CNS tumours; epidemiology, etiology and pathology

David Scheie

Avdeling for patologi,
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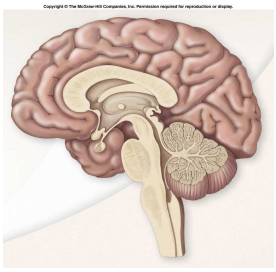
Brain tumours



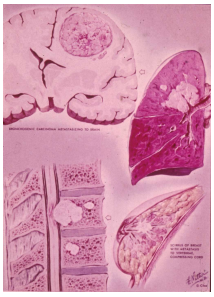
- **3.0% of all new cancer cases**
- **Causes are poorly understood**
- **Well-defined risk factors: Ionizing radiation, rare genetic syndromes**
- **Gliomas; 50%**
- **Meningiomas; 25%**

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
- Understimated; probably 10 times more common than primary CNS tumours
- 25-35% of all cancer patients
- Increase in incidence;
  -longer survival
  -increased incidence (epescially lung cancer, aging population)
  -improved diagnostics



CNS tumours; etiology

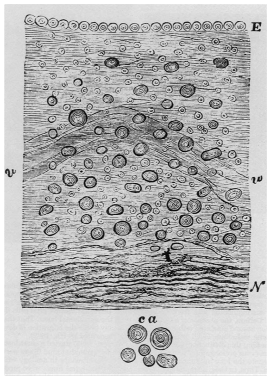
- Poorly understood
- Ionizing radiation is the only well-established causal environmental factor
- Contradictory/inconclusive reports: electromagnetic fields, mobile phones, microwaves, radars, occupational factors, diet, infections.
- Not associated: Smoking, alcohol consumption, dental X-ray, head 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 risc 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

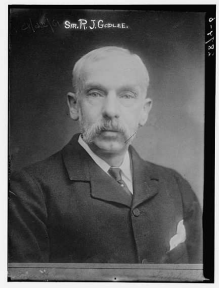
Rudolf Virchow

- **1856: "Nervenkitt"**
- **γλια (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 transparant lobulated tumour, perfectly isolated from the brain substance"
- Histology: Glioma
- The patient died of meningitis on the 28th postoperative day

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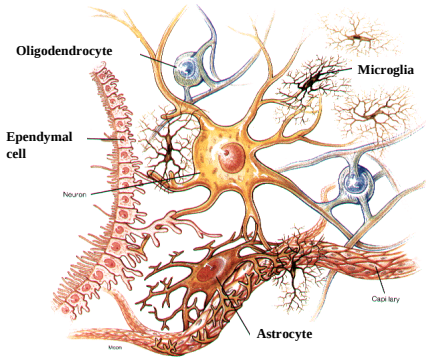
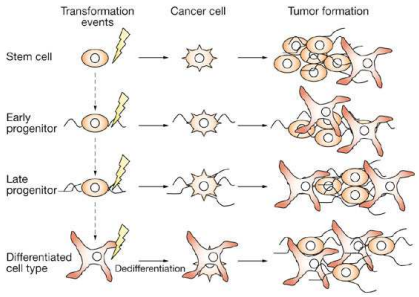
Glial cells

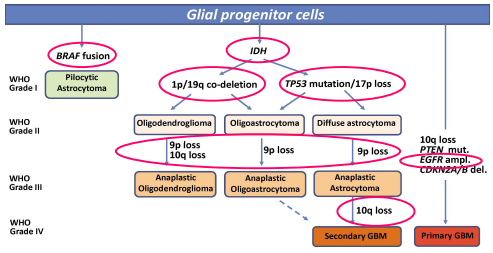


The histogenesis of gliomas is unknown



Dietrich J, *Nat Clin Pract Oncol*, 2008

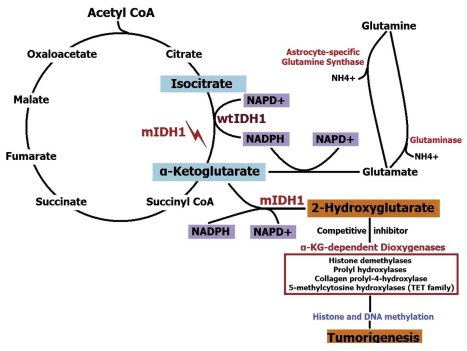
Molecular pathways and common genetic alterations in gliomas



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

Nikiforova MN, *Arch Pathol Lab Med*, 2011

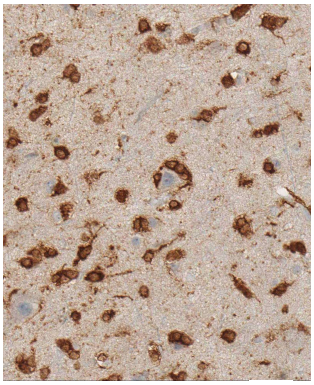
IDH mutation



Olar A, *Annals of Diagnostic Pathology*, 2011

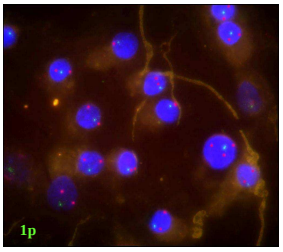
IDH mutation in diffuse gliomas

- 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

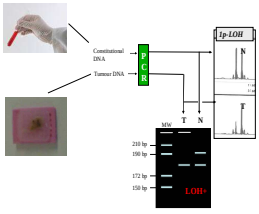


1p/19q loss in 50-80% of oligodendroglial tumours

FISH:



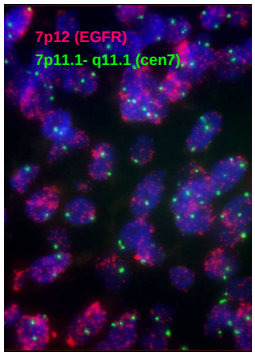
PCR:



Diagnostic, prognostic, predictive marker

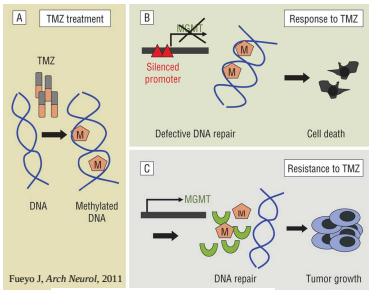
EGFR amplification

- **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
(O^6-methylguanine DNA methyltransferase; DNA repair enzyme)

Temozolomide damages tumour DNA by methylation



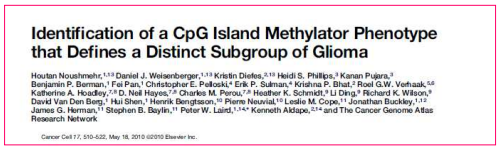
Hypermethylation of MGMT

-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

Houtan Noushmehr,[1,13] Daniel J. Weisenberger,[1,13] Kristin Diefes,[2,13] Heidi S. Phillips,[3] Kanan Pujara,[3] Benjamin P. Berman,[1] Fei Pan,[1] Christopher E. Pelloski,[4] Erik P. Sulman,[4] Krishna P. Bhat,[2] Roel G.W. Verhaak,[5,6] Katherine A. Hoadley,[7,8] D. Neil Hayes,[7,8] Charles M. Perou,[7,8] Heather K. Schmidt,[9] Li Ding,[9] Richard K. Wilson,[9] David Van Den Berg,[1] Hui Shen,[1] Henrik Bengtsson,[10] Pierre Neuvial,[10] Leslie M. Cope,[11] Jonathan Buckley,[1,12] James G. Herman,[11] Stephen B. Baylin,[11] Peter W. Laird,[1,3,4,*] Kenneth Aldape,[2,14] and The Cancer Genome Atlas Research Network

Cancer Cell 17, 510–522, May 18, 2010 ©2010 Elsevier Inc.

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

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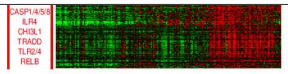
Gene expression profiling

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), *EGFRvIII*, *wt p53*, *CDKN2A* (deletion p16/p14arf) or aberrant *Rb/CDK4*	Neural and stem cells (notch, Sonic hedgehog)	Astrocytic
Mesenchymal	*NF1* (mutation, low expression), *PTEN* (mutation)	Mesenchymal (YKL40, MET), astrocytic (CD44), Schwann cell (S100A), tumor necrosis and NF-κB pathways	Undefined

[a]Data collected from results reported in Verhaak et al, 2010[5]



Verhaak RG, *Cancer Cell*, 2010

Response to therapy:

Greatest benefit: Classical type
No benefit: Proneural type

The first classification system of brain tumours

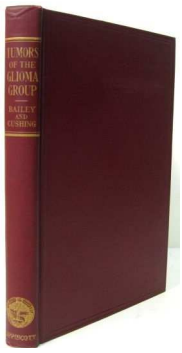
Percival Bailey

1892-1973

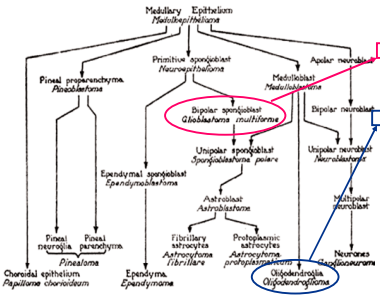
Harvey Cushing

1869-1939

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



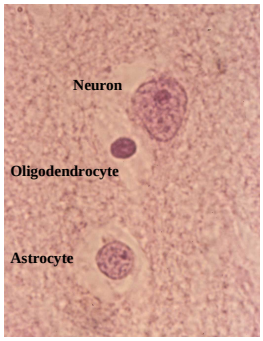
1926, Bailey and Cushing: "A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis"

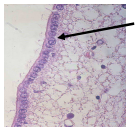


Type of tumour	Average survival period (mths)
Medulloepithelioma	8
Pineoblastoma	12
Spongioblastoma multiforme	12
Medulloblastoma	17
Pinealoma	18
Ependymoblastoma	19
Neuroblastoma	25
Astroblastoma	28
Ependymoma	32
Spongioblastoma polare	46
Oligodendroglioma	66
Astrocytoma protoplasmaticum	67
Astrocytoma fibrillare	86

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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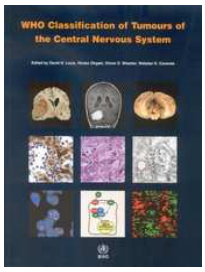
WHO 2007



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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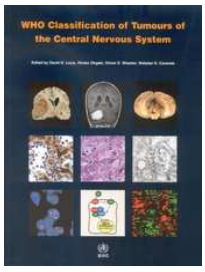
WHO 2007



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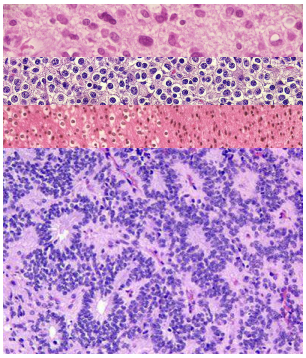
WHO 2007, Classification of gliomas:

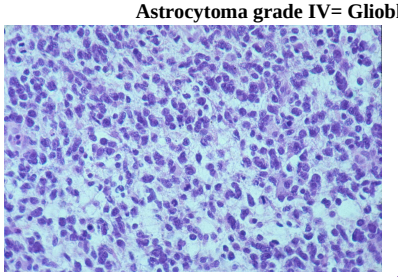
- **Astrocytoma, grade I-IV**
- **Oligodendroglioma, grade II and III**
- **Oligoastrocytoma, grade II and III**
- **Ependymoma, grade I-III**

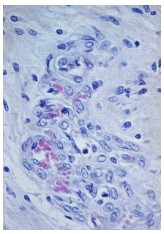


Grade is important for treatment:

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

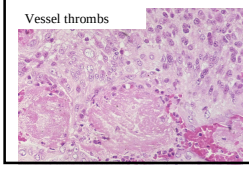
Astrocytoma grade IV= Glioblastoma



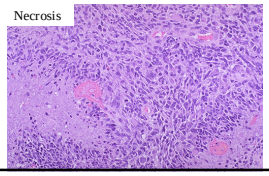


Microvaskulær proliferation

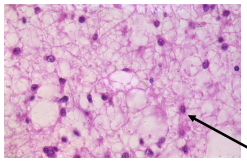
Vessel thrombs



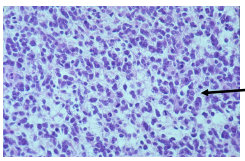
Necrosis

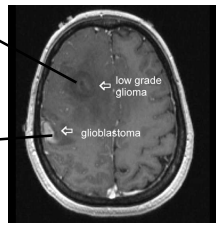


Tissue sampling: Biopsy from the most malignant part!

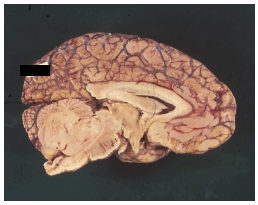


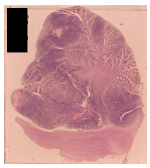
Representative biopsy?

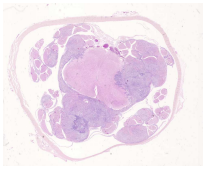


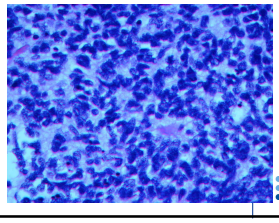


Medulloblastoma, WHO grade IV

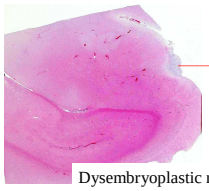


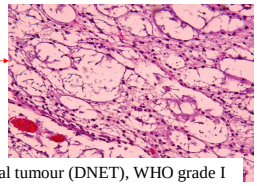




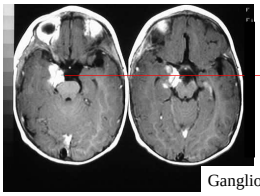


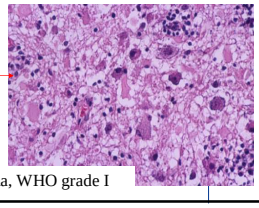
Combined glial and neuronal tumours





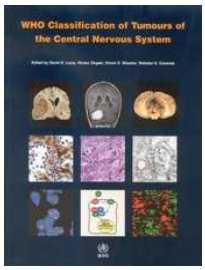
Dysembryoplastic neuroepithelial tumour (DNET), WHO grade I





Gangliogliomа, WHO grade I

WHO 2007



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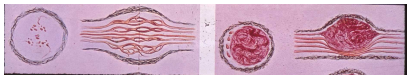
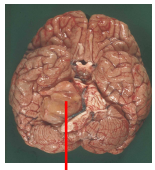
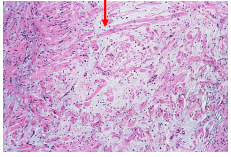
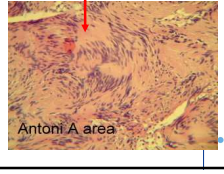
Neurofibroma Schwannoma

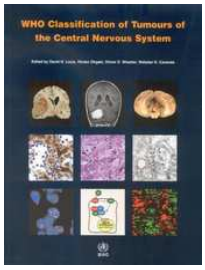








WHO 2007



Main groups:

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7. Metastatic tumours

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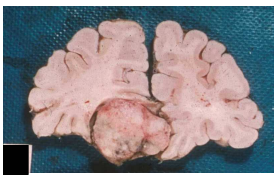
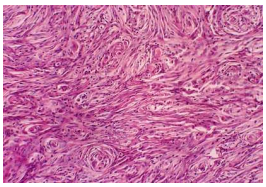
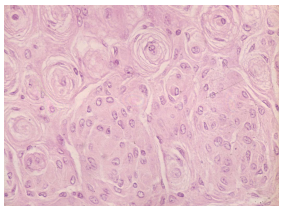
Meningioma







Women/men: 1.7/1.0

Ca.mamma.

Grade I

Grade II (atypical)

Grade III (anaplastic)

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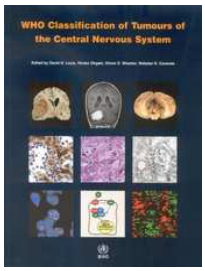
WHO 2007



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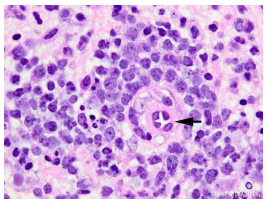
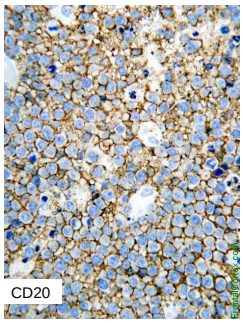
Primary CNS Lymphomas



Diffuse large cell B-cellelymphoma; >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

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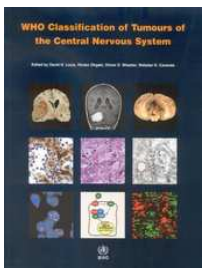
WHO 2007



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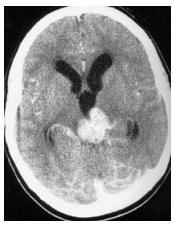
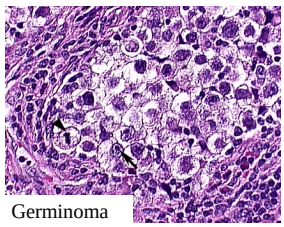
Germinal cell tumours





Germinoma

Other variants:

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

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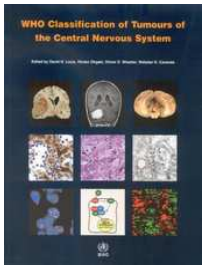
WHO 2007



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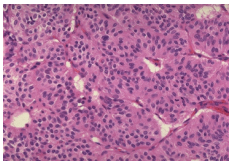
Tumours of the sellar region



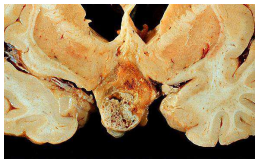
Pituitary adenoma

Prolactinoma: 25-30%.

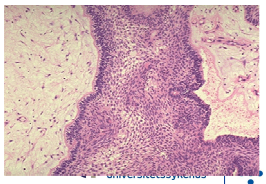
Non-hormone producing: 20-25%.

Growth hormone: 15-20%.

ACTH: 10-15%.



Craniopharyngeoma, WHO grade I



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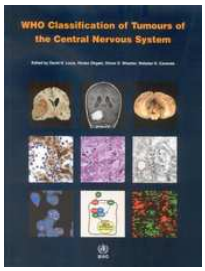

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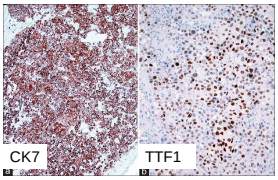
Brain metastases- primary focus

- Unknown primary focus at time of diagnosis: 16-20% av tilfellene
- 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

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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

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