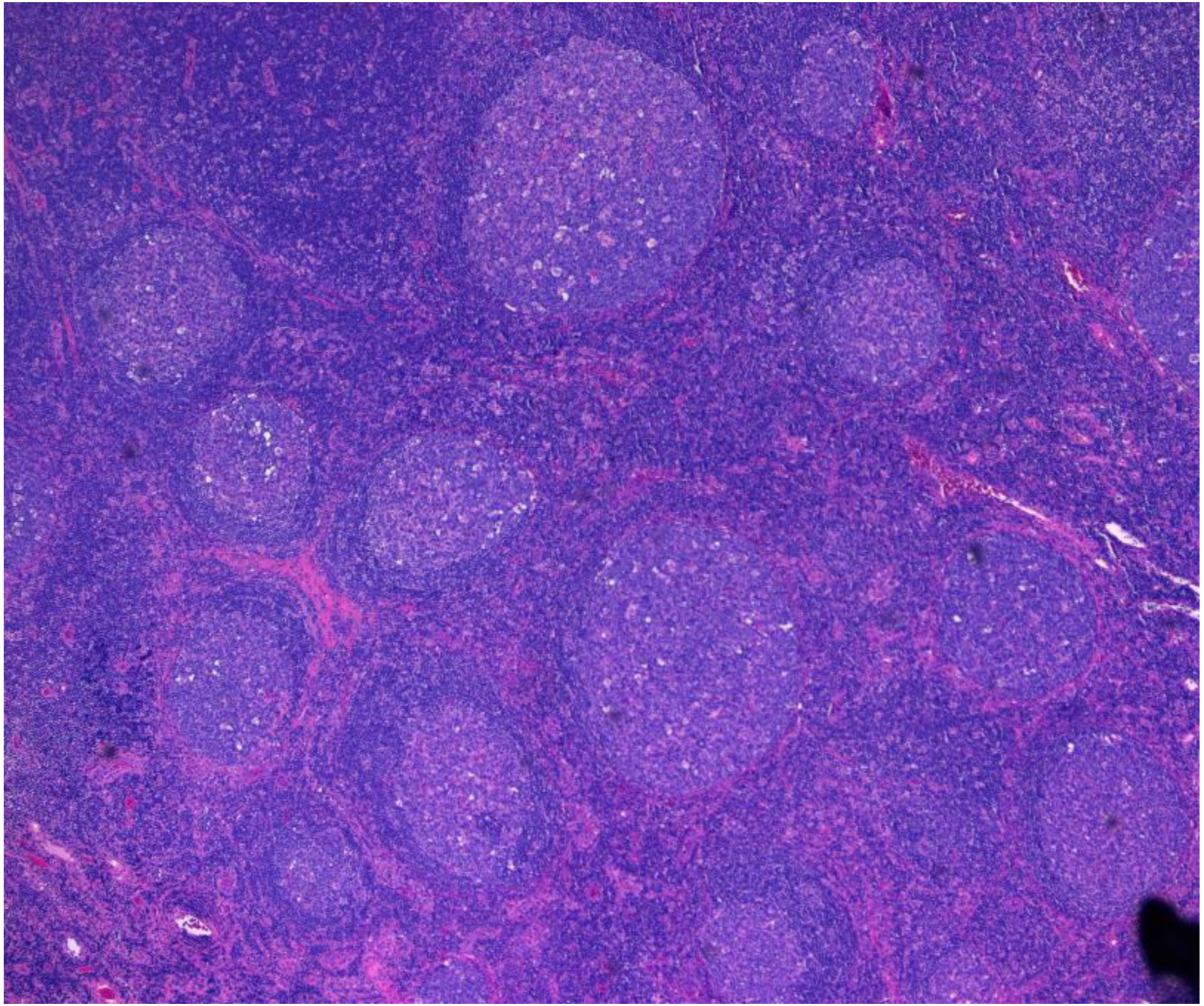
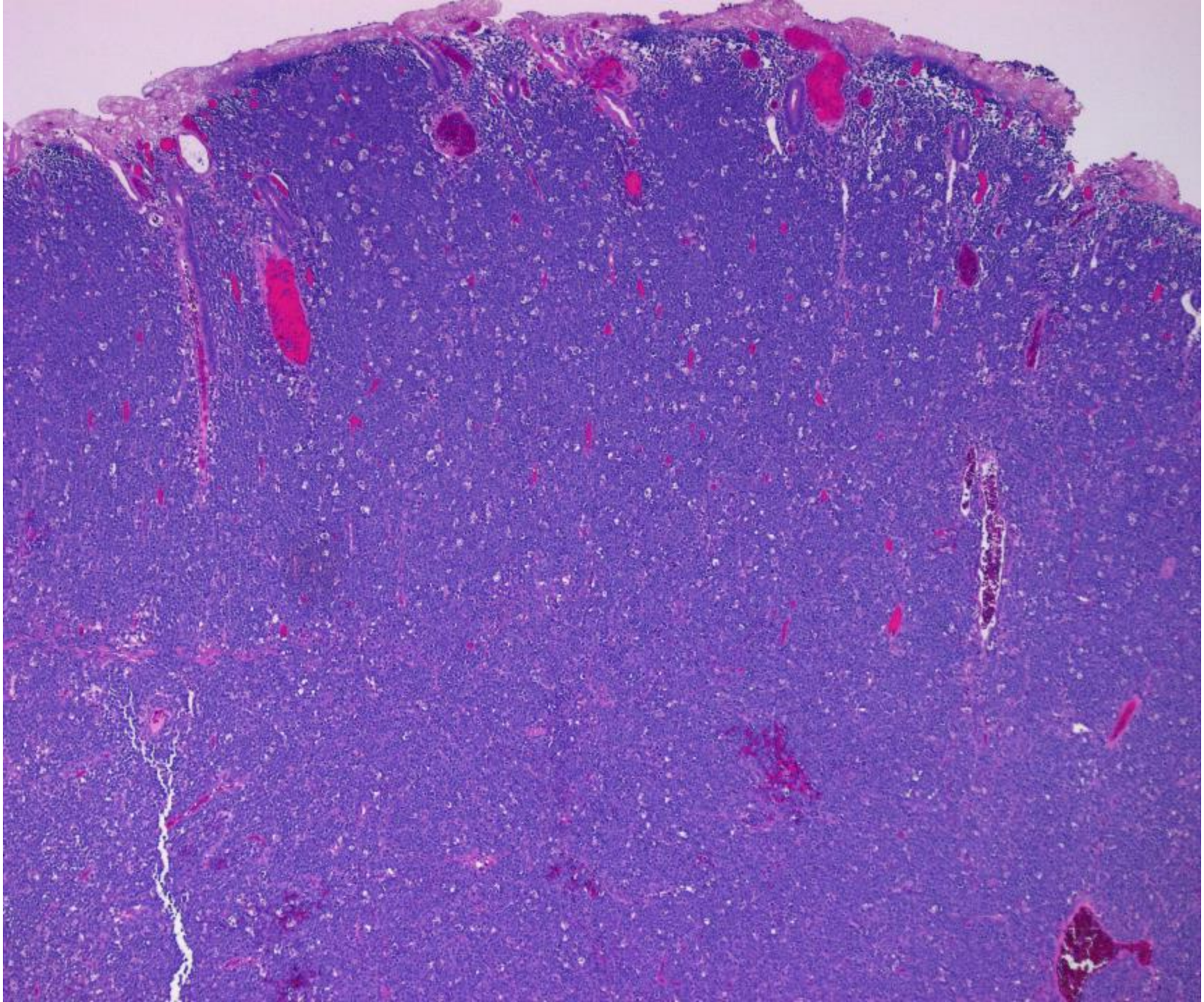
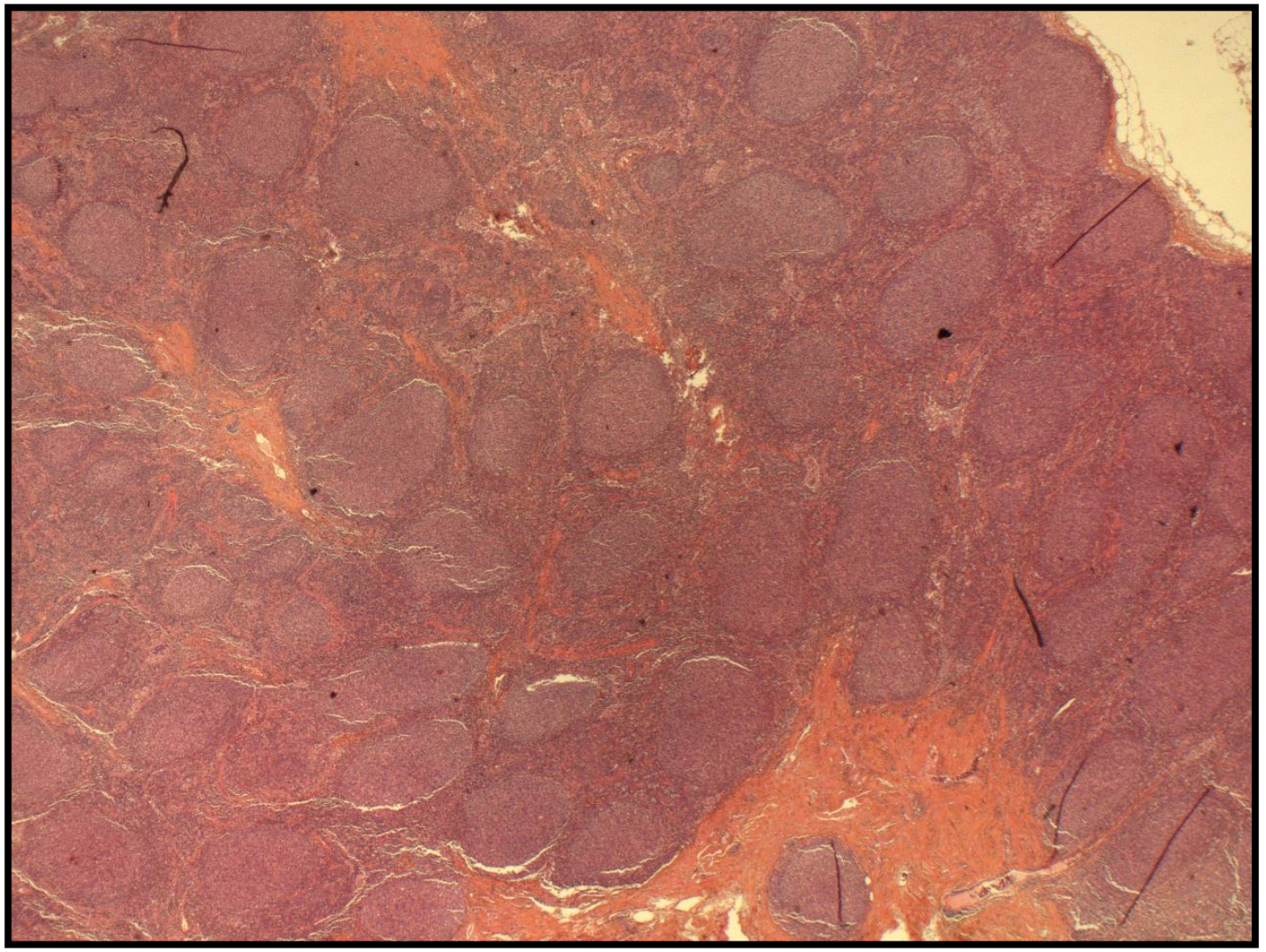
- Immunfenotype (immunhistokjemi/flowcytometri)
- Molekylærpatologi/genetiske avvik
- Klinikk

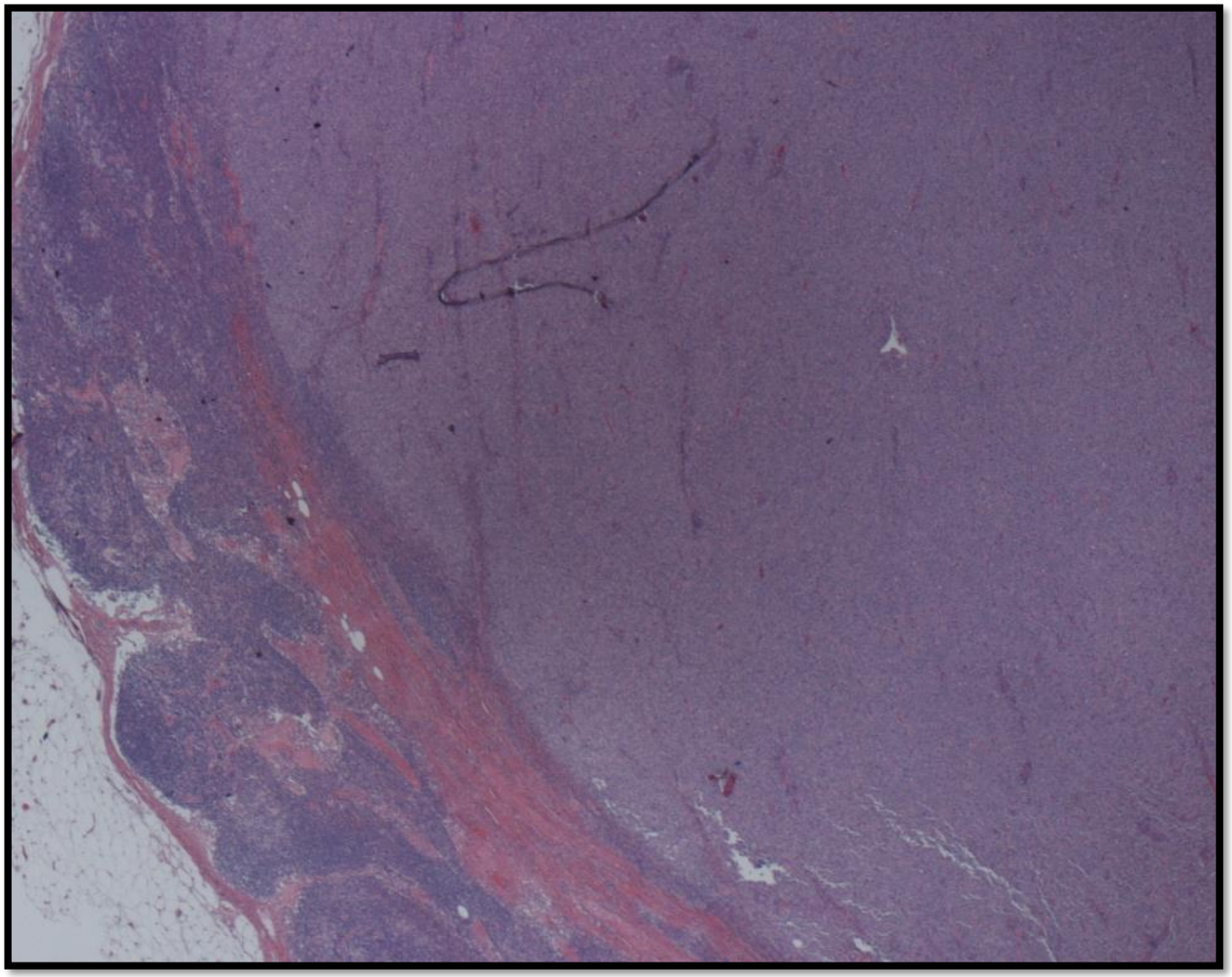




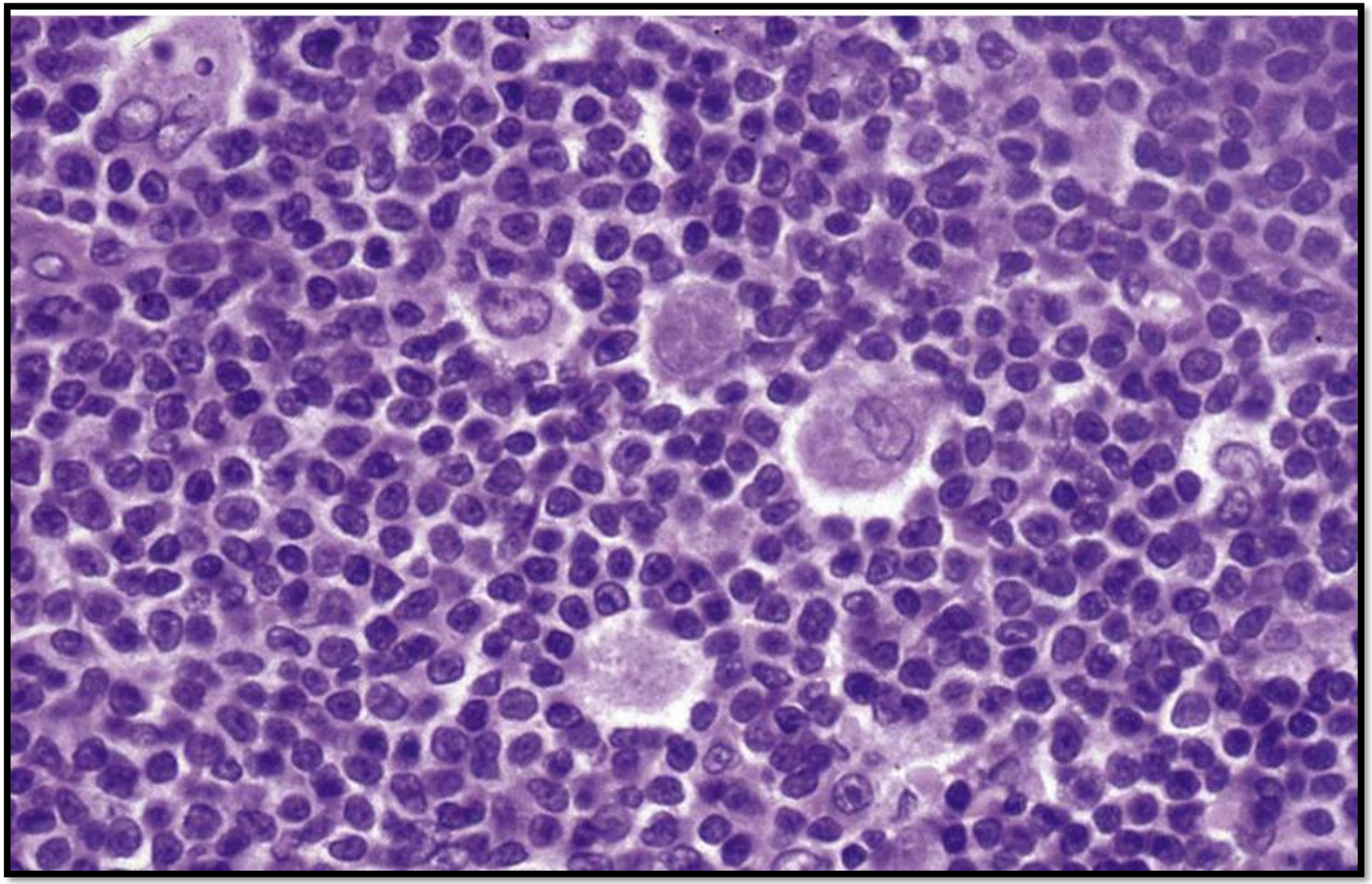
Vekstmønster-follikulært



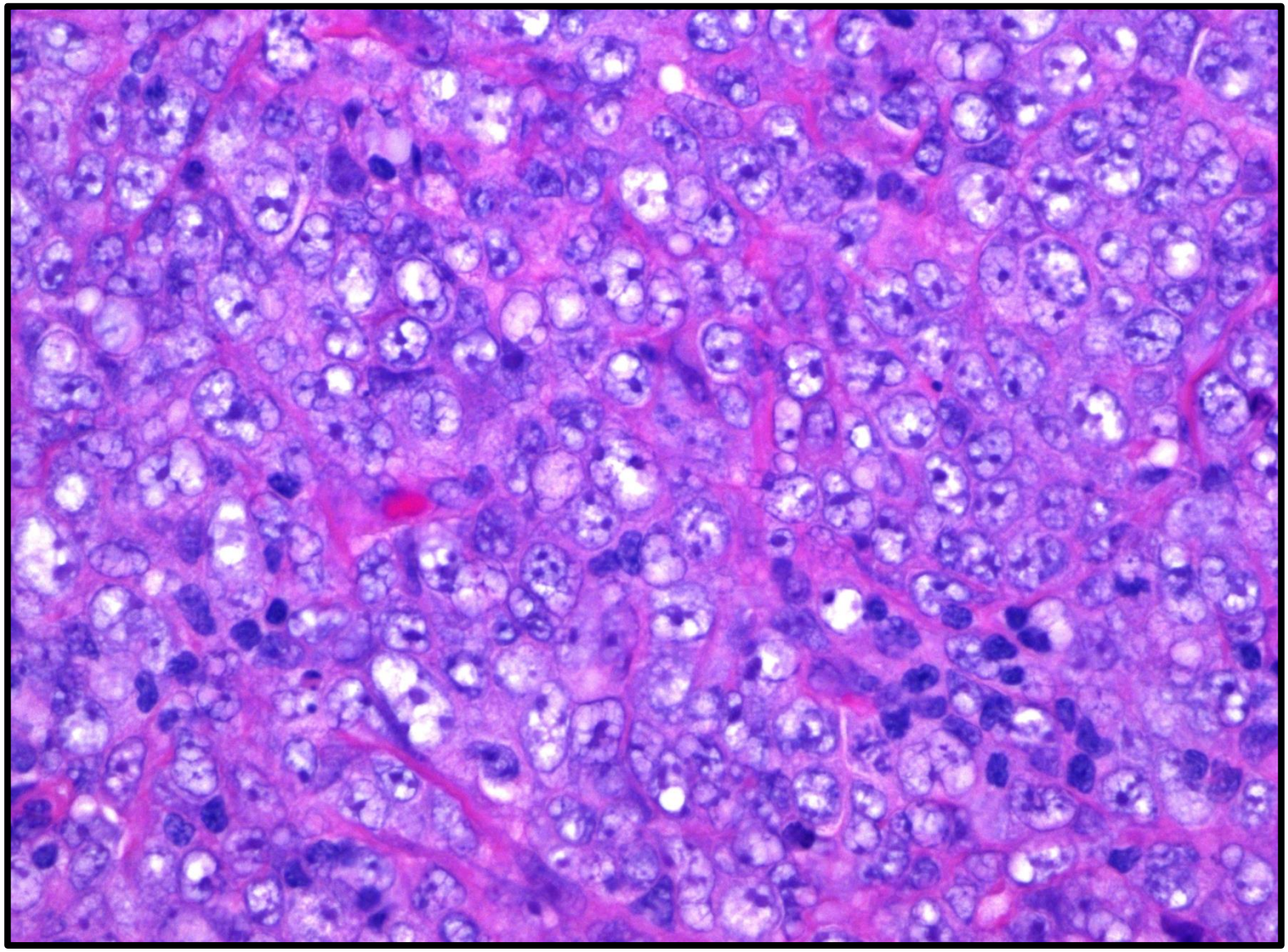
Vekstmønster - Diffust



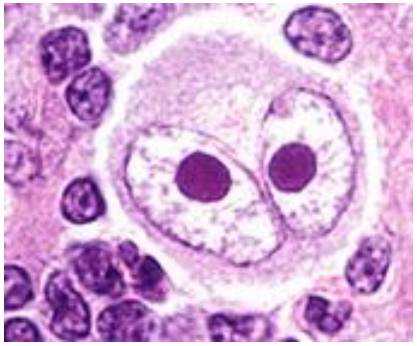
Morfologi-cytter

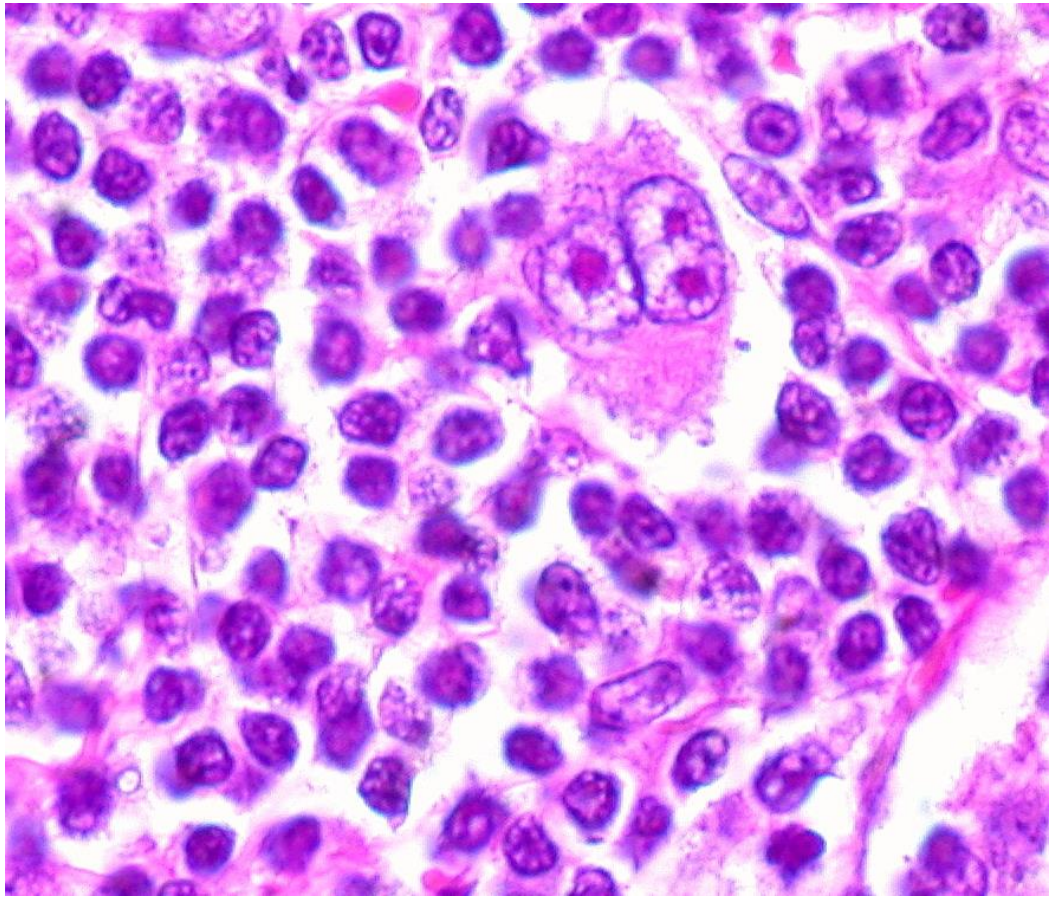


Morfologi-blaster



Morfologi: Reed-Sternbergceller

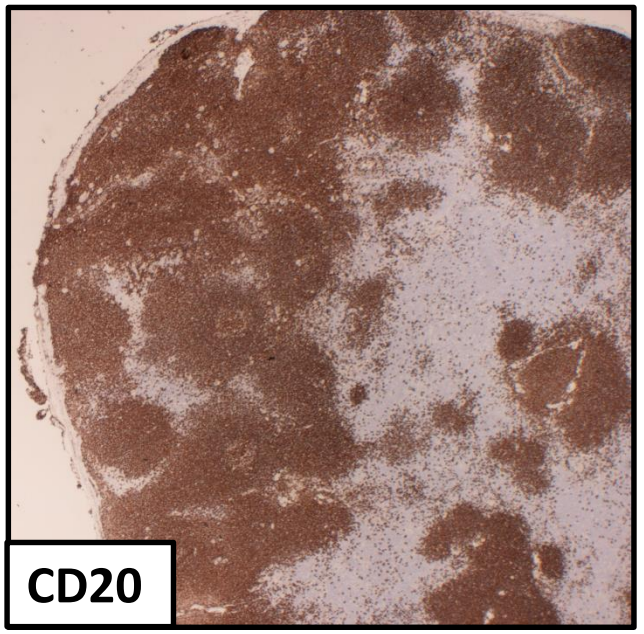




Hva bygger WHO-klassifikasjonen på

- Morfologi/histologi
- **Immunfenotype (immunhistokjemi/flowcytometri)**
- Molekylærpatologi/genetiske avvik
- Klinikk

Immunfenotype



- B-cellelymfomer
  - CD20, CD19, CD79a, Pax5
- T-cellelymfomer
  - CD3, CD2, CD5, CD7, CD4, CD8…..
- Myelomatose/plasmacelleneoplasi
  - CD138

  - En del lymfomer taper uttrykk av linjespesifikke antigener.

Immunfenotype ved småcellete B-cellelymfomer

	CD19/CD20/ Pax5	CD5	CD10	CD23	cyclinD1
Småcellet lymfocytært lymfom	+	+	-	+	-
Mantelcellelymfom	+	+	-	-	+
Follikulært lymfom	+	-	+	-	-
Marginalsonelymfom	+	-	-	-	-
Lymfoplasmacyttisk lymfom	+	-	-	-	-

Hva bygger WHO-klassifikasjonen på

- Morfologi/histologi
- Immunfenotype (immunhistokjemi/flowcytometri)
- **Molekylærpatologi/genetiske avvik**
- Klinikk

Molekylærpatologi

- Translokasjoner:
  - Burkitt lymfom - t(8;14)
  - Follikulært lymfom - t(14;18)
  - Mantelcellelymfom - t(11;14)
  - Anaplastisk storcellet lymfom, ALK+, - t(2;5) og varianter

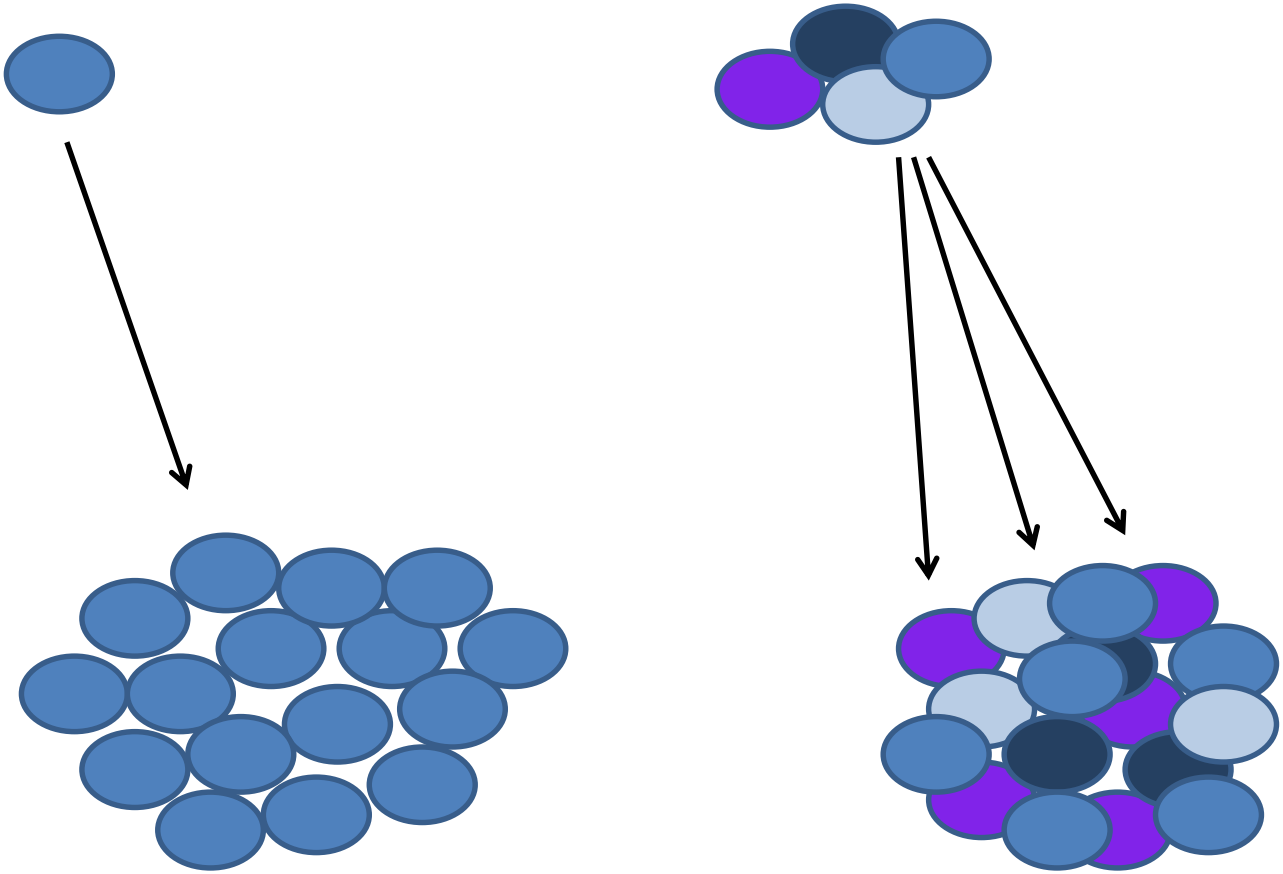
- Mutasjoner
  - Myd88L265P - Lymfoplasmacyttisk lymfom
  - BRAFV600E - Hårcelleleukemi

- Listen er lengre og under utvikling…

- «Tilgjengelige kriterier» variere fra type til type. Aberrasjonene er ikke spesifikke.

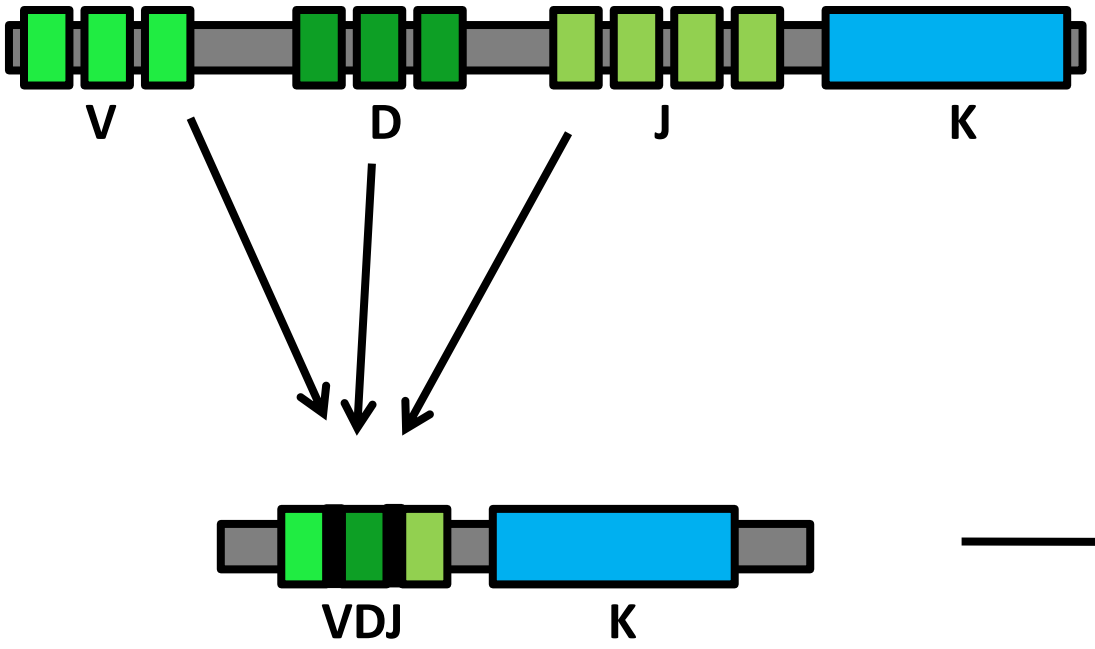
Klonalitetsundersøkelse

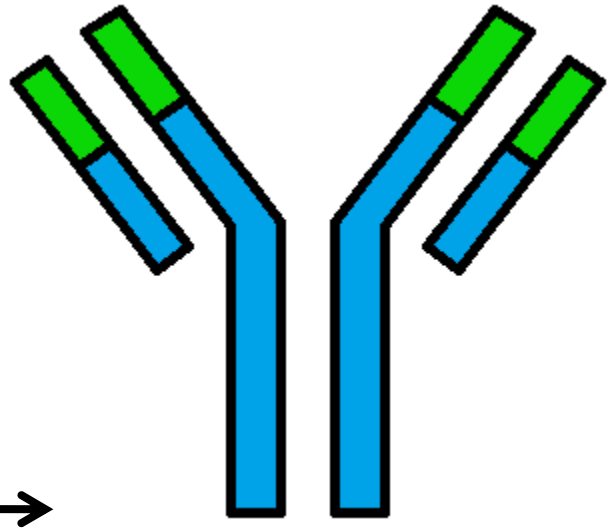
Monoklonal-Polyklonal

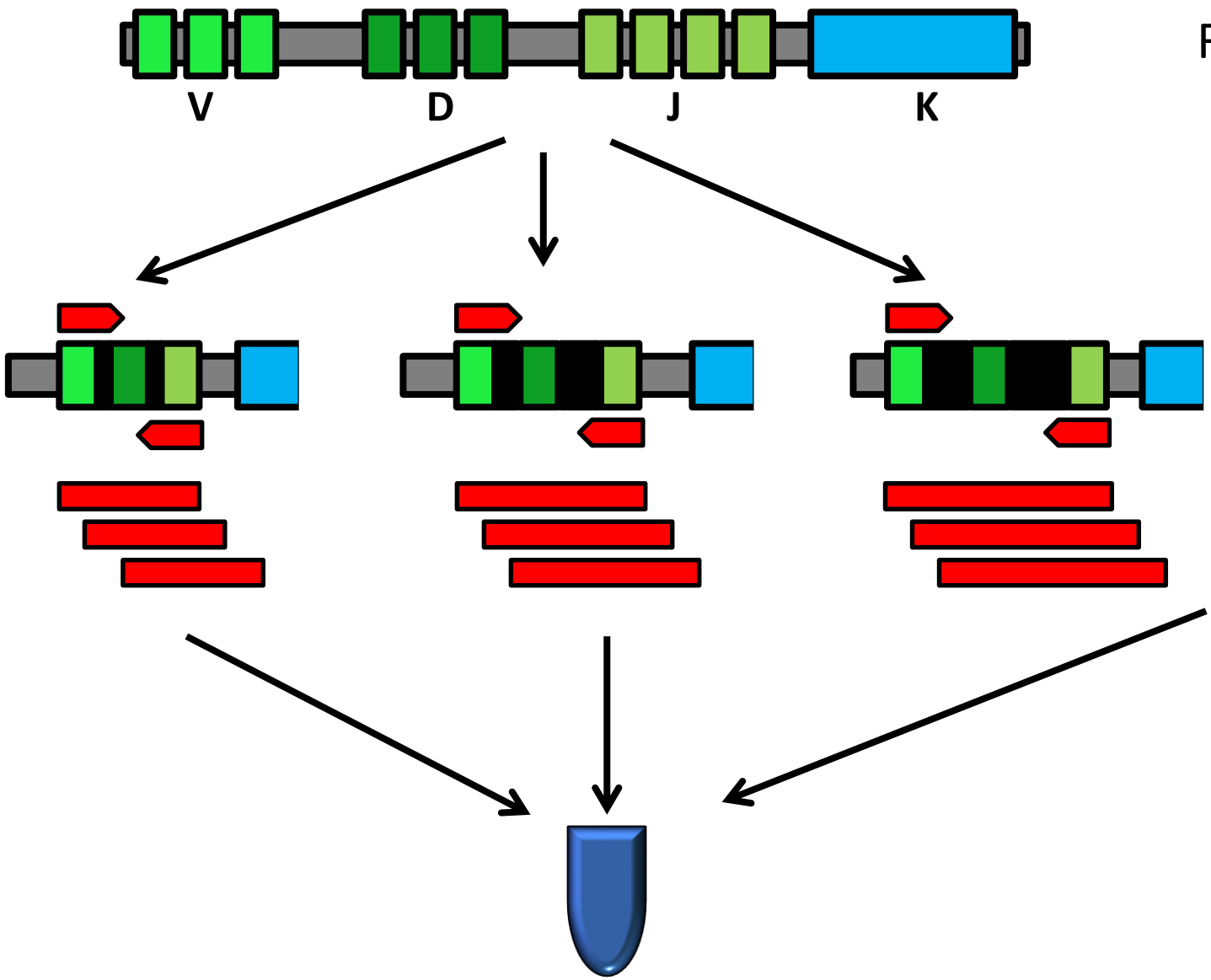


Grunnlag for klonalitetsanalyse: IgH

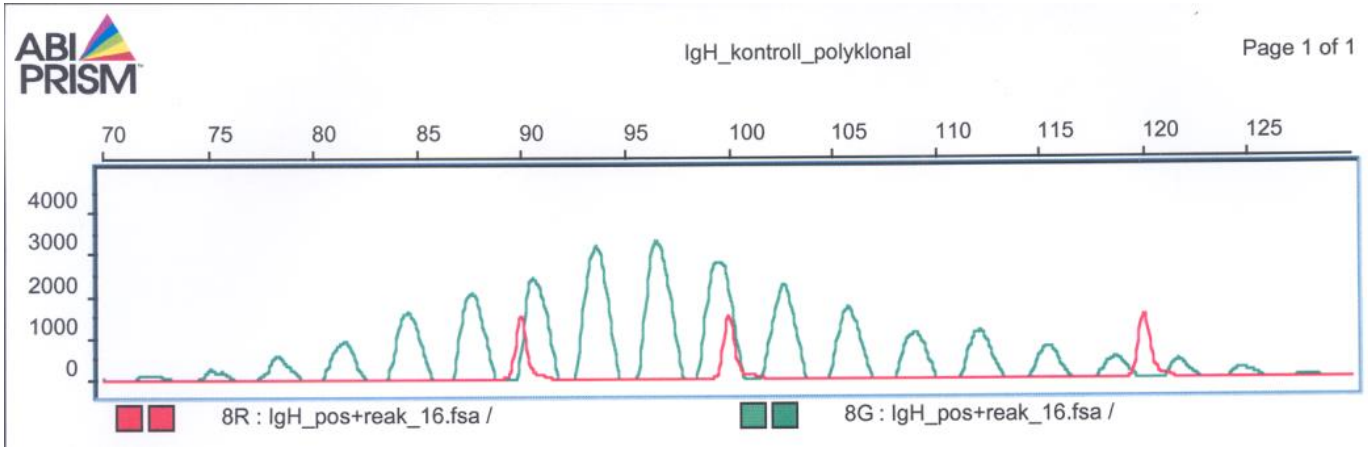
- Hver B-lymfocytt lager sitt spesifikke antistoff
- Hver T-lymfocytt lager sin spesifikke T-cellereseptor

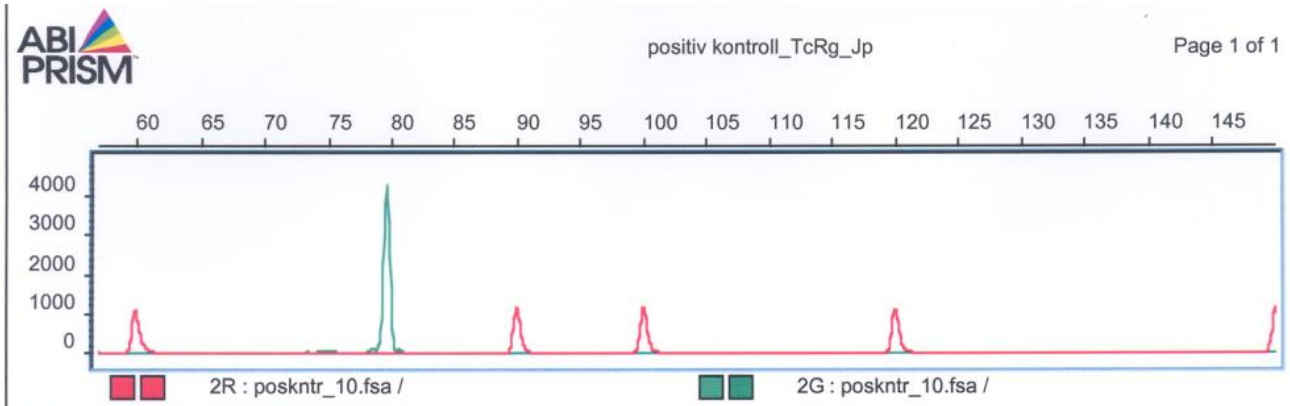





V
D
J
K
Før rearrangering
Multiple celler med rearrangerte gener
Amplifikasjon vha PCR

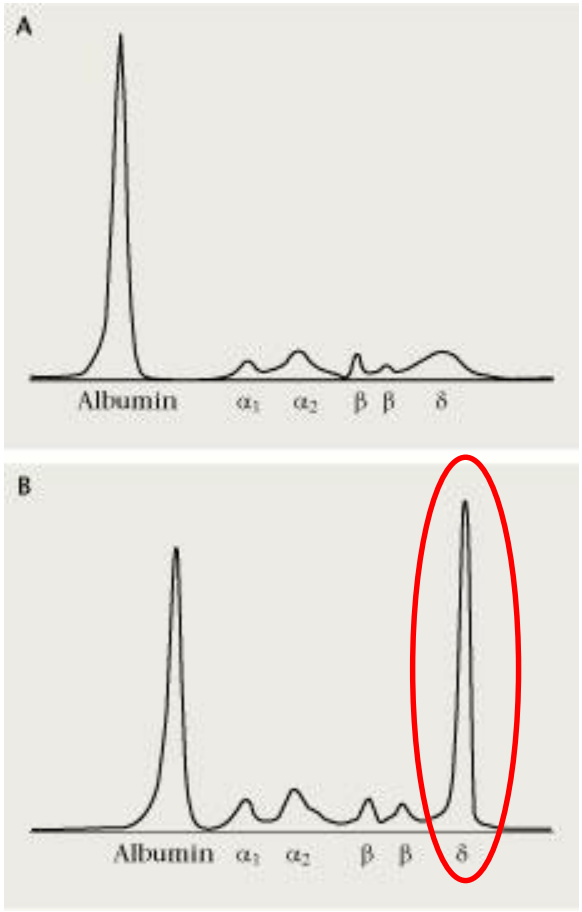
Resultat, PCR





Dye/Sample Peak	Minutes	Size	Peak Height	Peak Area	Data Point
2G, 7	7.35	79.72	4361	34639	2758

Serumproteinelektroforese



M-komponent
(=Monoklonal komponent)

Noen kjøreregler ved klonalitetsanalyse:

- En klon bør ha sitt morfologiske korrelat.
- Funn av klon betyr ikke at det er kreft.
- Fravær av monoklonalitet utelukker ikke kreft.
- I de fleste tilfellene er ikke klonalitetsundersøkelse nødvendig for diagnose

Klonalitetsanalyse-applikasjoner

- Skille mellom neoplastiske og reaktive infiltrat
- Avgjøre om flere samtidige lesjoner er samme eller forskjellige lymfomer.
- Stageing, benmargsinfiltrasjon: Avgjøre om morfologisk usikre benmargsinfiltrater er lymfominfiltrasjon eller ikke.
- Spørsmål om residiv eller nytt lymfom

Thomas Hodgkin

1798-1866

ON SOME

MORBID APPEARANCES

OF

THE ABSORBENT GLANDS

AND

SPLEEN.

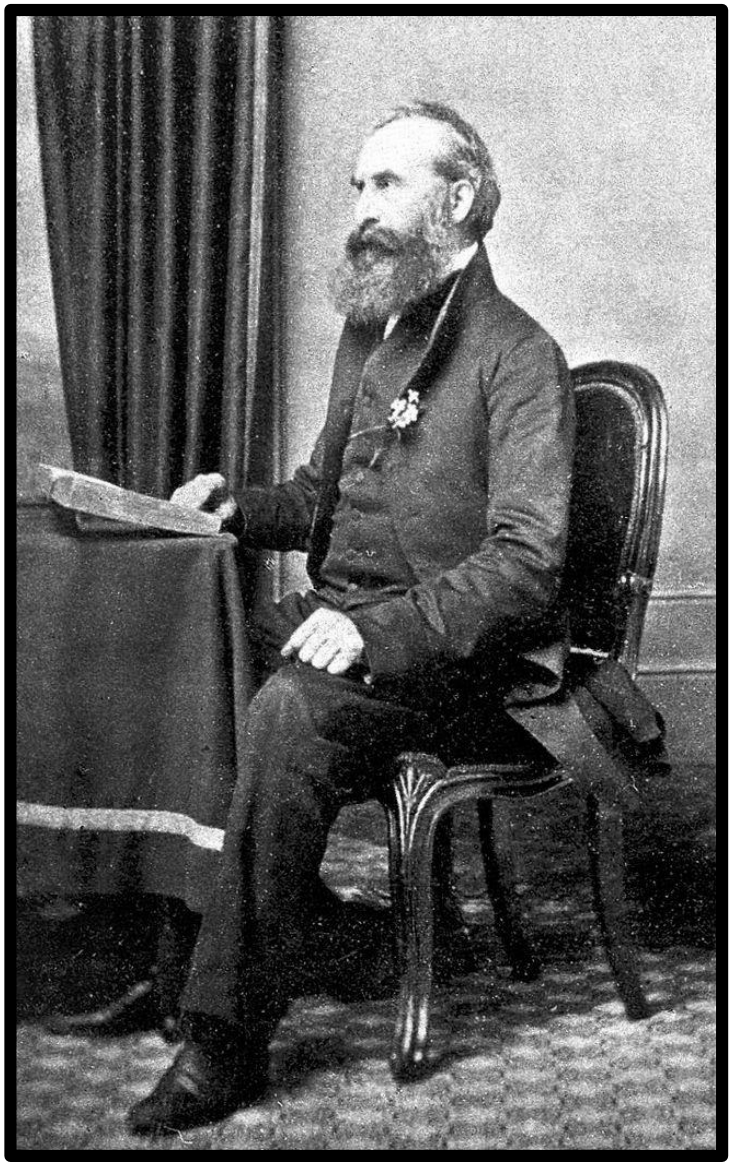
BY DR. HODGKIN.

PRESENTED

BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

THE morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

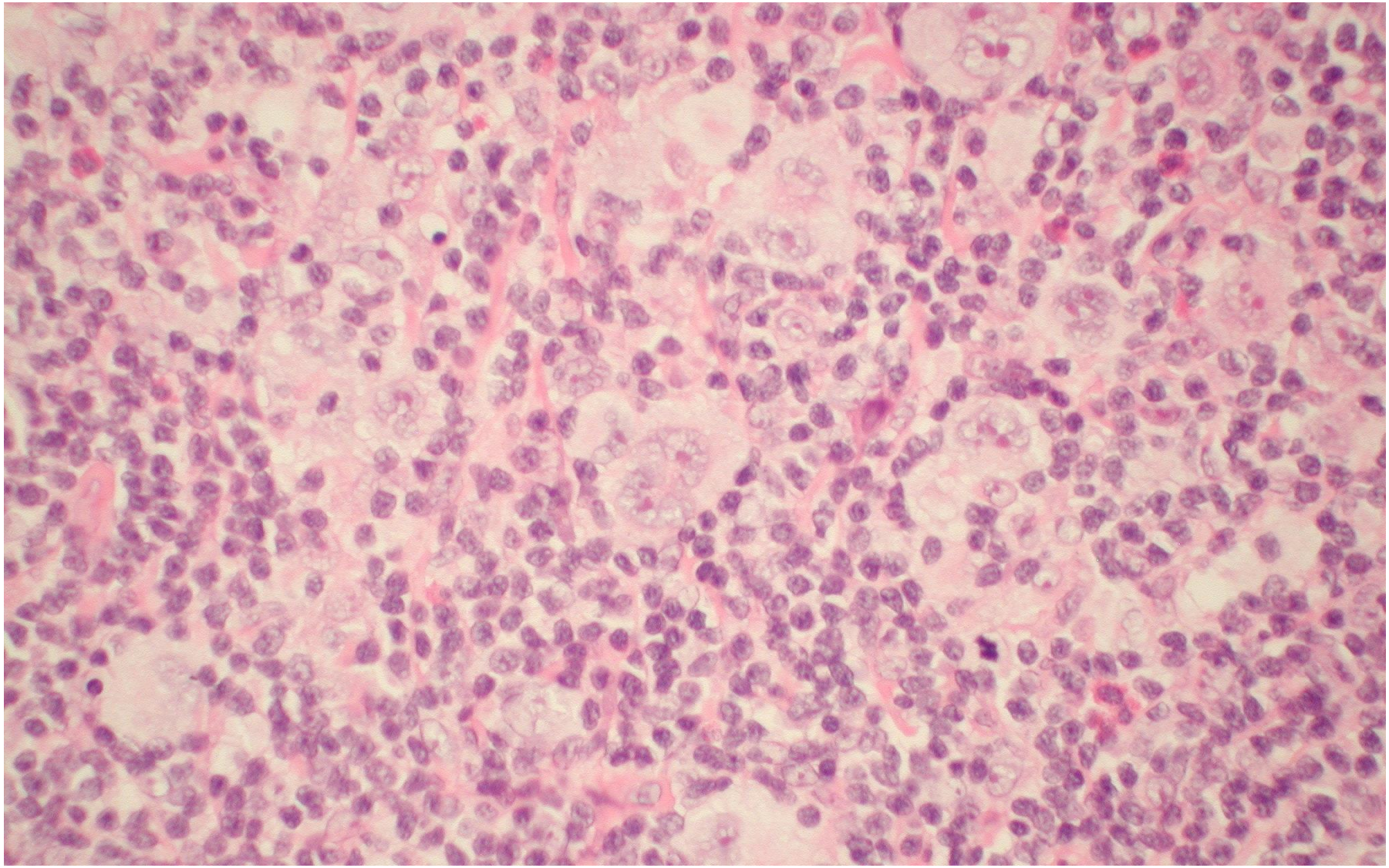


Med Chir Trans. 1832; 17: 68–114.

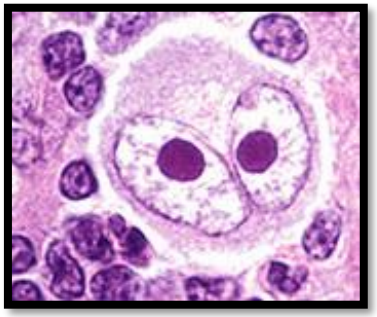
Hodgkin lymfom

- Klassisk Hodgkin lymfom
  - Nodulær sklerose – Vanligst, ofte mediastinal tumor
  - Blandet cellularitet
  - Lymfocyttrik
  - Lymfocyttfattig
- Nodulær lymfocyttrik Hodgkin lymfom

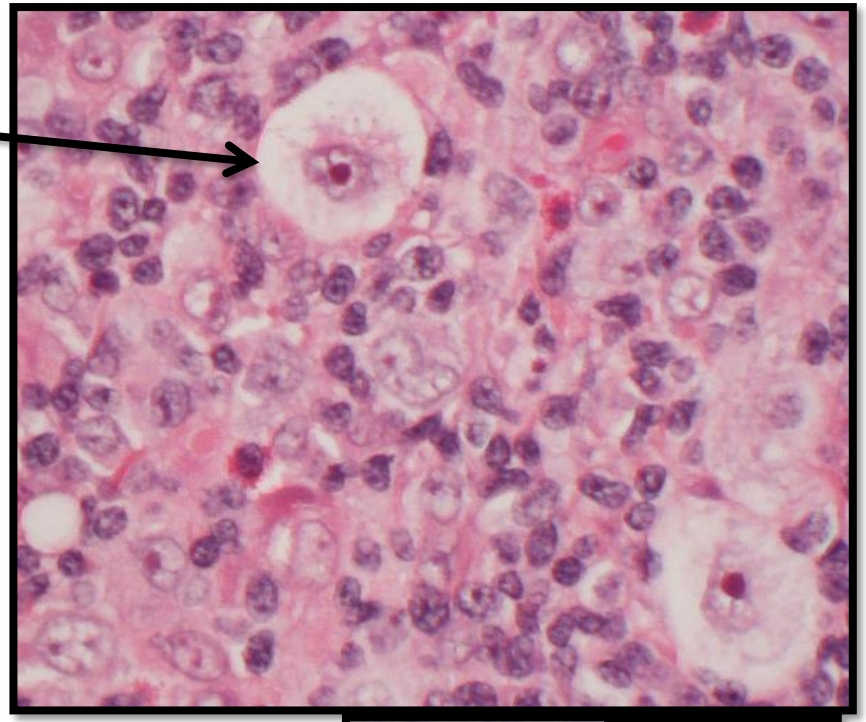
Klassisk Hodgkin lymfom, nodulær sklerose



Reed-Sternberg celle

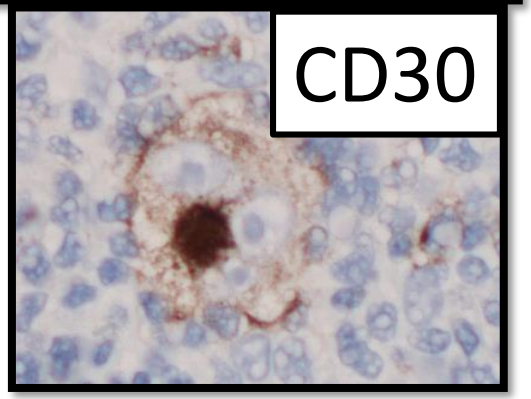


Hodgkin celle



Immunfenotype:

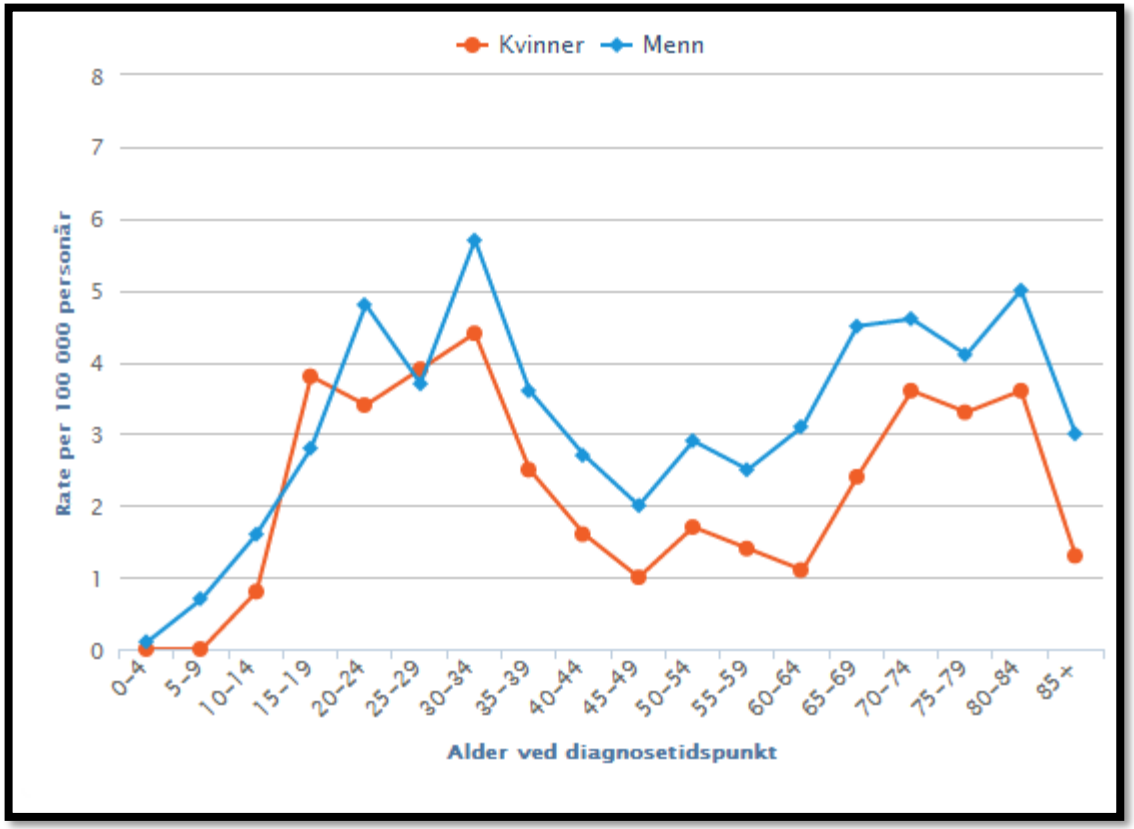
- CD30 +
- Pax5+
- LCA/CD45 –
- CD20 -/+



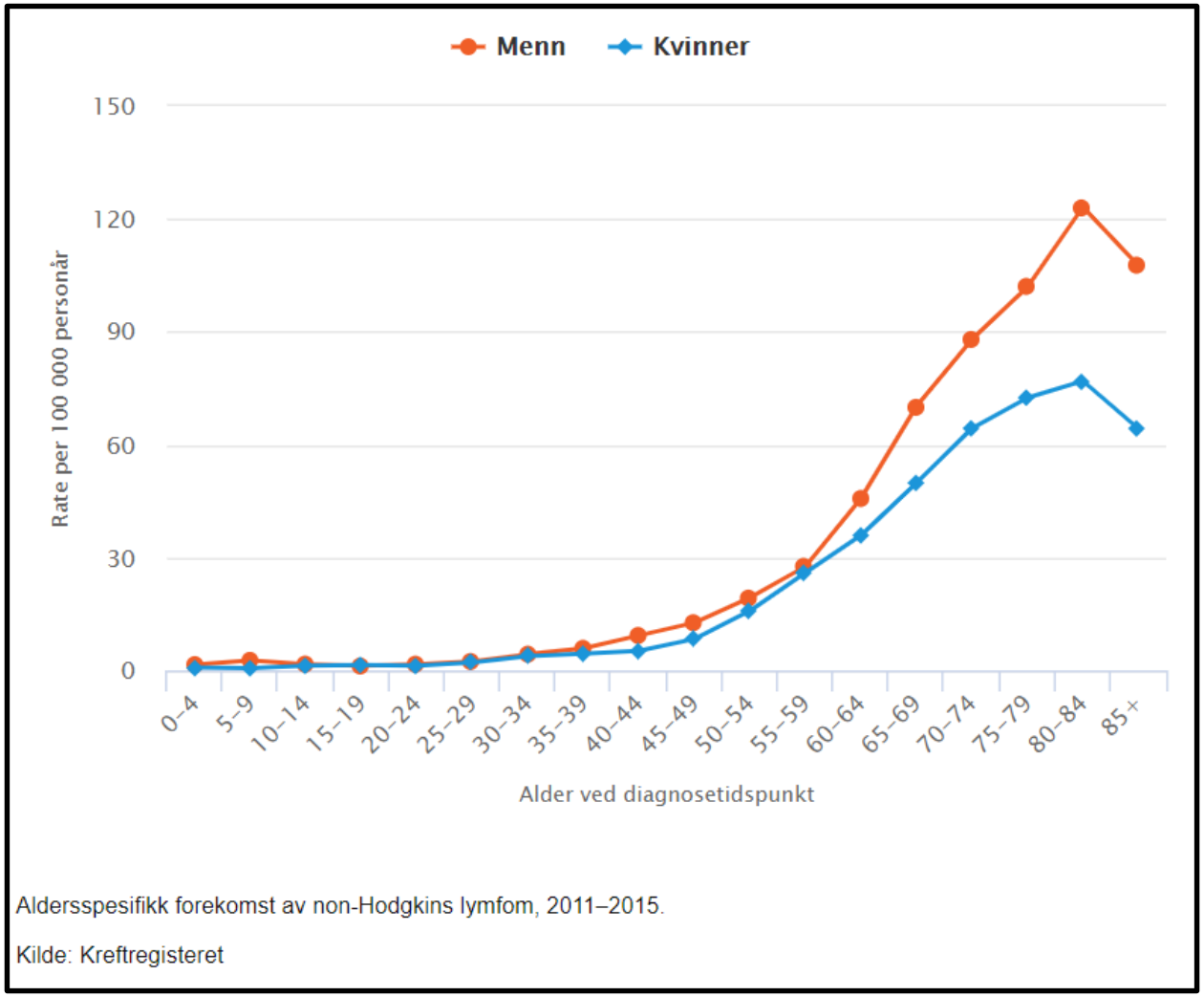
Typisk, men ikke spesifikk for klassisk Hodgkin

Hodgkin lymfom

- I 2011 var det 134 som fikk diagnosen HL, i overkant av 10% av maligne lymfomer



Non-Hodgkin lymfom



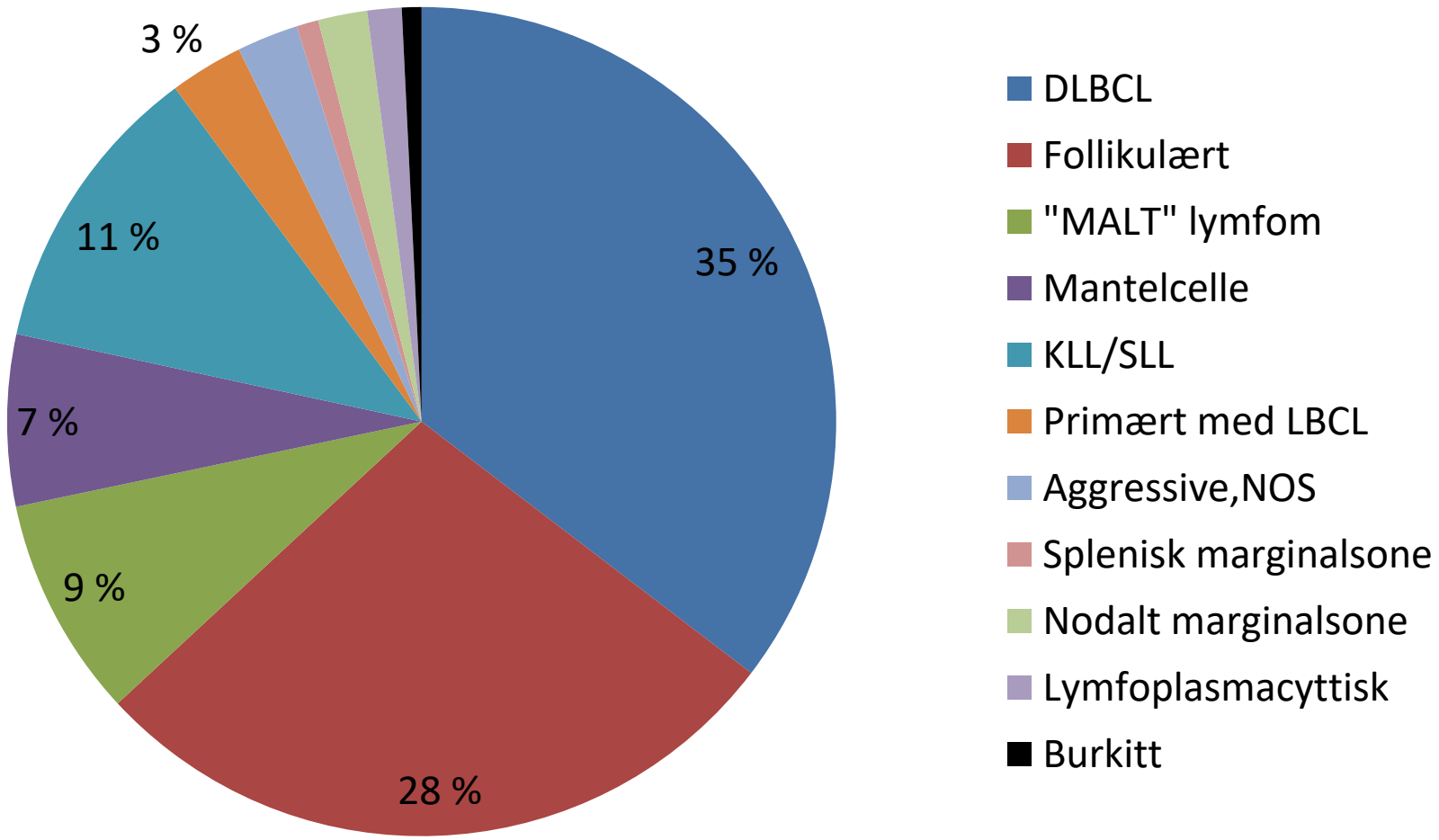
Aldersspesifikk forekomst av non-Hodgkins lymfom, 2011–2015.

Kilde: Kreftregisteret

Hovedinndeling

- Hodgkin lymfom: ca 10%
  - Nodulær lymfocyttrikt Hodgkin lymfom
  - Klassisk Hodgkin lymfom
- Non-Hodgkin lymfom: Ca 90%
  - B-NHL: ca 90% av NHL
    - B-lymfoblastlymfom/leukemi
    - B-NHL av moden/perifer type
  - T-NHL: ca 10% av NHL
    - T-lymfoblastlymfom/leukemi
    - T-NHL av moden/perifer type

Relativ frekvens av modne non-Hodgkin B-celle lymfomer hos voksne

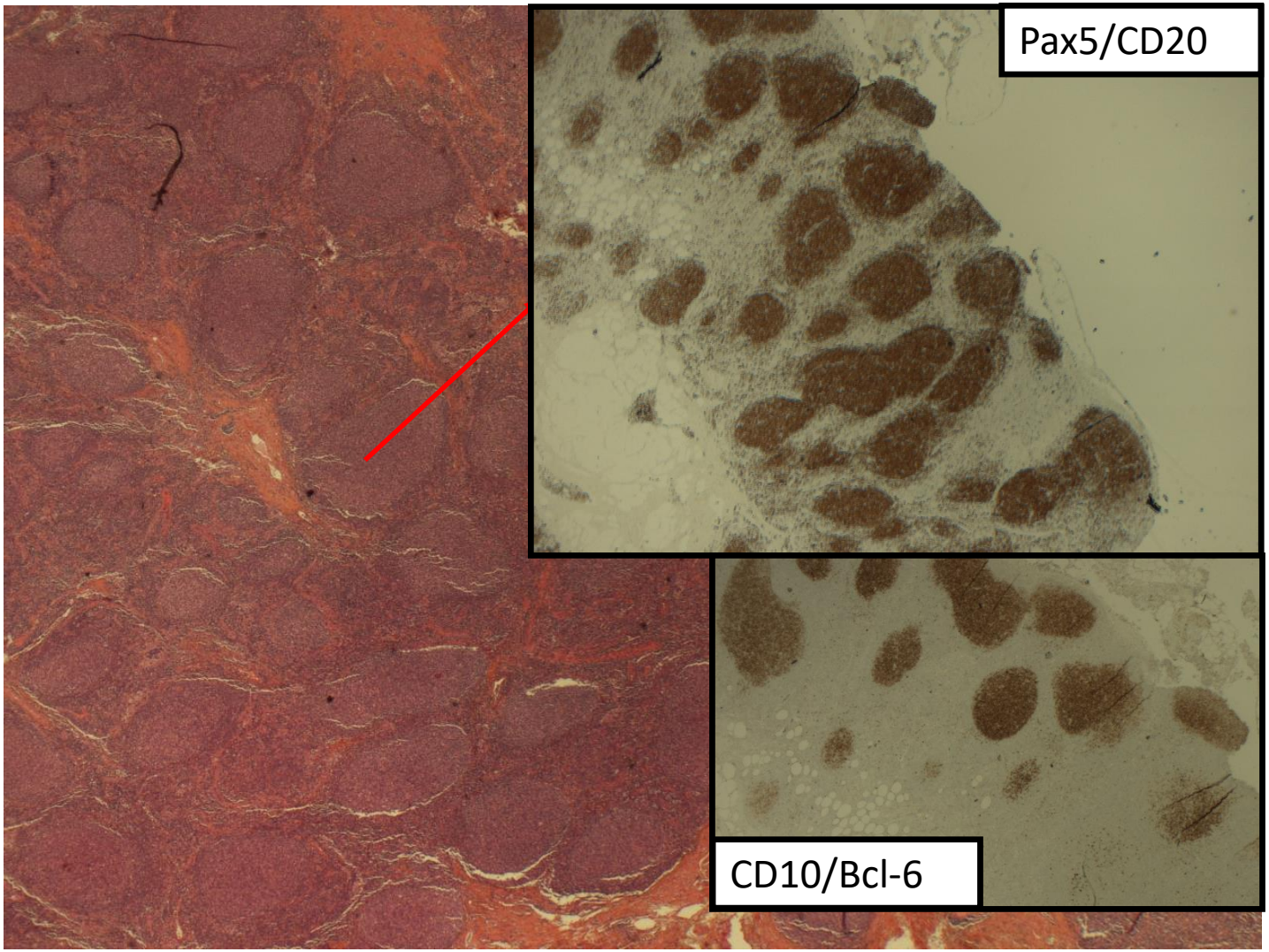


Indolente/lavgradig maligne non-Hodgkin B-cellelymfomer

- Follikulært lymfom
- Småcellet lymfocytært lymfom/kronisk lymfatisk leukemi
- Marginalsonelymfom
- Lymfoplasmacyttisk lymfom

- Mantelcellelymfom (NB! Mer aggressivt)

Follikulært lymfom



Tumor ”etterligner” en vanlig reaktiv follikkel (høyt differensiert).

Transformasjon

- Fra follikulært lymfom til høygradig B-cellelymfom (lavgradig til høygradig).
- Fra cytter til blaster
- Overgang til diffus vekstform.

- Alle lavgradig maligne B-cellelymfomer kan transformere til høygradig malignt B-cellelymfom.
- Annen behandling

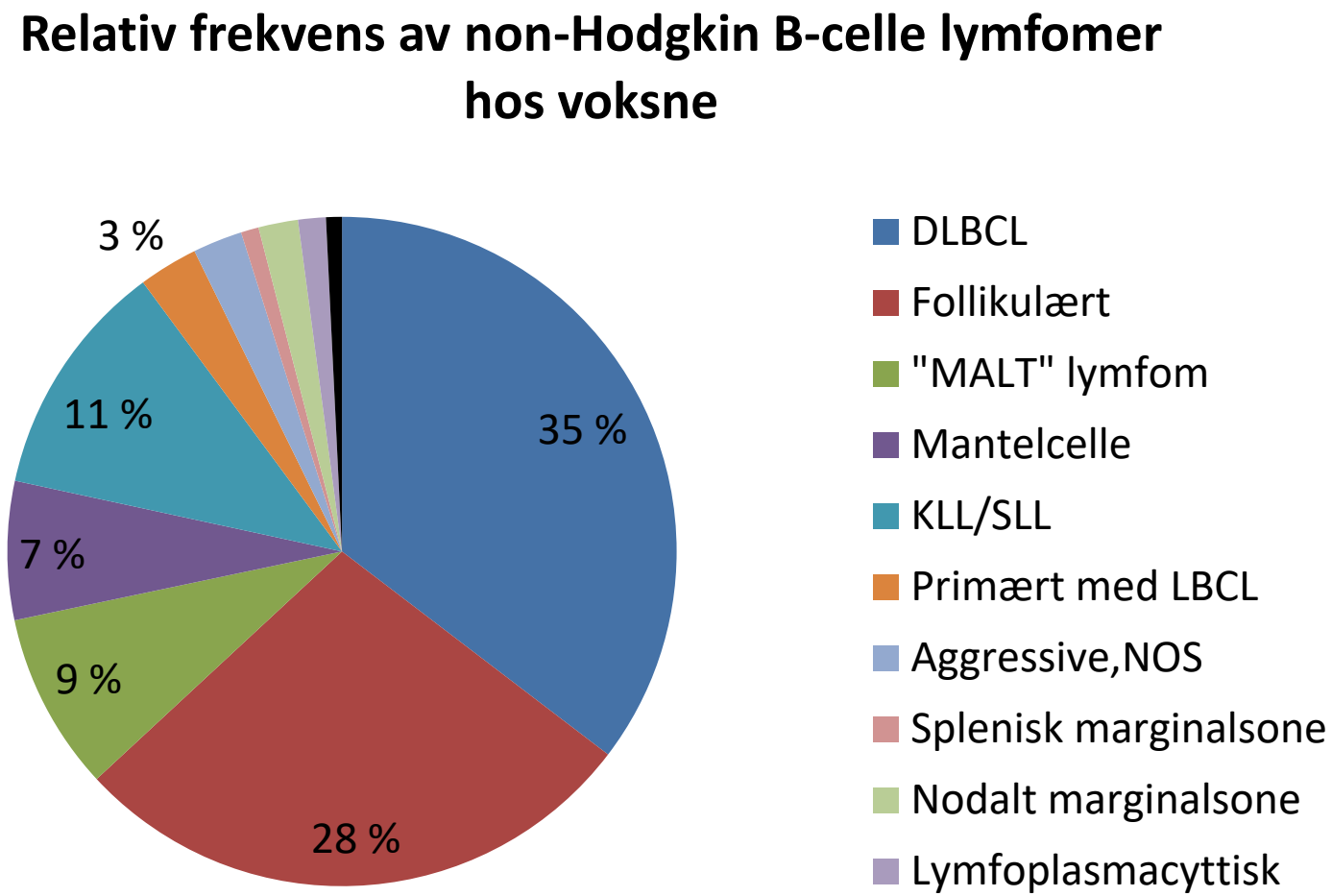
Aggressive non-Hodgkin B-cellelymfomer

- Diffust storcellet B-cellelymfom

  Skiller ut de med kombinasjoner av MYC-/BCL2-/BCL6-translokasjoner – ekstra aggressive

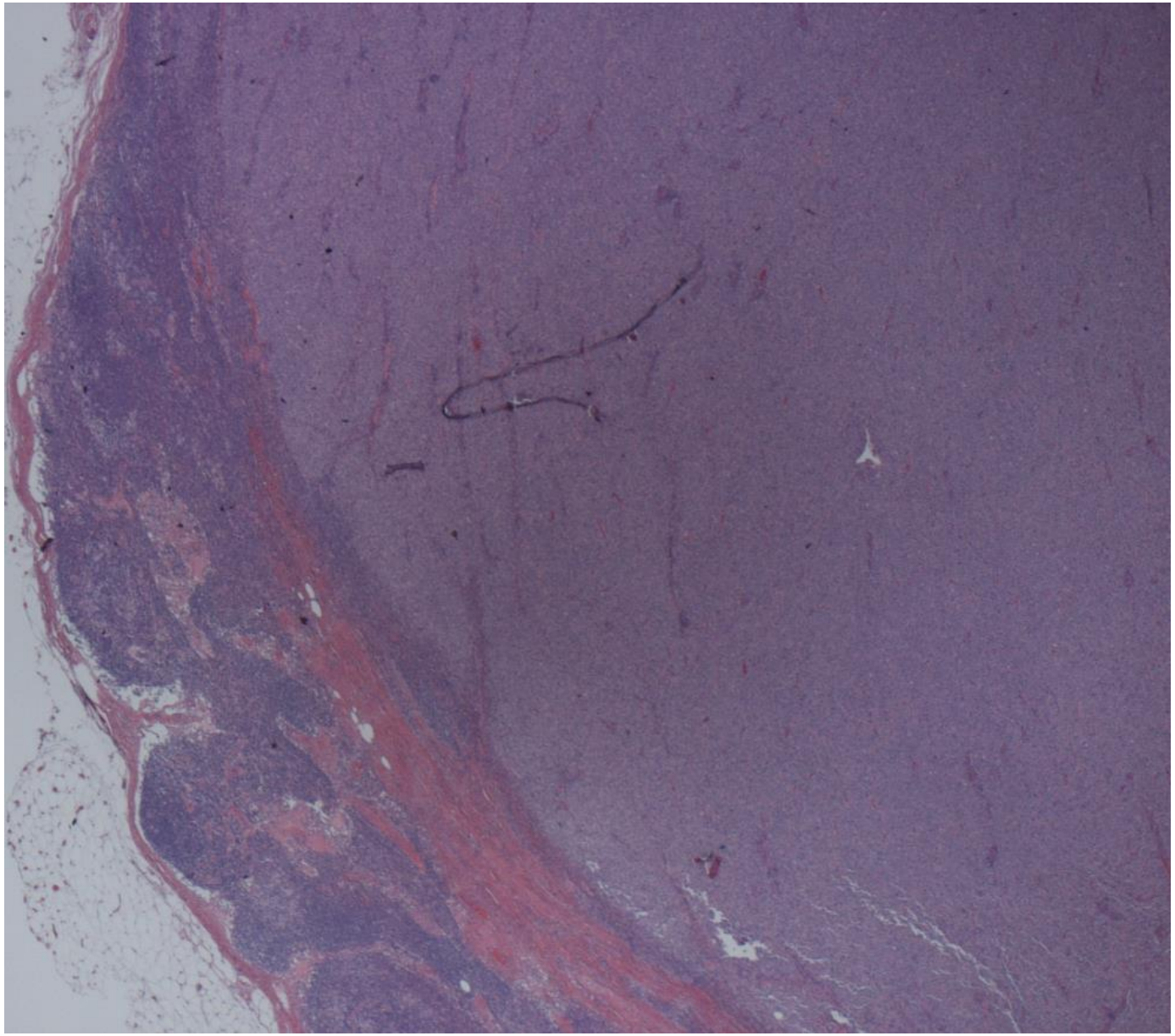
- Burkitts lymfom
- Mantelcellelymfom

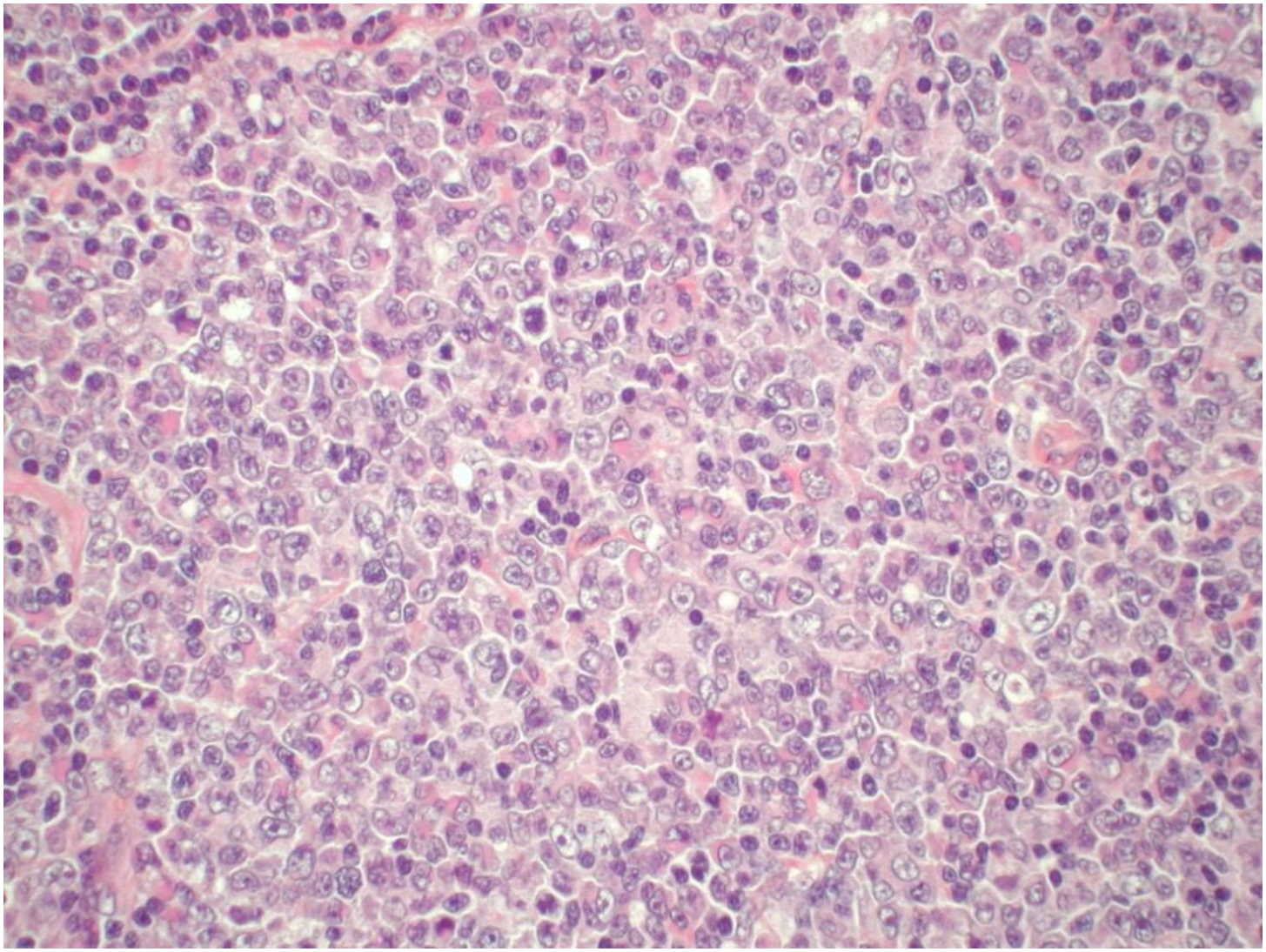
Diffust storcellet B-cellelymfom (DLBCL)

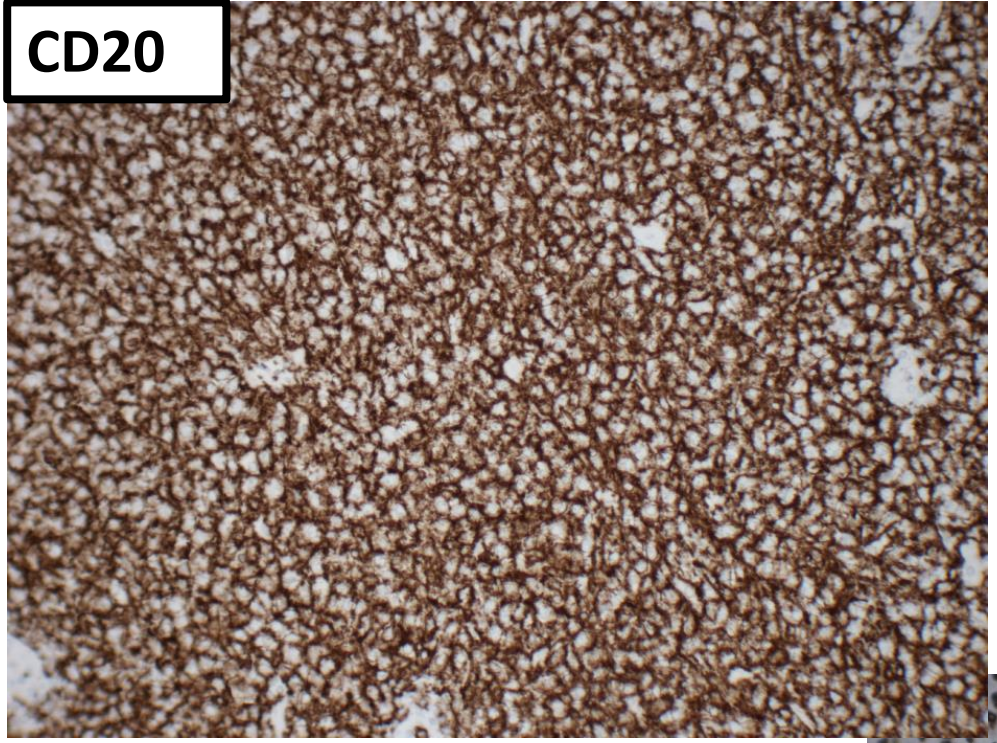


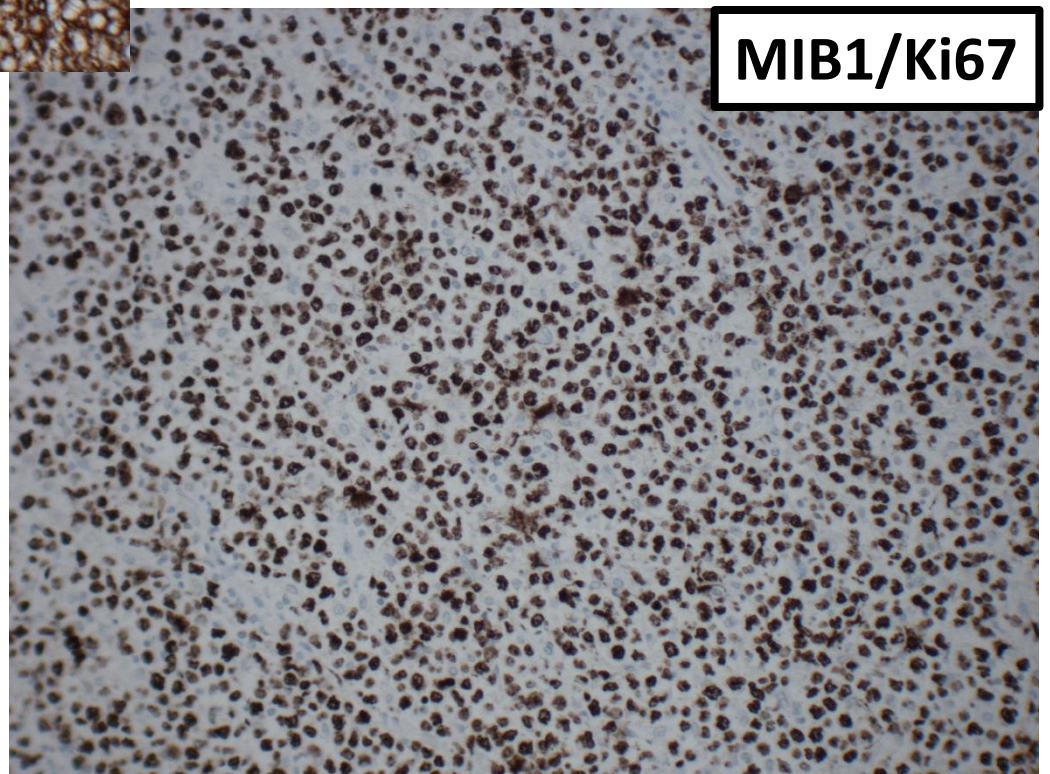
Diffust storcellet B-cellelymfom

- Median alder ved debut: ca 70 år
- Ca 60% nodale – ca 40% ekstranodale (oftest GI-tractus)
- Aggressiv sykdom
- Ofte kort sykehistorie (uker-få måneder)
- Rundt 50–60 % kan kureres



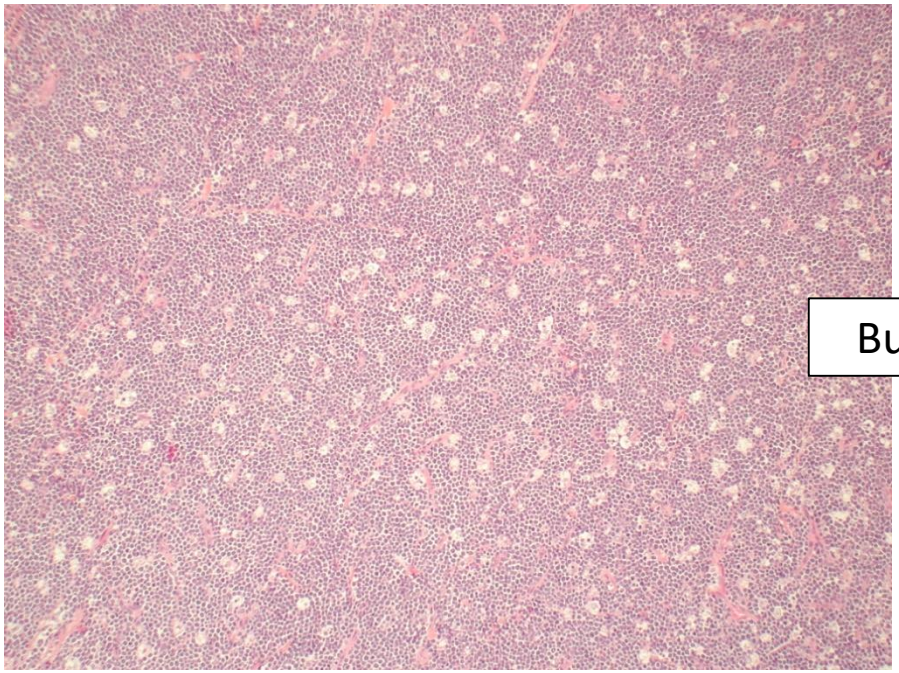



CD20

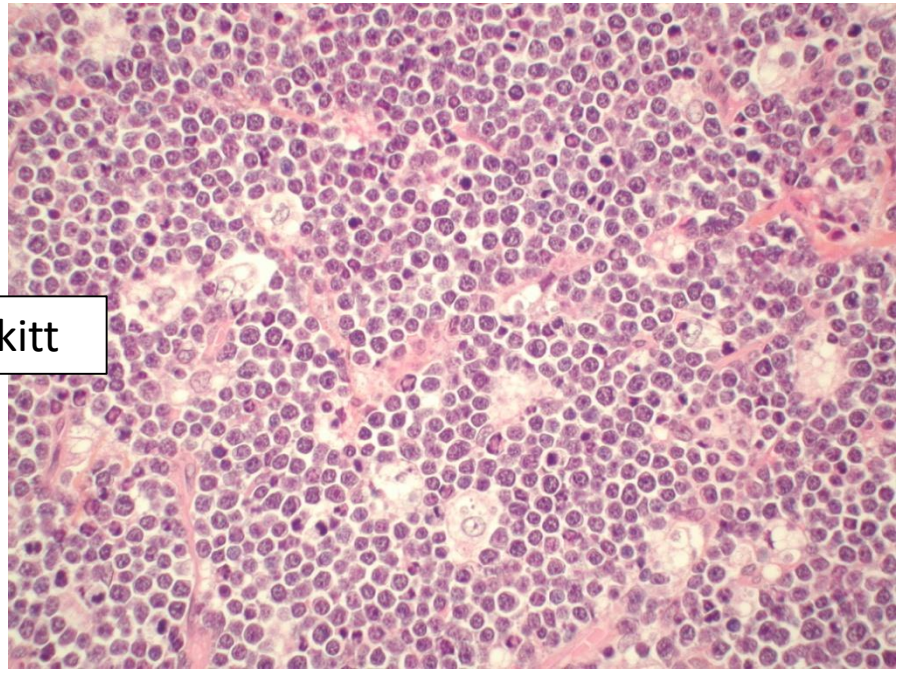

MIB1/Ki67

Burkitt lymfom (BL)
Sporadisk variant

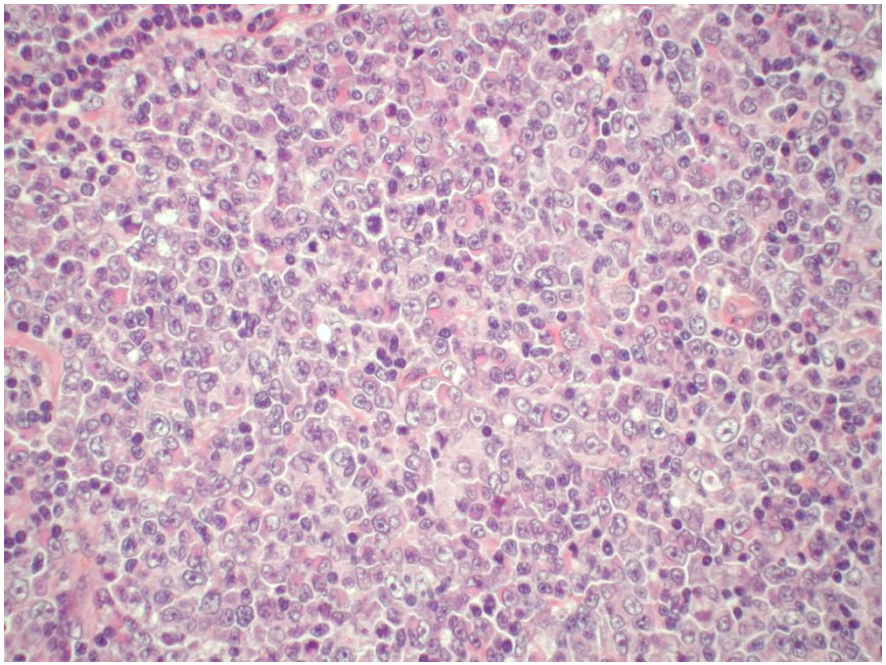
- Modent B-cellelymfom
- Svært aggressiv og hurtigvoksende tumor. Rask utredning. Skal ha annen behandling enn DLBCL.
- Svært sjelden diagnose, men ikke så sjelden diff.diagnose.
- Karakteristisk
  - Morfologi.
  - Immunfenotype.
  - Molekylærpatologiske funn

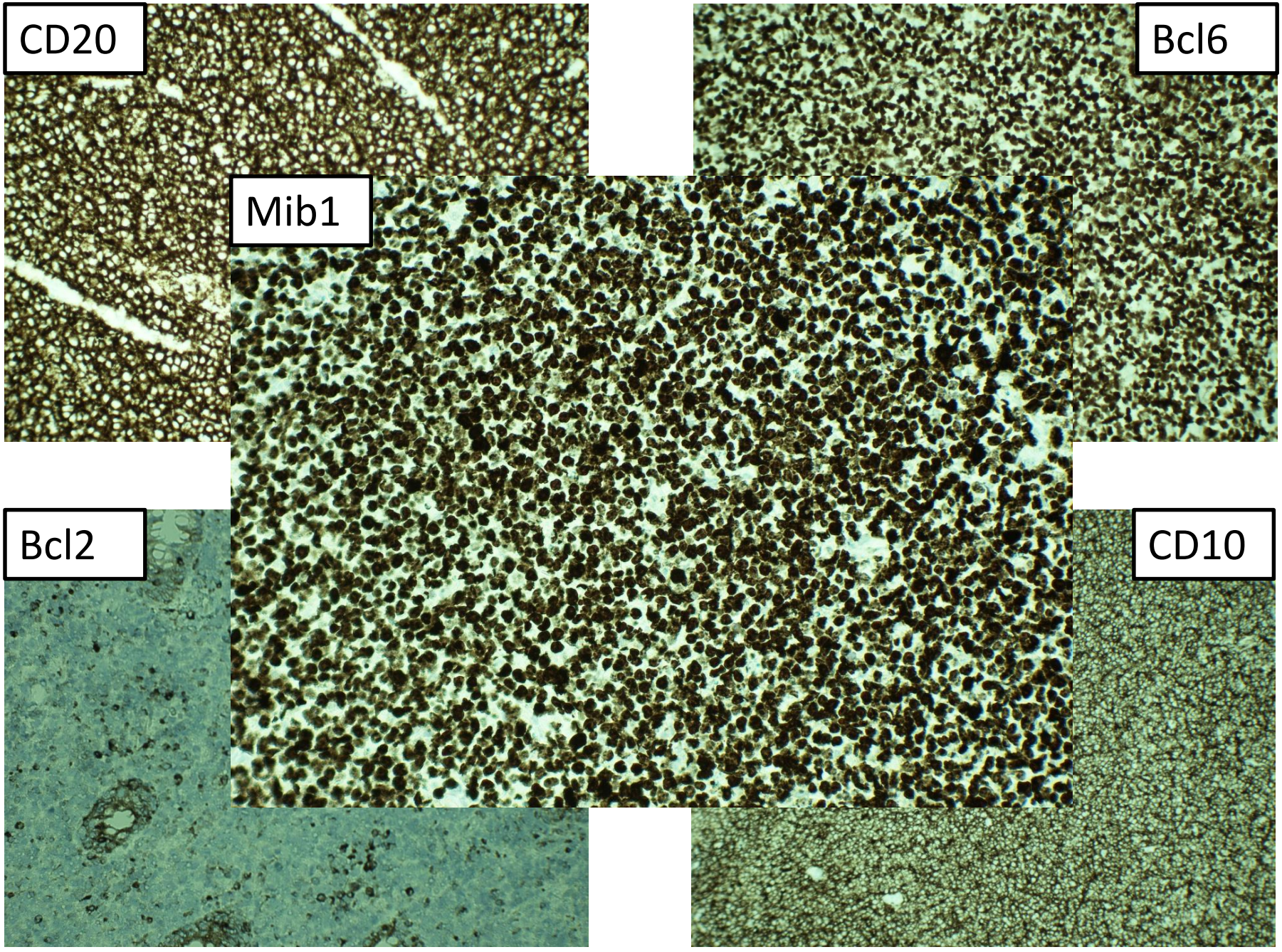


Burkitt



DLBCL

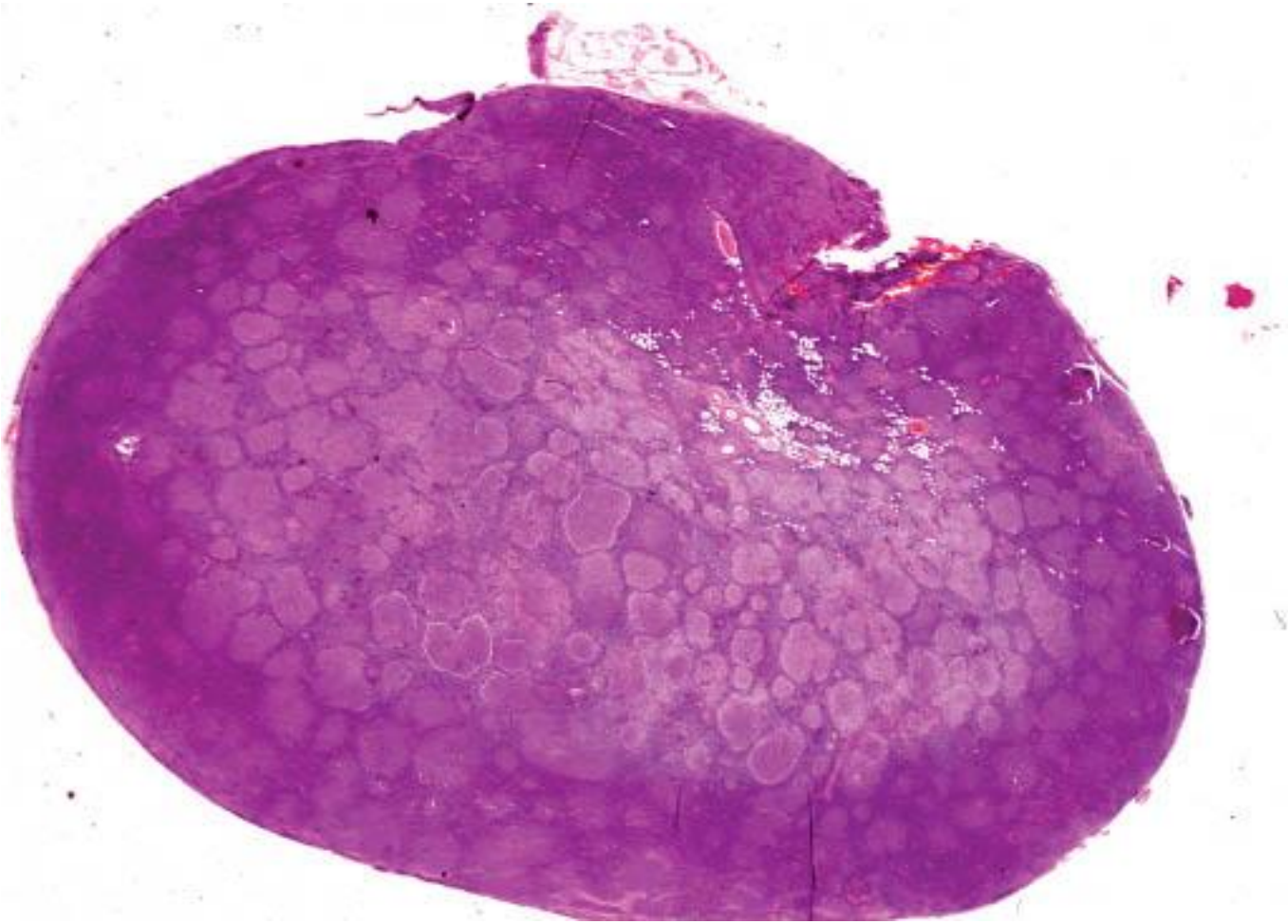


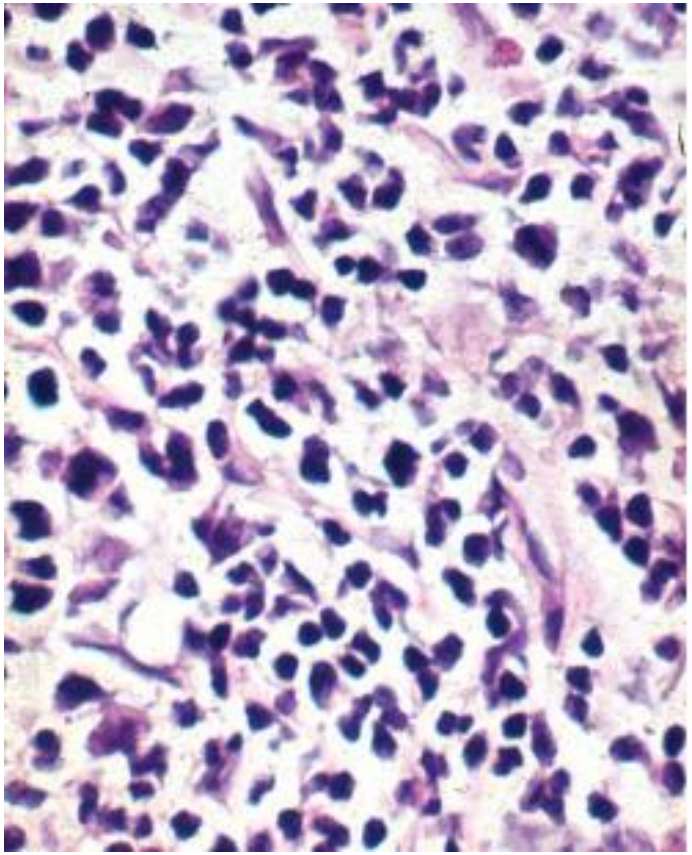

CD20
Bcl6
Mib1
Bcl2
CD10

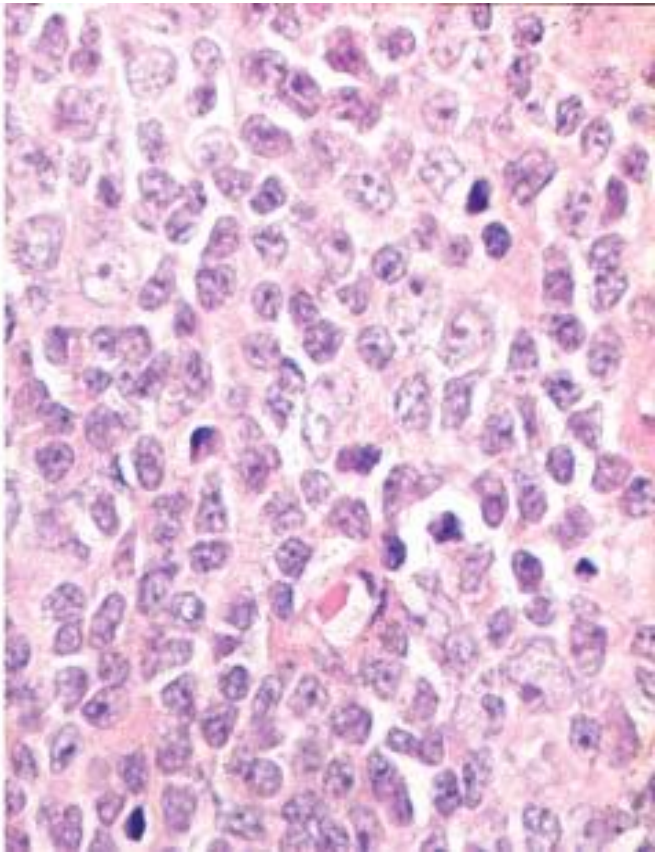
Forsendelse av ”lymfomprøver”
Ferskt vev

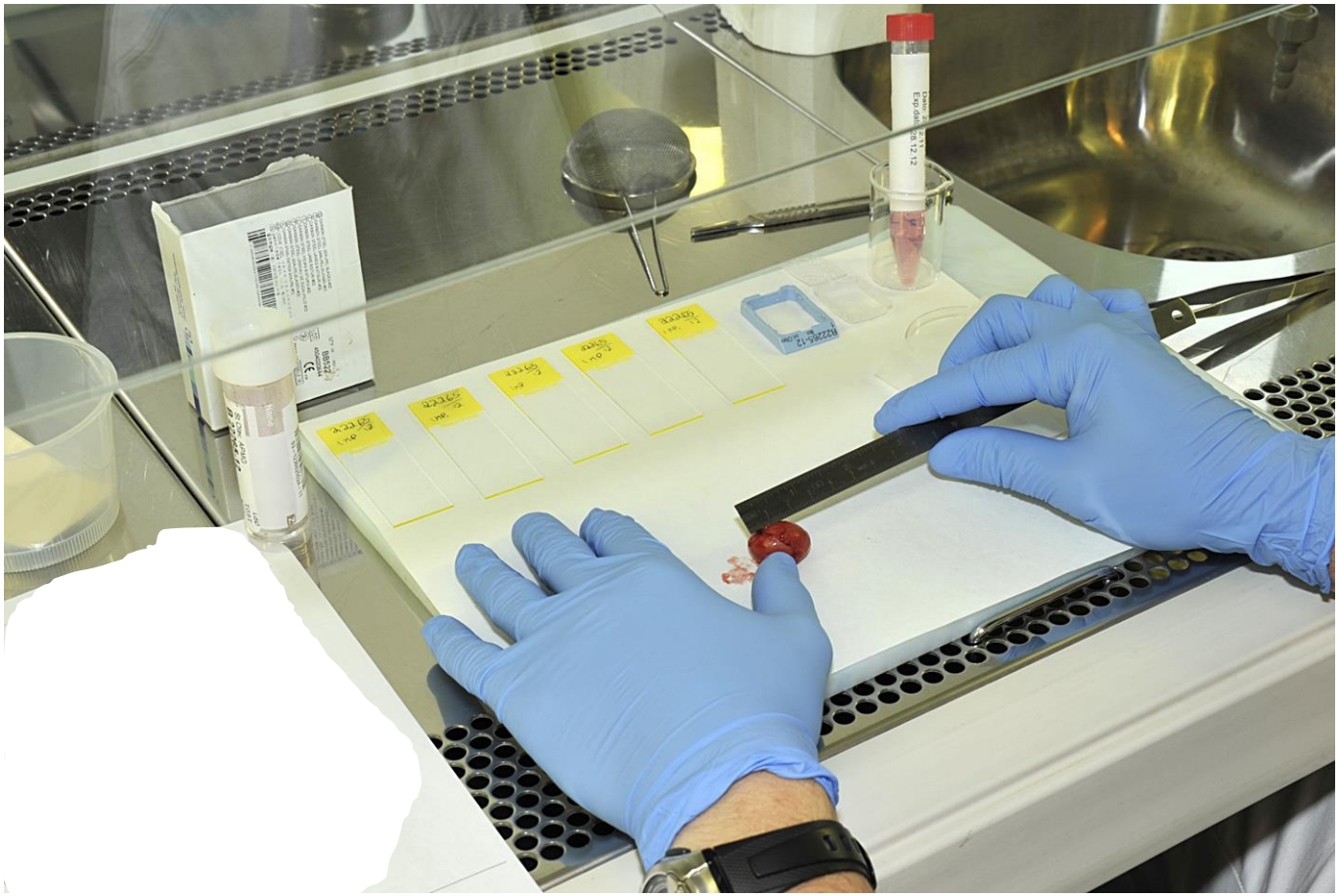
- Helst hele lymfeknuter, store eksisjoner
- Helst ferskt vev:
  - Sikre god og rask fiksering
  - Flowcytometri

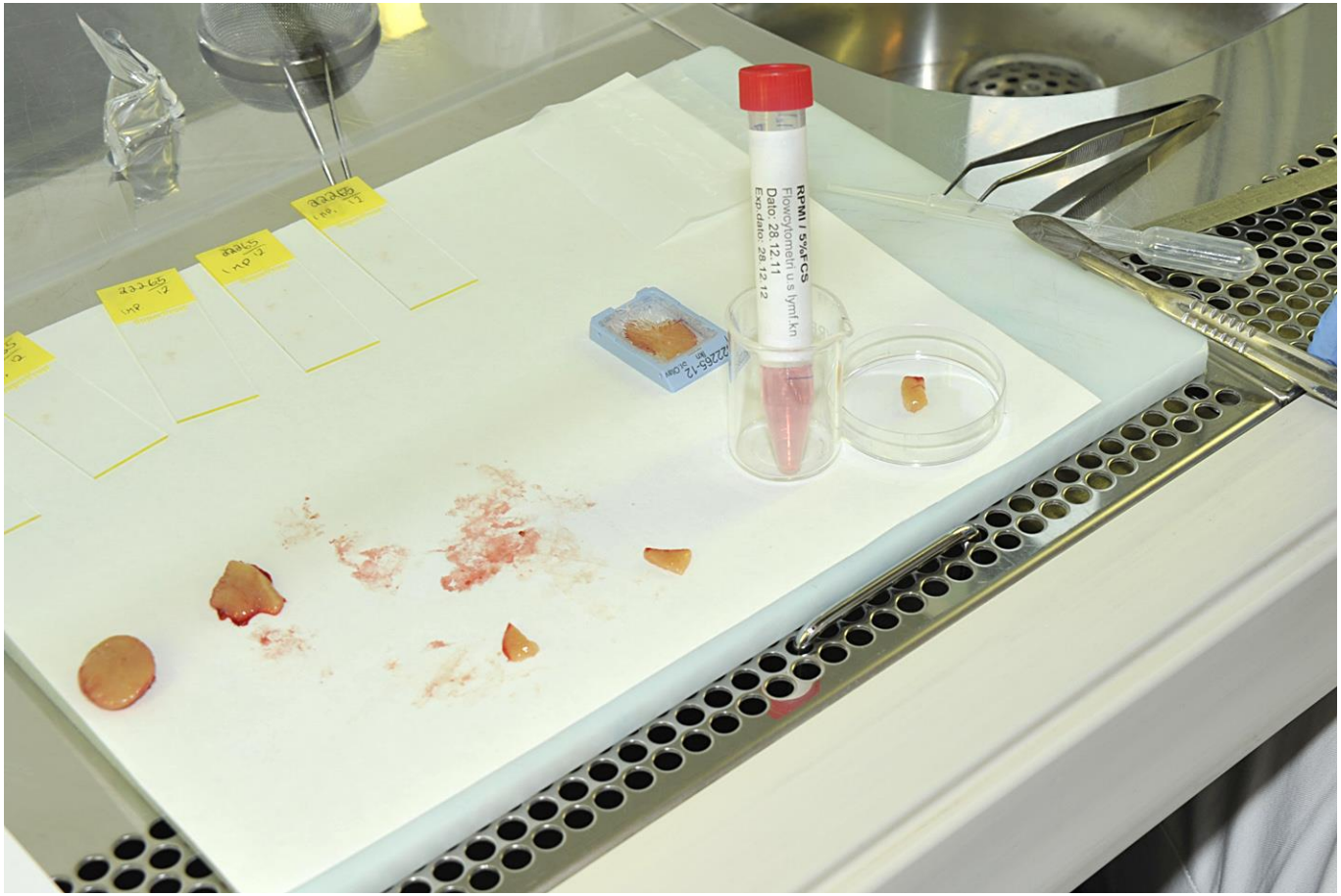
- Særlig viktig ved indolente tilstander









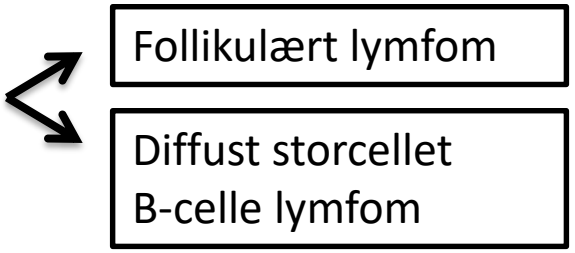

RPMI / 2%FCS
Flowcytometri u.s lymf.kn
Dato: 28.12.11
Exp.dato: 28.12.12

Avsluttende punkter

- Hvis noe ikke stemmer
  - Ring patologen før
    - den store sprøyta trekkes opp
    - pasienten går til allogen benmargstransplantasjon
    - svær kirurgi
- Kliniske opplysninger:
  - Histologi? («Shitologi» har forekommet)
  - Hva førte pasienten til legen
  - Immunsvikt!!!! Behandling, transplantasjon…
    - EBV

Hovedinndeling

- Hodgkin lymfom: ca 10%
  - Nodulær lymfocyttrikt Hodgkin lymfom
  - Klassisk Hodgkin lymfom
- Non-Hodgkin lymfom: Ca 90%
  - B-NHL: ca 90% av NHL
    - B-lymfoblastlymfom/leukemi
    - B-NHL av moden/perifer type
  - T-NHL: ca 10% av NHL
    - T-lymfoblastlymfom/leukemi
    - T-NHL av moden/perifer type



Quiz

- Mann 62 år.
- Store lymfeknuter på halsen