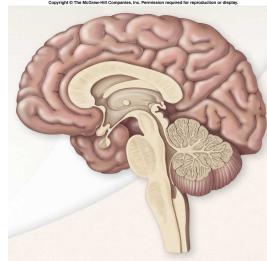


CNS tumours; epidemiology, etiology and pathology

David Scheie
Avdeling for patologi,
Oslo Universitetssykehus



Brain tumours



- 3.0% of all new cancer cases
- Causes are poorly understood
- Well-defined risk factors:
Ionizing radiation, rare genetic syndromes
- Gliomas; 50%
- Meningiomas; 25%



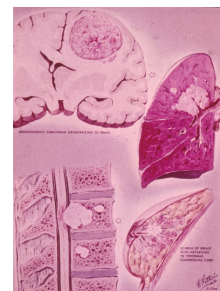
Epidemiology; Primary CNS tumours

- Incidence in Norway (2008), per 100 000: 16.6 in males, 18.7 in females
- 3.0% of all cancers in Norway (time period 1970-1999)
- Increase in incidence. Improved diagnostics. Aging population.
- Nordic countries > World
- Europe and North America > Africa, Asia and South America.
- Availability of health care technology is likely to explain at least some of the differences.



Epidemiology, Brain metastases

- Exact incidence unknown. Reported: 8.5-14.3 per 100 000
- Underestimated; probably 10 times more common than primary CNS tumours
- 25-35% of all cancer patients
- Increase in incidence;
 - longer survival
 - increased incidence (especially lung cancer, aging population)
 - improved diagnostics



CNS tumours; etiology

- Poorly understood
- Ionizing radiation is the only well-established causal environmental factor
- Contradictory/inconclusive reports: electromagnetic fields, mobile phones, microwaves, radars, occupational factors, diet, infections.
- Not associated: Smoking, alcohol consumption, dental X-ray, head injury
- Allergies/asthma and chicken pox have been associated with a decreased risk of glioma.
- Rare genetic syndromes in 1-2% of the cases; Li-Fraumeni, neurofibromatosis, tuberous sclerosis, nevoid basal cell carcinoma syndrome, familial polyposis, von Hippel-Lindau
- Two-fold increased risk in first degree relatives of patients with gliomas. Familial aggregation suggests a genetic aetiology but shared environmental exposure is also a possible explanation
- Virus; no causal role have been demonstrated in humans. Animal models; viruses can induce brain tumours. Humans: CMV and and polyomavirus have been isolated from brain tumours.

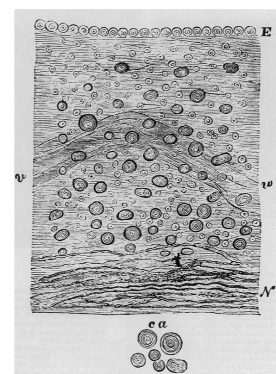


Glial cells and gliomas



Rudolf Virchow

- 1856: "Nervenkitt"
- γλιν (greek) = glue
- Neuroglia
- 1863-1865: Two main types of brain tumours:
 - glioma
 - sarcoma

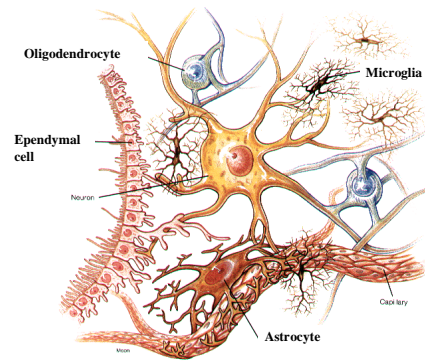


The first glioma operation

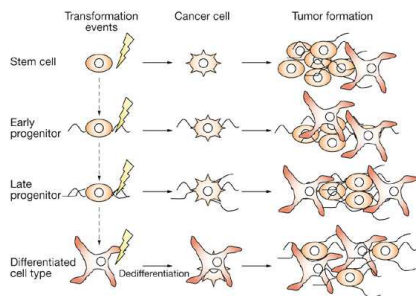


- 1884: Rickman J. Godlee, London
- 25-year-old man with seizures, pain attacks and paralysis of the left arm
- Dr A. Hughes Bennett:
Lesion in the right precentral gyrus
- "A transparent lobulated tumour, perfectly isolated from the brain substance"
- Histology: Glioma
- The patient died of meningitis on the 28th postoperative day

Glial cells

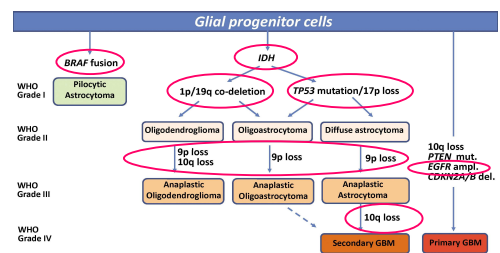


The histogenesis of gliomas is unknown



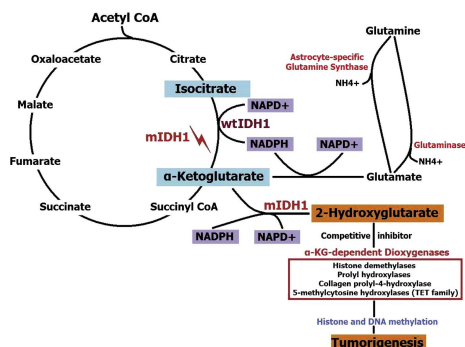
Dietrich J, Nat Clin Pract Oncol, 2008

Molecular pathways and common genetic alterations in gliomas



IDH: Isocitrate dehydrogenase
EGFR: Epidermal growth factor receptor
BRAF: v-rat murine sarcoma viral oncogene homologue B1

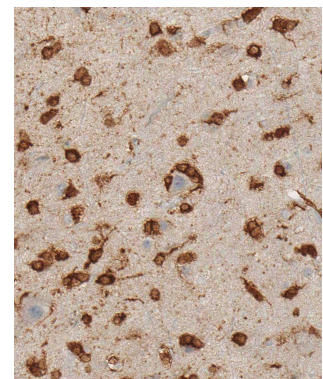
IDH mutation



Olur A, Annals of Diagnostic Pathology, 2011

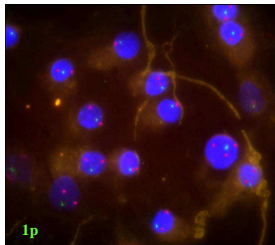
IDH mutation in diffuse gliomas

- Isocitrate dehydrogenase (IDH)
- Gliomas WHO grade II and III, secondary glioblastoma
- IDH1: 70-80% (IDH2: 5%)
- IDH1: >90%: R132H
- Monoclonal IDH1 R132H antibody
- Can distinguish between low-grade glioma and reactive glial proliferation
- Favourable prognostic factor in gliomas

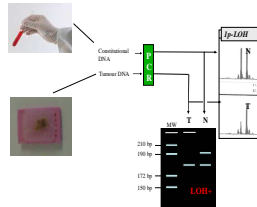


1p/19q loss in 50-80% of oligodendroglial tumours

FISH:



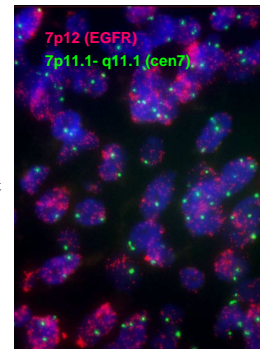
PCR:



Diagnostic, prognostic, predictive marker

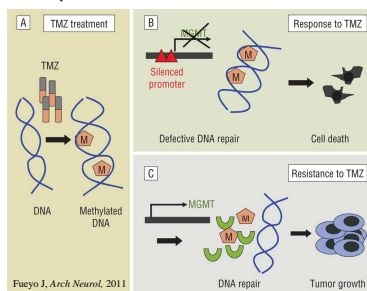
EGFR amplification

- Epidermal growth factor receptor (7p12)
- 30 - 40% of glioblastomas
- Highly suggestive of glioblastoma even if histologic criteria are not met
- Prognostic role is unclear



MGMT (O⁶-methylguanine DNA methyltransferase; DNA repair enzyme)

Temozolomide damages tumour DNA by methylation



Hypermethylation of MGMT

- occurs frequently in gliomas
- silences MGMT expression
- allows temozolomide to be cytotoxic

G-CIMP (CpG island methylator phenotype)

Identification of a CpG Island Methylator Phenotype that Defines a Distinct Subgroup of Glioma

Houten N, Nishikawa S, Doherty D, Watanabe T, Kretzschmar M, Haddad S, Phillips J, Karim P, Benjamin P, Barman V, Fan F, Christopher E, Poloski E, R. Sahu, Krishna P, Bhargava R, Verhaak, K, Haddad A, Haddad D, Haddad N, Haddad M, Haddad P, Haddad R, Haddad S, Haddad T, Haddad V, Haddad W, Haddad X, Haddad Y, Haddad Z, Haddad AA, Haddad AB, Haddad AC, Haddad AD, Haddad AE, Haddad AF, Haddad AG, Haddad AH, Haddad AI, Haddad AJ, Haddad AK, Haddad AL, Haddad AM, Haddad AN, Haddad AO, Haddad AP, Haddad AQ, Haddad AR, Haddad AS, Haddad AT, Haddad AU, Haddad AV, Haddad AW, Haddad AX, Haddad AY, Haddad AZ, Haddad BA, Haddad BB, Haddad BC, Haddad BD, Haddad BE, Haddad BF, Haddad BG, Haddad BH, Haddad BI, Haddad BJ, Haddad BK, Haddad BL, Haddad BM, Haddad BN, Haddad BO, Haddad BP, Haddad BQ, Haddad BR, Haddad BS, Haddad BT, Haddad BU, Haddad BV, Haddad BW, Haddad BX, Haddad BY, Haddad BZ, Haddad CA, Haddad CB, Haddad CC, Haddad CD, Haddad CE, Haddad CF, Haddad CG, Haddad CH, Haddad CI, Haddad CJ, Haddad CK, Haddad CL, Haddad CM, Haddad CN, Haddad CO, Haddad CP, Haddad CQ, Haddad CR, Haddad CS, Haddad CT, Haddad CU, Haddad CV, Haddad CW, Haddad CX, Haddad CY, Haddad CZ, Haddad DA, Haddad DB, Haddad DC, Haddad DD, Haddad DE, Haddad DF, Haddad DG, Haddad DH, Haddad DI, Haddad DJ, Haddad DK, Haddad DL, Haddad DM, Haddad DN, Haddad DO, Haddad DP, Haddad DQ, Haddad DR, Haddad DS, Haddad DT, Haddad DU, Haddad DV, Haddad DW, Haddad DX, Haddad DY, Haddad DZ, Haddad EA, Haddad EB, Haddad EC, Haddad ED, Haddad EE, Haddad EF, Haddad EG, Haddad EH, Haddad EI, Haddad EJ, Haddad EK, Haddad EL, Haddad EM, Haddad EN, Haddad EO, Haddad EP, Haddad EQ, Haddad ER, Haddad ES, Haddad ET, Haddad EU, Haddad EV, Haddad EW, Haddad EX, Haddad EY, Haddad EZ, Haddad FA, Haddad FB, Haddad FC, Haddad FD, Haddad FE, Haddad FF, Haddad FG, Haddad FH, Haddad FI, Haddad FJ, Haddad FK, Haddad FL, Haddad FM, Haddad FN, Haddad FO, Haddad FP, Haddad FQ, Haddad FR, Haddad FS, Haddad FT, Haddad FU, Haddad FV, Haddad FW, Haddad FX, Haddad FY, Haddad FZ, Haddad GA, Haddad GB, Haddad GC, Haddad GD, Haddad GE, Haddad GF, Haddad GG, Haddad GH, Haddad GI, Haddad GJ, Haddad GK, Haddad GL, Haddad GM, Haddad GN, Haddad GO, Haddad GP, Haddad GQ, Haddad GR, Haddad GS, Haddad GT, Haddad GU, Haddad GV, Haddad GW, Haddad GX, Haddad GY, Haddad GZ, Haddad HA, Haddad HB, Haddad HC, Haddad HD, Haddad HE, Haddad HF, Haddad HG, Haddad HH, Haddad HI, Haddad HJ, Haddad HK, Haddad HL, Haddad HM, Haddad HN, Haddad HO, Haddad HP, Haddad HQ, Haddad HR, Haddad HS, Haddad HT, Haddad HU, Haddad HV, Haddad HW, Haddad HX, Haddad HY, Haddad HZ, Haddad IA, Haddad IB, Haddad IC, Haddad ID, Haddad IE, Haddad IF, Haddad IG, Haddad IH, Haddad II, Haddad IJ, Haddad IK, Haddad IL, Haddad IM, Haddad IN, Haddad IO, Haddad IP, Haddad IQ, Haddad IR, Haddad IS, Haddad IT, Haddad IU, Haddad IV, Haddad IW, Haddad IX, Haddad IY, Haddad IZ, Haddad JA, Haddad JB, Haddad JC, Haddad JD, Haddad JE, Haddad JF, Haddad JG, Haddad JH, Haddad JI, Haddad JJ, Haddad JK, Haddad JL, Haddad JM, Haddad JN, Haddad JO, Haddad JP, Haddad JQ, Haddad JR, Haddad JS, Haddad JT, Haddad JU, Haddad JV, Haddad JW, 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Haddad UK, Haddad UL, Haddad UM, Haddad UN, Haddad UO, Haddad UP, Haddad UQ, Haddad UR, Haddad US, Haddad UT, Haddad UU, Haddad UV, Haddad UW, Haddad UX, Haddad UY, Haddad UZ, Haddad VA, Haddad VB, Haddad VC, Haddad VD, Haddad VE, Haddad VF, Haddad VG, Haddad VH, Haddad VI, Haddad VJ, Haddad VK, Haddad VL, Haddad VM, Haddad VN, Haddad VO, Haddad VP, Haddad VQ, Haddad VR, Haddad VS, Haddad VT, Haddad VU, Haddad VV, Haddad VW, Haddad VX, Haddad VY, Haddad VZ, Haddad WA, Haddad WB, Haddad WC, Haddad WD, Haddad WE, Haddad WF, Haddad WG, Haddad WH, Haddad WI, Haddad WJ, Haddad WK, Haddad WL, Haddad WM, Haddad WN, Haddad WO, Haddad WP, Haddad WQ, Haddad WR, Haddad WS, Haddad WT, Haddad WU, Haddad WV, Haddad WW, Haddad WX, Haddad WY, Haddad WZ, Haddad XA, Haddad XB, Haddad XC, Haddad XD, Haddad XE, Haddad XF, Haddad XG, Haddad XH, Haddad XI, Haddad XJ, Haddad XK, Haddad XL, Haddad XM, Haddad XN, Haddad XO, Haddad XP, Haddad XQ, Haddad XR, Haddad XS, Haddad XT, Haddad XU, Haddad XV, Haddad XW, Haddad XX, Haddad XY, Haddad XZ, Haddad YA, Haddad YB, Haddad YC, Haddad YD, Haddad YE, Haddad YF, Haddad YG, Haddad YH, Haddad YI, Haddad YJ, Haddad YK, Haddad YL, Haddad YM, Haddad YN, Haddad YO, Haddad YP, Haddad YQ, Haddad YR, Haddad YS, Haddad YT, Haddad YU, Haddad YV, Haddad YW, Haddad YX, Haddad YY, Haddad YZ, Haddad ZA, Haddad ZB, Haddad ZC, Haddad ZD, Haddad ZE, Haddad ZF, Haddad ZG, Haddad ZH, Haddad ZI, Haddad ZJ, Haddad ZK, Haddad ZL, Haddad ZM, Haddad ZN, Haddad ZO, Haddad ZP, Haddad ZQ, Haddad ZR, Haddad ZS, Haddad ZT, Haddad ZU, Haddad ZV, Haddad ZW, Haddad ZX, Haddad ZY, Haddad ZZ.

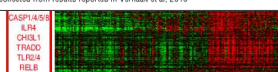
- Subset of gliomas: hypermethylation of CpG islands in >1500 gene loci
- Highly associated with IDH-mutations
- Favourable prognosis



Gene expression profiling

Table 1. Subtypes of Glioblastomas ^a			
Subtypes	Differential Genetic Alterations	Molecular Markers	Cellular Signature
Proneural	IDH1 (point mutation), PDGFRA, p53 (mutation, LOH)	Oligodendrocytic development (PDGFRA), proneural development (SOX)	Oligodendrocytic
Neural	Several genetic abnormalities (no significant differences with other subtypes)	Neural (similar to normal brain) (NEFL, GABRA1)	Oligodendrocytic, astrocytic, and neural
Classical	EGFR (amplification), NF1 (mutation), low expression, PTEN (mutation)	Neural and stem cells (notch, Sonic hedgehog)	Astrocytic
Mesenchymal	NF1 (mutation), low expression, PTEN (mutation)	Mesenchymal (VHL, MET), astrocytic (CD44), Schwann cell (S100A), tumor necrosis and NF-κB pathways	Undefined

^aData collected from results reported in Verhaak et al, 2010¹⁰



Verhaak RG, Cancer Cell, 2010

Response to therapy:
Greatest benefit: Classical type
No benefit: Proneural type

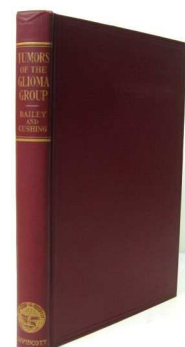
The first classification system of brain tumours



Percival Bailey
1892-1973

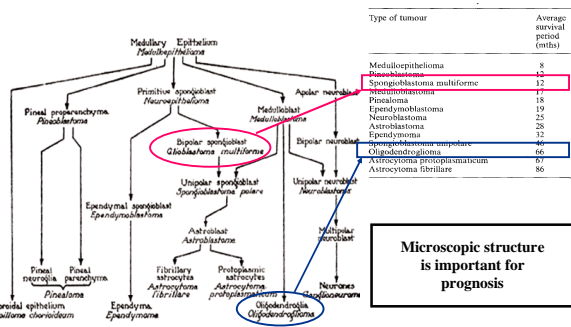


Harvey Cushing
1869-1939



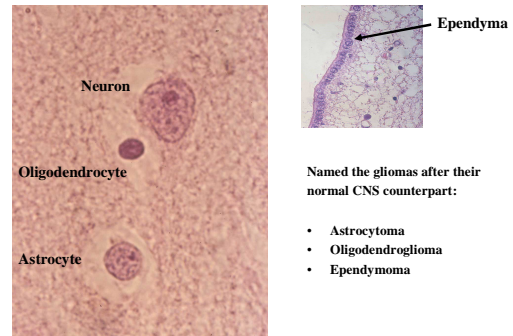
1926: "A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with A Correlated Study of Prognosis"

1926, Bailey and Cushing: "A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis"



Microscopic structure is important for prognosis

Glial cells and glioma

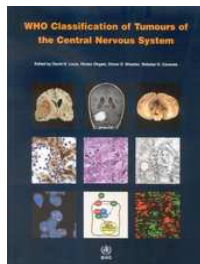


Named the gliomas after their normal CNS counterpart:

- Astrocytoma
- Oligodendroglioma
- Ependymoma

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WHO 2007



Main groups:

1. Neuroepithelial tumours
2. Tumours of cranial and paraspinal nerves
3. Tumours of the meninges
4. Lymphomas and haematopoietic neoplasms
5. Germ cell tumours
6. Tumours of the sellar region
7. Metastatic tumours

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WHO grading CNS tumors, I-IV:

Grade I:

- Low proliferative potential.
- Possibility of cure following surgical resection.

Grade II:

- Infiltrative.
- Recur despite low-level proliferative activity.
- Progress to higher grades.
- Typically survive > 5 years.

Grade III:

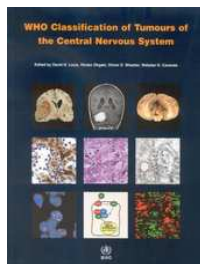
- Histological evidence of malignancy; nuclear atypia and brisk mitotic activity.
- In most settings tumors need adjuvant therapy.
- Typically survive 2-3 years.

Grade IV:

- Cytologically malignant, mitotically active, necrosis-prone
- Rapid pre- and postoperative disease evolution and a fatal outcome.
- The prognosis depends largely upon whether effective treatment regimens are available (glioblastoma vs. germinoma).

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WHO 2007



Main groups:

1. Neuroepithelial tumours
2. Tumours of cranial and paraspinal nerves
3. Tumours of the meninges
4. Lymphomas and haematopoietic neoplasms
5. Germ cell tumours
6. Tumours of the sellar region
7. Metastatic tumours

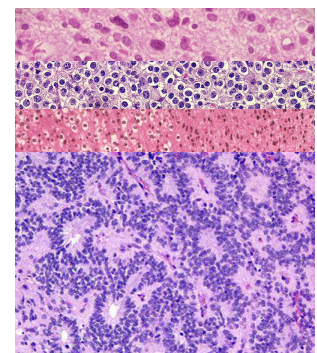
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WHO 2007, Classification of gliomas:

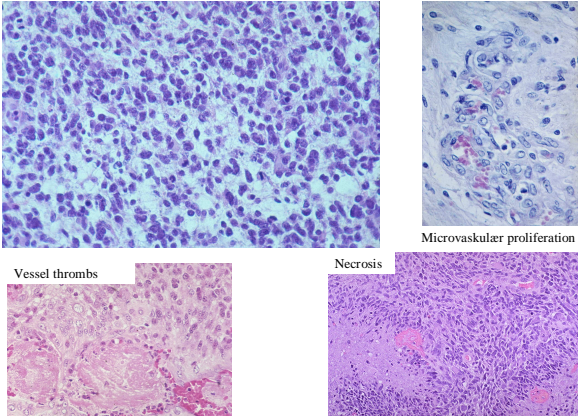
- Astrocytoma, grade I-IV
- Oligodendroglioma, grade II and III
- Oligoastrocytoma, grade II and III
- Ependymoma, grade I-III

Grade is important for treatment:

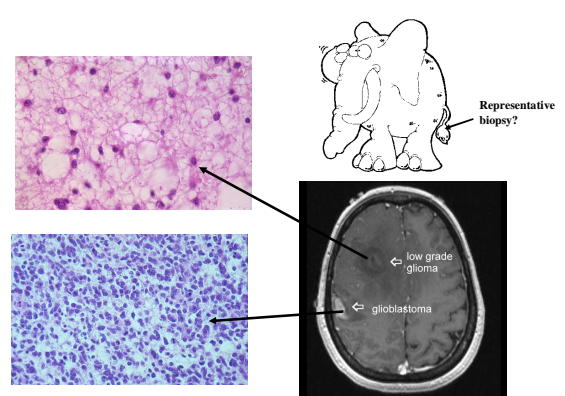
- Low-grade (I and II): Observation
- High-grade (III and IV): Additional therapy



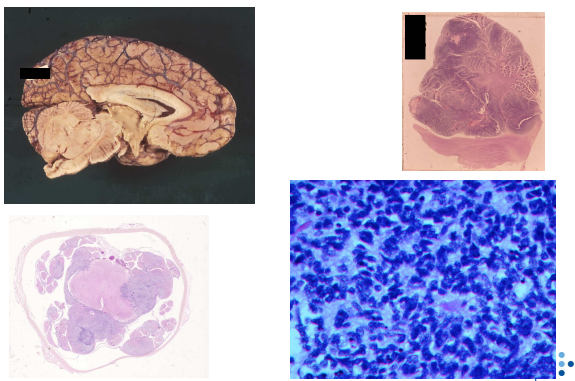
Astrocytoma grade IV= Glioblastoma



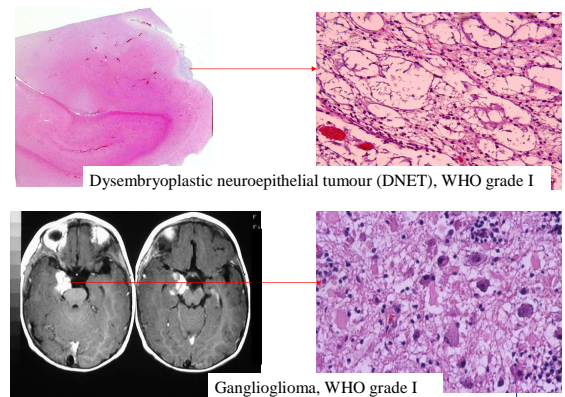
Tissue sampling: Biopsy from the most malignant part!



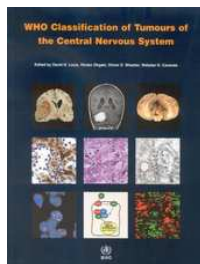
Medulloblastoma, WHO grade IV



Combined glial and neuronal tumours



WHO 2007

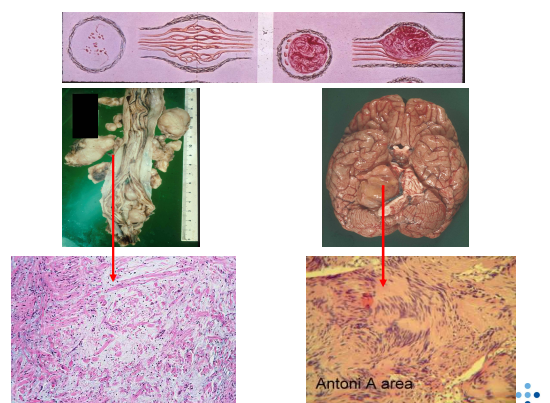


Main groups:

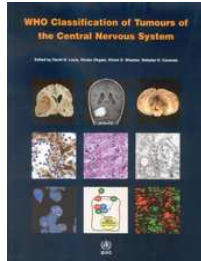
1. Neuroepithelial tumours
2. Tumours of cranial and paraspinal nerves
3. Tumours of the meninges
4. Lymphomas and haematopoietic neoplasms
5. Germ cell tumours
6. Tumours of the sellar region
7. Metastatic tumours

Neurofibroma

Schwannoma



WHO 2007

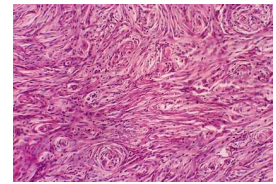


Main groups:

1. Neuroepithelial tumours
2. Tumours of cranial and paraspinal nerves
3. Tumours of the meninges
4. Lymphomas and haematopoietic neoplasms
5. Germ cell tumours
6. Tumours of the sellar region
7. Metastatic tumours



Meningioma



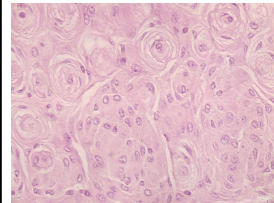
Women/men: 1.7/1.0

Ca.mamma.

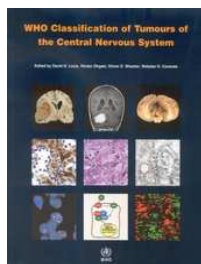
Grade I

Grade II (atypical)

Grade III (anaplastic)



WHO 2007

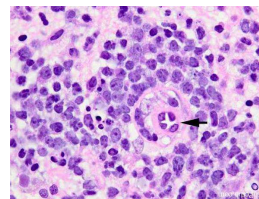


Main groups:

1. Neuroepithelial tumours
2. Tumours of cranial and paraspinal nerves
3. Tumours of the meninges
4. Lymphomas and haematopoietic neoplasms
5. Germ cell tumours
6. Tumours of the sellar region
7. Metastatic tumours

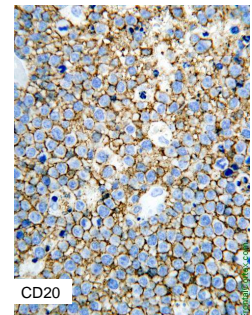


Primary CNS Lymphomas



Diffuse large cell B-cell lymphoma;
>90% of the cases

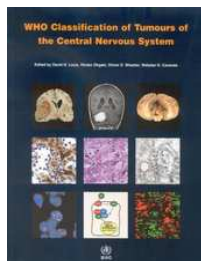
OBS; Prebiopsy steroid treatment have a profound apoptosis-based effect on tumour cells, vastly reducing their numbers. In extreme cases, only a sea of macrophages remain



CD20



WHO 2007

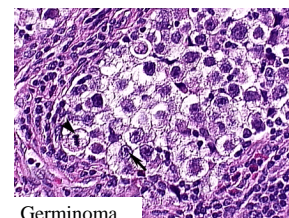
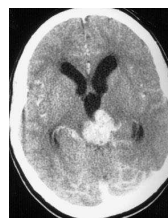


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Germinal cell tumours



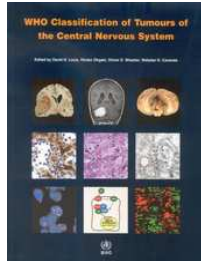
Germinoma

Other variants:

teratoma, embryonal carcinoma,
yolk sac tumour, choriocarcinoma,
mixed tumours



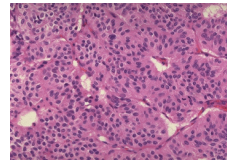
WHO 2007



Main groups:

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Tumours of the sellar region



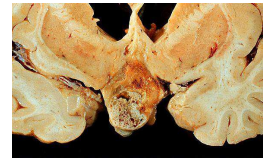
Pituitary adenoma

Prolactinoma: 25-30%.

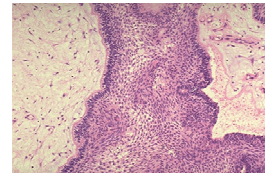
Non-hormone producing: 20-25%.

Growth hormone: 15-20%.

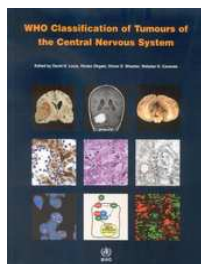
ACTH: 10-15%.



Craniopharyngeoma, WHO grade I



WHO 2007



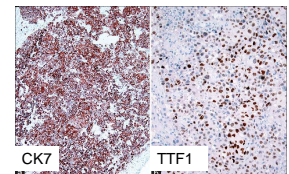
Main groups:

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Brain metastases- primary focus

- Unknown primary focus at time of diagnosis: 16-20% av tilfelle
- In approx 4% the primary focus is not found
- Lung; 20%
- Mamma; 5%
- Melanoma; 6.5%
- Kidney; 6.8%
- GI-tract; 1.8%

- Very uncommon:
- Prostatic carcinoma
 - Sarcoma (Only 3% av sarcoma patients develop CNS metastasis ("alveolar soft part sarcoma", osteosarcoma))



Pulmonary adenocarcinomas are the most frequent primary tumour

Brain tumour diagnosis – current status

Gold standard: Light microscopy

The WHO classification is useful:

- High-grade tumours are more aggressive
- Astrocytomas are more aggressive than grade-matched oligodendrogliomas

The WHO classification has limitations:

- Variable behaviour among tumours with identical histology
- High interobserver variability regarding subtyping and grading of gliomas

Advances in neurosurgery, radiation and chemotherapy have provided only small improvements in clinical outcome in gliomas

Need for objective markers of diagnostic, prognostic and predictive value!

Classification of gliomas in the future

Histology, patient age, 1p/19q status account for 70-80% of the prognostic variability in gliomas (Vitucci M, *Br J Cancer*, 2011)

Key factors for implementing new molecular markers in future classification systems are to

- account for the remaining 20-30% of prognostic variability
- identify molecular subsets of tumours uniquely responsive to specific therapies

Improved technology will allow gene expression profiling also in formalin-fixed, paraffin-embedded tissue (Colman H, *Neuro Oncol*, 2010)

Looking forward to a new and improved WHO classification in 2015/16