ENCR-JRC Training on Data Coding

25 September 2018 • Copenhagen • Denmark

Sarcoma, NET, CNS tumours & haematological malignancies

Coding issues

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European Commission

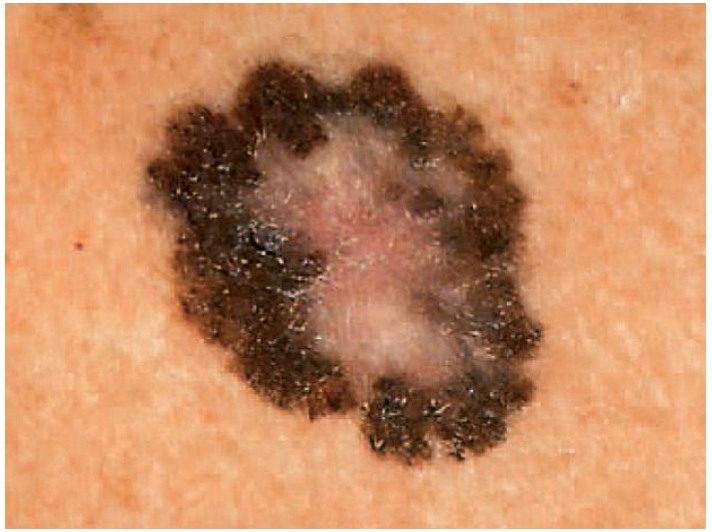
Introduction

- For most (solid) cancers, the primary site of the most important factor for the prognosis and the choice of treatment
- For other cancers, especially haematological malignancies, but also for an increasing number of solid cancers, the morphological classification is the most important factor

How is a cancer diagnosis made?

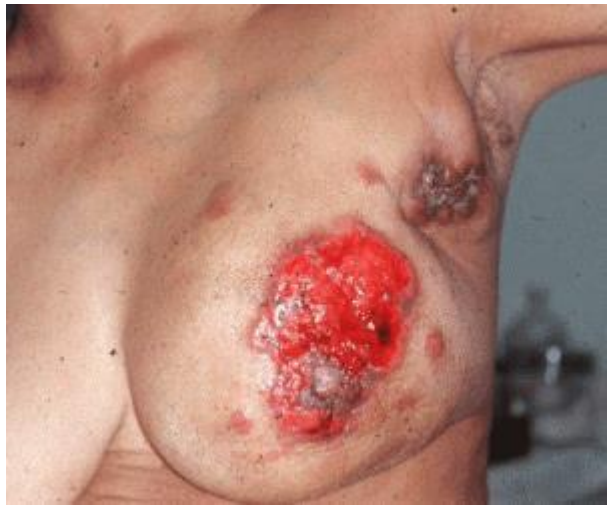
1. Clinical features
2. Microscopy
   - Large cells / small cells
   - Specific characteristics (colour, amount of cytoplasm, type of cell nucleus, etc)
3. Specific tests for proteins in the cytoplasm/cell nucleus/on the surface (immunohistochemistry)
4. Immunophenotyping
5. Cytogenetics

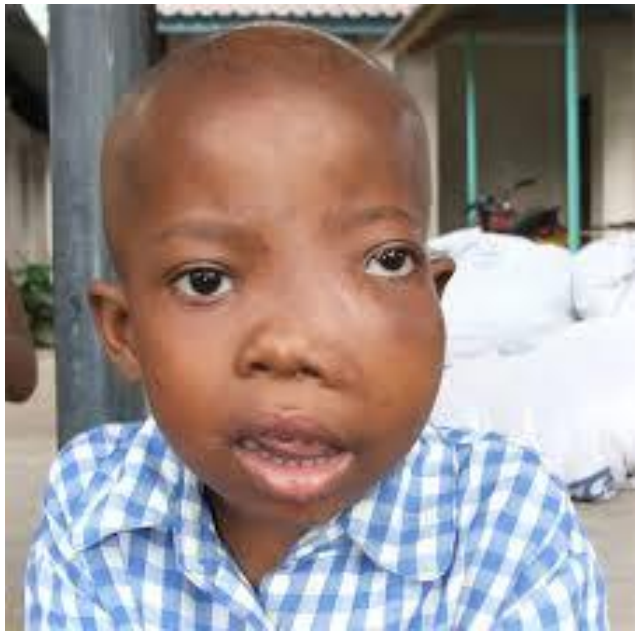
1. Clinical diagnosis



melanoma

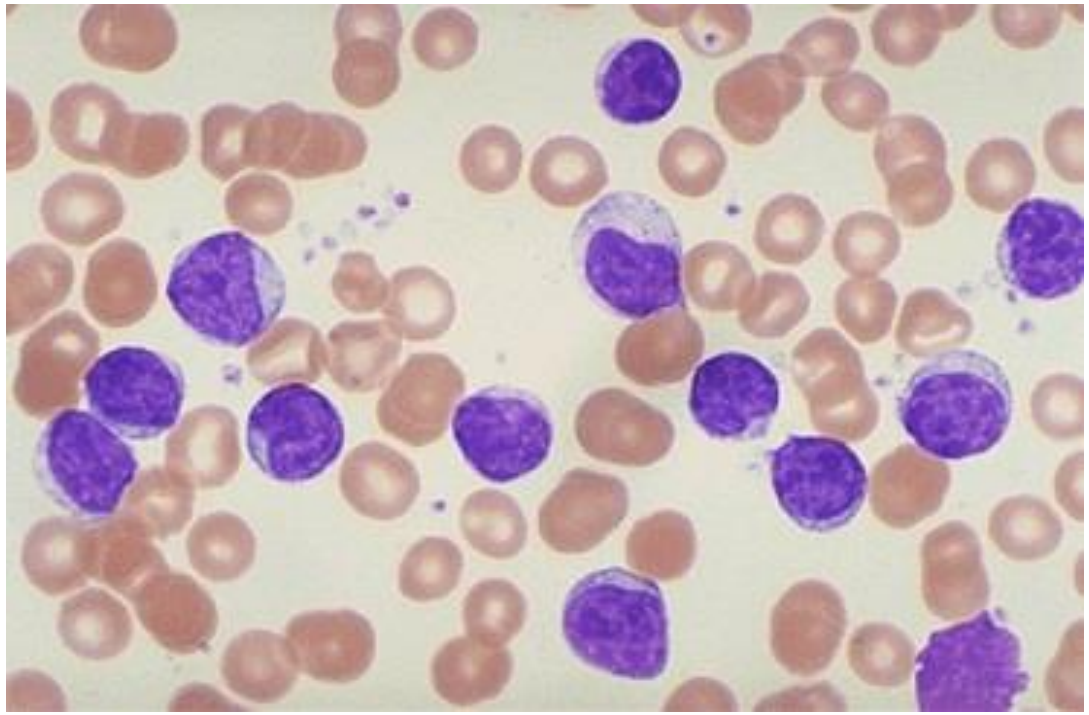
breast cancer



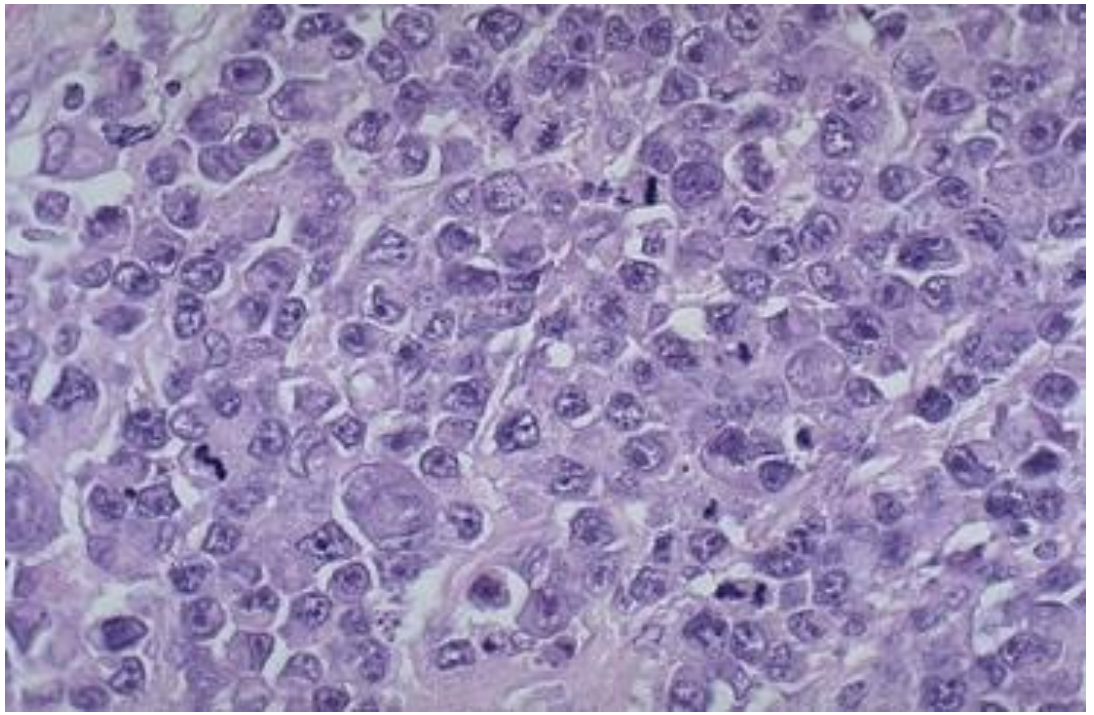


Burkitt lymphoma

2. Microscopy

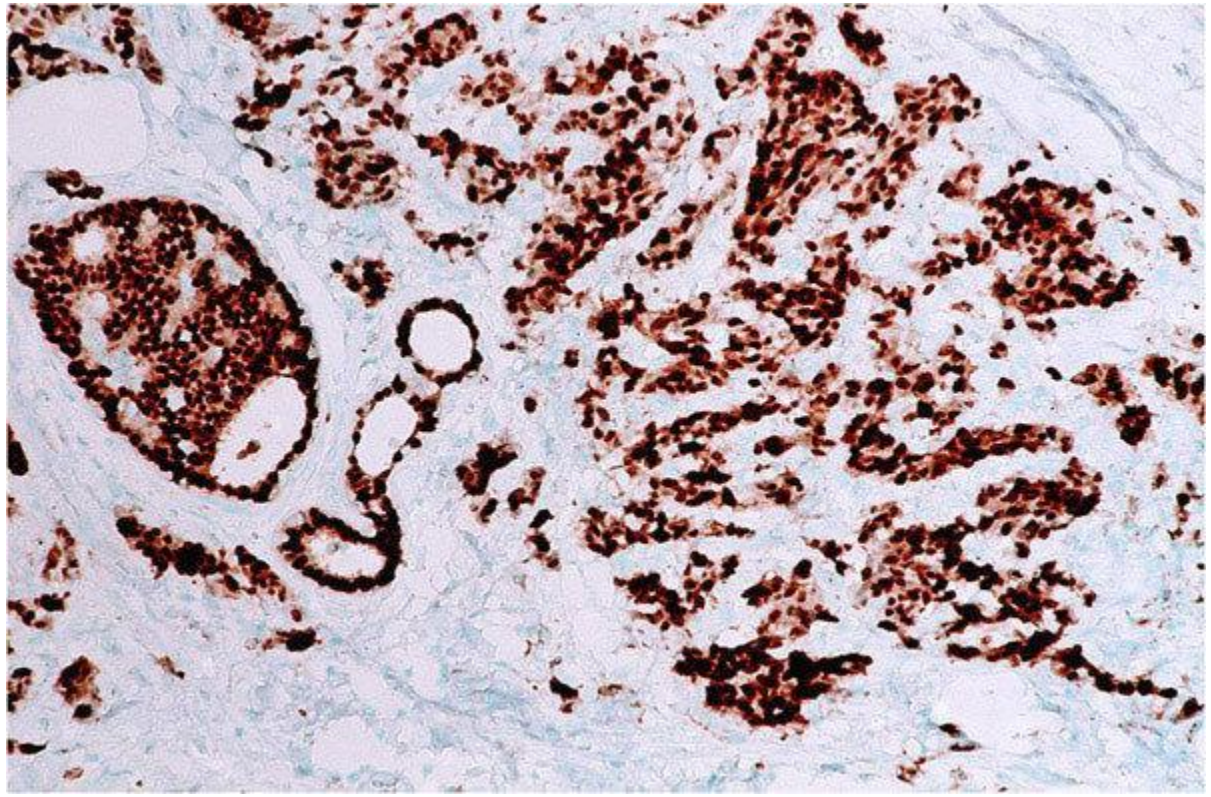


Small, mature cells with little cytoplasm, no mitoses (CLL)



Large cells (cytoplasm ++), prominent nucleoli, mitoses (DLBCL)

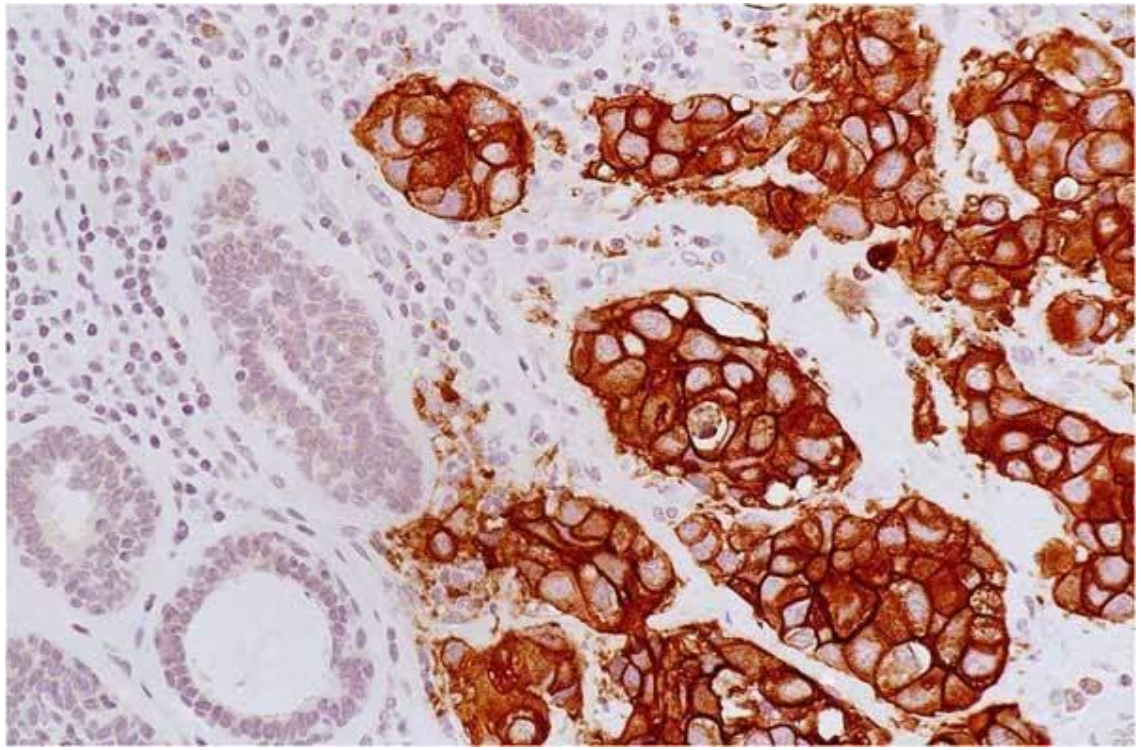
3. Immunohistochemistry



Expression of the estrogen receptor (ER) by using an immunostain for ER.

The immunostain binds to the ER protein in the nucleus of the cancer cells and is detected by a positive brown colour

3. Immunohistochemistry



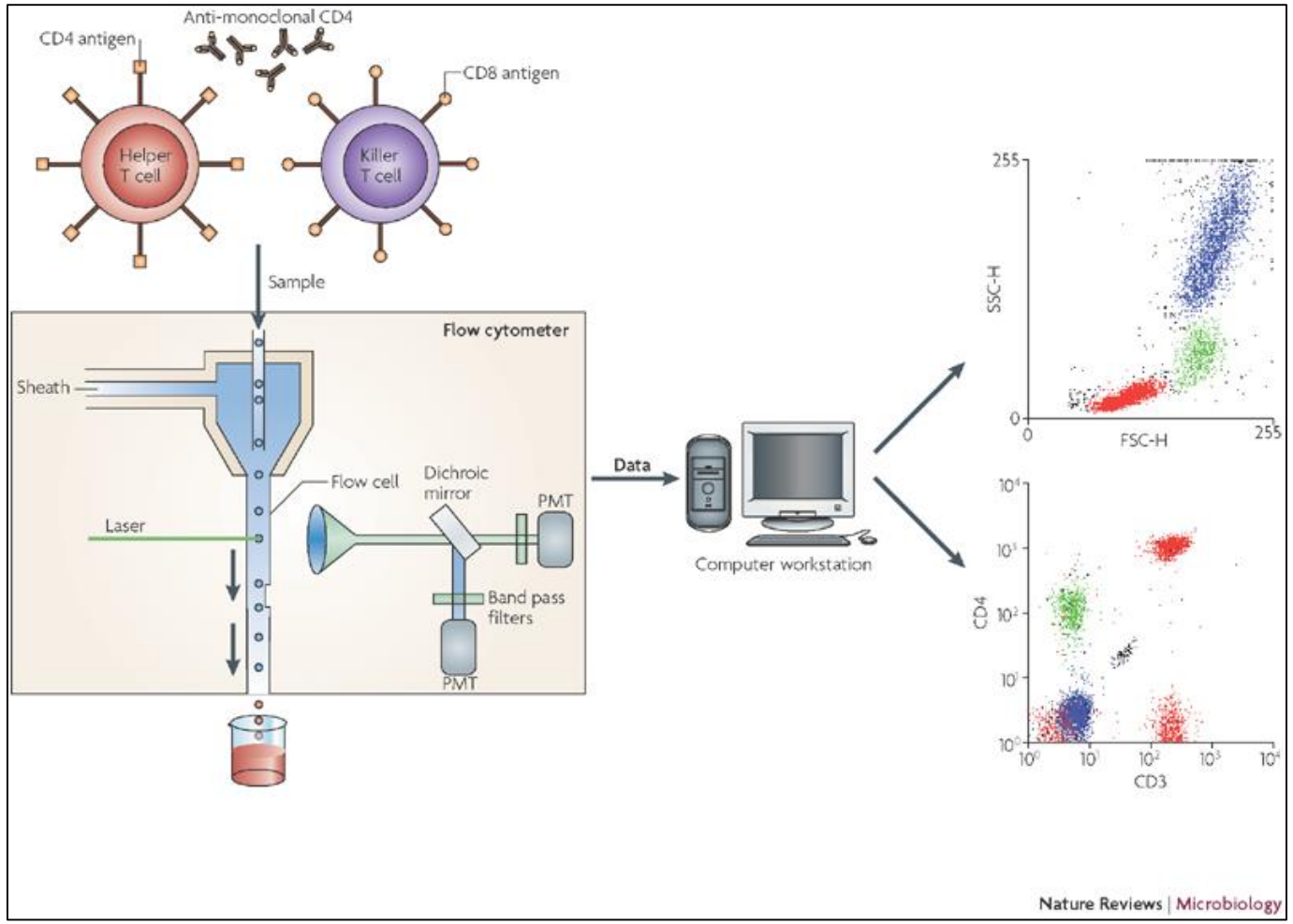
Expression of HER2 by using an immunostain for HER2.

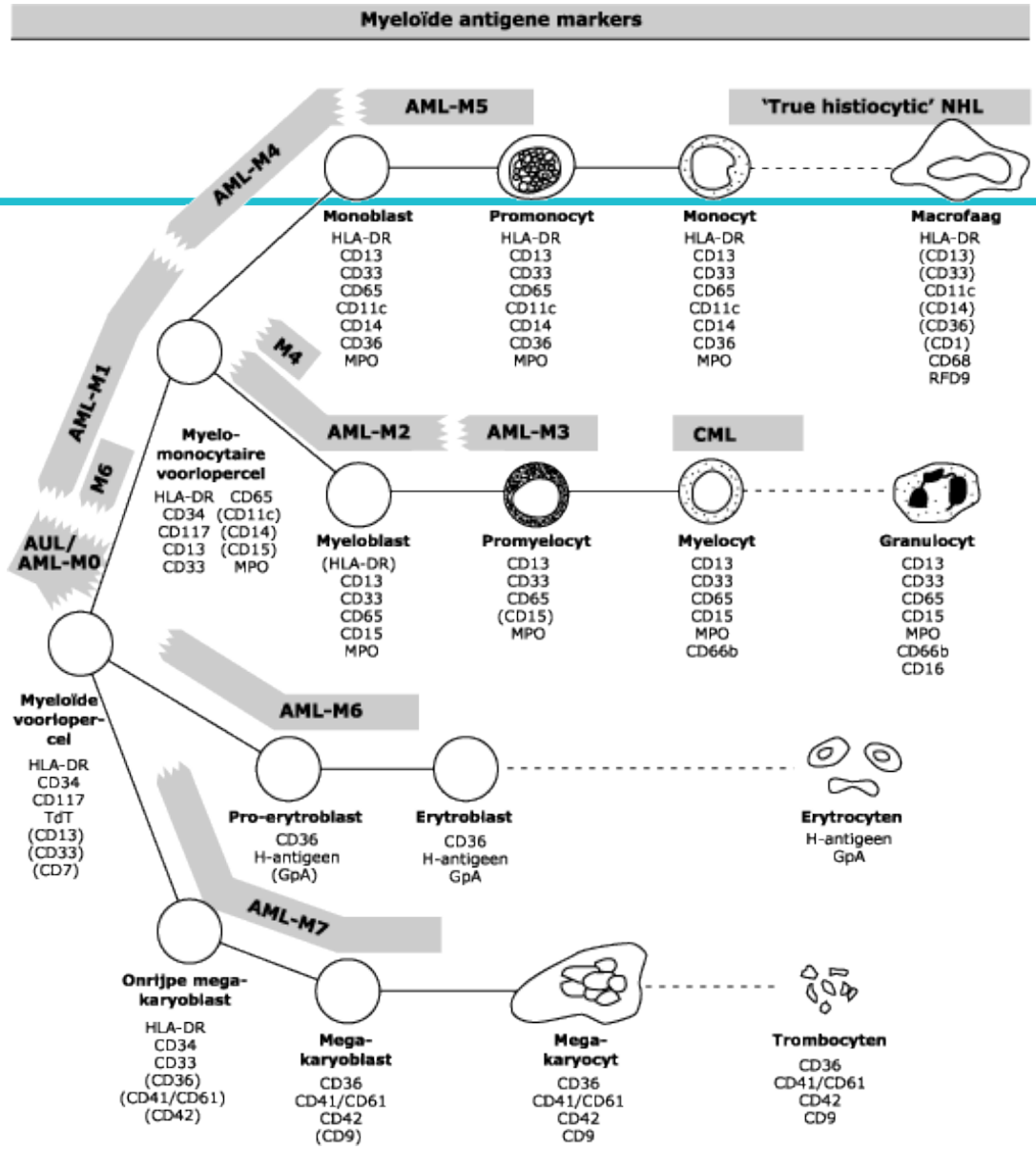
The immunostain binds to the HER2 protein on the surface of the cancer cells and is detected by a positive brown colour

4. Immunophenotyping

- Technique for the detection of proteins in the cell membrane of cancer cells
  - Tissue
  - Blood
  - Bone marrow
- If a certain protein is absent of present this gives an indication for the type of cell

4. Immunophenotyping

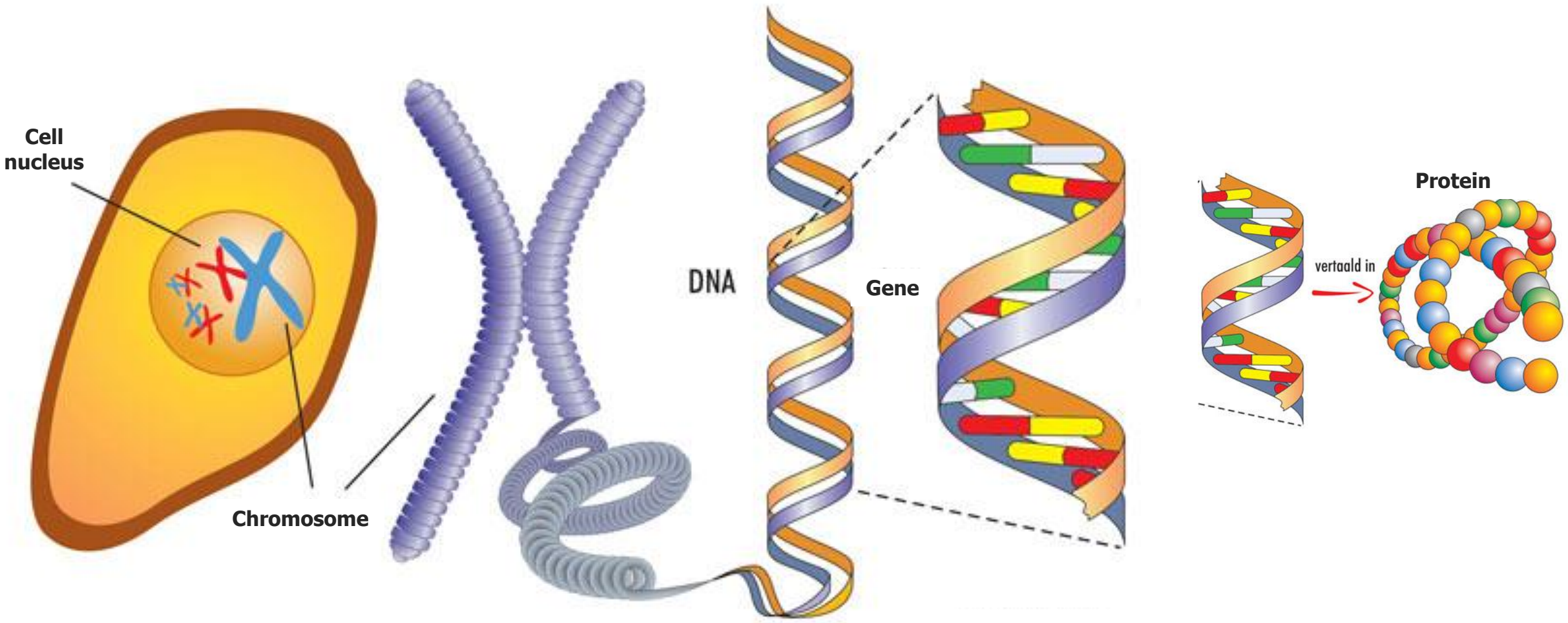




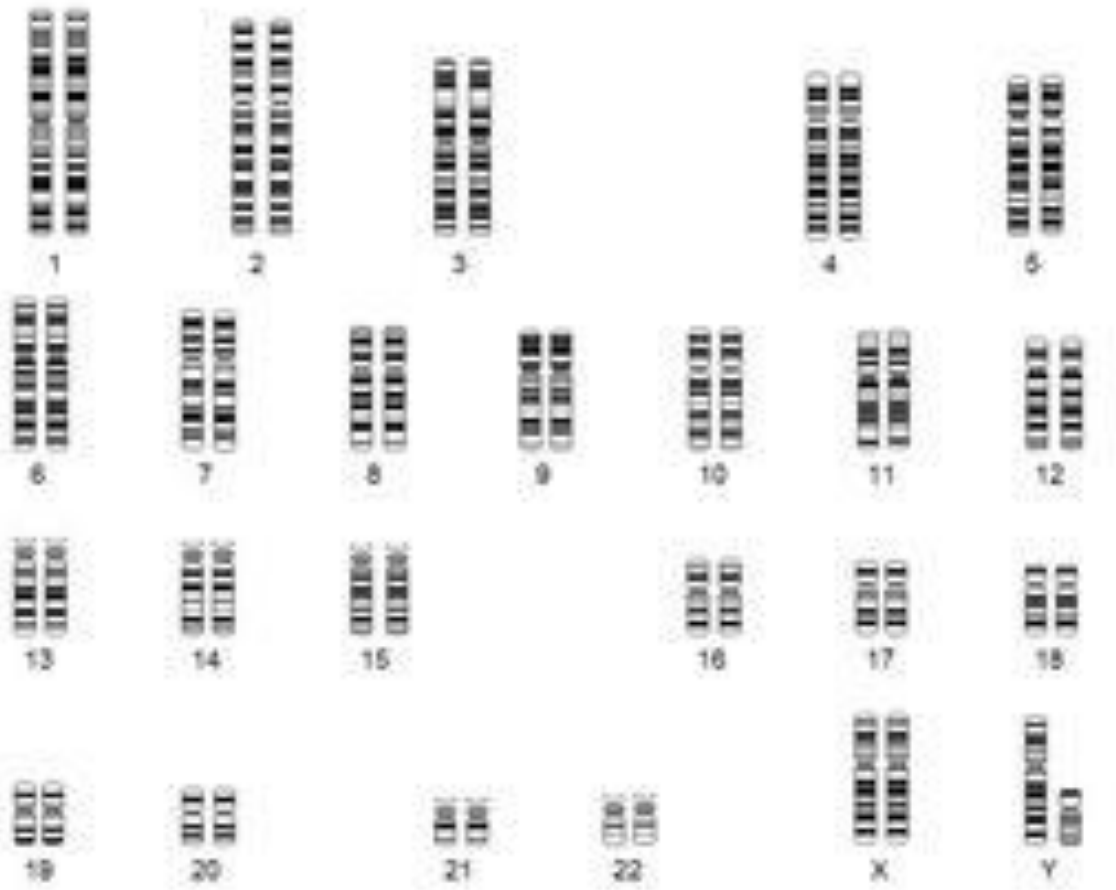
5. Cytogenetics & molecular diagnostics

- Most cancer cells have 'errors' in the DNA (cytogenetic aberrations)
- With cytogenetics & molecular diagnostics these aberrations can be detected
- Many aberrations are not clinically relevant, but others are, because specific drugs can target specific cytogenetic aberrations, e.g. imatinib for BCR-ABL+ chronic myeloid leukaemia ('targeted therapy')
- Often, aberrations can be detected with different techniques

5. Cytogenetics & molecular diagnostics



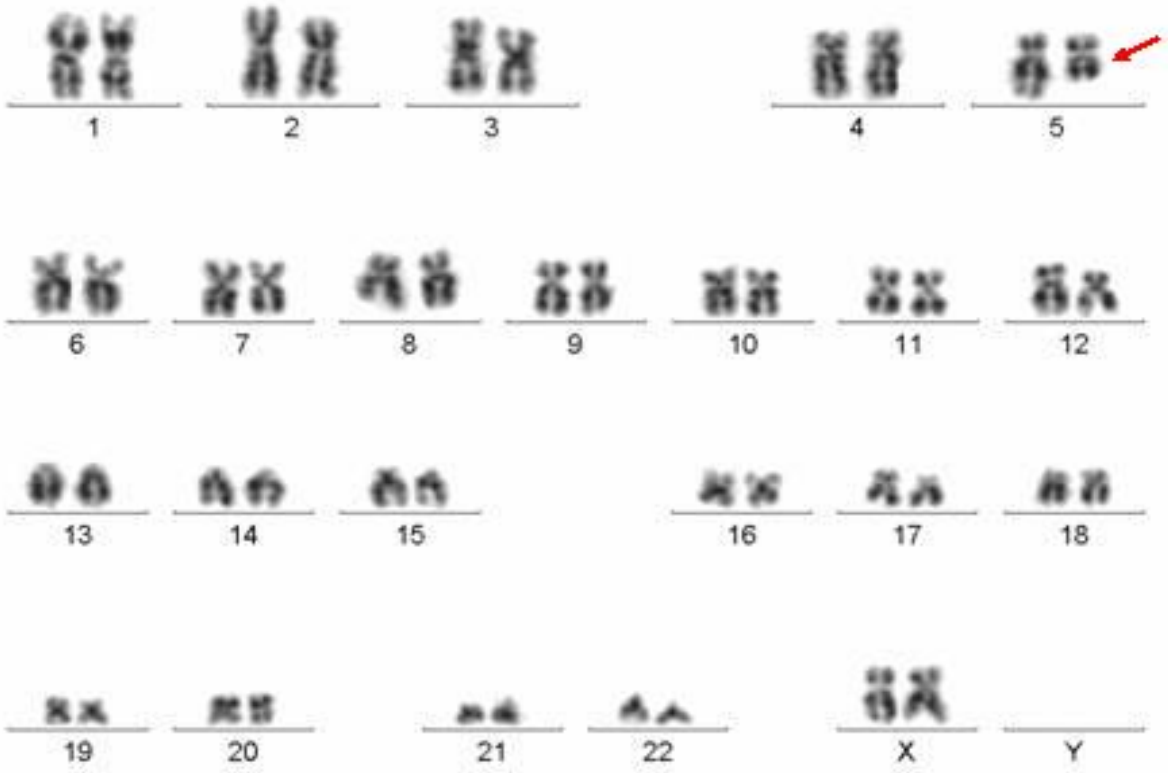
5. Cytogenetics: karyotyping



- Photo of the chromosomes
- Each (normal) cell has 46 chromosomes
- In cancer cells a (part of a) chromosome can be missing, duplicated or displaced

5. Karyotyping: example

- Patient with MDS
- A part the long arm (q) of chromosome 5 is missing (=deletion)
- Diagnosis: MDS with 5q-
- Morphology code: 9986

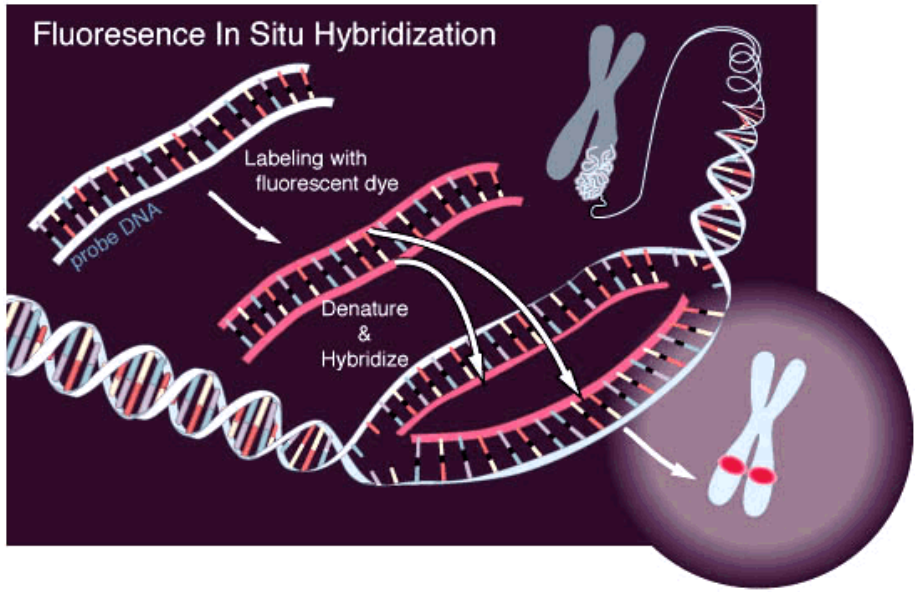


5. Aberrations visible with karyotyping

- Deletion→ MDS with 5q- = M9986
- Translocation → t(9;22) in CML =M9875
- Inversion → AML with inv(3) = M9869
- Trisomy (3 chromosomes in stead of 2) → Down syndrome (trisomy 21)
- Monosomy (1 chromosome in stead of 2)
- Hypodiploidy (<46 chromosomes) → hypodiploid ALL = M9816
- Hyperdiploidy (>46 chromosomes) → hyperdiploid ALL = M9815

5. Cytogenetics: Fluorescence *in situ* hybridisation (FISH)

- A fragment of RNA ('probe') is labelled with a fluorescent dye
- The probe binds to specific parts of the DNA (a gene or a larger part of the DNA)
- If the probe binds to a gene or part of DNA you see a fluorescent dot



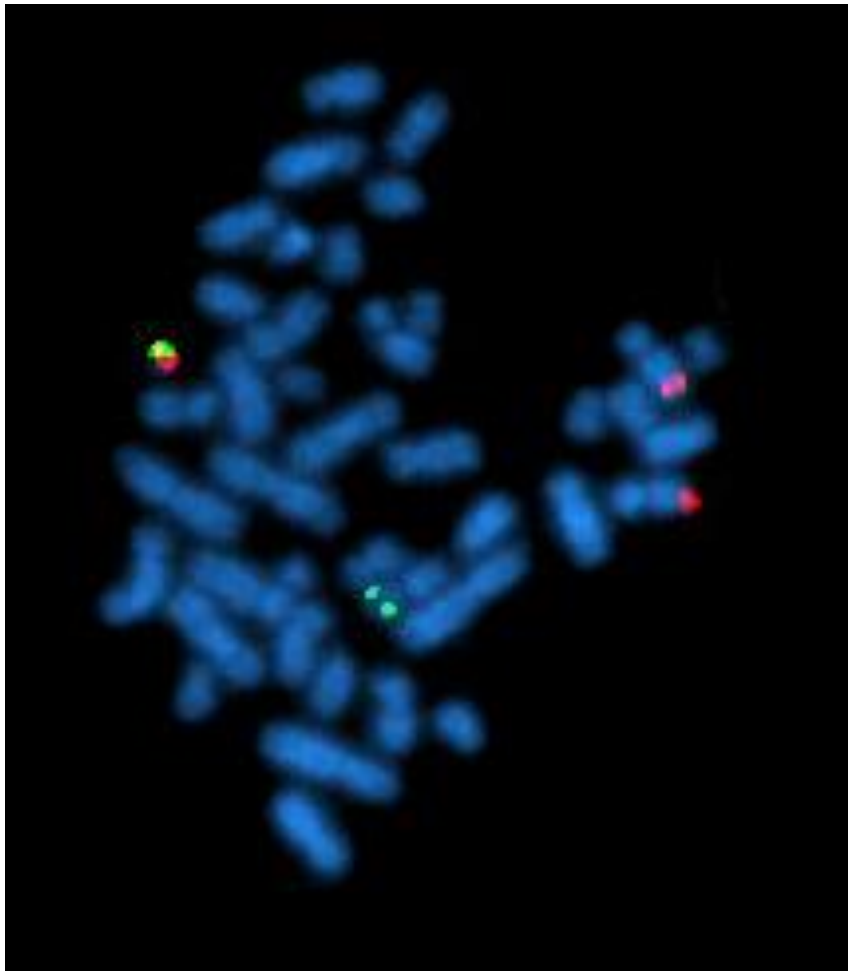
5. FISH: example

In CML there is a translocation of chromosomes 9 and 22 = t(9;22)

Chromosome 9 is labelled red and chromosome 22 green.

The normal situation is that you see 2 pairs of dots of the same colour (4 dots in total of each colour).

If there is a combination red/green, the translocation is present.



5. Molecular diagnostics

If a gene (or combination of genes = 'fusion genes') codes for a specific protein, you can also use molecular diagnostics to detect the protein.

The fusion gene in CML produces the protein BCR-ABL, which can be detected in blood.

Sarcoma

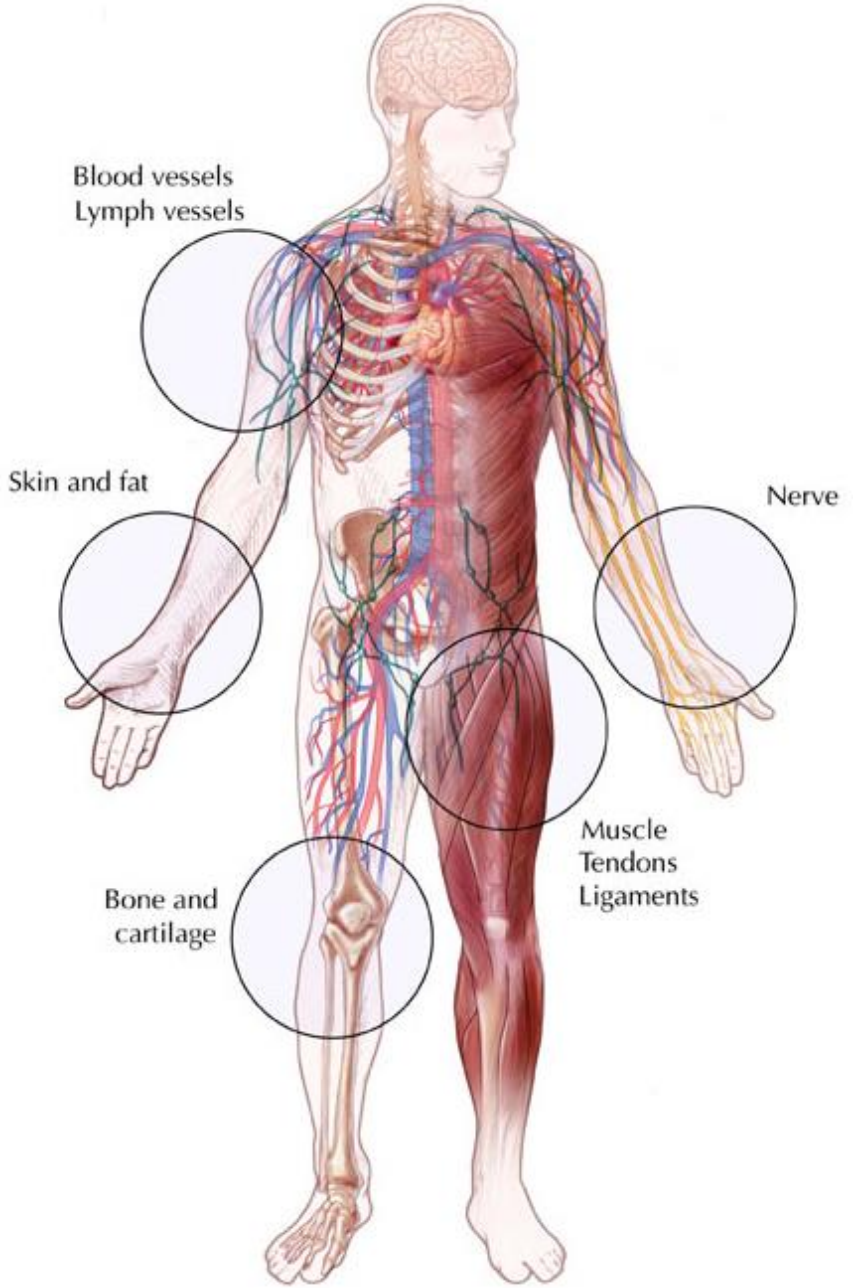
European Commission

What is a sarcoma?

- A sarcoma is a malignant tumour that arises in tissues that were formed from the mesoderm, the 'middle' germ layer of the embryo
- In those tissues no 'basal membrane' is present
- Therefore, the behaviour of the tumour (the potency to metastasize) cannot be determined on the basis of invasion of the basal membrane (as in all epithelial cancers), but has to be determined on other factors

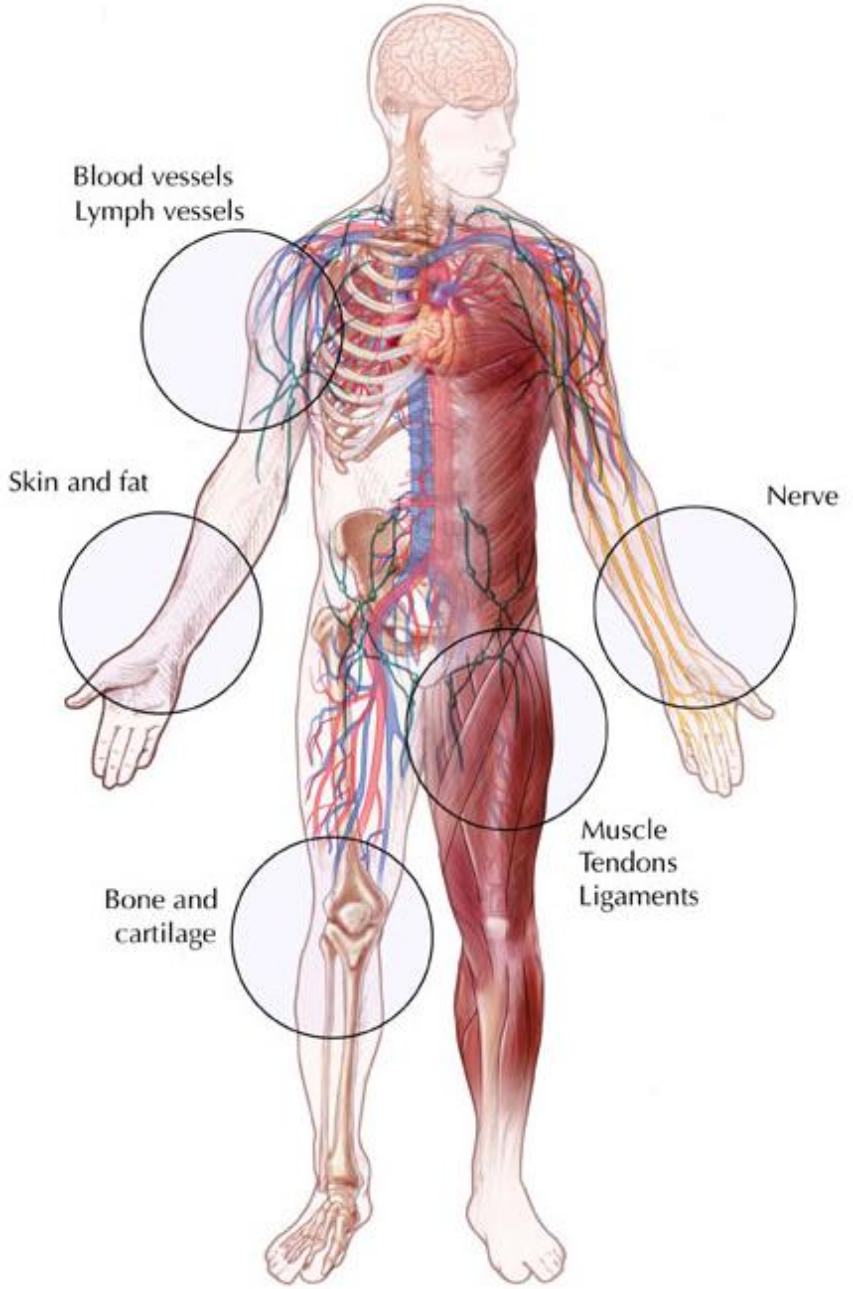
Sarcoma: main sites

- Bone and cartilage
- 'Soft tissues'
  - Skin and subcutaneous tissues
  - Blood and lymph vessels
  - Muscles, tendons, ligaments
  - Nerves
- Organs
  - Stomach, uterus, etc.



Sarcoma: main sites

- Bone and cartilage → C40, C41
- 'Soft tissues'
  - Soft tissues → C49
  - Peripheral nerves & ANS → C47
  - Retroperitoneum → C48.0
  - Mediastinum → C38.1-3
- Organs
  - Stomach, uterus, etc. → code to the specific organ, e.g. C16, C54, etc.



Sarcoma: main histological types

- Bone → osteosarcoma; cartilage → chondrosarcoma
- 'Soft tissues'
  - Skin and subcutaneous tissues (fat → liposarcoma; connective tissue → fibrosarcoma)
  - Blood and lymph vessels → (lymph)angiosarcoma
  - Muscles → rhabdomyosarcoma (striated muscle) or leiomyosarcoma (smooth muscle); tendons → synoviosarcoma
  - Nerves → malignant peripheral nerve sheath tumour (MPNST)
- In organs, almost all types can occur as in most organs all kinds of soft tissues are present (fat, connective tissue, muscle, blood vessel)

Sarcoma: other/rare types

- Stromal cells → gastrointestinal stromal tumour (GIST), stromal sarcoma
- Osteoclasts → osteoclastoma (giant cell tumour of bone)
- Peripheral neuroectoderm → peripheral neuroectodermal tumour (PNET)
- Small blue round cell tumours, such as Ewing's sarcoma [t(11;22)] and desmoplastic small round cell tumour
- Kaposi's sarcoma (a blood vessel tumour of the skin; often with multiple lesions)
- Remnants of the chorda → chordoma (considered as a bone tumour)

Sarcoma: other/rare types

- Mesothelium → mesothelioma
- Meninges → meningioma

Sarcoma: a-specific types

- Spindle cell sarcoma
- Pleomorphic cell sarcoma
- Small cell sarcoma
- Giant cell sarcoma (except of bone)
- Epithelioid sarcoma
- Undifferentiated sarcoma
- Malignant fibrous histiocytoma

If there is a specific diagnosis and an a-specific diagnosis, the specific diagnosis has preference.

Sarcoma: grade

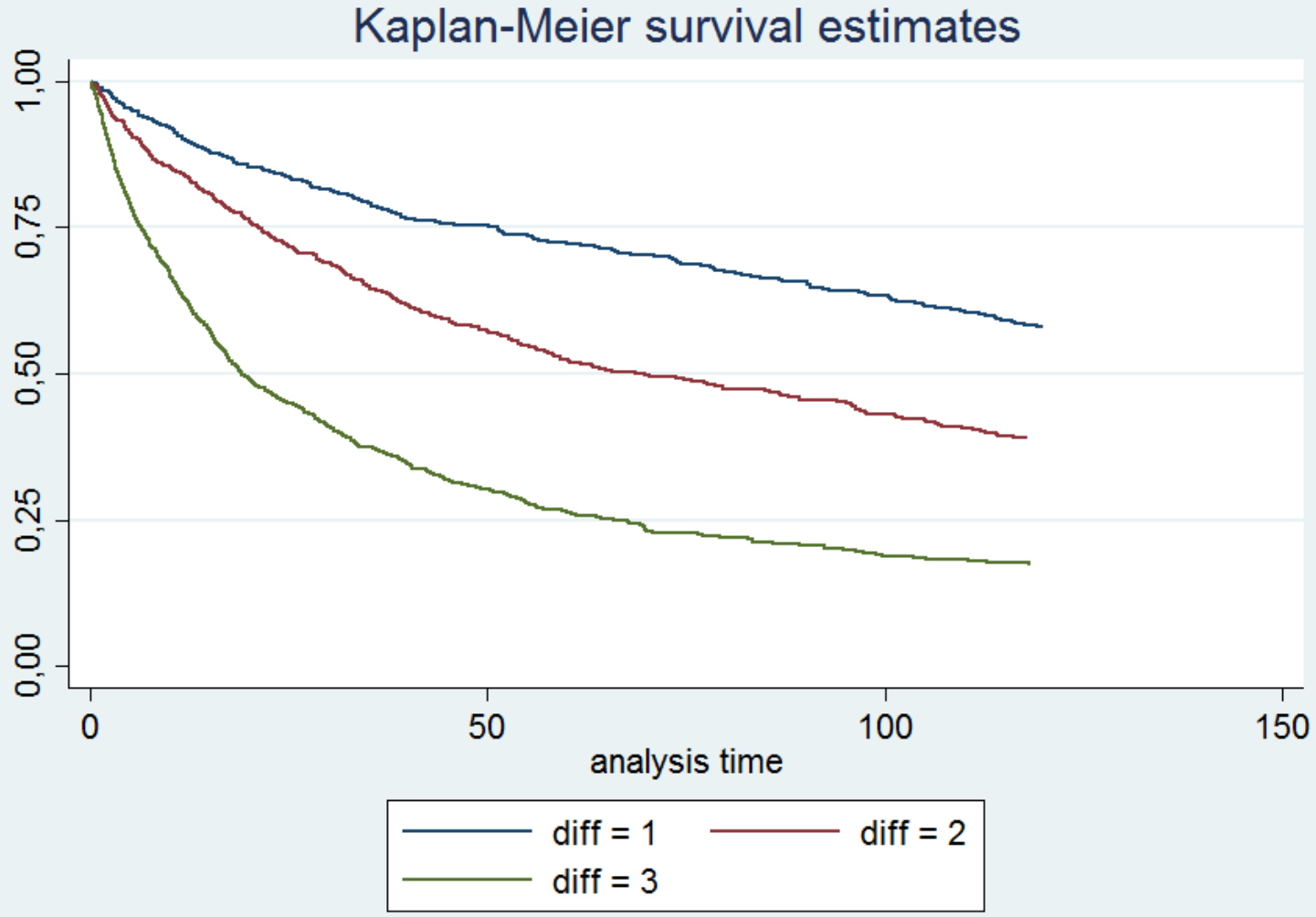
- For most sarcomas a grading system is used by the pathologist to indicate the potency for recurrence and/or distant metastasis (grade 1: low; grade 2: intermediate; grade 3: high)
- Most relevant for
  - liposarcoma, fibrosarcoma,
  - leiomyosarcoma, chondrosarcoma,
  - GIST
- Always considered high grade
  - rhabdomyosarcoma, osteosarcoma, angiosarcoma,
  - PNET, Ewing sarcoma

Survival of leiomyosarcoma according to grade

Grade 1: 10-year survival ~60%

Grade 2: 10-year survival ~40%

Grade 3: 10-year survival ~20%



Grade 1 liposarcoma and chondrosarcoma

According to the latest version of the WHO classification of sarcomas grade 1 liposarcoma (8850/31 or 8851/31) and grade 1 chondrosarcoma (9220/31) are no longer considered malignant and should be classified with behaviour code 1 (8850/11 and 9222/11, respectively).

For international comparison the behaviour code is of less relevance as long as the correct grade is coded.

GIST

The potency for recurrence or metastases of GIST is dependent of

- size of the tumour
- number of mitoses

Small tumours without mitosis are considered benign (/0), large tumours or tumours with many mitoses are considered malignant (/3); the intermediate group is considered borderline malignant (/1).

Rules for the exact classification will be drawn up later, as not all pathologist use the same rules.

It is recommended to register the tumour size and the number of mitosis

Combination of topography and morphology

Typical bone tumours can also occur in organs or soft tissues ('extraskeletal osteosarcoma', etc.): code to the site of origin and not on bone.

Example:

osteosarcoma primary to the duodenum → topography C17.0

Typical soft tissue tumours can also occur in organs or bone

Example:

Fibrosarcoma primary to the humerus→ topography C40.0

Combination of topography and morphology

Chordoma is considered a bone tumour

Examples:

- *pre-pontine chordoma/ near the cerebellum / sella region→ topography C41.0*
- *sacral chordoma → topography C41.4*

Combination of topography and morphology

PNET can occur in the CNS and in bone/soft tissue but has different morphology codes

- PNET in CNS: M9473 ('central PNET')
- PNET in bone/soft tissue: M9364 ('peripheral PNET')

Rhabdoid tumours can occur in the CNS and in bone/soft tissue but have different morphology codes

- Rhabdoid tumour in CNS: M9508 ('atypical teratoid/rhabdoid tumour')
- Rhabdoid tumour outside CNS: M8963 ('malignant rhabdoid tumour'/'rhabdoid sarcoma')

EXERCISES

European Commission

NET & NEC (neuroendocrine tumour & carcinoma)

European Commission

Endocrine or neuro-endocrine?

- Endocrine cells release hormones into the blood but do not receive neural input
- Neuro-endocrine cells receive neural input (neurotransmitters from nerve cells) and release hormones into the blood
- NET = tumour of neuro-endocrine cells
- Neuro-endocrine cells can be found everywhere in the body where there is epithelium, so not in the CNS, bone or soft tissues

Hormone production

- As neuro-endocrine tumours can produce (a large variety of) hormones, patients can have all kinds of symptoms related to the hormone production
- 'carcinoid syndrome' (serotonin production)

Most common sites of NET/NEC

Lungs (mostly NEC)

Gastro-intestinal tract

- ileum/jejunum
- appendix
- pancreas

Thyroid gland

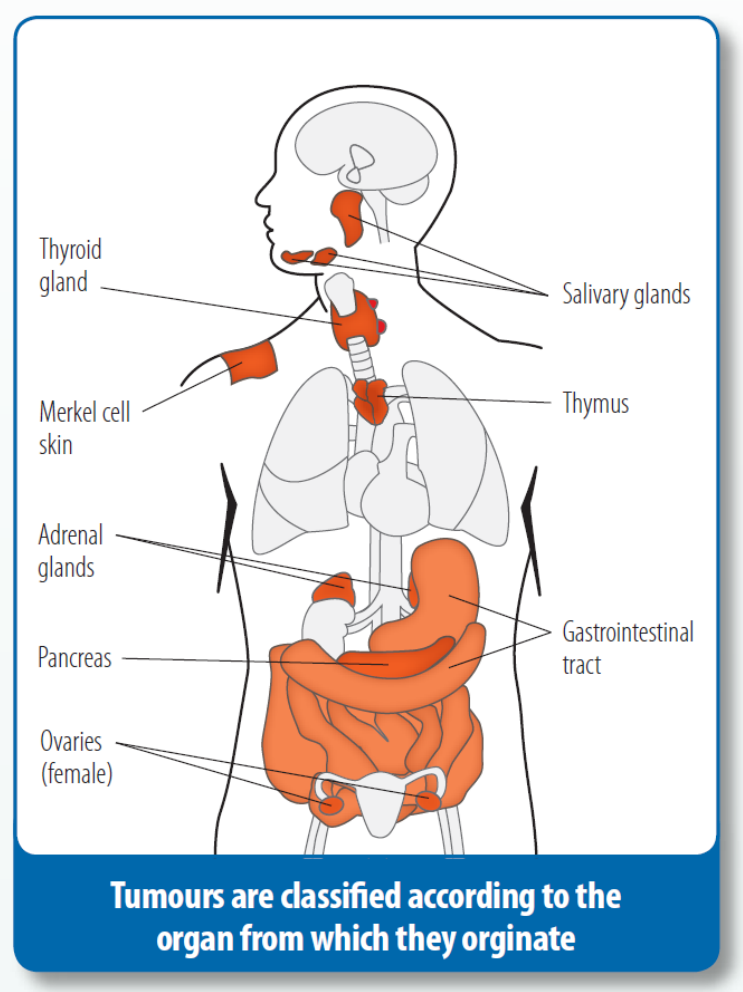
Skin

Salivary glands

Thymus

Adrenal gland (cortex)

Ovaries

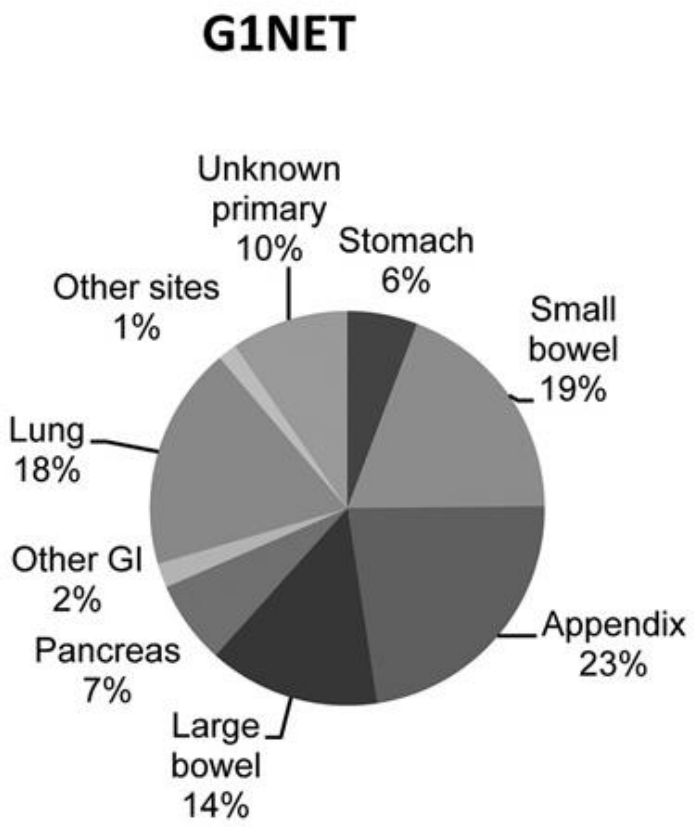


G1NET

Grade 1

- carcinoid
- NET
- well differentiated NET
- NET grade 1
- NEC grade 1

→ Code as M8240/3(1)

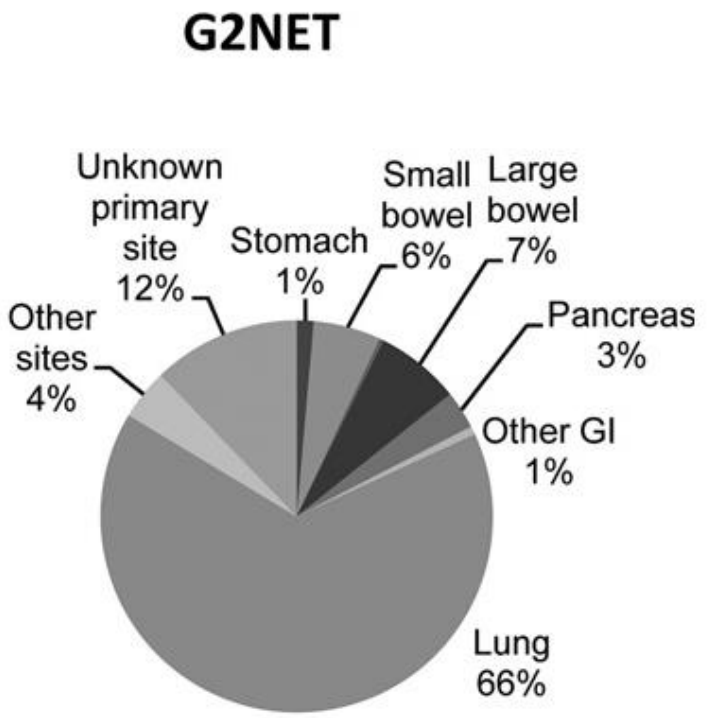


G2NET

Grade 2

- atypical carcinoid
- moderately differentiated NET
- NET grade 2
- NEC grade 2

→ Code as M8249/3(2)

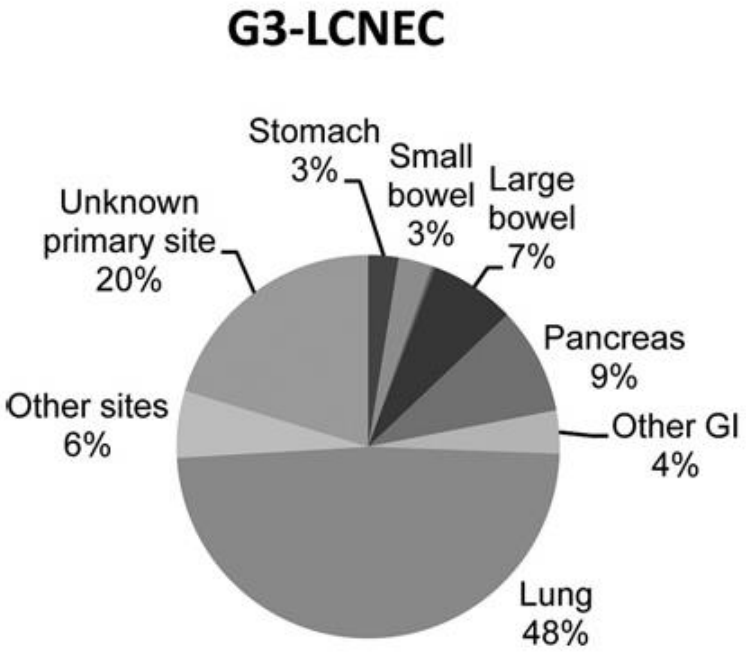


G3-LCNEC

Grade 3

- grade 3 large cell neuroendocrine carcinoma
- poorly differentiated neuroendocrine carcinoma
- grade 3 neuroendocrine carcinoma
- large cell neuroendocrine carcinoma

→ Code as M8013/3(3)

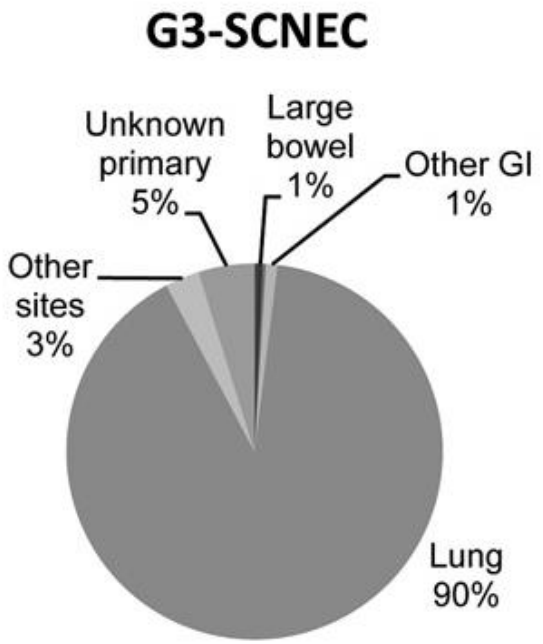


G3-SCNEC

Grade 4

- Grade 3 small cell neuroendocrine carcinoma
- undifferentiated neuroendocrine carcinoma
- small cell neuroendocrine carcinoma
- small cell carcinoma

→ Code as M8041/3(4)



Grade unknown

Grade unknown

- neuroendocrine carcinoma

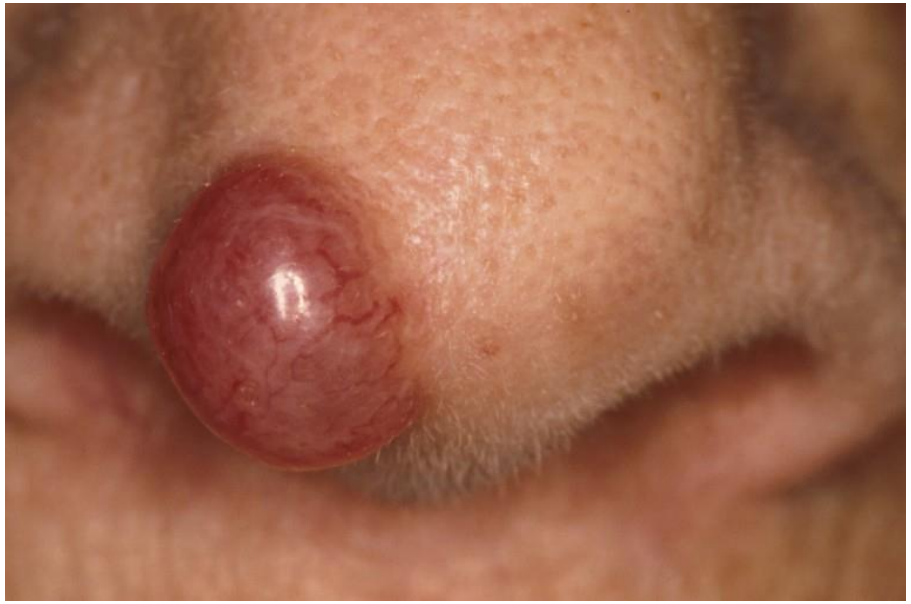
→ Code as M8246/3

NET/NEC of the skin

NET or NEC (all grades) primary to the skin

→Code as M8247/3 (Merkel cell carcinoma)

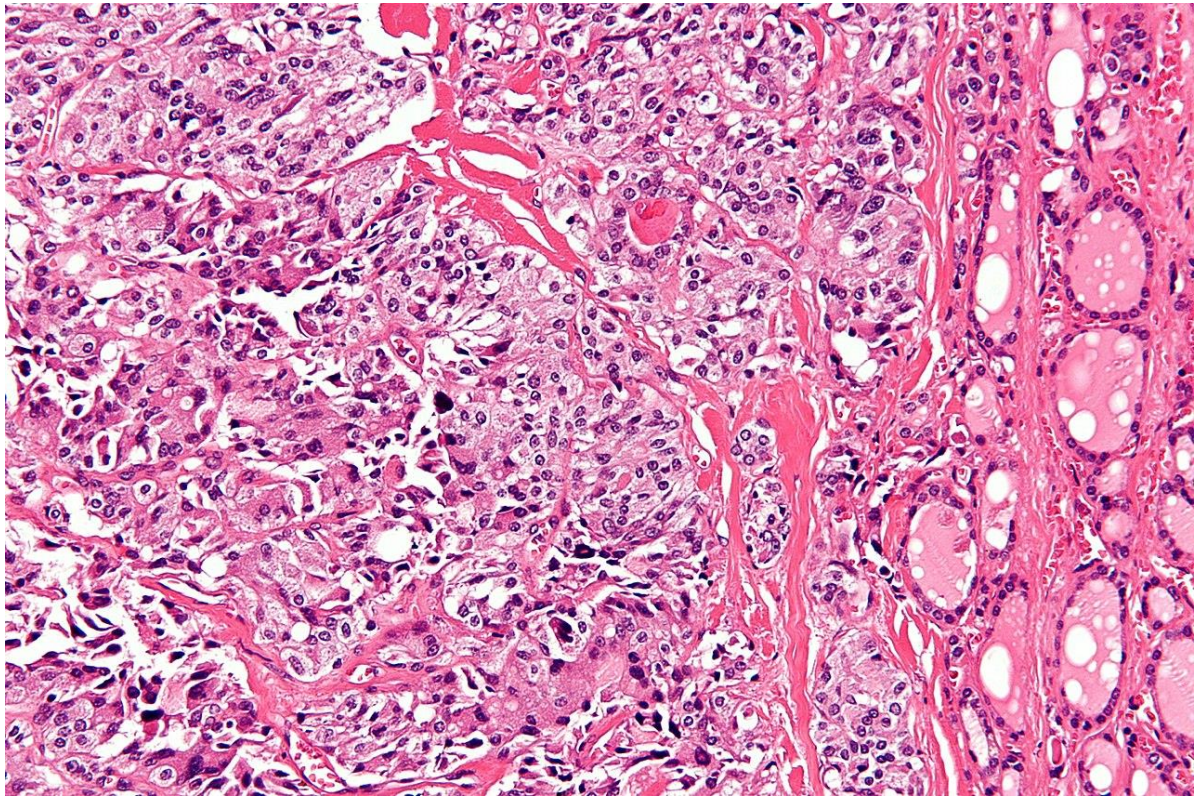
Merkel cell carcinoma is the most aggressive skin cancer!



NET/NEC of the thyroid

NET or NEC (all grades) primary to the thyroid

→ Code as M8345/3 (Medullary carcinoma of the thyroid)



Functional (=hormone producing) NET/NEC

Code to the specific morphology in case of hormone production

Not for all hormones a specific morphology code is available

Example

NET of the pancreas , gastrin-producing → M8153/3 (gastrinoma)

EXERCISES

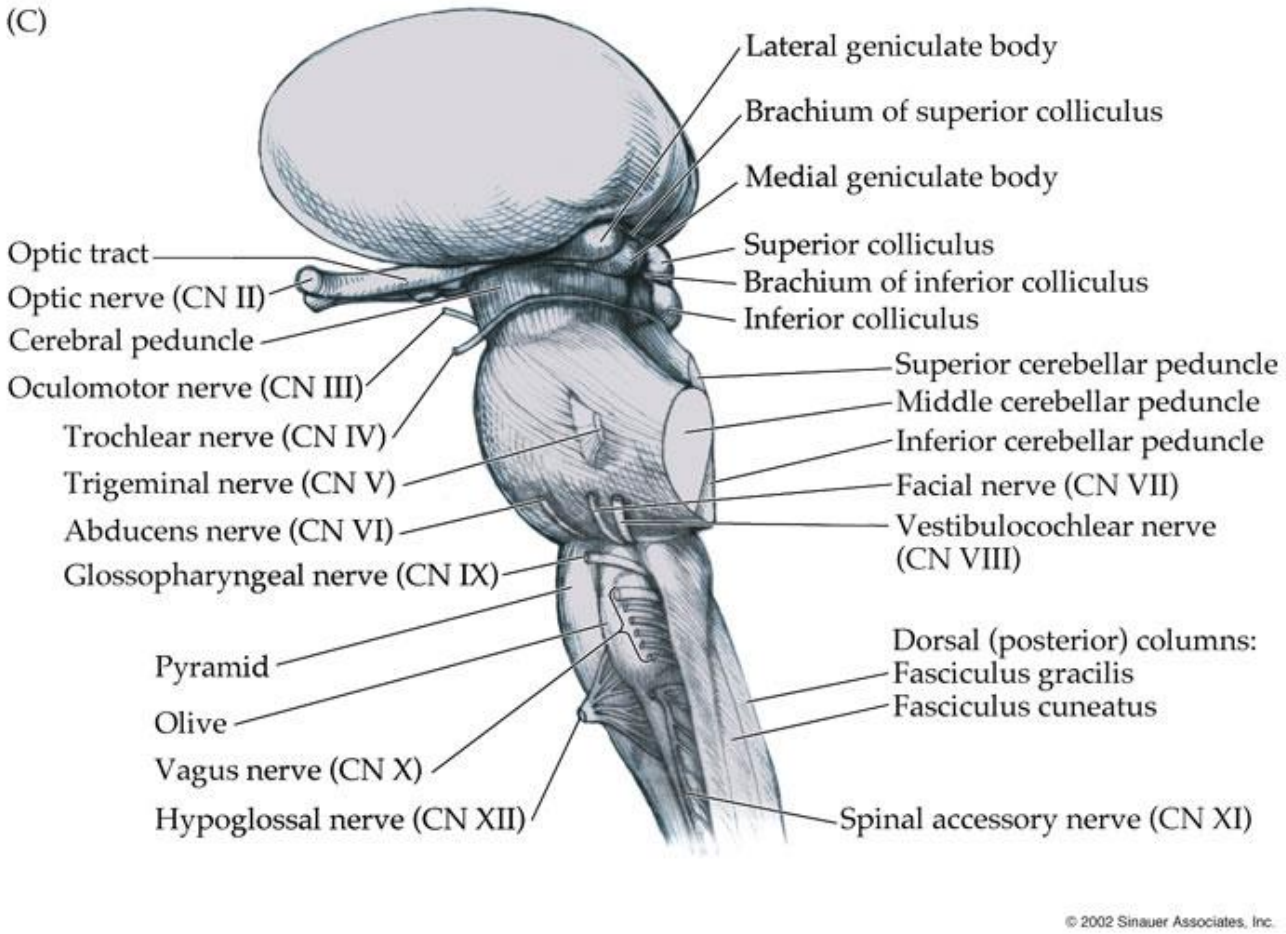
European Commission

Tumours of the central nervous system (CNS)

European Commission

Cranial nerves

- Olfactory nerve (I) C72.2
- Optic nerve (II) C72.3
- Acoustic nerve (VIII) C72.4
- Other cranial nerves C72.5

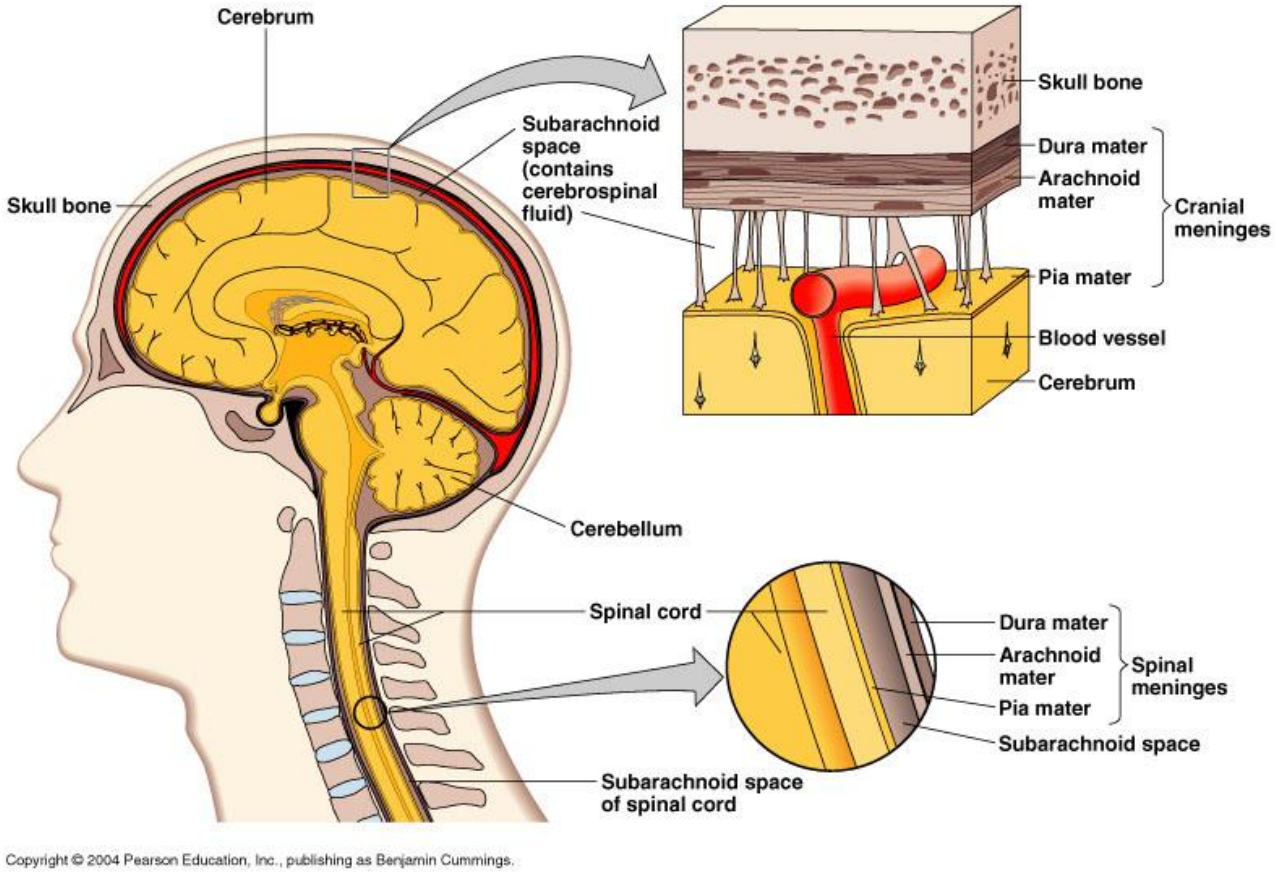


Tumours of the cranial nerves

- Pilocytic astrocytoma (optic nerve)
  - in children
  - may be bilateral or in the chiasma
- Schwannoma (mostly acoustic nerve, but also in other cranial nerves)
  - vestibular schwannoma, acoustic neurinoma
  - benign in the vast majority of cases (M9560/0)
  - malignancy extremely rare (MPNST=M9540/3)
  - often the diagnosis is made on imaging only
  - may be bilateral

Meninges

- Cerebral meninges C70.0
- Spinal meninges C70.1



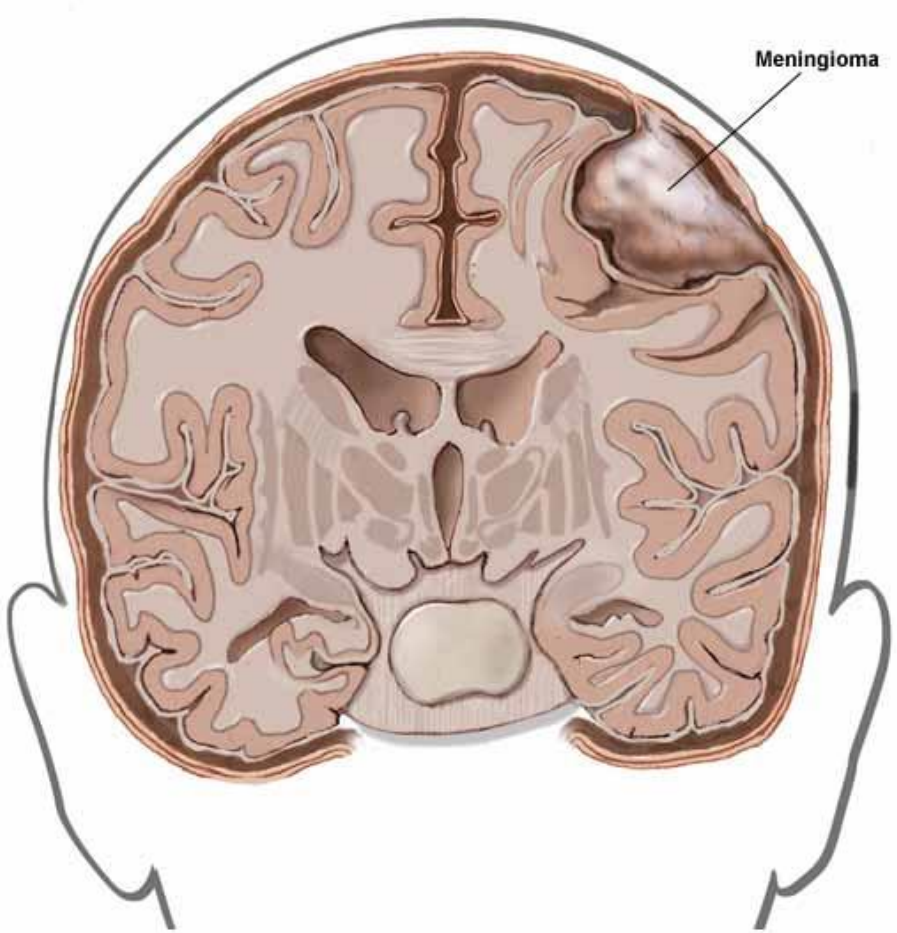
Tumours of the meninges

- Meningioma
  - Mostly benign (9530/0 – 9537/0)
  - Atypical (9538/1)
  - Rarely malignant (malignant meningioma = 9530/3 or meningial sarcomatosis = 9539/3)
- Hemangiopericytoma
  - vestibular schwannoma, acoustic neurinoma
- Melanoma
  - Solitary (8720/3) or diffuse (8728/0, 8728/1, 8728/3)

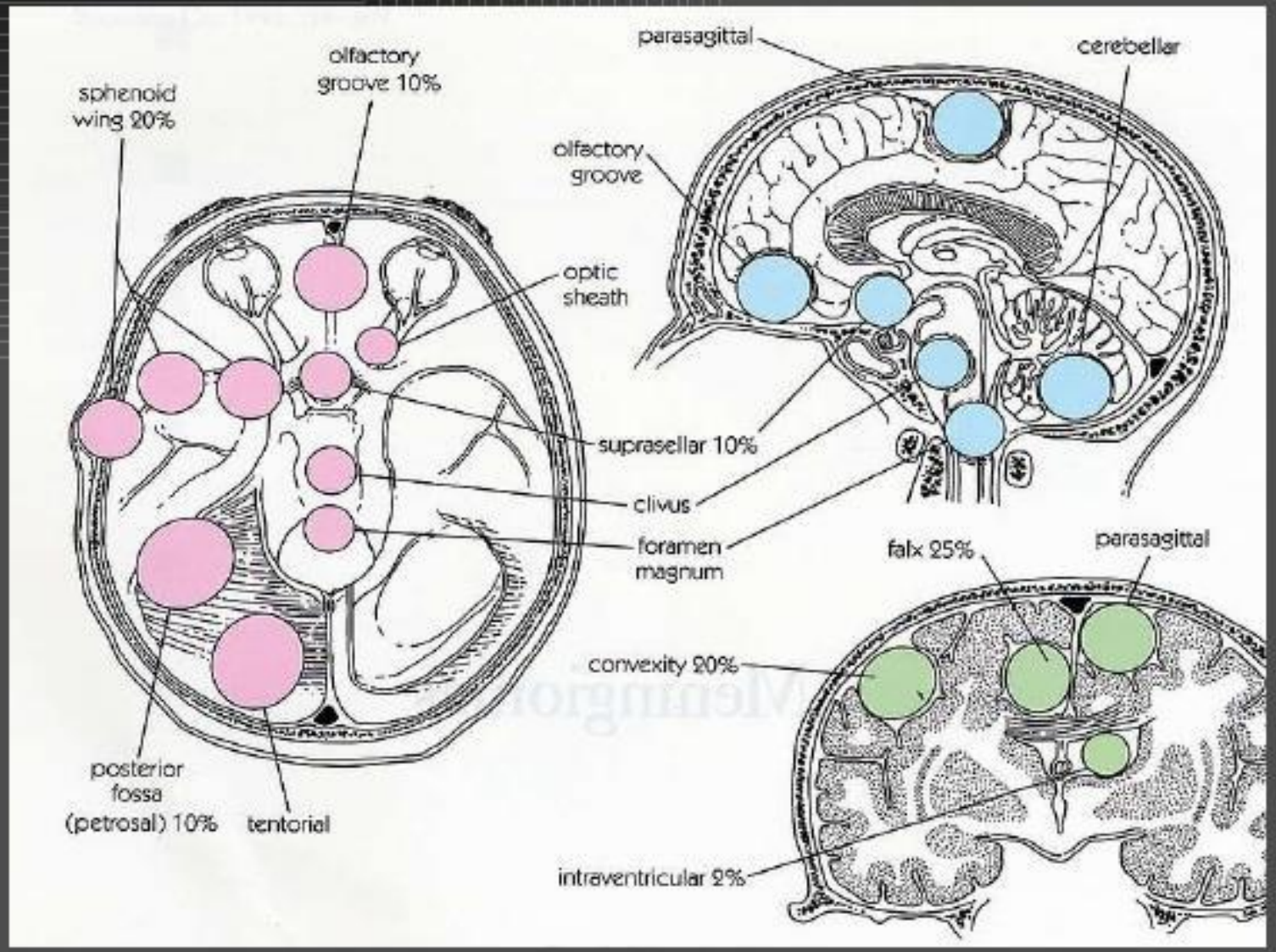
Tumours of the meninges

A meningioma of the CNS should always be coded on C70!

- 'Meningioma of the brain' = C70.0
- 'Meningioma of the spinal cord' = C70.1

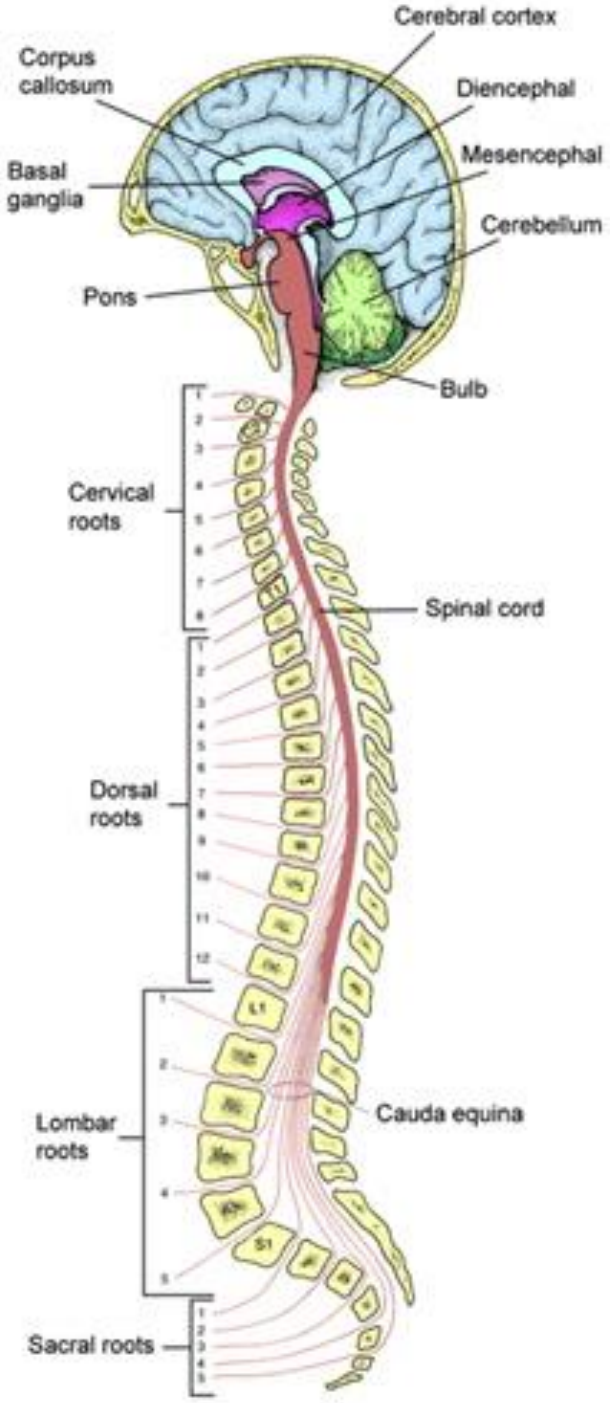


Location


parasagittal
cerebellar
olfactory groove 10%
sphenoid wing 20%
olfactory groove
optic sheath
suprasellar 10%
clivus
foramen magnum
falx 25%
parasagittal
convexity 20%
posterior fossa (petrosal) 10%
tentorial
intraventricular 2%

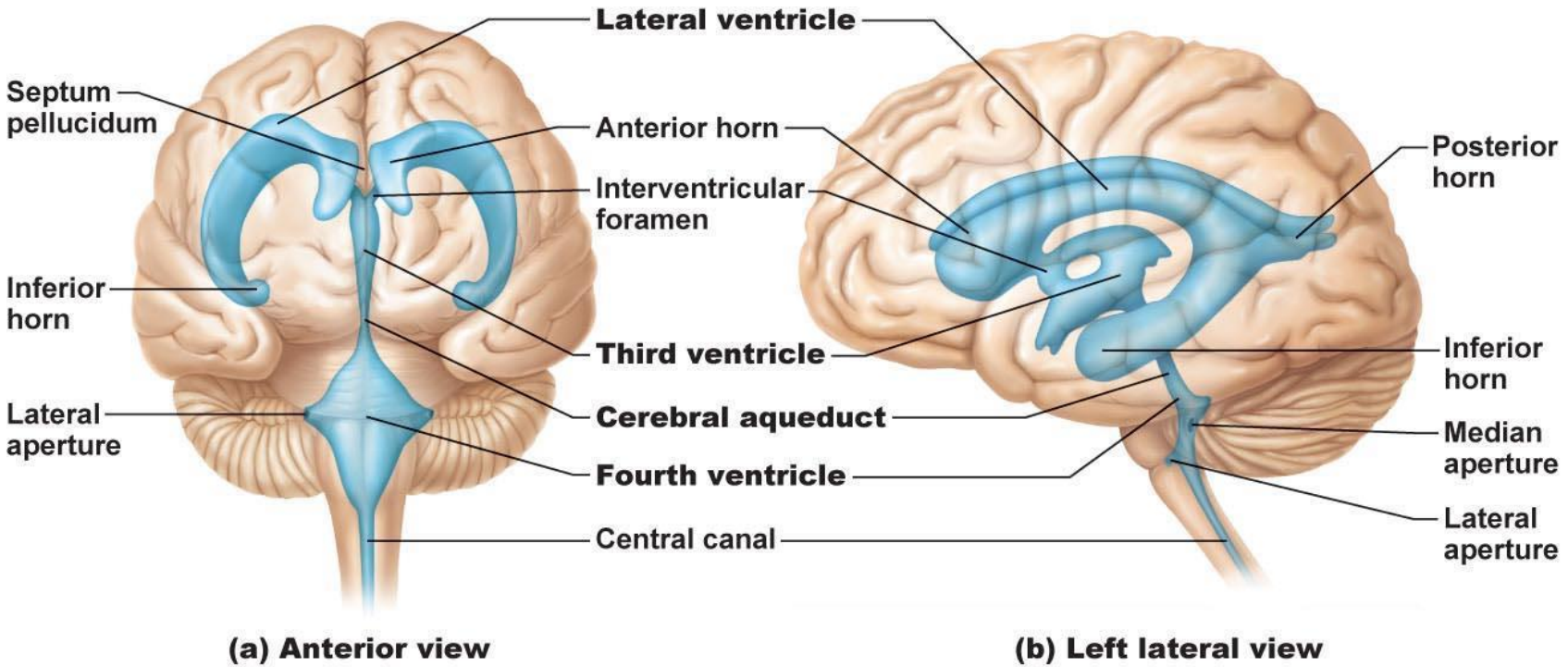
Brain and spinal cord

- Cortex
  - Frontal lobe (C71.1)
  - Temporal lobe (C71.2)
  - Parietal lobe (C71.3)
  - Occipital lobe (C71.4)
- Basal ganglia (C71.0)
- Cerebellum (C71.6)
- Brain stem (C71.7)
- Ventricles (C71.5)
- Spinal cord/cauda equina (C72.0/C72.1)

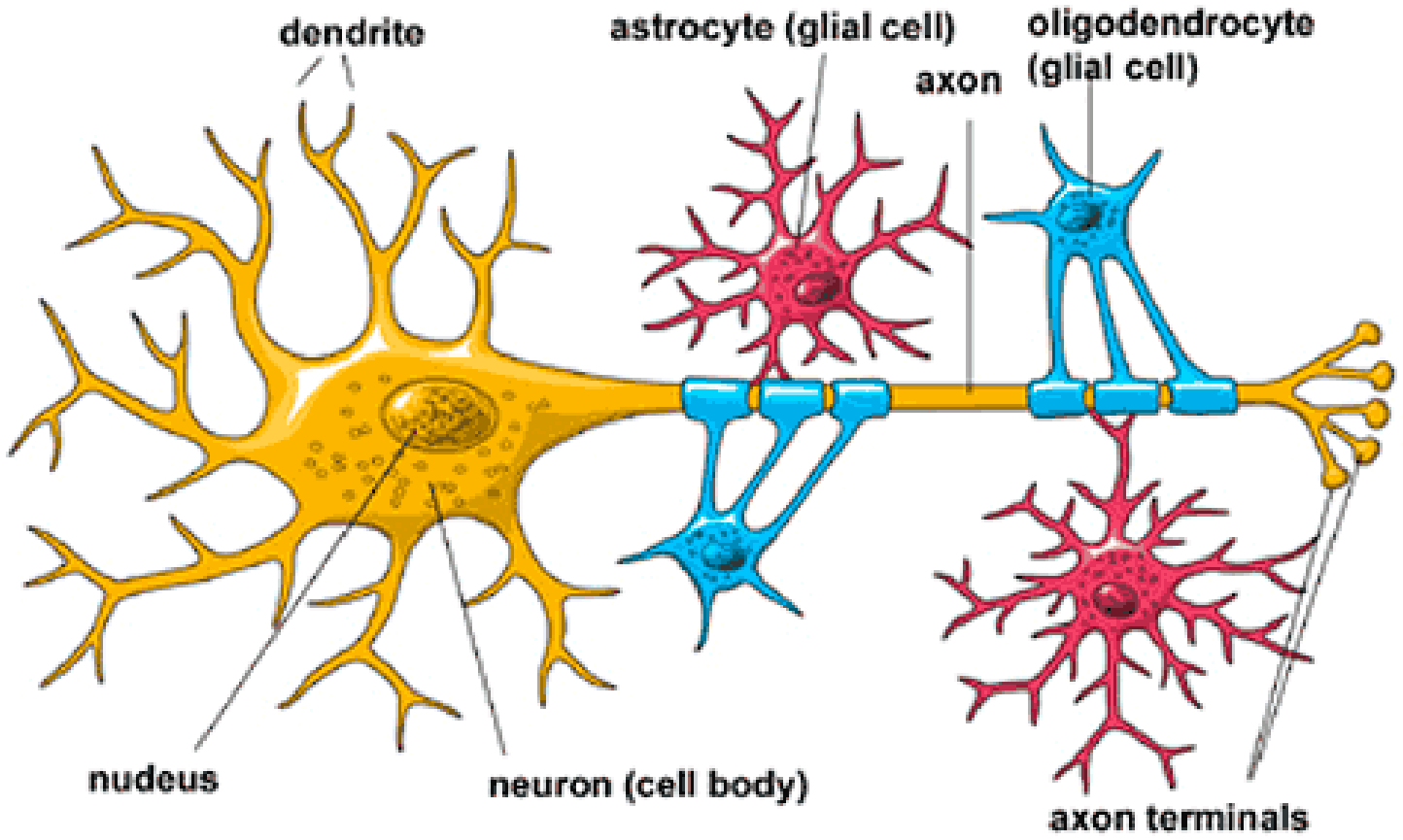


The ventricles of the brain

- The ventricles are filled with fluid; the only anatomical structure in the ventricles is the choroid plexus



Brain cells


dendrite
astrocyte (glial cell)
axon
oligodendrocyte
(glial cell)
nucleus
neuron (cell body)
axon terminals

Neuro-epithelial tumours of the brain and spinal cord

- Gliomas (glioma=‘tumour of glial cell’)
  - Astrocytic tumours
  - Oligodendroglial tumours
  - Oligo-astrocytic tumours
  - Ependymal tumours
  - Choroid plexus tumours
- Neuronal and mixed neuronal-glial tumours
- Tumours of the epiphysis
- Embryonal tumours

WHO grade

The grade aims to predict the biological behaviour of the tumour

- Grade I: tumour with low proliferation and potential cure after resection
- Grade II: infiltrative tumour with low proliferation but with risk of recurrence after resection
- Grade III: histological malignant tumour (nuclear atypia & many mitoses) which requires (adjuvant) Rt and/or Ct after resection
- Grade IV: histological malignant tumour with necrosis and fast progression with fatal outcome

Transformation from a lower to a higher grade can occur (as in HM)

Grading in CNS tumours differs from other cancers

- low grade = WHO grade 2
- high grade = WHO grade 3
- 'anaplastic' = WHO grade 3

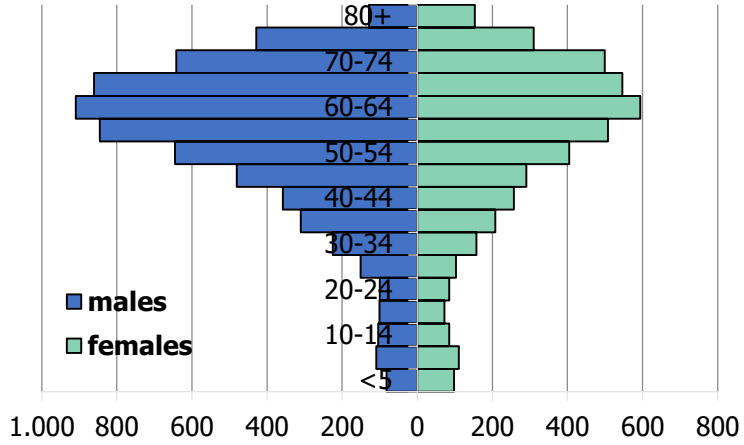
- *a specific WHO grade overrules a descriptive term*

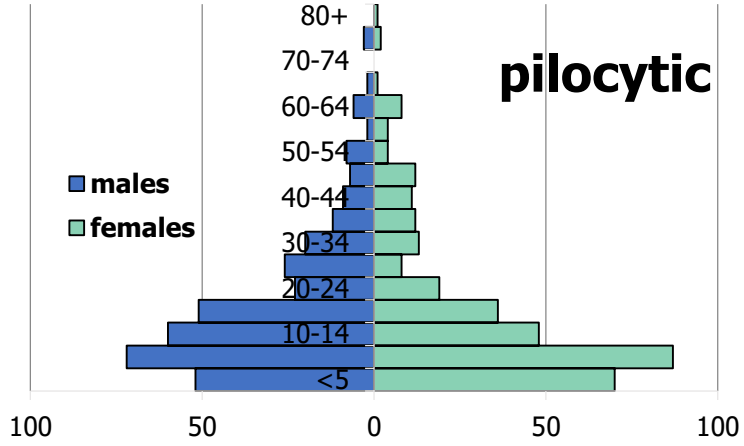
Site of the tumour

- Astrocytoma: 98% cerebral
- Oligodendroglioma: 99% cerebral
- Ependymoma: 50% cerebral (the wall of the ventricles), 50% spinal (the spinal canal)
  - Subependymoma & anaplastic ependymoma mostly cerebral
  - Myxopapillary ependymoma mostly spinal (cauda equina/filum terminale)
- Choroid plexus tumor: always cerebral (ventricle)

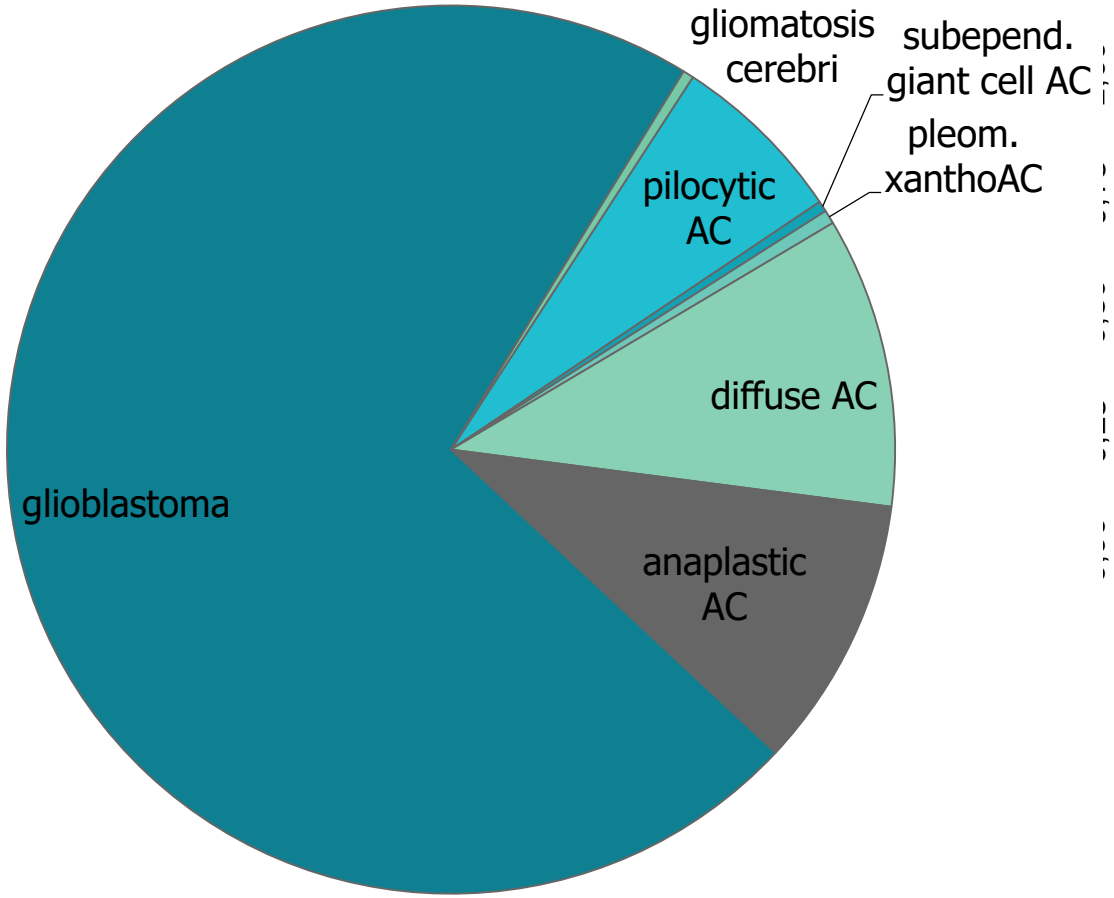
Astrocytoma: classification and age distribution

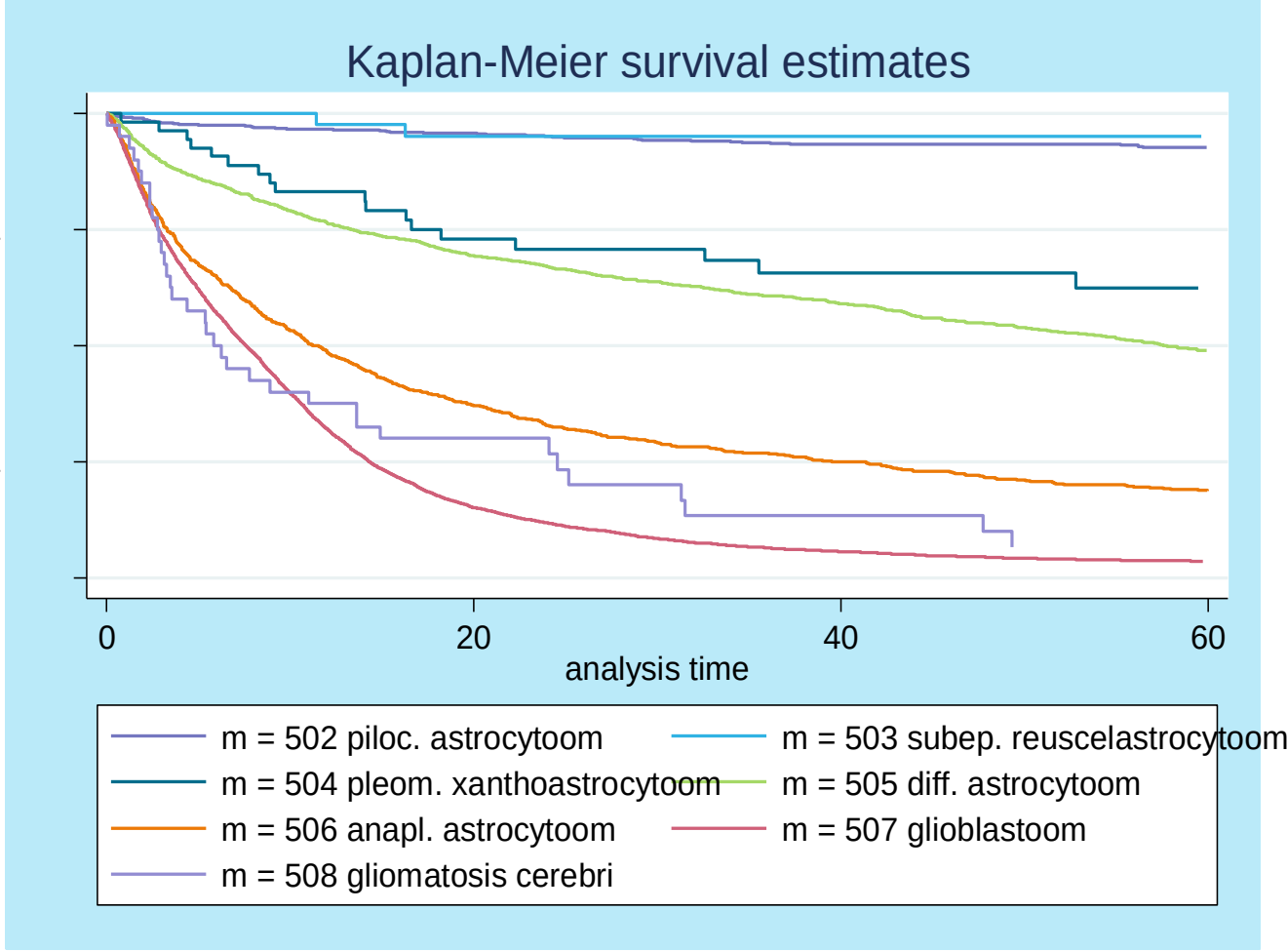
type	Morphology	WHO grade
Pilocytic astrocytoma subtype: pilomyxoid astrocytoma (9425/3, grade II)	9421/1	I
Subependymal giant cell astrocytoma	9384/1	I
Pleomorphic xanthoastrocytoma	9424/3	II
Diffuse astrocytoma subtypes: fibrillary, gemistocytic, protoplastic	9400/3 9420/3, 9411/3, 9410/3	II
Anaplastic astrocytoma	9401/3	III
Glioblastoma subtypes: giant cell glioblastoma, gliosarcoma	9440/3 9441/3, 9942/3	IV
Gliomatosis cerebri	9381/3	mostly III





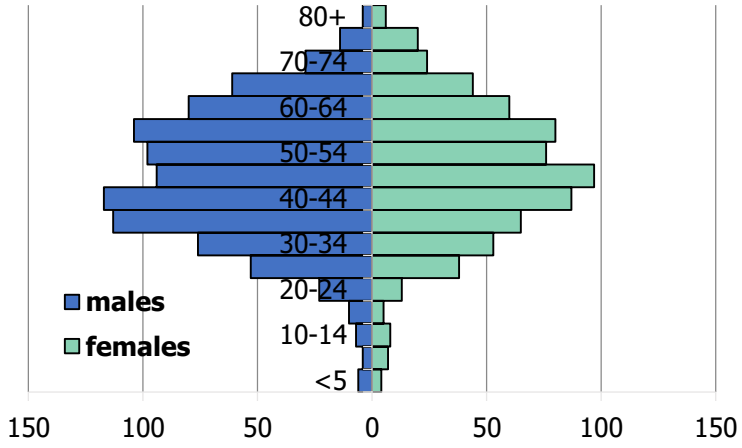
Astrocytoma



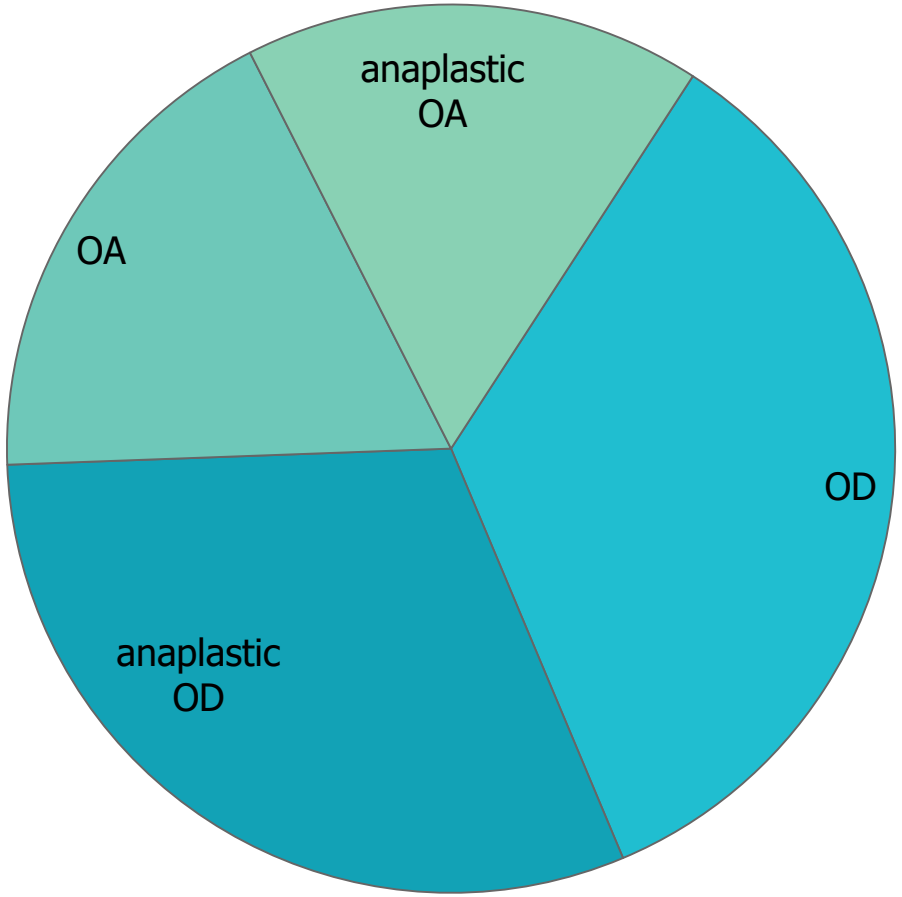


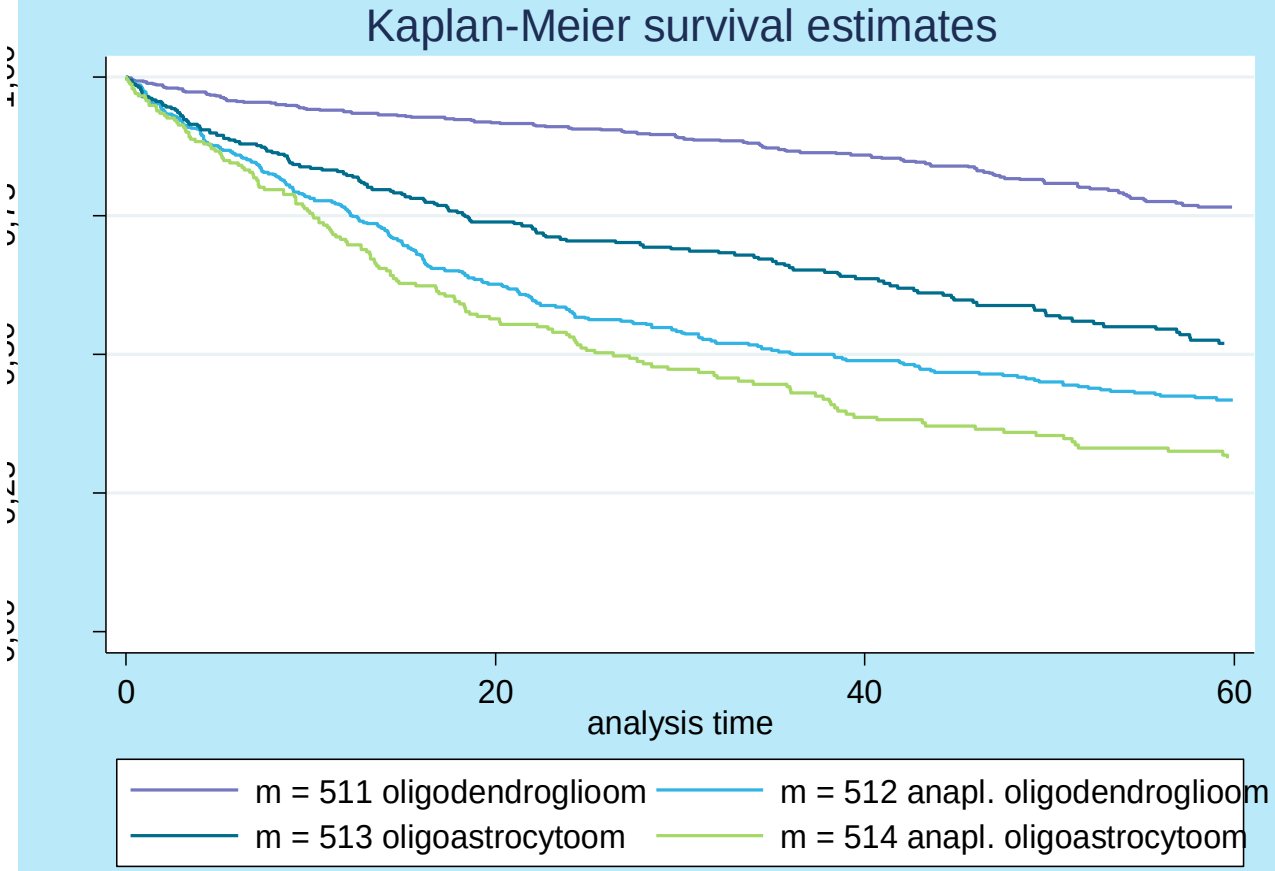
Oligodendroglioma: classification and age distribution

type	Morphology	WHO grade
Oligodendroglioma	9450/3	II
Anaplastic oligodendroglioma	9451/3	III
Oligoastrocytoma	9382/3	II
Anaplastic oligoastrocytoma	9382/3	III



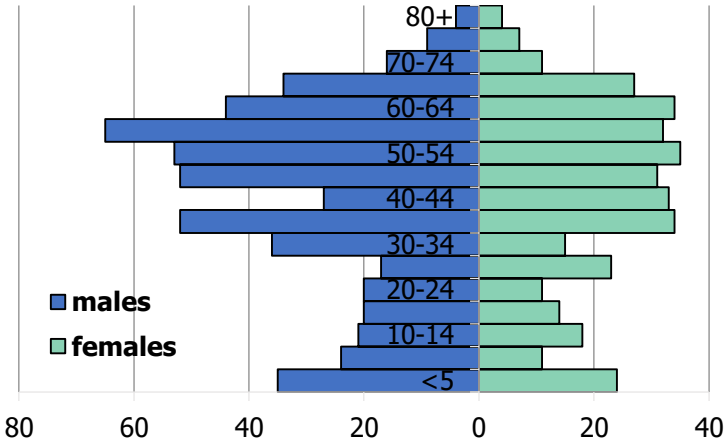
Oligodendroglioma



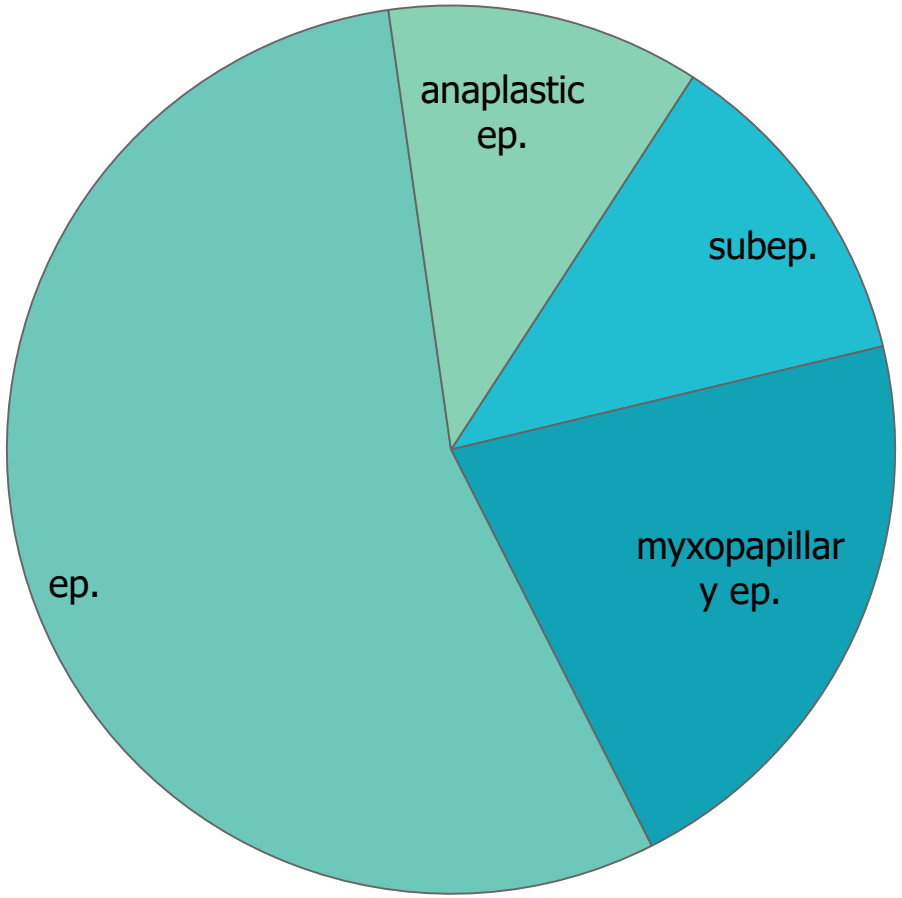


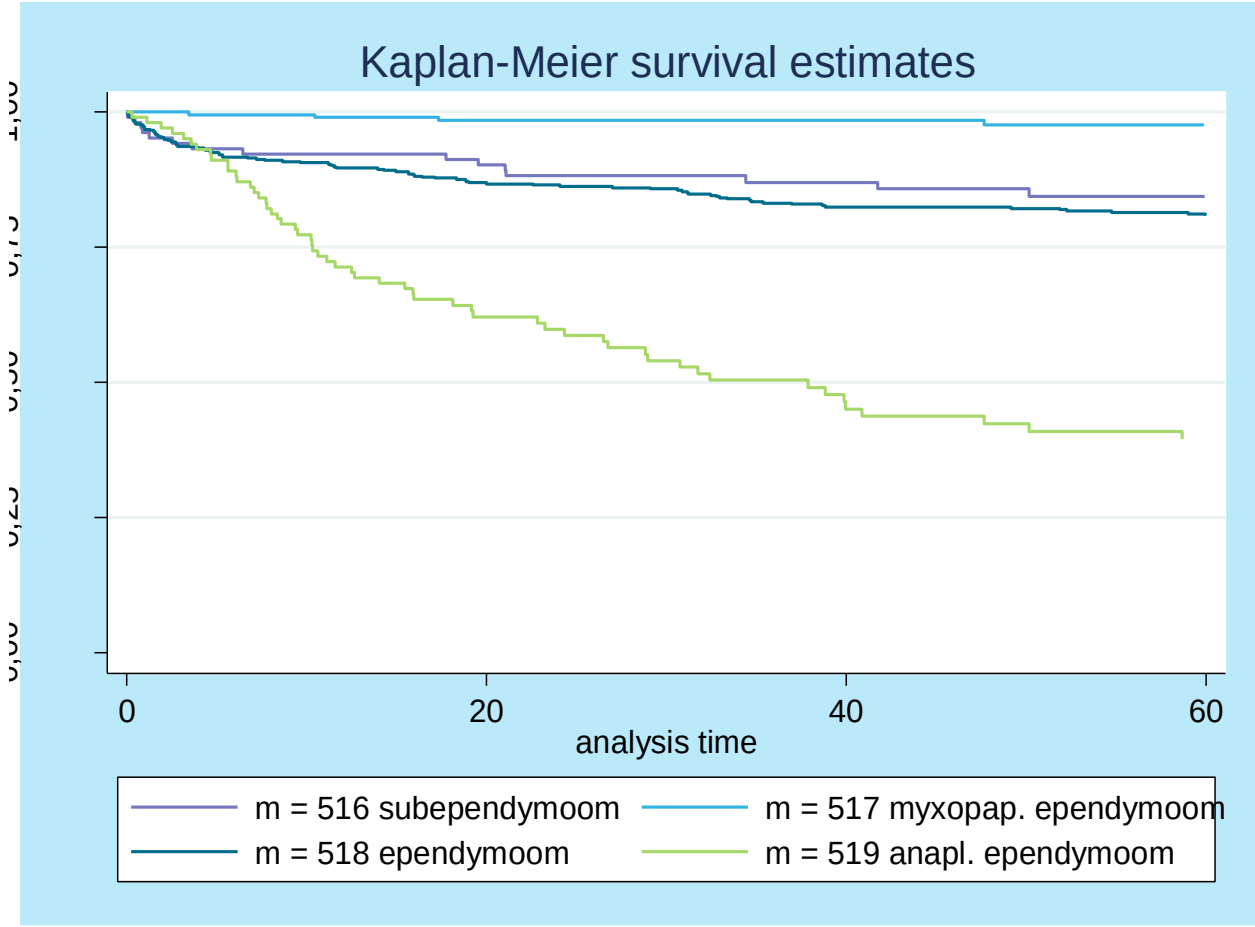
Ependymoma: classification and age distribution

type	Morphology	WHO grade
Subependymoma	9383/1	I
Myxopapillary ependymoma	9394/1	I
Ependymoma (subtypes: cellulai, papillary (9393/3), clear cell, tanycytic)	9391/3	II
Anaplastic ependymoma	9392/3	III



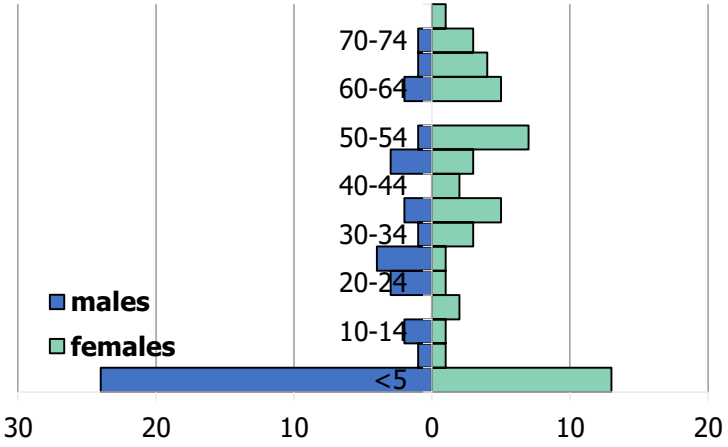
Ependymoma


anaplastic ep.
subep.
myxopapillary ep.
ep.

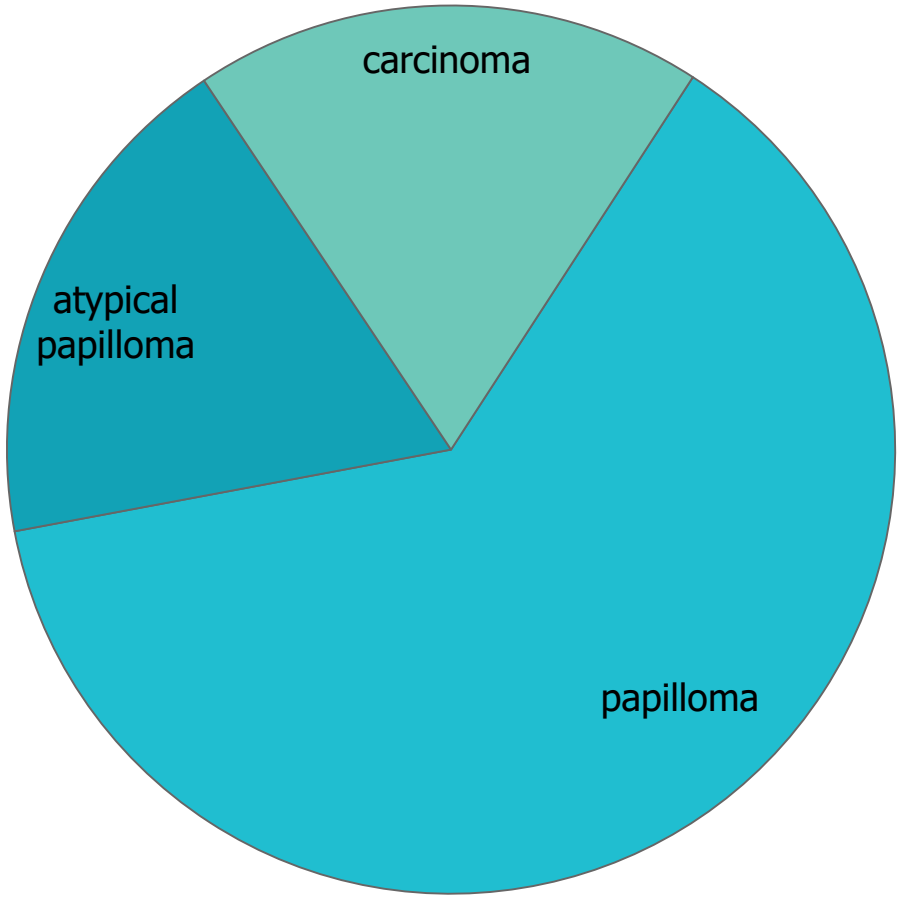

Kaplan-Meier survival estimates
0
20
40
60
analysis time
m = 516 subependymoom
m = 517 myxopap. ependymoom
m = 518 ependymoom
m = 519 anapl. ependymoom

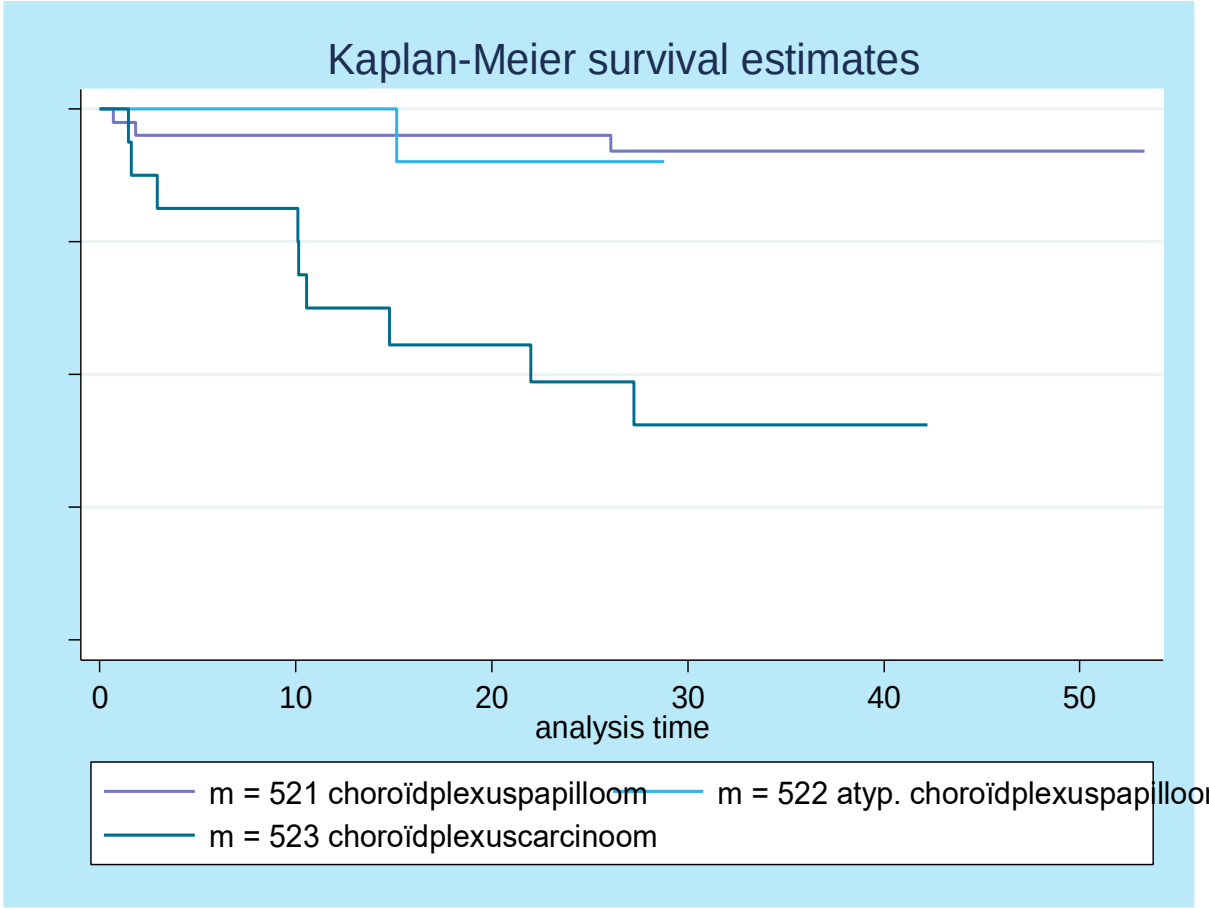
Choroid plexus tumours: classification and age distribution

type	Morphology	WHO grade
Choroid plexus papilloma	9390/0	I
Choroid plexus papilloma, atypical	9390/1	II
Choroid plexus carcinoma	9390/3	III



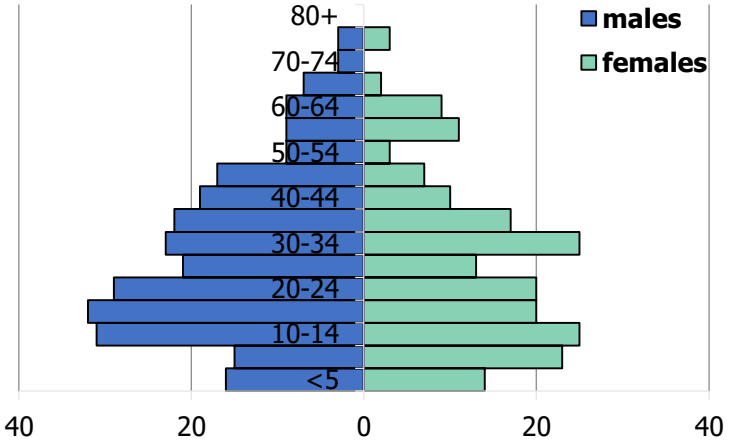
Choroid plexus tumours





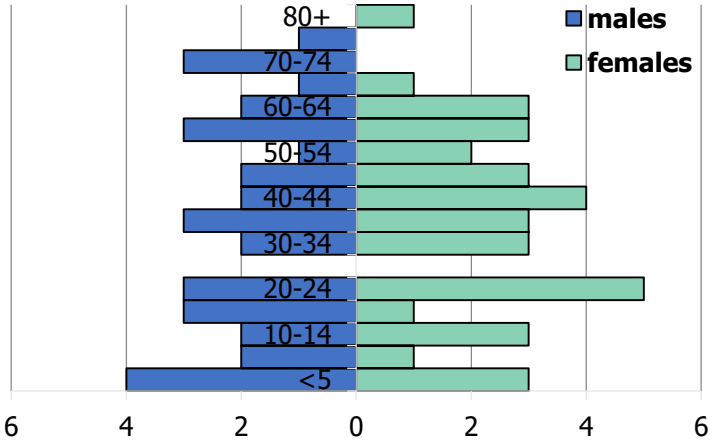
Neuronal & mixed neuronal-glial tumours: classification and age distribution

type	Morphology	WHO grade
Dysplastic gangliocytoma of the ce rebellum	9493/0	I
Desmoplastic infantila astrocytoma/ganglioglioma	9412/1	I
Dysembryoplastic neuroepithelial tumour	9413/0	I
Gangliocytoma	9492/0	I
Ganglioglioma	9505/1	I (or II)
Anaplastic ganglioglioma	9505/3	III
Neurocytoma (central, extraventicular, cerebellar)	9506/1	I or II
Papillary glioneural tumour	9509/1	I
Spinal paraganglioma	8680/1	I

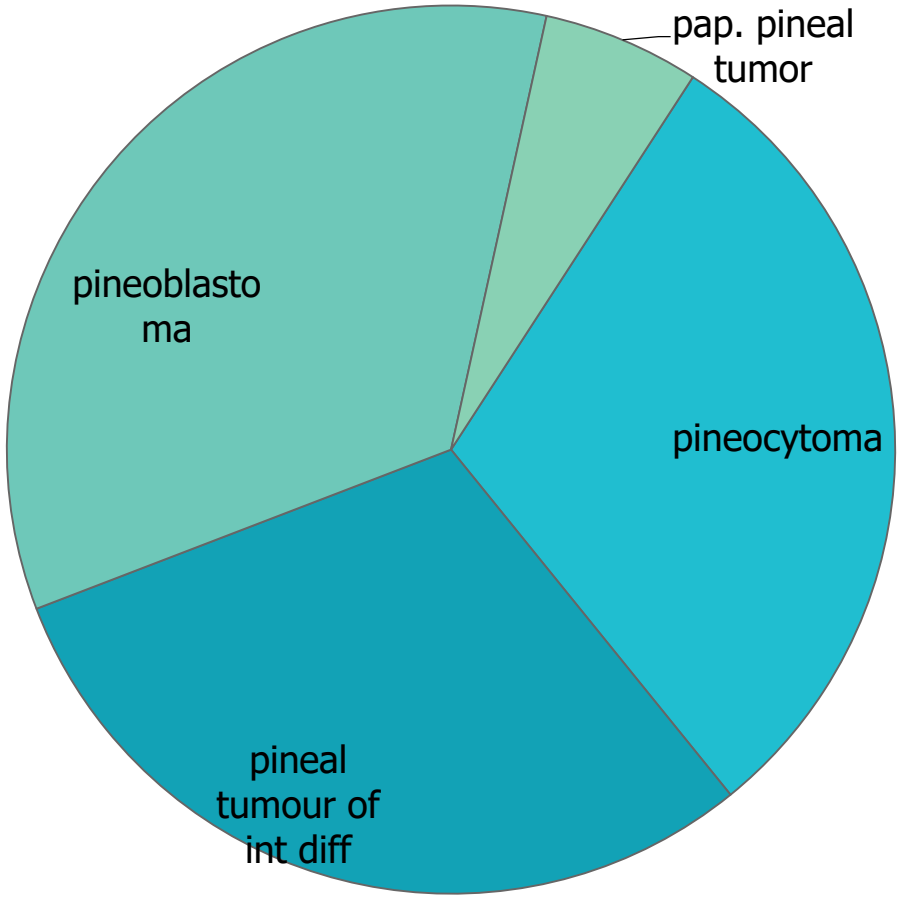


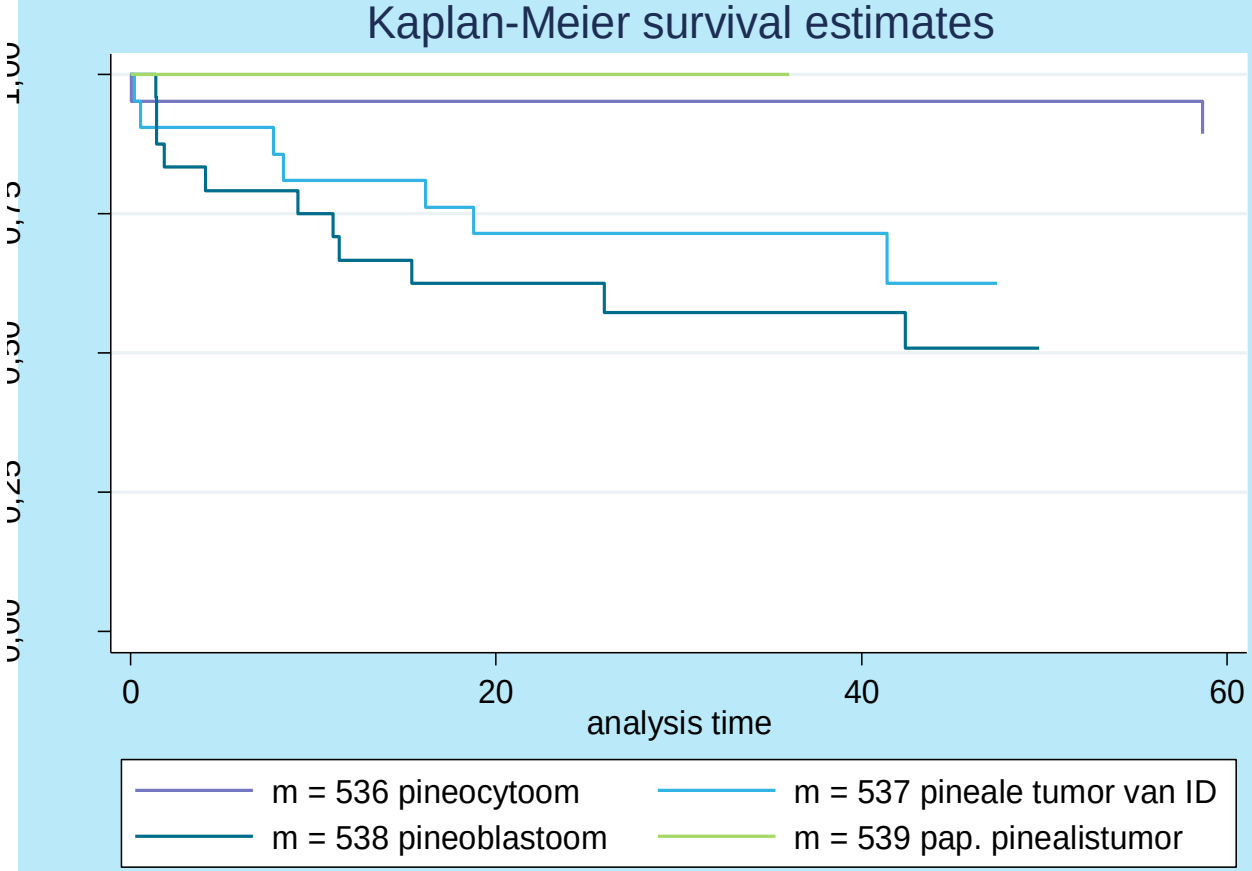
Tumours of the pineal region: classification and age distribution

type	Morphology	WHO grade
Pineocytoma	9361/1	I (was II)
Pineal parenchymal tumour of intermediate differentiation	9362/3	II of III (was III of IV)
Pineoblastoma	9362/3	IV
Papillary tumour van de pinealis region	9395/3	II of III



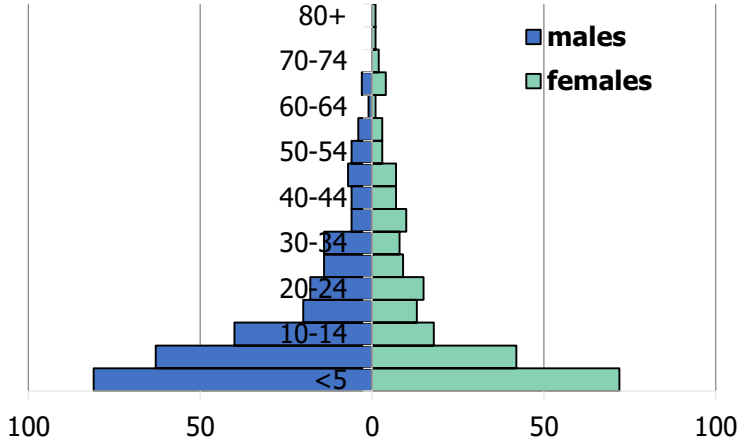
Tumours of the pineal region



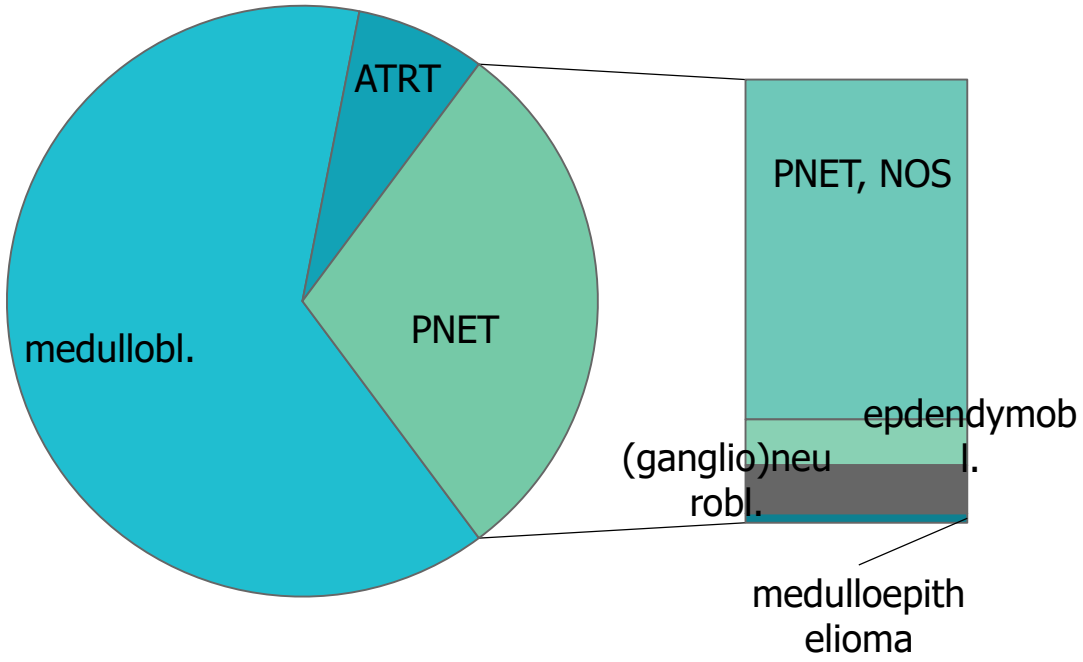


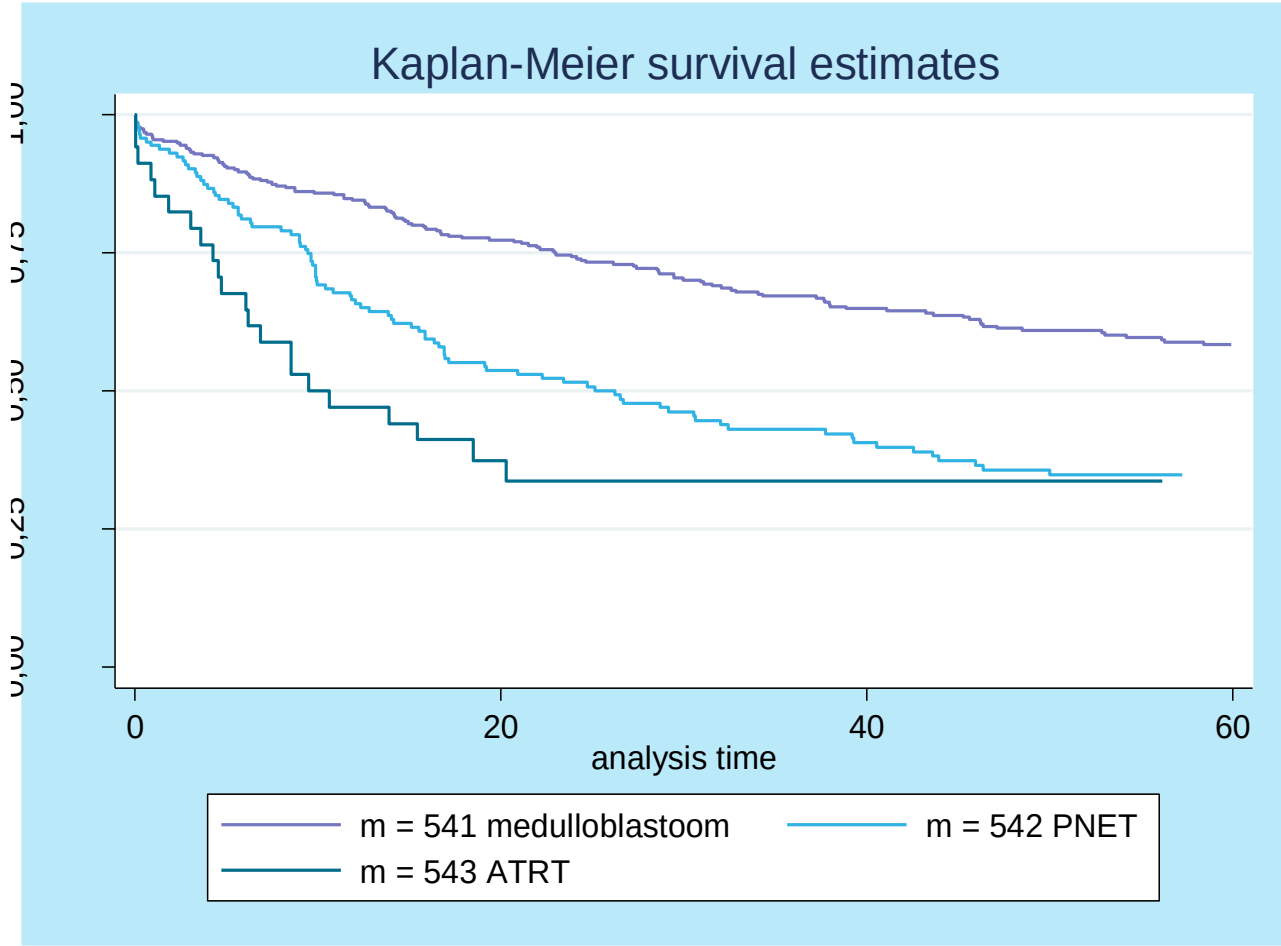
Embryonal tumours: classification and age distribution

type	Morphology	WHO grade
Medulloblastoma (subtypes: desmoplastic/nodular, anaplastic/large cell)	9470/3 (9471/3, 9474/3)	IV
PNET of the CNS (subtypes: neuroblastoma, ganglioneuroblastoma, medullo-epithelioma, ependymoblastoma)	9473/3 (9500/3, 9490/3, 9501/3, 9392/3)	IV
Atypical teratoid / rhabdoid tumour	9508/3	IV



Embryonal tumours





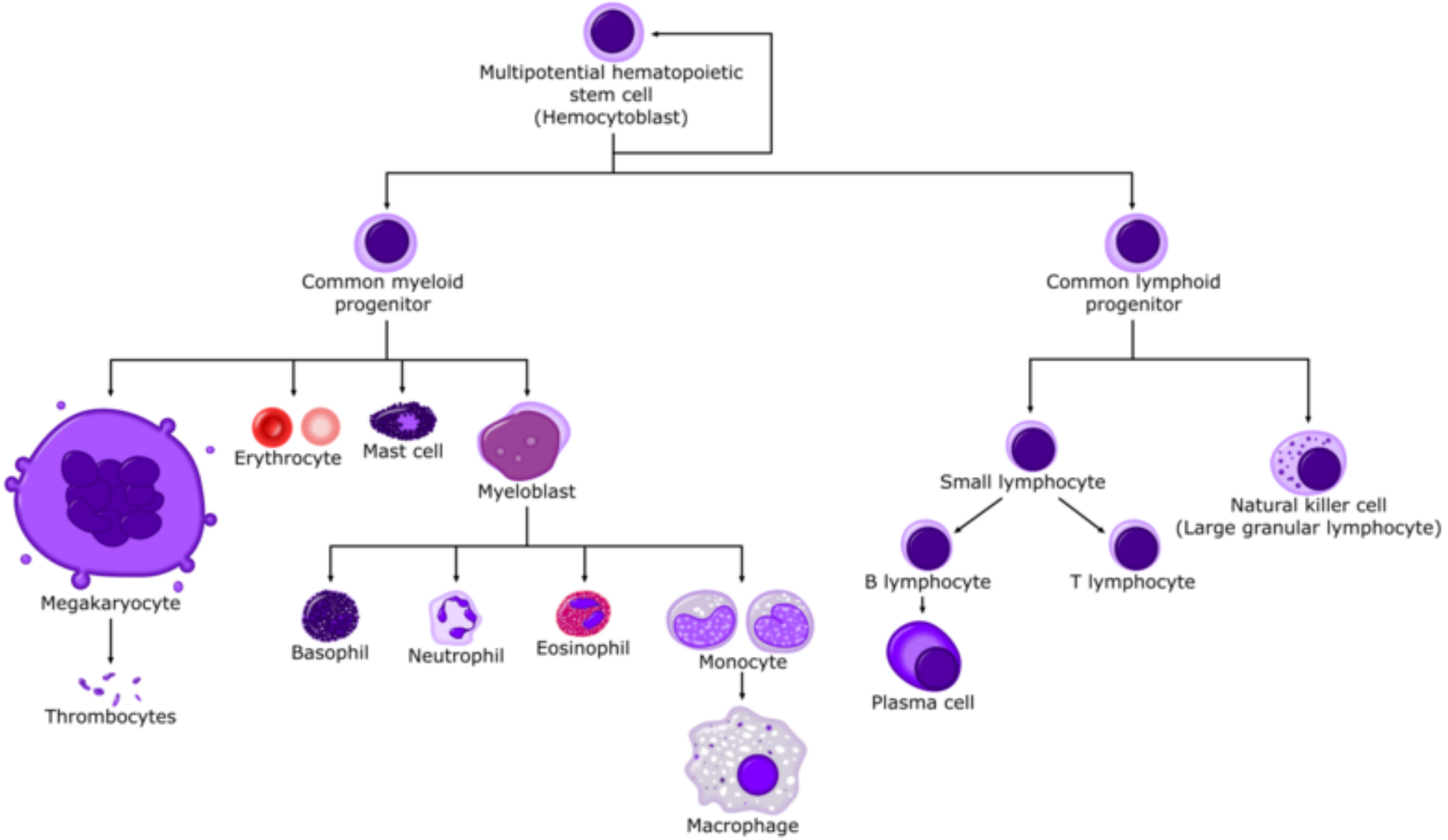
EXERCISES

European Commission

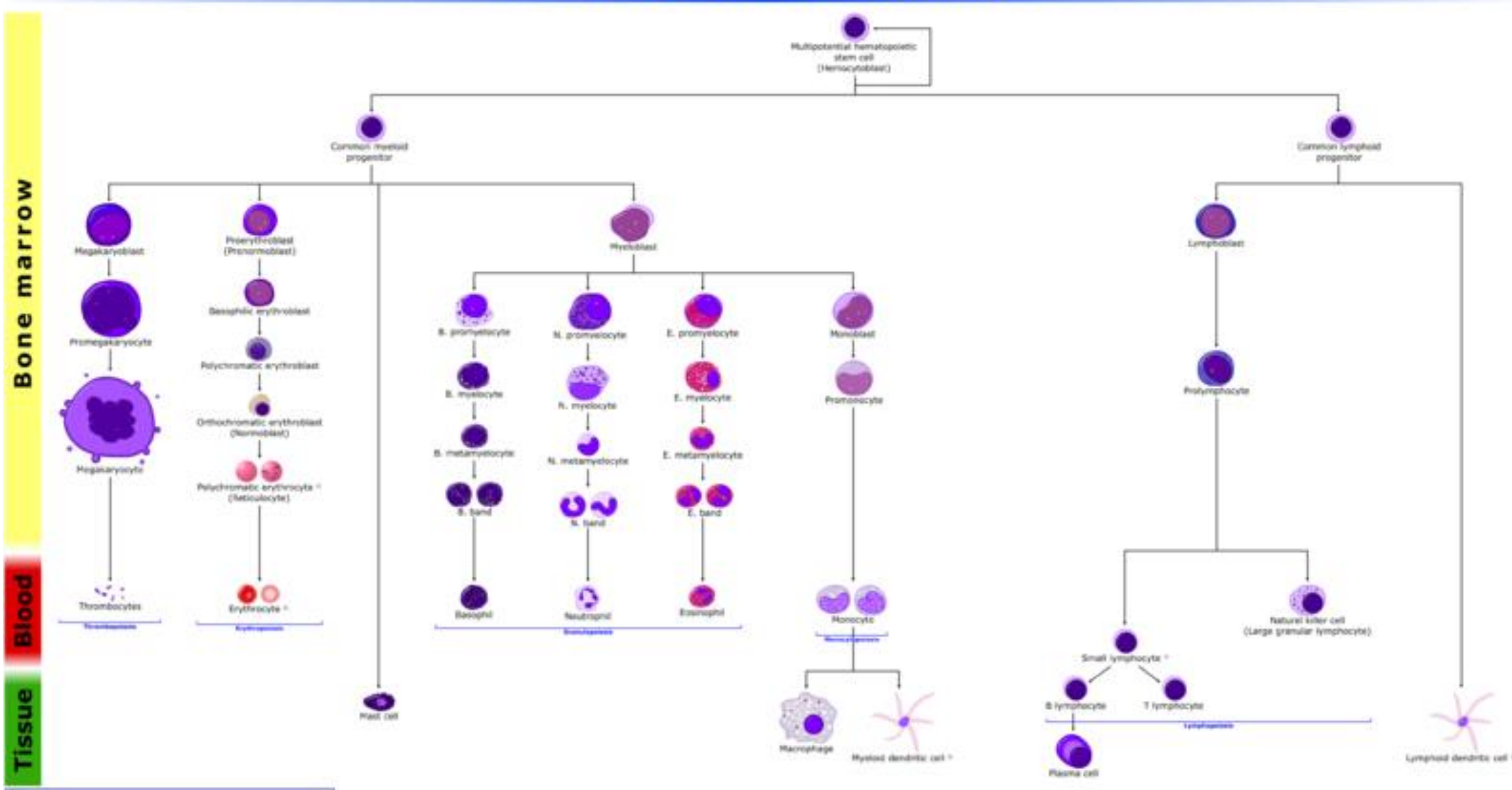
Haematological malignancies

European Commission

Haematopoiesis (overview)



Hematopoiesis in humans



Classification of haematological malignancies

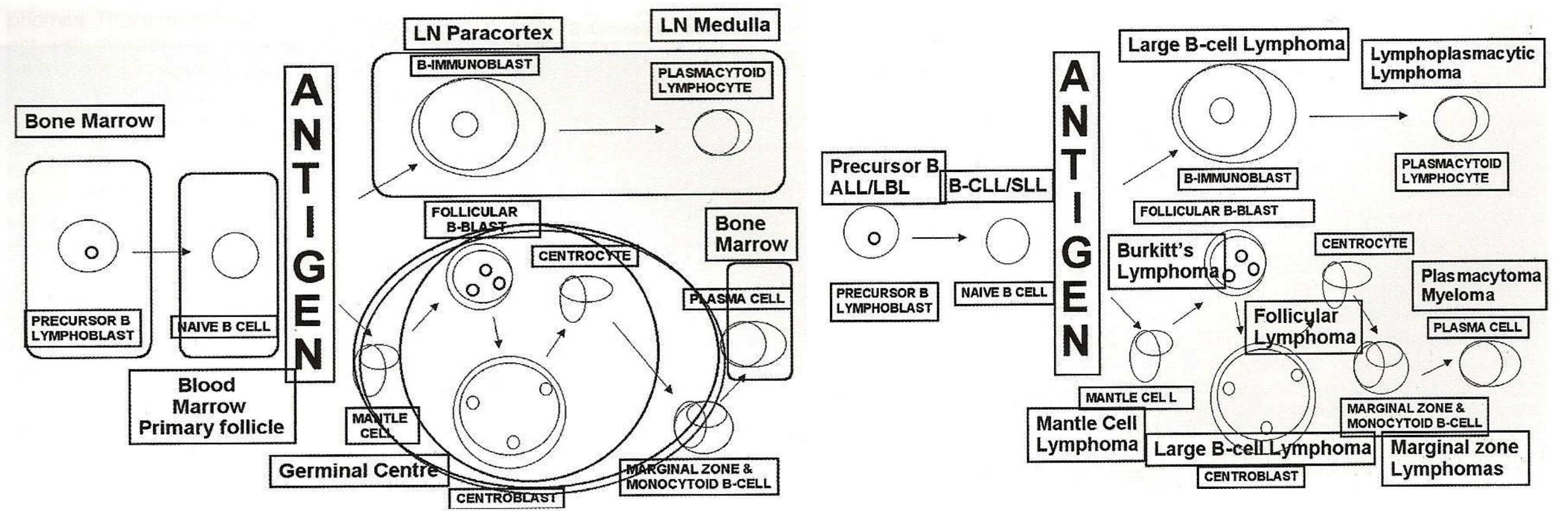
Aim:

- To determine the cell type and ‘the normal counterpart’
- To determine subtypes which are relevant for the prognosis and/or the treatment

Examples

Haematological malignancy	Normal counterpart
Multiple myeloma	plasma cell
Follicular lymphoma	germinal centre B-cell
B-ALL	haematopoietic stem cell or a B-cell progenitor cell
Mantle cell lymphoma	peripheral B-cell of the inner mantle zone (of a lymph node)

B-lymphocyte development with the malignant counterpart



Rules for classification

- Classify to the most specific (WHO) diagnosis
- Use all information from the different diagnostics
- Take into account that indolent haematological malignancies can transform to aggressive haematological malignancies
- For lymphoid malignancies the site of the tumour (lymph node, bone marrow) can also give an indication for the tumour type

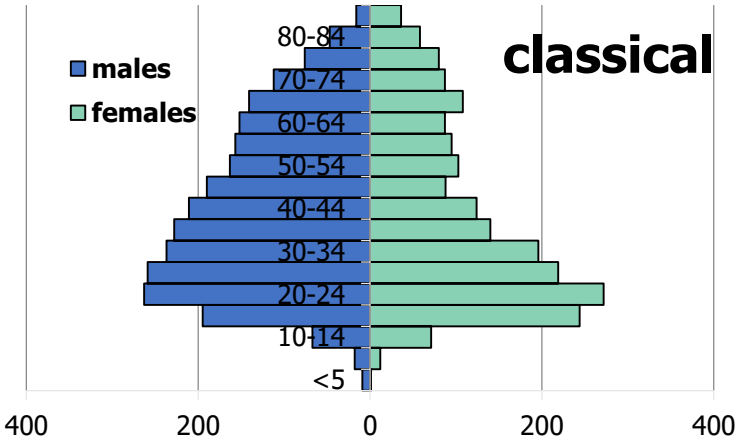
Site of lymphoma

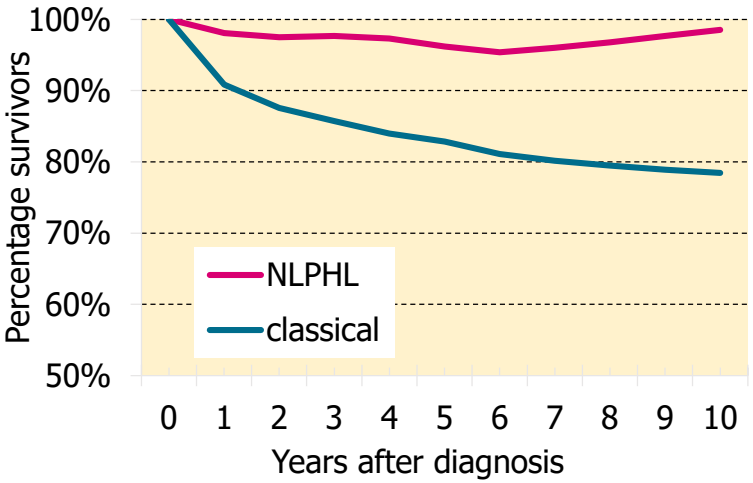
- Hodgkin lymphoma → lymph nodes
- Follicular lymphoma → mostly lymph nodes
- Lymphoplasmocytic lymphoma → bone marrow
- DLBCL → any site (including extranodal sites)
- T-ALL/LBL → bone marrow, thymus/mediastinal nodes

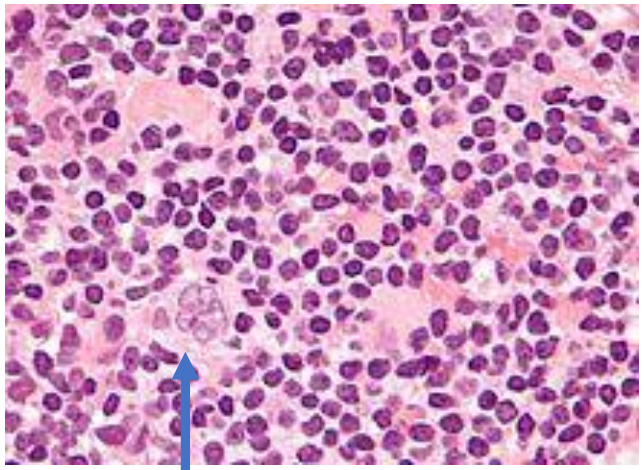
Hodgkin lymphoma: NLPHL versus classical HL

NLPHL (~8% of all cases)

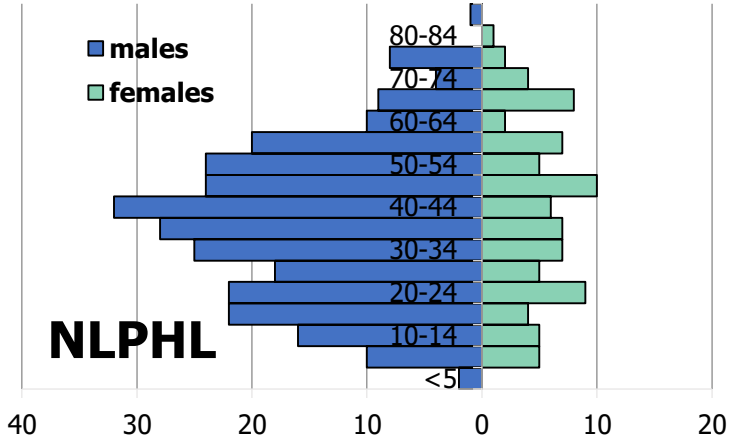
- higher survival, less aggressive treatment
- In the long run: risk of transformation to DLBCL







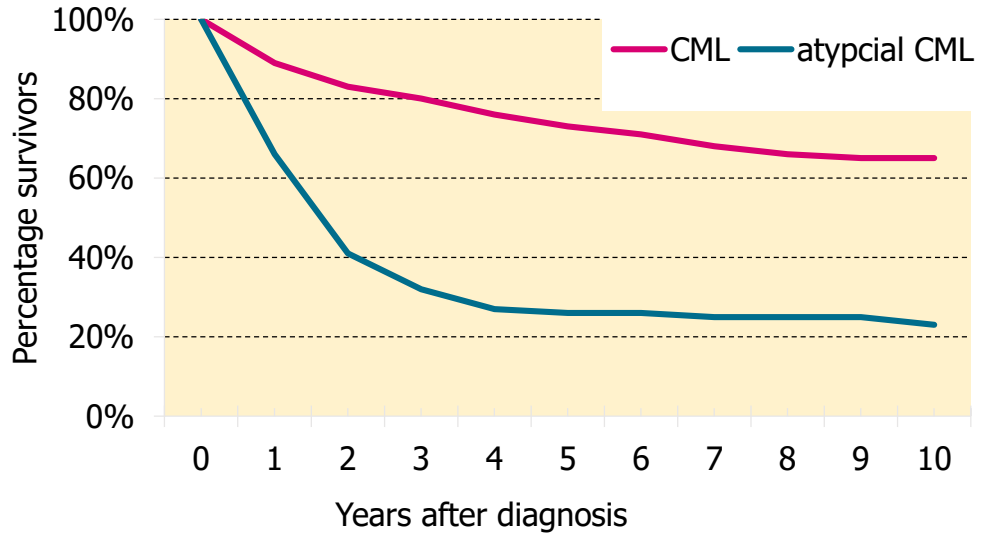
Reed-Sternberg cell (1900)

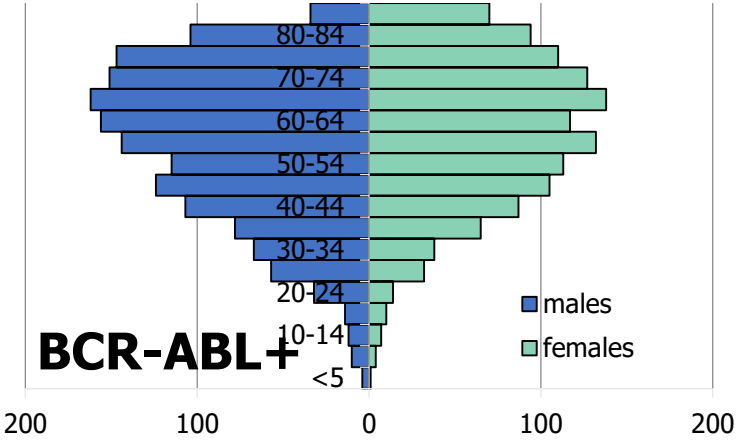


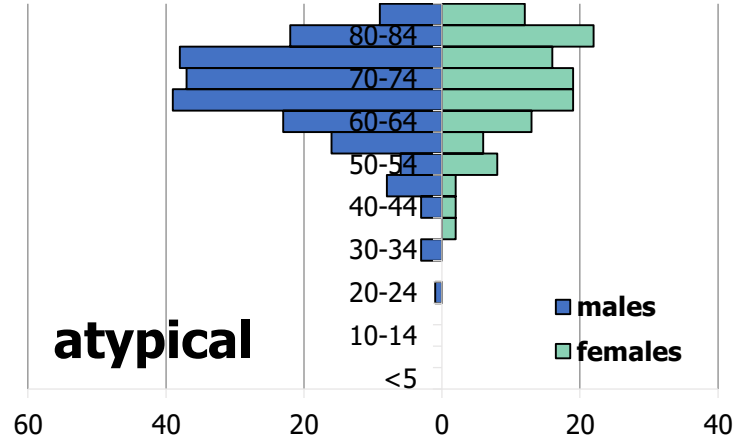
CML: BCR-ABL+ versus atypical

Atypical CML (~10% of all 'CML')

- Absence of t(9;22)
- No treatment with TKI (imatinib) → poor survival







Acute myeloid leukaemia

- *De novo* or as transformation of MDS or MPN
- In case of multiple diagnoses, code to the most specific category (1 > 2 > 3 > 4)
  1. With cytogenetic aberrations (9865, 9866, 9869, 9871, 9896, 9897, 9912)
  2. Myelodysplasia related (9895)
  3. Therapy related (9920)
  4. Other, not specified

Acute myeloid leukaemia

Examples

- Acute megakaryoblastic leukaemia (9910), therapy related (9920) → 9920
- Acute myeloid leukaemia, t(8;21) (9896), therapy related (9920) → 9896
- Acute myelomonocytic leukaemia (9867), t(8;21) (9896) → 9896

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