Imperial College London

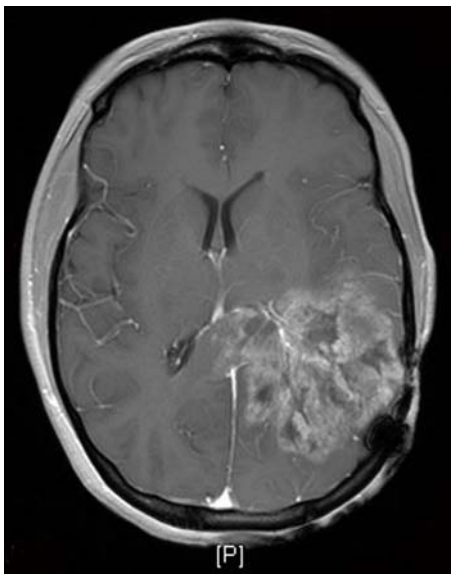
13 December 2012

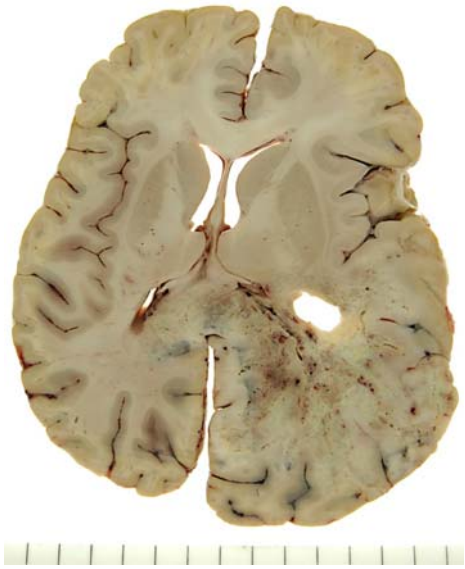
BSc Neuroscience – Module 2

Tumours of the Central Nervous System

Federico Roncaroli

Brain cancer is a devastating disease





Key concepts to understand the CNS

- **Complexity**
- **Diversity**
- **Connectivity**
- **Plasticity**
- **Uniqueness**

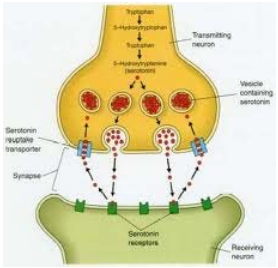
NORMAL CELL TYPES

- **Neurons**
- **Astrocytes**
- **Oligodendrocytes** } ***Glia (glue)***
- **Microglia**

- **Ependyma**
- **Choroid plexus epithelium** } ***Interface with CSF***
- **Meninges**

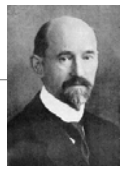
- **Endothelium & pericytes** } ***Interface with blood***

FUNCTIONAL CLASSIFICATION - NEUROTRANSMITTERS

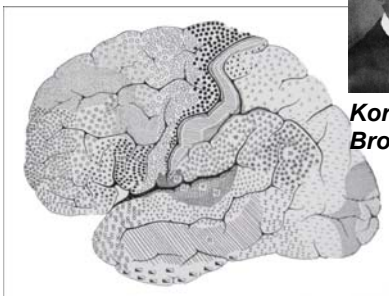


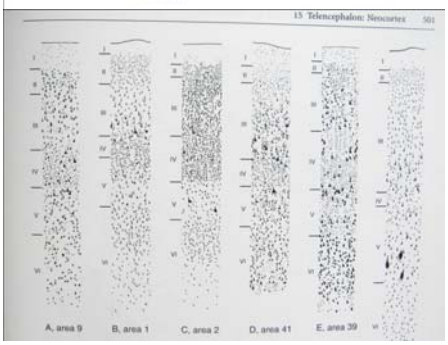
- More than 50 peptides
- GABA - Inhibitory
- Glutamate – Excitatory
- Acetylcholine
- Dopamine
- Serotonin

Cytoarchitecture

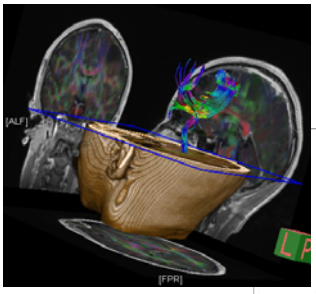


Korbinian Brodmann

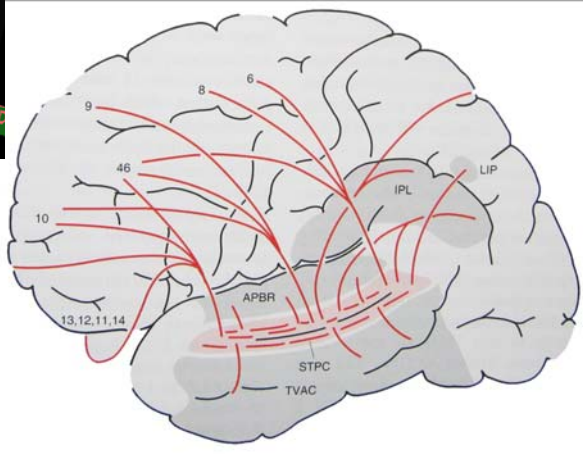




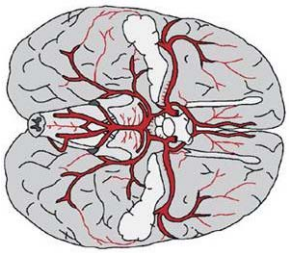
CONNECTIVITY

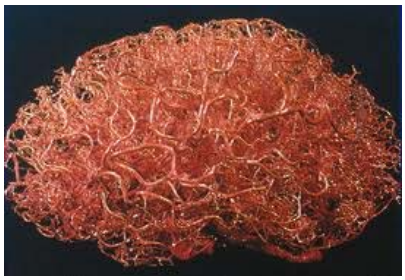


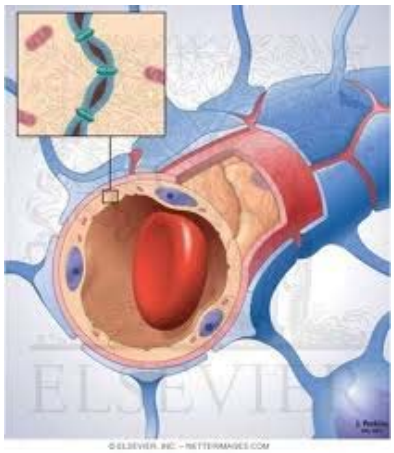
Functional pathways
Hierarchy of functions
Plasticity



BLOOD BRAIN BARRIER





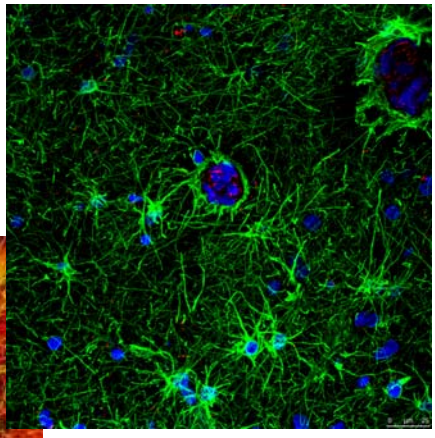


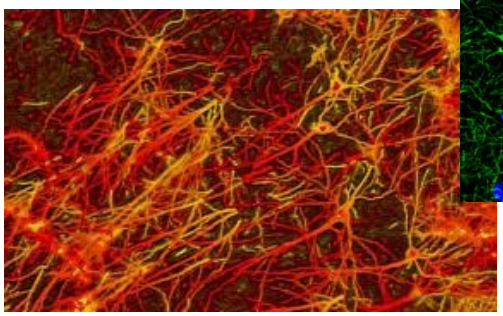
BBB unique to CNS

Tight junctions between endothelial cells, pericytes and astrocytes

It ensures that the homeostasis within the brain is maintained

THE COMPLEXITY OF THE CNS CAN AFFECT YOUR SCIENCE



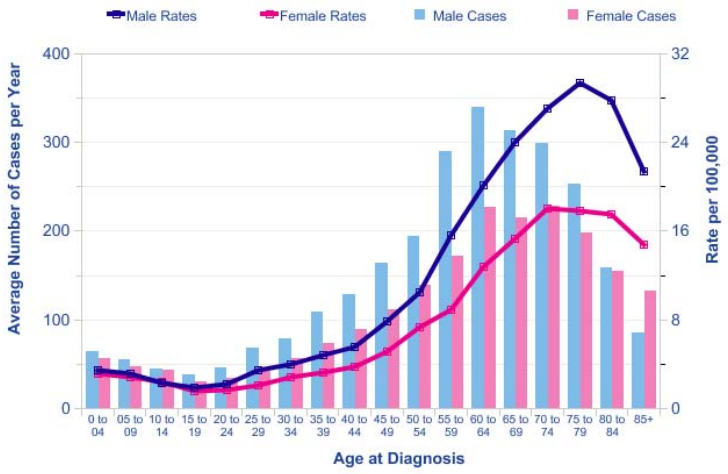


CNS tumours in adults

BRAIN TUMOURS: INCIDENCE, SURVIVAL, AND AETIOLOGY
P A McKinney

Breast	41300	(15%)
Lung	38190	(14%)
Large bowel	35410	(13%)
Prostate	24710	(9%)
Bladder	12470	(5%)
Stomach	9750	(4%)
Non-Hodgkin's lymphoma	9010	(3%)
Head and neck	7780	(3%)
Oesophagus	7230	(3%)
Pancreas	6990	(3%)
Ovary	6790	(3%)
Leukaemia	6660	(2%)
Kidney	6000	(2%)
Malignant melanoma	5990	(2%)
Body of uterus	5200	(2%)
Brain and CNS	4400	(2%)
Multiple myeloma	3350	(1%)
Cervix	3200	(1%)
Other	32850	(13%)
Persons: all malignant neoplasms excluding non-melanoma skin cancer (NMSC)	267450	(100%)

CANCER RESEARCH UK



About 5,000 new adult cases x year of primary CNS cancer
No data on metastases

CNS tumour in children

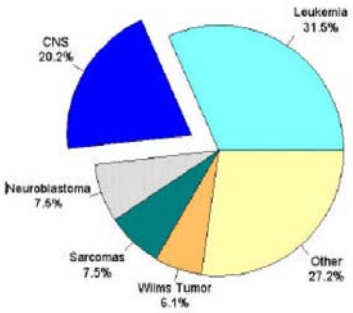
CNS tumours account for about 20% of all neoplasms in children under 15 years

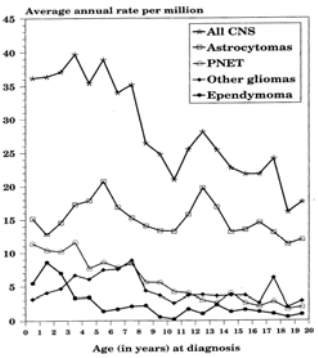
Second most common paediatric cancer after leukaemia - Leading cause of cancer deaths in paediatric oncology patients

Incidence of 3.3 cases per 100,000 in the US - about 2-3,000 children diagnosed annually (CBTRUS)

One third presents before the age of 5, and three-quarters before age 10

Increase in the diagnosis over the last 30 years due to the increased use of MRI imaging and improved imaging technologies





The important of data collection

National Brain Tumour Registry

part of ECRIC: The Eastern Cancer Registration and Information Centre

About NBTR

Welcome to the National Brain and CNS Tumour Registry (NBTR) one of the site-specific cancer registries established to support the National Cancer Intelligence Network. The National Brain and CNS Tumour Registry is run and managed by the Eastern Cancer Registry and Information Centre and is part of the UK Cancer Registries.

The need for the National Brain Tumour Registry is strongly supported by all the professional groups involved in the treatment of these patients and the brain tumour charities representing the patients. It will be a population-based registry for England that will eventually hold all the data items in the new Cancer Dataset which is currently in development.

The information collected by the NBTR covers both benign and malignant primary brain cancer, arising in the central nervous system (CNS), the skull base or pituitary gland. Data is collected under the permissions granted to the English Cancer Registries by the National Information Governance Board. See Legislation.


Dr Jem Rashbass

Staff of about 20 people dedicated to looking at clinical records
Process about thousands of records x year
Supplied by other Cancer Registries & Hospital records
Excellent quality of data

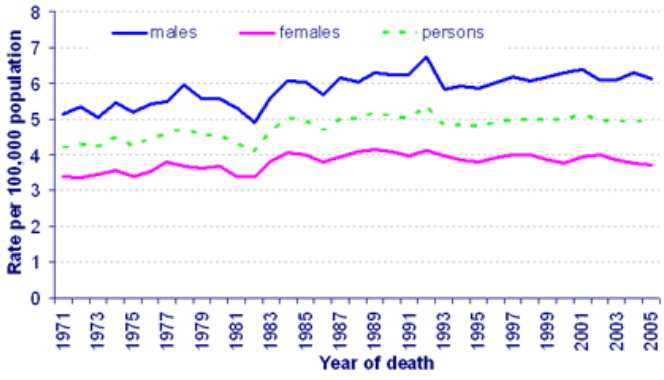
Metastases now registered
Data on mortality, progression & morbidity

A CNS tumour is bad news

- High and severe morbidity
- High mortality
- Severe effects of treatment

Central Nervous System tumours cause over 3,400 deaths each year in the UK.

Figure 2.2: Age standardised (European) mortality rates, brain and other central nervous system tumours, by sex, UK, 1971-2005



Refers mostly to gliomas – little data on benign tumours and metastases

Genetic predisposition to CNS tumours

- ***Neurofibromatosis 2 (22q12)***
- *Tuberous Sclerosis 1 (9q34)*
- *Tuberous Sclerosis 2 (16p13)*
- *Turcot's syndrome (APC 5q21) (PMS2 7p22) (MHL1 Chr3 & 2 Chr2)*
- *Li-Fraumeni (p53 17p13)*
- *Cowden syndrome PTEN (10q23.3)*
- *Gorlin syndrome PTCH1 (9q31)*
- ***Von Hippel Lindau (3q25)***

Clinical/family history
Adequate genetic screening
Surveillance and early diagnosis

Topical Review Article

Neurooncology of Familial Cancer Syndromes

Andreas F. Hottinger, MD, PhD, and Yasmin Khakoo, MD

The majority of tumors of the nervous system are sporadic. However, a subset of patients with tumors and their families are predisposed to developing cancers of the central nervous system and other organs because of a germline mutation. In the last decade, many of the genes responsible for these typically autosomal dominant familial tumor syndromes have been identified. Additionally, our understanding of the mechanisms of carcinogenesis in these syndromes has increased, allowing for more targeted therapies for these patients as well as those with sporadic cancers. Because these patients present a unique set of issues regarding diagnosis and neurooncological management, the most common familial cancer syndromes involving the nervous system are reviewed: neurofibromatosis type 1 and 2, tuberous sclerosis complex, von Hippel Lindau, Li-Fraumeni, Gorlin, and Turcot syndrome.

Keywords: central nervous system tumor; familial cancer syndromes; neurooncology

1953

60th Anniversary Edition of *Cancer*

Supplement to ***Cancer***

Brain Tumor Epidemiology: Consensus From the Brain Tumor Epidemiology Consortium

MOBILE PHONES

Radiofrequency (RF) signals which fall within the microwave region of the electromagnetic spectrum are emitted and received by mobile phone handsets. The energy levels of these waves are insufficient to damage or disrupt cellular DNA. However, public concern over the possible detrimental health effects of using mobile phones have resulted in a number of investigations of possible links with brain tumours.

When assessing the literature on this topic interpretation of a small number of early studies from the USA and Sweden must be cautious. They were conducted on relatively small populations, relating to a time when analogue phones predominated, they had relatively short follow up periods, or they suffered from methodological shortcomings. To date five further reports from substantial well conducted studies in the USA, Finland, and Denmark using different epidemiological methods have observed the same outcome. They found no increased risk of brain cancers or any subtype of brain tumour associated with exposure to mobile phones using measures of the type of phone, duration and frequency of use, and cumulative hours of use. Thus, so far the consensus of evidence is that mobile phone use does not increase the risk of developing a brain tumour. However, with the exponential increase in the ownership and duration of use of these hand held devices it will be important to continue investigations with respect to digital phones, allowing for a latent period of several decades in the development of a tumour.

?

Environmental factors

IONISING RADIATION

Ionising radiation given in therapeutic doses is one of the few known risk factors for brain tumours. The now discontinued low dose radiation treatment of tinea capitis and skin disorders in children increased the risk of brain tumours well into adulthood as does radiotherapy for childhood cancers and leukaemia. Survivors of the atomic bomb in Hiroshima have increased risks of meningioma in proportion to their level of exposure. In utero exposure does not appear to affect the risk for the developing fetus. Diagnostic *x* rays do not appear to be linked to gliomas, but full mouth dental *x* rays have been associated with meningiomas in a small number of studies.

NEW INTEREST IN COMORBIDITIES

- **Association between CNS and non-CNS cancer – possible but not proven –** *?role of p53*
- **Inverse association between neurodegenerative conditions (Alzheimer's;** *?Parkinson's Disease***) and CNS cancer**
- **No clear association between neuroinflammatory conditions (mainly MS) and CNS cancer**
- **Low risk of CNS cancer in patients with allergies – ?role of IgE**
- **Possible role of viral infection (CMV & HHV6)**

CLASSIFICATION OF CNS TUMOURS

- **PRIMARY** *(Any tumour that only occurs in the CNS)*
- **SECONDARY** *(Metastases)*

PRIMARY

EXTRA-AXIAL (COVERINGS)

Tumours of bone, cranial soft tissue, meninges and nerves

INTRA-AXIAL (PARENCHYMA)

Derived from the major normal cell populations of the CNS (*astrocytes, oligodendrocytes, neurons, ependyma***)**

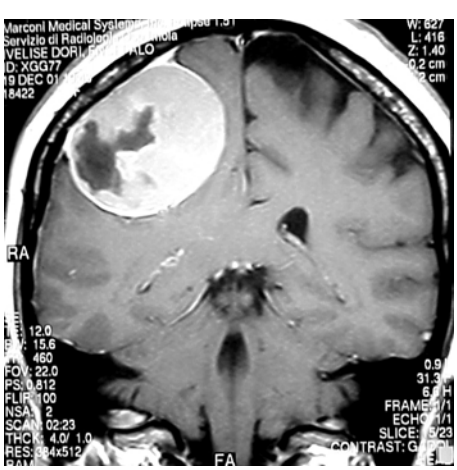
Derived from other cells types (*lymphocytes, vessels, connective tissue) (same name as extra-CNS tumours***)**

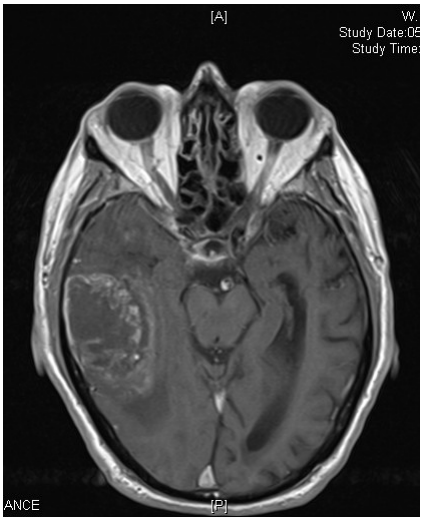
Derived from embryonal (?stem) cells

PRAGMATIC BUT HELPFUL DISTINCTION

- ***Compressive lesions***
- ***Marginally infiltrative***
- ***Diffusely infiltrative***

What is the intra-axial one?

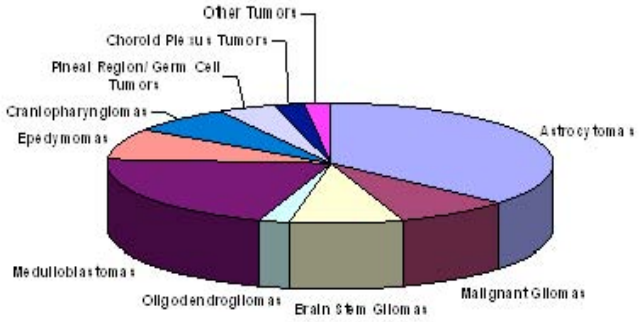




SITE AND AGE

- Brain tumours have certain predilection for or only occur in some sites of the CNS
- Some brain tumours are very rare or do not occur at all in certain ages

•About 60% paediatric CNS tumours occur in posterior fossa (lower brain stem and cerebellum)
•Hemispheric WHO grade I and I astrocytomas more common than high grade (Oligodendrogliomas are exceptional)
•Meningiomas are very rare
•Choroid plexus carcinomas and PNET typically under 2 years



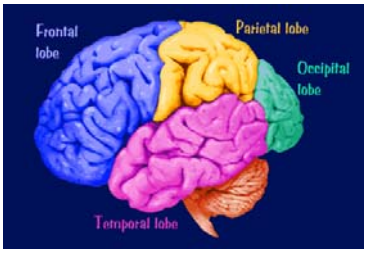
SIGNS AND SYMPTOMS ARE OFTEN NOT SPECIFIC

Supratentorial tumours

- **Focal neurological deficit**
- **Seizure (CAUSE STILL UNCLEAR)**
- **Headache**
- **Change mental status**

Subtentorial

- **Cerebellar Ataxia**
- **Long tract signs**
- **Cranial nerve palsy**



Signs and symptoms can be subtle

They can be underestimated

Non-neoplastic lesions can mimic CNS cancer

Collecting the correct history from patients is important

Brain tumours in children

Signs and Symptoms

- a seizure not related to high fever
- staring, repetitive automatic movements
- persistent vomiting without any known cause (projectile vomiting), nausea
- progressive weakness or clumsiness; neck tilt, squint
- walking, balance problems
- precocious puberty; growth retardation
- sleep apnea
- vision problems
- headache, especially that wakes the child up at night or is early in the morning
- pain, especially back pain, which should be taken seriously in a child
- changes in personality, irritability, listlessness
- excessive thirst and excessive urination (rare, if the tumor is pressing against the pituitary)

What To Do

Take your child to the doctor. The doctor should listen carefully to your description of your child's behavior and ask you pertinent questions. If symptoms warrant, vision and other tests should be performed. The tumor probably will not be felt. The doctor should order tests.

- MRI
- CT scan

Both of these tests are expensive, and therefore doctors will likely not order them until they rule out all other possibilities. As a parent, you may need to be quite insistent that they be performed. Any brain tumor will show up on an MRI; the CT scan misses some tumors.

NEUROIMAGING

- **CT-SCAN**
- **MR-SCAN**
- **PHYSIOLOGICAL MRI**
- **FUNCTIONAL MRI**
- **TRACTOGRAPHY**
- **SPECTROSCOPY (metabolism) (useful as ancillary technique)**
- **PET-SCAN (traces compounds - research)**

- **Assess tumour type**
- **Guide resection**
- **Guide biopsies**
- **Identify transformation**
- **Assess response to treatment**
- **Assess recurrences**

MRI in treatment of adult gliomas

John W Henson, Paola Gaviani, R Gilberto Gonzalez

Lancet Oncol 2005; 6: 167–75

Division of Neuroradiology and Steven E and Catherine Pappas Center for Neuro-oncology (J W Henson MD, P Gaviani MD); and Division of Neuroradiology (R G Gonzalez MD).

Diffuse astrocytomas of the adult cerebral hemispheres are unique among tumours in human beings in the extent to which their imaging features are related to histopathological characteristics and clinical behaviour. However, understanding is still restricted about the value of imaging features in the measurement of response and of progression in these tumours. The present approach used in clinical trials, which consists of an anatomical

NEUROIMAGING TO MONITOR TREATMENT

Efficacy of radio / chemotherapy

Distinguish between progression and pseudoprogression

Distinguish between progression and radiation induces changes

Feasibility of reintervention

VOLUME 28 · NUMBER 11 · APRIL 10 2010

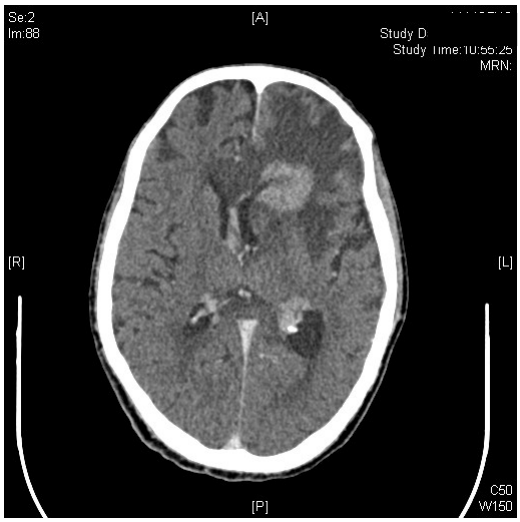
JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

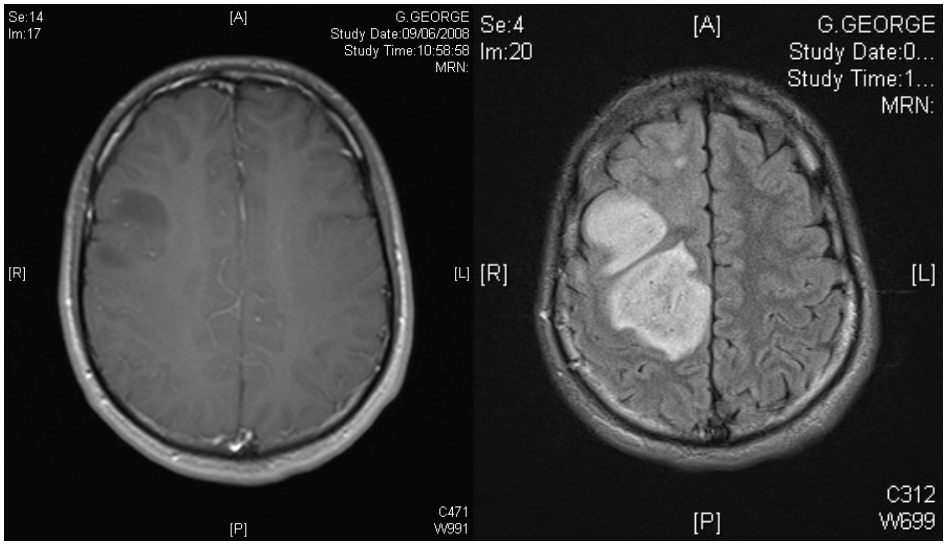
Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group

Patrick Y. Wen, David R. Macdonald, David A. Reardon, Timothy F. Cloughesy, A. Gregory Sorensen, Evanthia Galanis, John DeGroot, Wolfgang Wick, Mark R. Gilbert, Andrew B. Lassman, Christina Tsien, Tom Mikkelsen, Eric T. Wong, Marc C. Chamberlain, Roger Stupp, Kathleen R. Lamborn, Michael A. Vogelbaum, Martin J. van den Bent, and Susan M. Chang

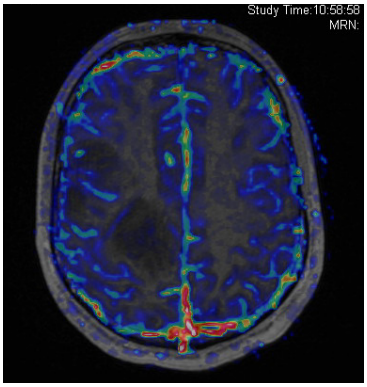
From the Center for Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, Division of Neurology, Brigham and Women's Hospital, Department of Radiology, Massachusetts General Hospital, Brain Tumor Center, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA; Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC; Neuro-Oncology Program

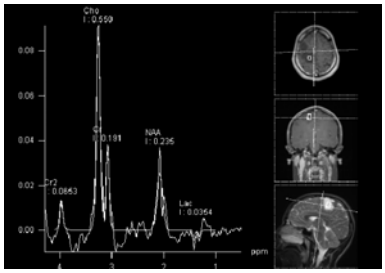


Structural imaging – MRI (T1, T2, contrast, flair)

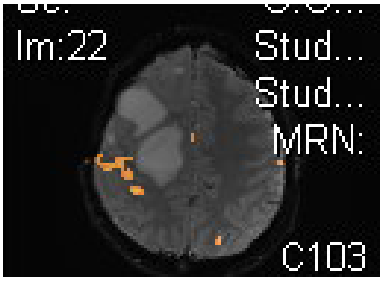


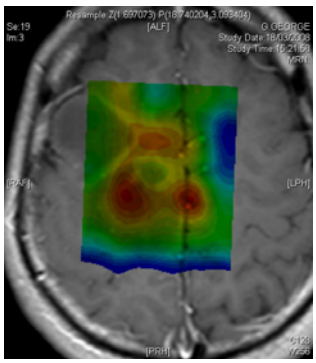
Physiological

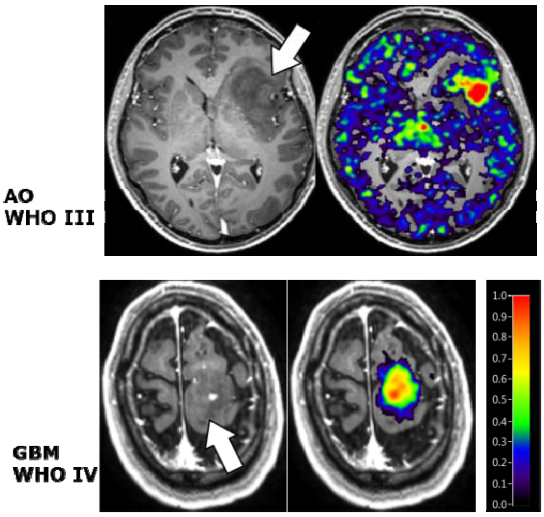




Functional







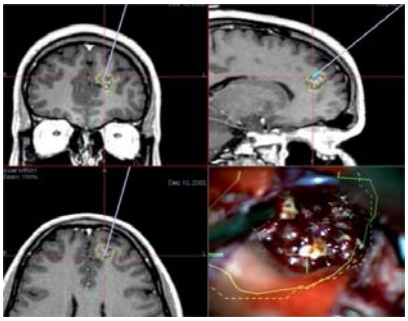
Molecular Imaging (PET-scan)

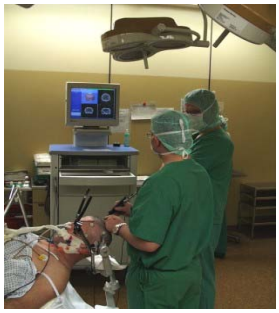
Use of radioactive tracers to target molecules of interest

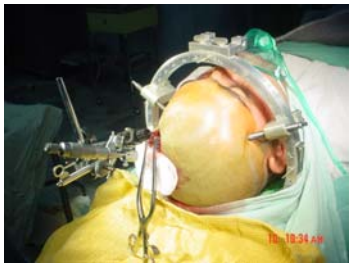
NEUROSURGERY

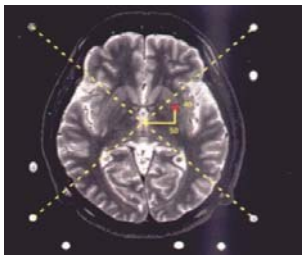
- **Stereotactic biopsy – inoperable tumours (about 0.5cm tissue)**
- **Open biopsy – inoperable but approachable tumours (about 1cm)**
- **Craniotomy for debulking (as much as tissue as possible)**

Stereotactic Biopsy - Neuronavigation

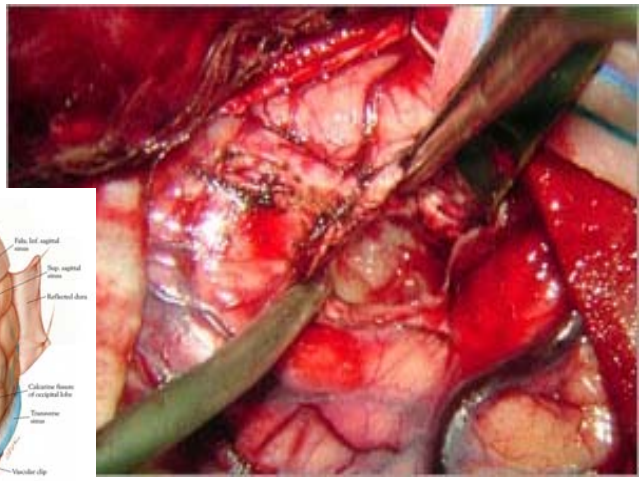


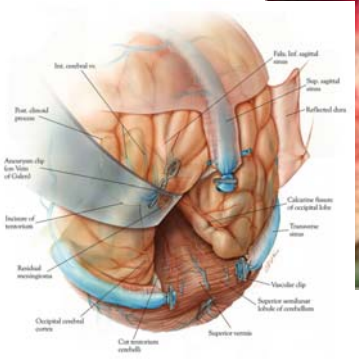






Debulking or open biopsy



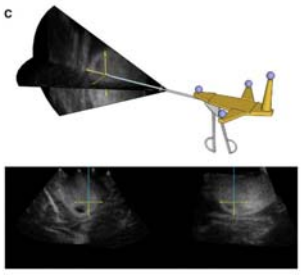


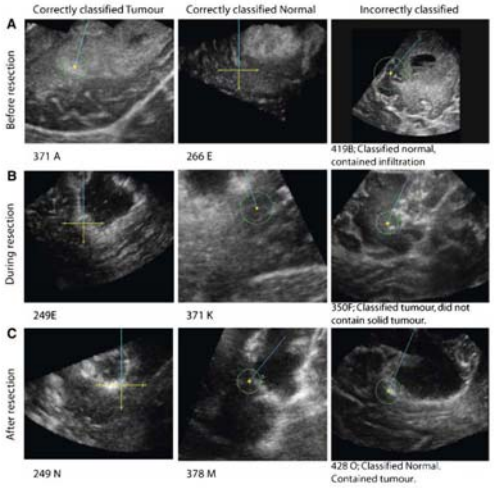
Acta Neurochir (Wien) (2008) 150:1033–1042
DOI 10.1007/s00701-008-0017-3

CLINICAL ARTICLE

Comparison of navigated 3D ultrasound findings with histopathology in subsequent phases of glioblastoma resection

Ola Morten Rygh · Tormod Selbekk · Sverre Helge Torp · Stian Lydersen · Toril Anita Nagelhus Hernes · Geirmund Unsgaard





"Maximally safe surgery aims to obtain an extensive excision with minimal damage to the patient"

REVIEW

Glioma Extent of Resection and Its Impact on Patient Outcome

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Reprint requests:
Nader Sanai, M.D., Department of Neurological Surgery, University of California at San Francisco, 300 Parnassus Avenue, M-779, Box 0112, San Francisco, CA 94143-0112.

OBJECTIVE: There is still no general consensus in the literature regarding the role of extent of glioma resection in improving patient outcome. Although the importance of resection in obtaining tissue diagnosis and alleviating symptoms is clear, a lack of Class I evidence prevents similar certainty in assessing the influence of extent of resection.

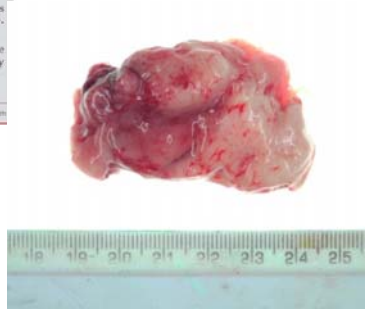
METHODS: We reviewed every major clinical publication since 1990 on the role of extent of resection in glioma outcome.

RESULTS: Twenty-eight high-grade glioma articles and 10 low-grade glioma articles were examined in terms of quality of evidence, expected extent of resection, and survival benefit.

CONCLUSION: Despite persistent limitations in the quality of data, mounting evidence suggests that more extensive surgical resection is associated with longer life expectancy for both low- and high-grade gliomas.

KEY WORDS: Extent of resection, High-grade glioma, Low-grade glioma, Tumor volume

Neurosurgery 62:753–764, 2008 DOI: 10.1227/01.NEU.0000316766.20846.8D www.neurosurgery-online.com



POST-OPERATIVE TREATMENT

- Conventional fractionated radiotherapy
- Gamma knife (common for metastases)
- Proton bean
- Steroids (usually pre-op)
- Chemotherapy (Temozolomide)
- Anti-angiogenic factors (Avastin)
- Drugs to control symptoms (epilepsy)
- Vaccines

2010: neuro-oncology is moving!

Roger Stupp[a] and Michael Weller[b]

[a]Department of Neurosurgery, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne and [b]Department of Neurology, University Hospital Zurich, Zurich, Switzerland

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Current Opinion in Neurology 2010, 23:553–555

The first randomized phase III trial in patients with primary central nervous system lymphoma was reported for the first time at the 2010 annual meeting of the American Society of Clinical Oncology, and concluded that the omission of whole brain radiotherapy from first-line treatment does not compromise survival. Two randomized trials investigated tailored treatment strategies for elderly patients with glioma and reached opposite conclusions. Novel treatment approaches in recurrent glioblastoma with alternating tumour treatment fields (NovoTTF), or antiangiogenic agents (cilengitide and bevacizumab) have been reported and updated. The role of vascular endothelial growth factor-inhibiting strategies in the management of recurrent glioma remains unclear and controversial.

Curr Opin Neurol 23:553–555

1350-7540

Paradigm shift

Molecular Heterogeneity in Glioblastoma: Therapeutic Opportunities and Challenges

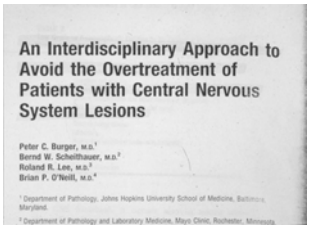
M. Kelly Nicholas,[a] Rimas V. Lukas,[a] Steven Chmura,[b] Bakhtiar Yamini,[c] Maciej Lesniak,[c] and Peter Pytel[d]

Glioblastoma (GBM) has been recognized as a clinical and pathologic entity for more than a century. Throughout its history, its cells of origin have been in question. Its behavior is aggressive and despite decades of effort, median survival is just beginning to improve. Surgical techniques and radiotherapy schemas continue to be refined, but the most recent progress has been achieved through improved medical therapies. These are the result of both pharmacological advances and a deeper understanding of the biological characteristics of GBM. Due to a combination of its complex phenotype and organ-specific clinical manifestations, efforts to refine GBM treatment with targeted therapies largely have been frustrated. In this review, we discuss recent attempts to exploit new molecular insights, consider the reasons for slow progress in developing better treatments, and examine future therapeutic options.
Semin Oncol 38:243-253.

"magic bullets"

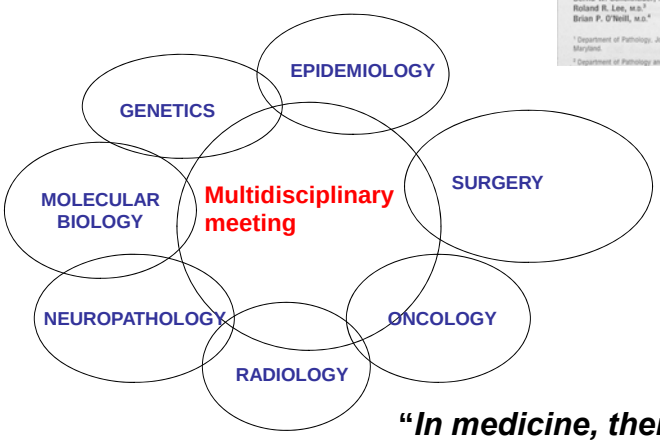
"individualised treatment"

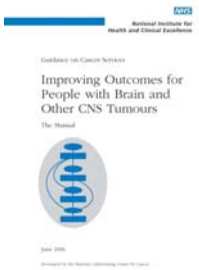
Decision making pathway


An Interdisciplinary Approach to Avoid the Overtreatment of Patients with Central Nervous System Lesions

Peter C. Burger, M.D.[1]
Bernd W. Scheithauer, M.D.[2]
Roland R. Lee, M.D.[3]
Brian P. O'Neill, M.D.[4]

[1] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland.
[2] Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, Minnesota.




NHS
National Institute for Health and Clinical Excellence

Guidance on Cancer Services

Improving Outcomes for People with Brain and Other CNS Tumours

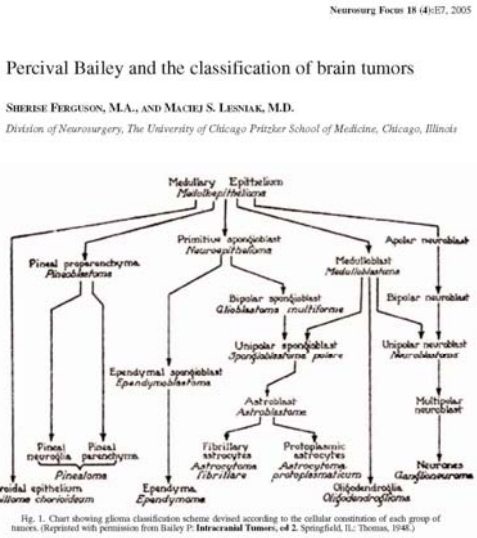
The Manual

June 2006

Developed by the National Collaborating Centre for Cancer

"*In medicine, there are not stupid questions but there are silly mistakes*" (Film: School of Medicine)

How do we name a CNS tumour?


Neurosurg Focus 18 (4):E7, 2005

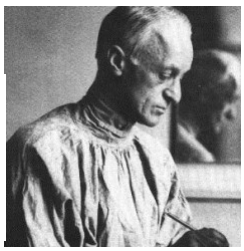
Percival Bailey and the classification of brain tumors

SHERISE FERGUSON, M.A., AND MACIEJ S. LESNIAK, M.D.

Division of Neurosurgery, The University of Chicago Pritzker School of Medicine, Chicago, Illinois

Medullary Epithelium
Medulloepithelioma
Primitive spongioblast
Neuroepithelioma
Apolar neuroblast
Pineal parenchyma
Pineoblastoma
Medulloblast
Medulloblastoma
Bipolar spongioblast
Gioblastoma multiforme
Bipolar neuroblast
Unipolar spongioblast
Spongioblastoma polare
Unipolar neuroblast
Neuroblastoma
Ependymal spongioblast
Ependymoblastoma
Astroblast
Astroblastoma
Multipolar neuroblast
Pineal neuroglia
Pineal parenchyma
Pinealoma
Fibrillary astrocytes
Astrocytoma fibrillare
Protoplasmic astrocytes
Astrocytoma protoplasmaticum
Neurones
Ganglioneuroma
Choroidal epithelium
Papilloma choroideum
Ependyma
Ependymoma
Oligodendroglia
Oligodendroglioma

Fig. 1. Chart showing glioma classification scheme devised according to the cellular constitution of each group of tumors. (Reprinted with permission from Bailey P: **Intracranial Tumors**, ed 2. Springfield, IL: Thomas, 1948.)



H Cushing ***P Bailey***

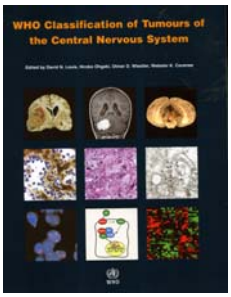
Names derive from putative cell of origin

Differentiation

Descriptive

WHO classification of CNS tumours

- Neuroepithelial tumors.
  - Glial tumors.
    - Astrocytic tumors.
      - Pilocytic astrocytoma.
      - Diffuse astrocytoma (including fibrillary, protoplasmic, and gemistocytic).
      - Anaplastic astrocytoma.
      - Glioblastoma (including giant cell glioblastoma, and gliosarcoma).
      - Pleomorphic xanthoastrocytoma.
      - Subependymal giant cell astrocytoma.
    - Oligodendroglial tumors.
      - Oligodendroglioma.
      - Anaplastic oligodendroglioma.
    - Mixed gliomas.
      - Oligoastrocytoma.
      - Anaplastic oligoastrocytoma.
    - Ependymal tumors.
      - Myxopapillary ependymoma.
      - Subependymoma.
      - Ependymoma (including cellular, papillary, clear cell, and tanycytic).
      - Anaplastic ependymoma.
    - Neuroepithelial tumors of uncertain origin.
      - Astroblastoma.
      - Chordoid glioma of the third ventricle.
      - Gliomatosis cerebri.



    - Neuronal and mixed neuronal-glial tumors (some glial component may be present).
      - Gangliocytoma.
      - Ganglioglioma.
      - Desmoplastic infantile astrocytoma/ganglioglioma.
      - Dysembryoplastic neuroepithelial tumor.
      - Central neurocytoma.
      - Cerebellar liponeurocytoma.
      - Paraganglioma.
    - Nonglial tumors.
      - Embryonal tumors.
        - Ependymoblastoma.
        - Medulloblastoma.
        - Supratentorial primitive neuroectodermal tumor (PNET).
      - Choroid plexus tumors.
        - Choroid plexus papilloma.
        - Choroid plexus carcinoma.
      - Pineal parenchymal tumors.
        - Pineoblastoma.
        - Pineocytoma.
        - Pineal parenchymal tumor of intermediate differentiation.
- Meningeal tumors.
  - Meningioma.
  - Hemangiopericytoma.
  - Melanocytic lesion.
- Germ cell tumors.
  - Germinoma.
  - Embryonal carcinoma.
  - Yolk-sac tumor (endodermal-sinus tumor).
  - Choriocarcinoma.
  - Teratoma.
  - Mixed germ cell tumor.
- Tumors of the sellar region.
  - Pituitary adenoma. (Refer to the PDQ summary on Pituitary Tumor Treatment for more information.)
  - Pituitary carcinoma.
  - Craniopharyngioma.
- Tumors of uncertain histogenesis.
  - Capillary hemangioblastoma.
- Primary CNS lymphoma. (Refer to the PDQ summary on Primary CNS Lymphoma Treatment for more information.)
- Tumors of peripheral nerves that affect the CNS.
  - Schwannoma.
- Metastatic tumors.

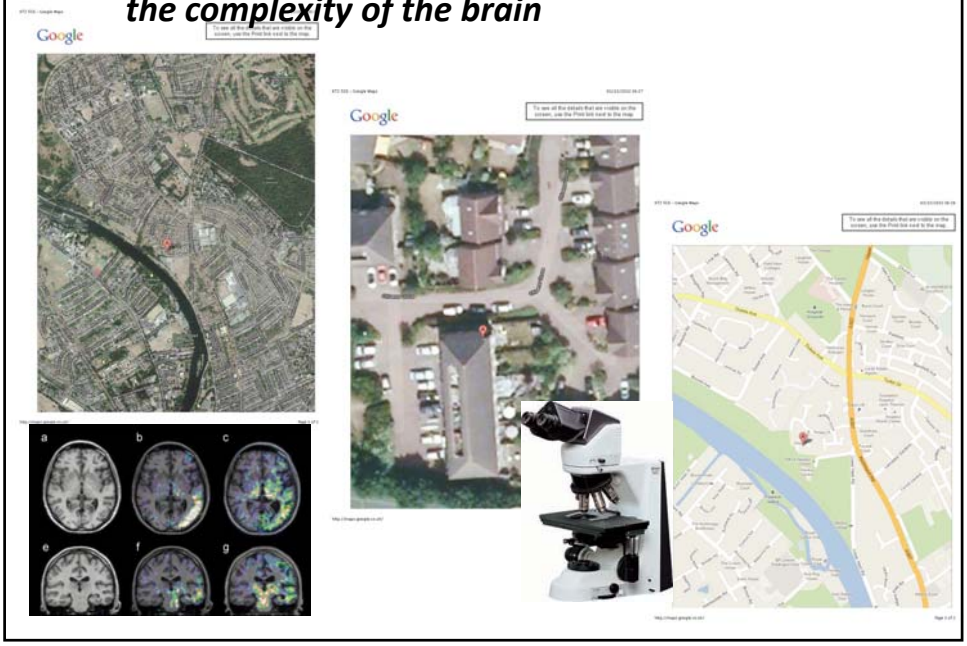
More and more variant are documented

Fibrillary astrocytoma
Gemistocytic astrocytoma
Granular cell astrocytoma
Astroblastoma
Angiocentric glioma
Pleormorphic xanthoastrocytoma
Pilocytic astrocytoma
Pilomyxoid astrocytoma
Anaplastic pilocytic astroctyoma

Giant cell GBM
Gliosarcoma
Small cell GBM
GBM with PNET component
GBM with adipocytic differentiation
GBM with oligo-like component
GBM with neuronal differentiation
GBM with signed-ring cells

Oigodendroglioma
Oligodendroglioma with neurocytic features
Oligoastrocytoma
Oligodendrosarcoma

The microscope is a great tool to help unravelling the complexity of the brain



Brain Pathology ISSN 1015-6305

CONTROVERSIES IN NEUROPATHOLOGY

The 2007 WHO Classification of Tumors of the Nervous System: Controversies in Surgical Neuropathology

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Keywords
brain tumors, classification, controversial issues, pathology, World Health Organization.

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doi:10.1111/j.1750-3639.2008.00179.x

Abstract

Controversy surrounds the recent 2007 WHO Classification of Tumours of the Nervous System. A number of nosologic issues remain to be resolved, some a reflection of conceptual disagreement, others the result of inadequate data to permit their definitive resolution. Among these and discussed herein are (i) the nosologic place of highly anaplastic oligoastrocytic tumors, (ii) the forms and significance of microvascular changes in high-grade gliomas, (iii) the makeup of the glioneuronal tumors category, (iv) the subclassification of pineal parenchymal tumors of intermediate type, and (v) the classification of principle forms of mesenchymal neoplasms, specifically hemangiopericytoma and solitary fibrous tumor. These issues and others are the substance of this and an upcoming companion article.

Brain Pathology ISSN 1015-6305

REVIEW ARTICLE

The Evolution of Our Understanding on Glioma

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Keywords
glioma, history, review.

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Received 13 November 2007; accepted 16 November 2007.

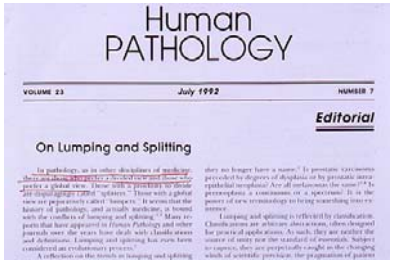
doi:10.1111/j.1750-3639.2008.00136.x

Abstract

The description of neuroglia by Virchow in 1848 may be considered the starting point of our understanding of primary brain tumors. At the beginning of the 20th century, surgical removal of primary brain tumors became possible, and therefore, tissue for microscopic analysis and clinical data on survival became available. During this time, research on gliomas beyond improving surgical procedures focused on their classification. The classification schemes developed emphasized parameters for sorting tumors with regard to (i) cytological aspects; (ii) presumed tumor cell origin; (iii) histological appearance of the tissue; or (iv) clinical outcome. Over the years, experimental studies have greatly improved our knowledge on gliomas. Gliomas induced by viruses, chemicals, radiation, transgenes and knock-out technology contributed to the understanding of their pathogenesis and still serve as preclinical models for the testing of novel therapies. Recent advances in developmental neurobiology and the identification of stem cells provided new insights into the origin of brain tumors and the molecular mechanisms of tumor formation. This review briefly compiles the evolution of our concepts on gliomas, focusing on the latest developments.

Perhaps we went a bit too far

Need of a clarification between neuropathologists



Human PATHOLOGY

VOLUME 23 — July 1992 — NUMBER 7

Editorial

On Lumping and Splitting

The concept of grading

Note: Grading comes after defining the histotype

There is no staging system for CNS tumours (*extension of the disease is not considered – no metastasis***)**

ESSENTIAL CONCEPTS

- The grading system is an attempt of stratifying tumours by outcome
- It is based on their natural history
- It is based on histopathological criteria (essentially proliferative activity)
- Grading does not consider tumour morbidity (difference between “biological” and “clinical” outcome)
- Evolving concept

Brain Pathology ISSN 1015-6305

HISTORICAL PERSPECTIVE

Development of the WHO Classification of Tumors of the Central Nervous System: A Historical Perspective

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Department of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, Mi.

Keywords
brain tumors, classification, historical development, World Health Organization.

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Received 23 April 2008; accepted 29 May 2008.

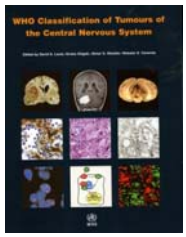
doi:10.1111/j.1750-3639.2008.00192.x

Abstract

The classification of brain tumors has undergone numerous changes over the past half century. The World Health Organization has played a key role in the effort. Four versions of its *Classification of Tumours of the Central Nervous System* have been published. The present work chronicles their progress, placing emphasis on the historical context of the earliest effort.

Fist WHO working group in Cologne - 1976

ESSENTIAL CONCEPTS

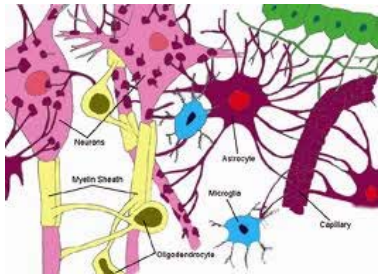


- Long-term survival / cured – Grade I
- Cause death in more than 5 yrs – Grade II
- Cause death within 5 yrs – Grade III
- Cause death within 6 mo-1yr – Grade IV

- Avoid overtreatment!

- Two to Four tier system
- Result of a consensus meeting
- Not universal
- Relates to histotype
- Some tumour types have only one possible grade
- Limited by size of biopsies
- Reliable only for diffuse astrocytomas and meningiomas
- New insight from molecular / genetics

CNS tumours are heterogenous



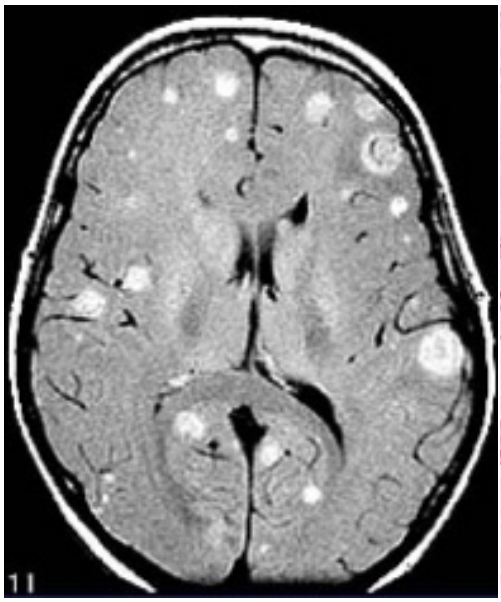
- Several types
- Intertumoural heterogeneity (same histotype but different genetics / molecular pathways)
- Intratumoural heterogeneity
- Heterogeneity of microenvironment

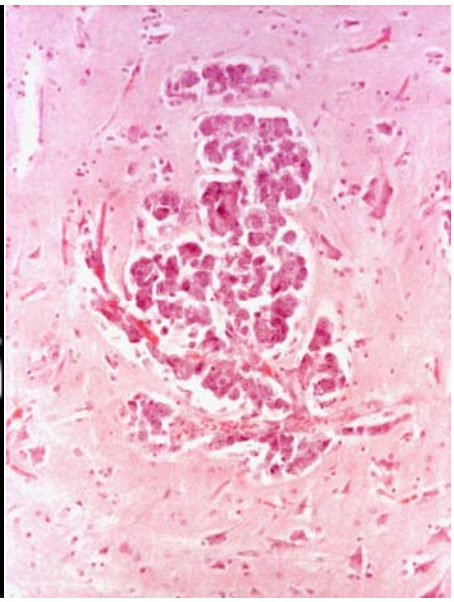
- ***Several levels of complexity***

METASTASES TO CNS

- Commonest CNS tumour
- Increasing incidence due to longer survival
- Any site, including meninges and bone
- Any tumour can potentially give CNS metastases
- Most frequent tumours are: Lung ca, melanoma, breast ca, renal ca and colon ca.
- May be the first presentation of the disease
- No grading

- New research interest in CNS metastases





Neurosurg Focus 22 (3):E1, 2007

Molecular events of brain metastasis

JUSTIN G. SANTARELLI, M.D., VAHE SARKISSIAN, M.D., LEWIS C. HOU, M.D., ANAND VEERAVAGU, B.S., AND VICTOR TSE, M.D., PH.D.
Department of Neurosurgery, Stanford University School of Medicine, Stanford, California

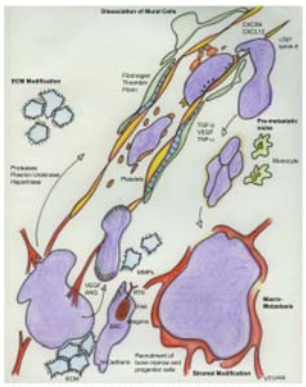
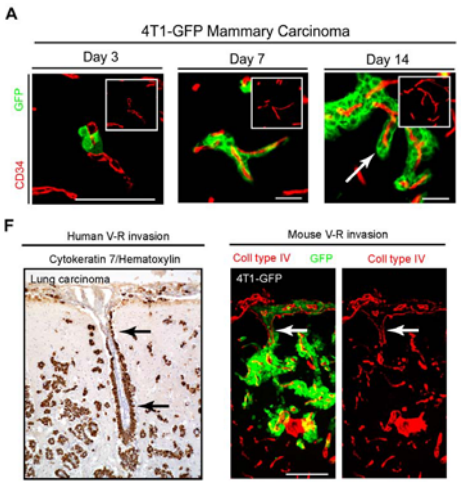


FIG. 1. Schematic depicting the major events and participating molecules in the process of metastasis: invasion; epithelial-mesenchymal transition; circulation shielding; anchoring and extravasation; dormancy and macrometastasis. ANG = angiopoi; ECM = extracellular matrix; RTK = receptor tyrosine kinase; TGF = transforming growth factor.

OPEN ACCESS Freely available online PLoS one

The Vascular Basement Membrane as "Soil" in Brain Metastasis

W. Shawn Carbonell[1]*, Olaf Ansorge[2], Nicola Sibson[1], Ruth Muschel[1]
1 Gray Institute for Radiation Oncology and Biology, University of Oxford, Oxford, United Kingdom, 2 Department of Neuropathology, University of Oxford, Oxford, United Kingdom



CCR FOCUS

CNS Metastasis: An Old Problem in a New Guise

Jeanny B. Aragon-Ching and Jo Anne Zujewski

Table 1. Therapeutic approaches to CNS disease

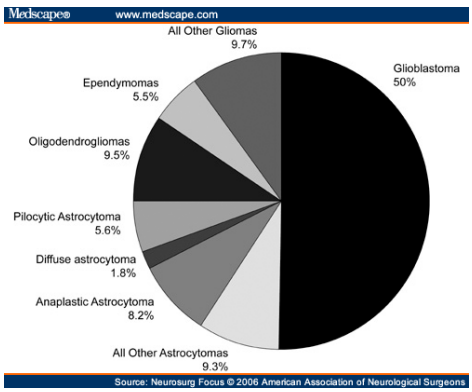
- Surgical excision
- Radiosurgery
- Radiation sensitizers
- Cytotoxic chemotherapy
- Targeted therapies
- Novel drug delivery techniques

Table 2. Critical areas for research

- Preclinical models for site-specific metastasis
- Molecular profiling of tumors with site-specific metastases
- Host effects, including pharmacogenomics
- Effective anticancer strategies for sanctuary sites
- Assays to detect drug accumulation in CNS or other sanctuary site
- Therapeutic strategies for treatment of micrometastatic disease (prevention of CNS metastasis)
- Strategies to avoid long-term CNS complications of therapy (systemic and CNS directed)
- Behavioral tools for anticipating/measuring long-term neurocognitive defects
- Quality of life assessment of long-term effect of systemic and CNS-directed therapies

Break

GLIAL TUMOURS: 75% primary intrinsic tumours in adults



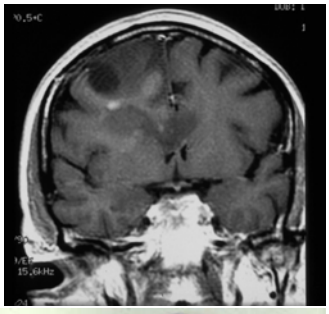
Diffuse infiltration

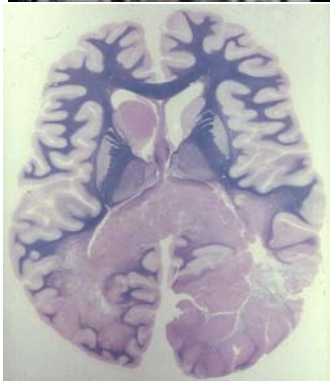
- Fibrillary, gemistocytic astrocytoma (all grades)
- Oligodendroglioma (all grades)
- Mixed oligo-astrocytoma

Compressive margins

- Pilocytic astrocytoma
- Pleomorphic xantoastrocytoma
- Subependymal astrocytoma

- Ganglioglioma
- Ependymoma





Infiltrative growth makes resection impossible and post-op treatment very difficult

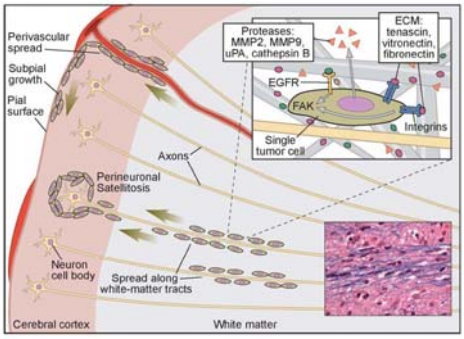


Figure 2
Invasion. Malignant glioma cells show preferential invasion along white-matter tracts, around neurons and blood vessels, and in the subpial region. The photomicrograph (*lower right corner*; Luxol fast blue H&E stain, 400X) illustrates individual elongated, hyperchromatic tumor nuclei oriented along myelinated axons (which stain bright blue with the Luxol fast blue stain). The inset at the top right illustrates molecular events relating to the invasion of single cells: elaboration of proteases such as matrix metalloproteinases MMP2 and MMP9, urokinase-type plasminogen activator (uPA), and cathepsin B; expression of integrins that interact with extracellular matrix (ECM) components such as tenascin, vitronectin, and fibronectin that are themselves expressed by tumor cells; and activation of focal adhesion kinase (FAK)-mediated cellular signaling pathways via epidermal growth factor receptor (EGFR) or integrin signaling (*see text*).

" INFILTRATIVE" ASTROCYTOMAS

- Any site of the CNS – cerebral hemispheres are the far more common sites

- Account for about 80% of gliomas
- Occur more commonly between 30-40 years
- WHO grade II to IV
- De novo grade IV (glioblastoma)
- WHO Grade II progress to higher grade in 5-7 years to become eventually GBM

- 70% of low grades have p53 mutations
- 85% mutations of IDH1

- De novo GBM have complex genotype

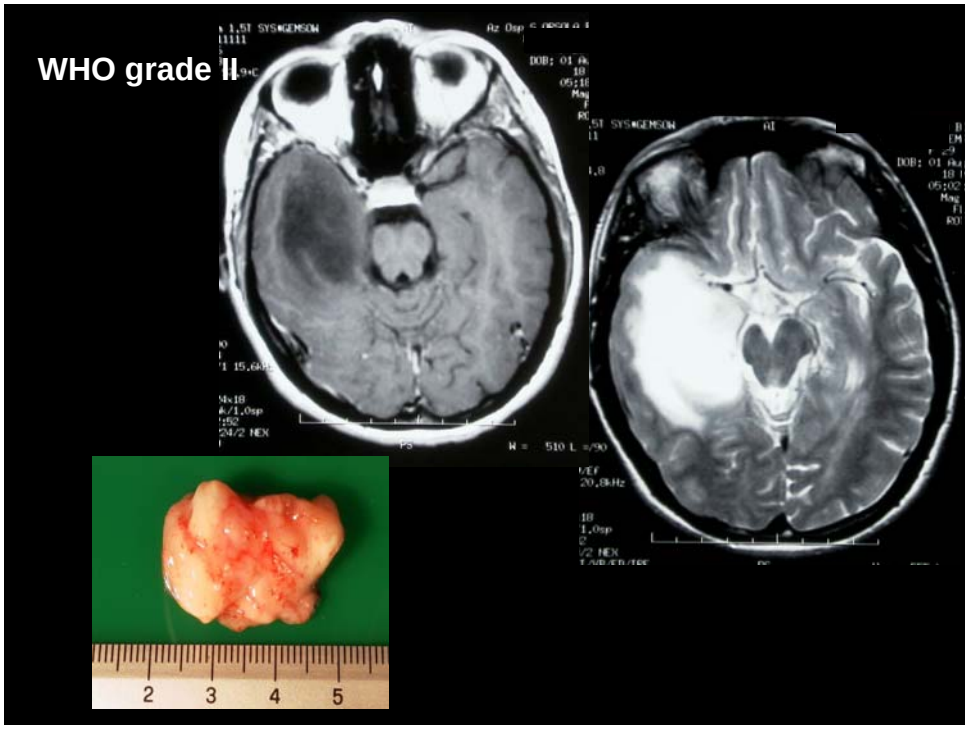
TABLE 1
WHO Classification of Tumors of the Nervo

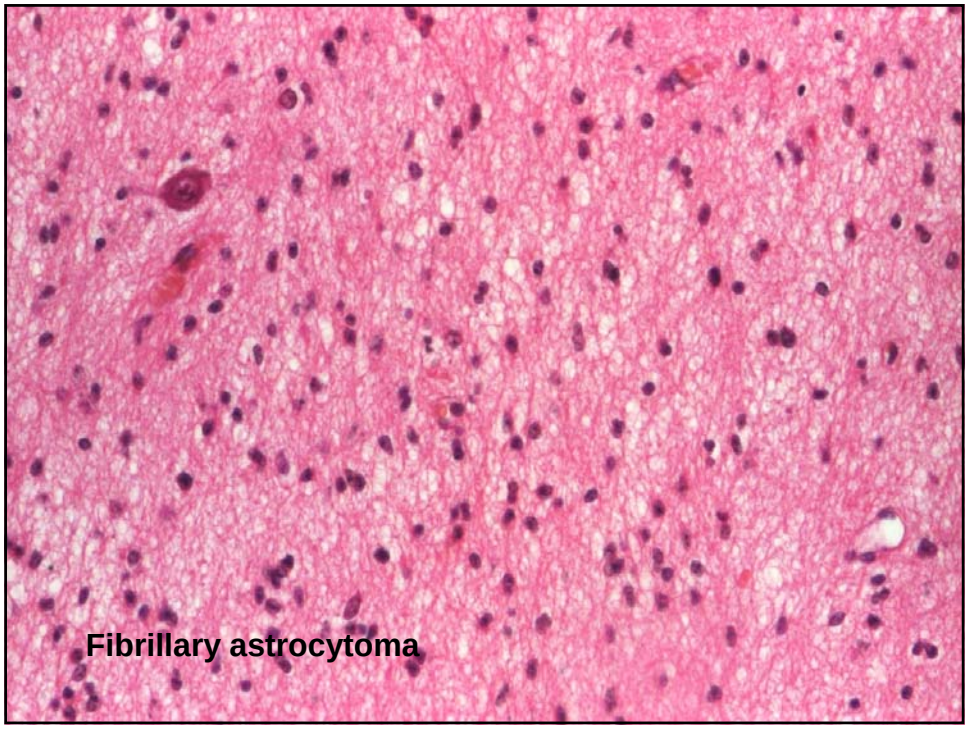
Tumors of Neuroepithelial Tissue

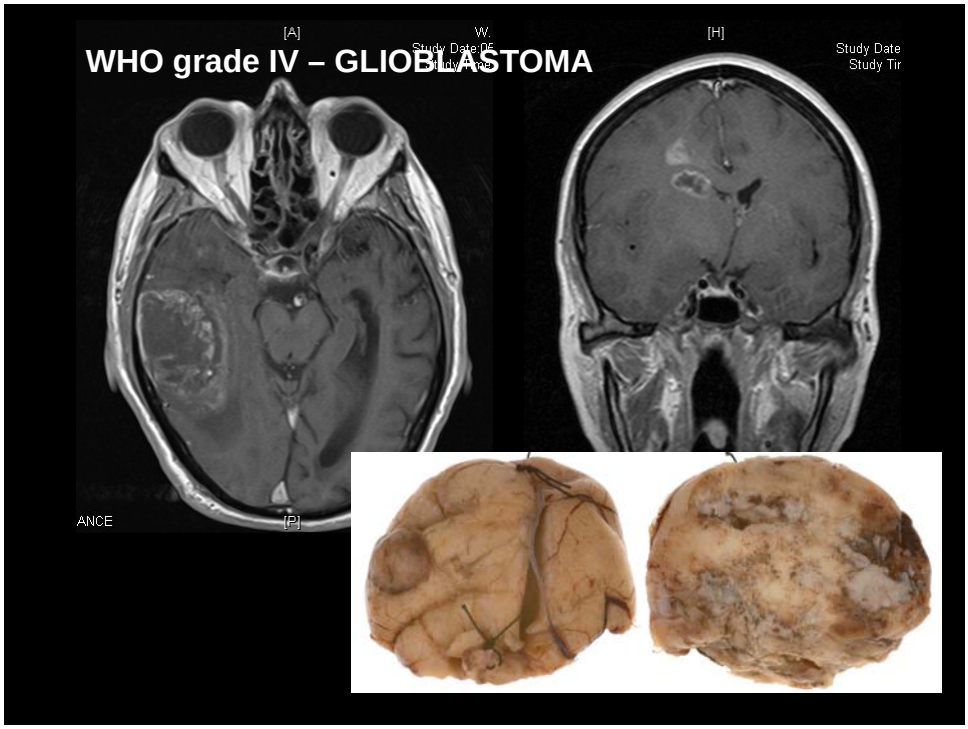
Astrocytic tumors
Diffuse astrocytoma
Fibrillary astrocytoma
Protoplasmic astrocytoma
Gemistocytic astrocytoma
Anaplastic astrocytoma
Glioblastoma
Giant cell glioblastoma
Gliosarcoma

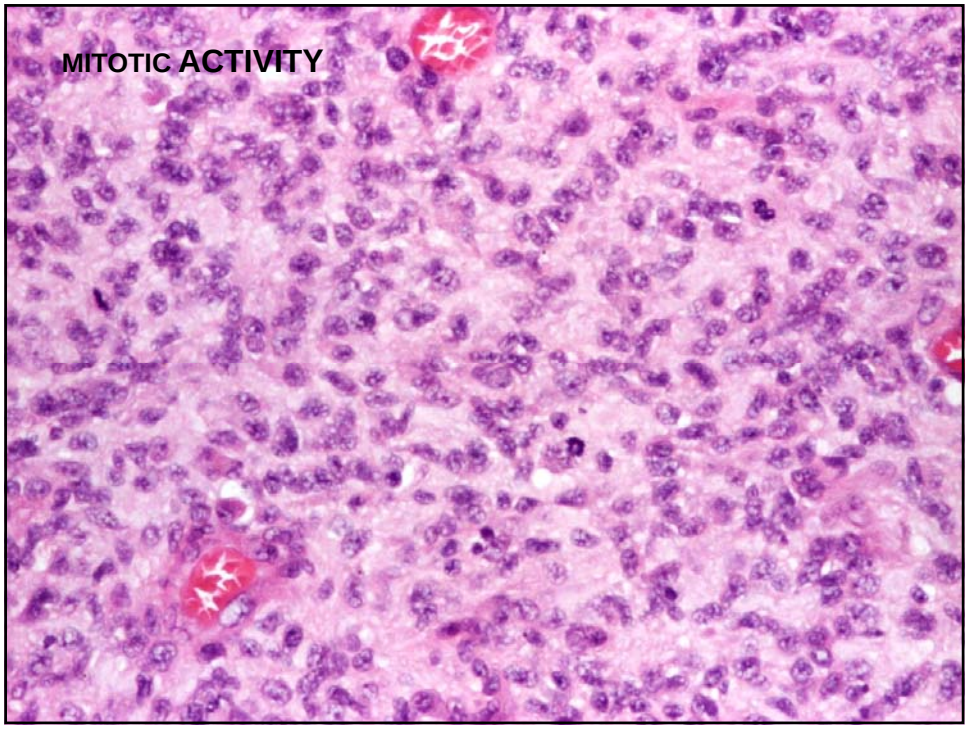
GRADING ASTROCYTIC TUMOURS

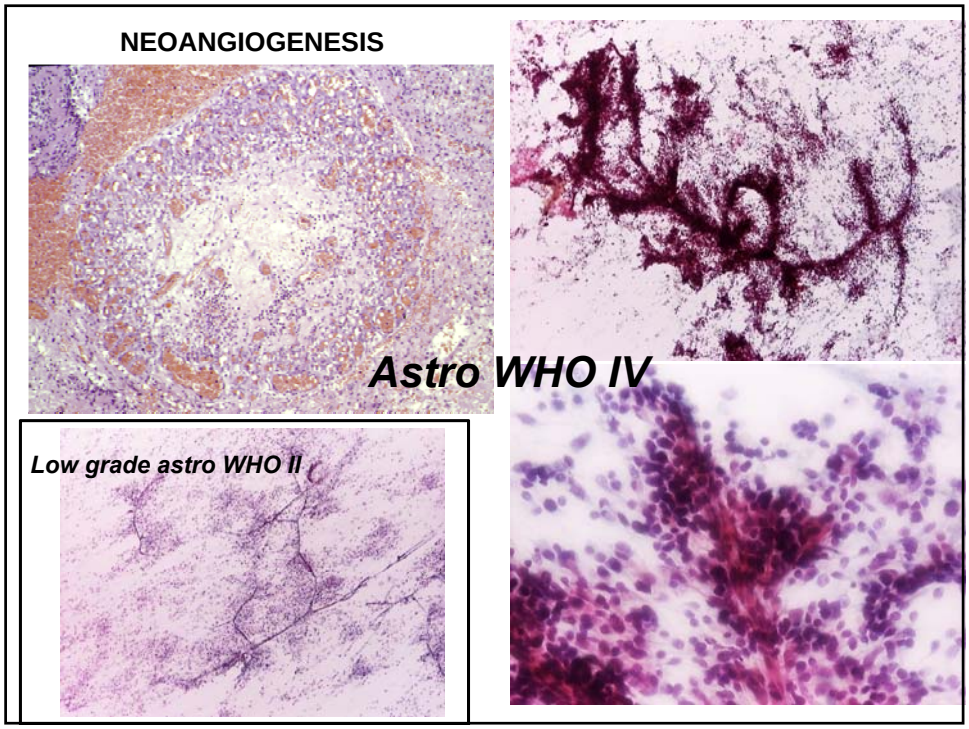
- *CELLULARITY*
- *NUCLEAR ATYPIA* *Grade II to III*
- **MITOSES**
- **==========**
- **ENDOTHELIAL PROLIFERATION**
- **VASCULAR PROLIFERATION**
- **NECROSIS WITH PALISADING FEATURES**
- *Grade III to IV*

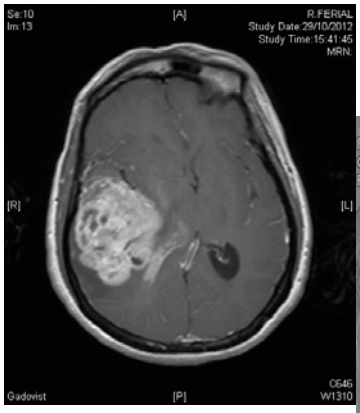



Fibrillary astrocytoma


WHO grade IV – GLIOBLASTOMA
[A]
[H]
Study Date
Study Tir
ANCE
[P]


MITOTIC ACTIVITY


NEOANGIOGENESIS
Astro WHO IV
Low grade astro WHO II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Gadovist
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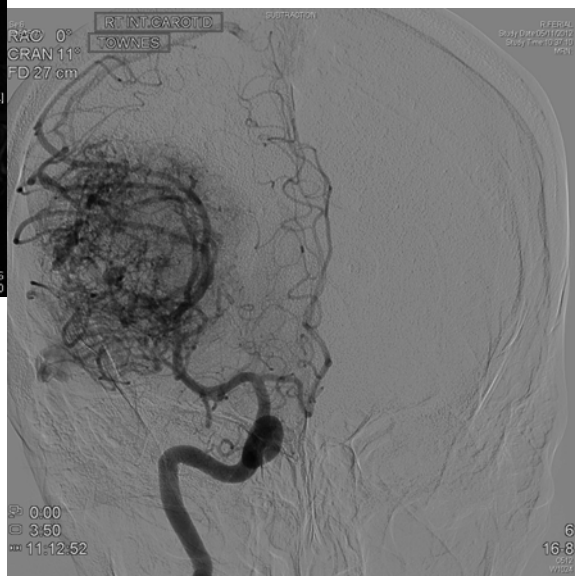
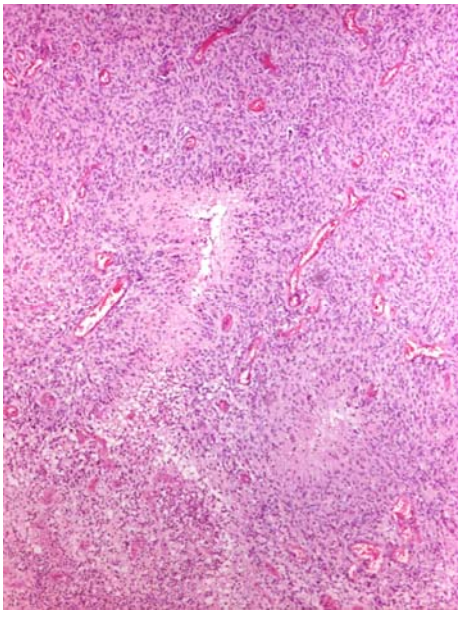
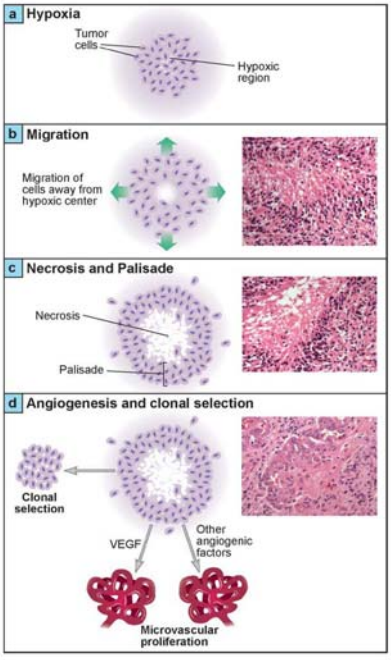
W1310

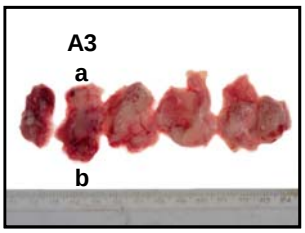

RT INT CAROTID
TOWNES
RAO 0°
CRAN 11°
FD 27 cm
0.00
3.50
11:12.52
6
16:8

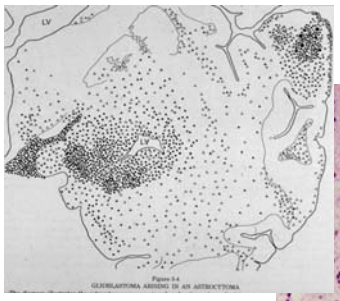
NECROSIS

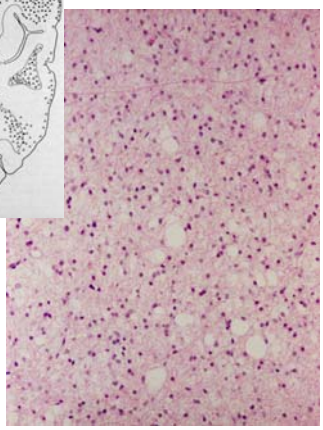


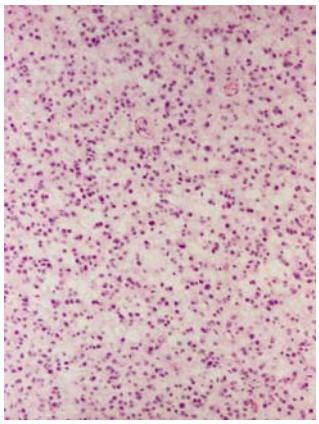

a Hypoxia
Tumor cells
Hypoxic region
b Migration
Migration of cells away from hypoxic center
c Necrosis and Palisade
Necrosis
Palisade
d Angiogenesis and clonal selection
Clonal selection
VEGF
Other angiogenic factors
Microvascular proliferation

About 10% of GBMs results from progression of a lower grade astrocytoma (secondary GBM)





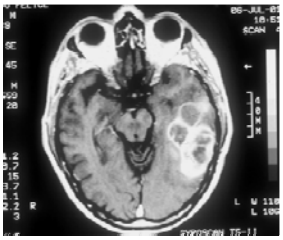


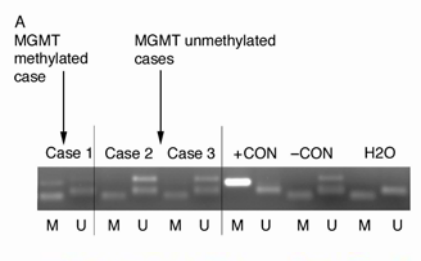


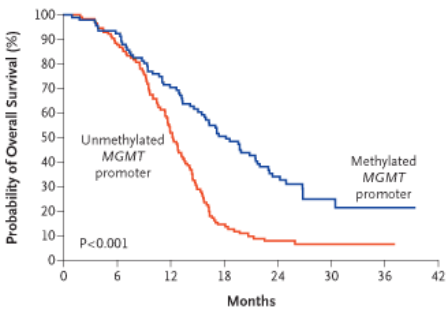
Astrocytomas in uncommon location

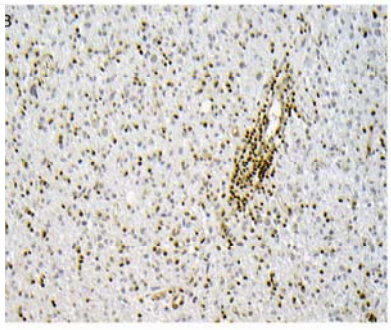
- Cerebellum – account for about 10% of diffuse astrocytomas
- Brain stem – rare, inoperable – often not suitable of biopsy – all ages but more common in children and young adults
- Spinal cord – rare – clinically more aggressive because of location

O6-methyguanine methyltransferase *MGMT1* – Repairs DNA after chemotherapy







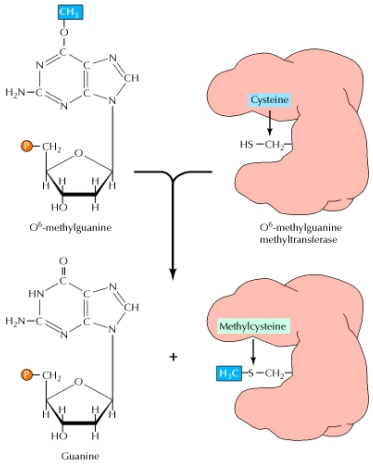


REVIEWS

MGMT promoter methylation in malignant gliomas: ready for personalized medicine?

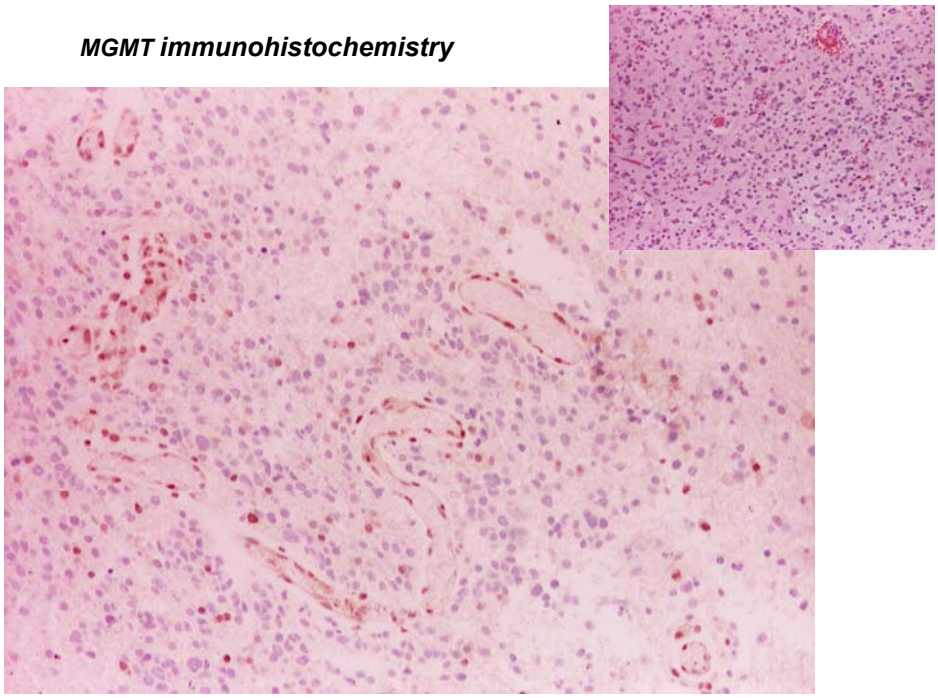
Michael Weller, Roger Stupp, Guido Reifenberger, Alba A. Brandes, Martin J. van den Bent, Wolfgang Wick and Monika E. Hegi

Highly conserved - Chr 10q26
Rapidly reverses alkylation, including methylation, at the O6 position of guanine by transferring the alkyl group to the active site of the enzyme

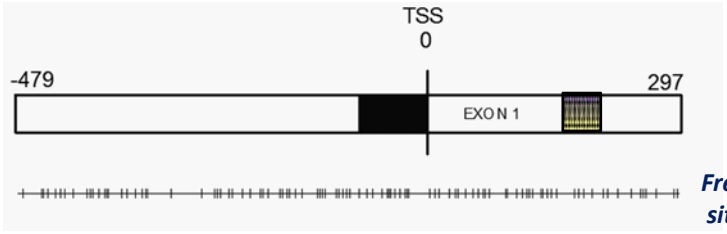


Similarly to many housekeeping genes, and contains a CpG island. CpG islands are genomic regions, typically of 300 –3,000 bp

MGMT immunohistochemistry



777-bp O6-methylguanine-DNA methyltransferase gene (MGMT) cysteine-phosphate-guanine (CpG) island with 97 CpG sites



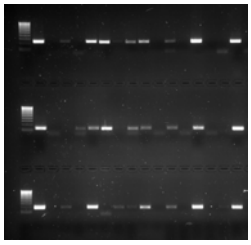
Frequency of CpG sites

MSP region

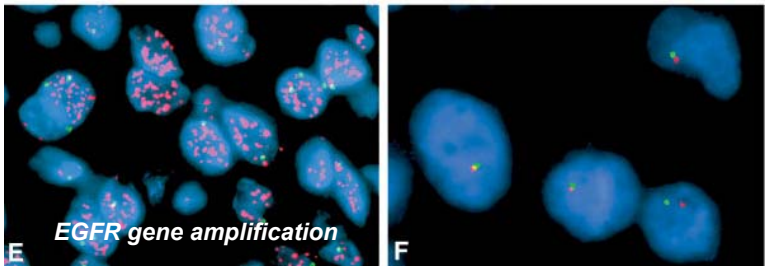
Minimal promoter

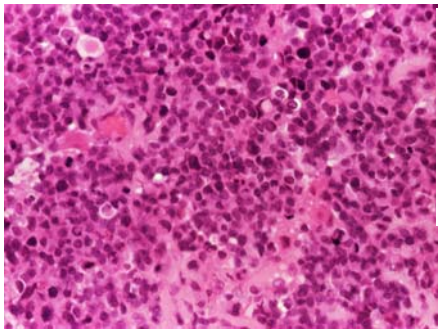
First noncoding exon

Minimal enhancer



Starting from molecular/genetic features





Small Cell Astrocytoma: An Aggressive Variant That Is Clinicopathologically and Genetically Distinct from Anaplastic Oligodendroglioma

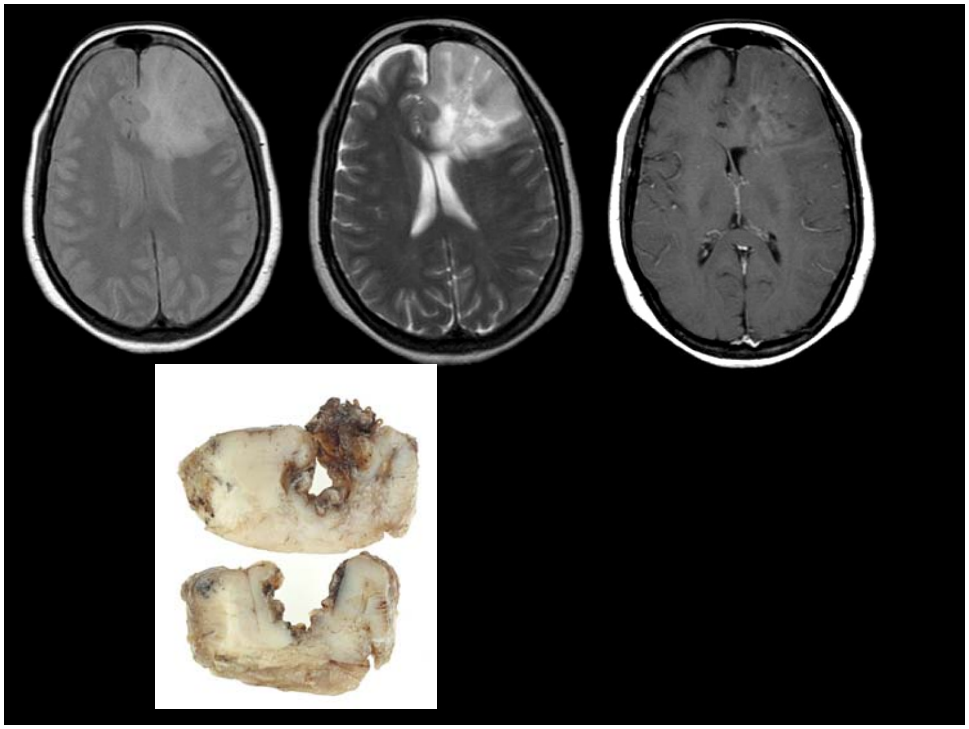
Arie Perry, M.D.[1]
Kenneth D. Aldape, M.D.[2]
David H. George, M.D.[3]
Peter C. Burger, M.D.[4]

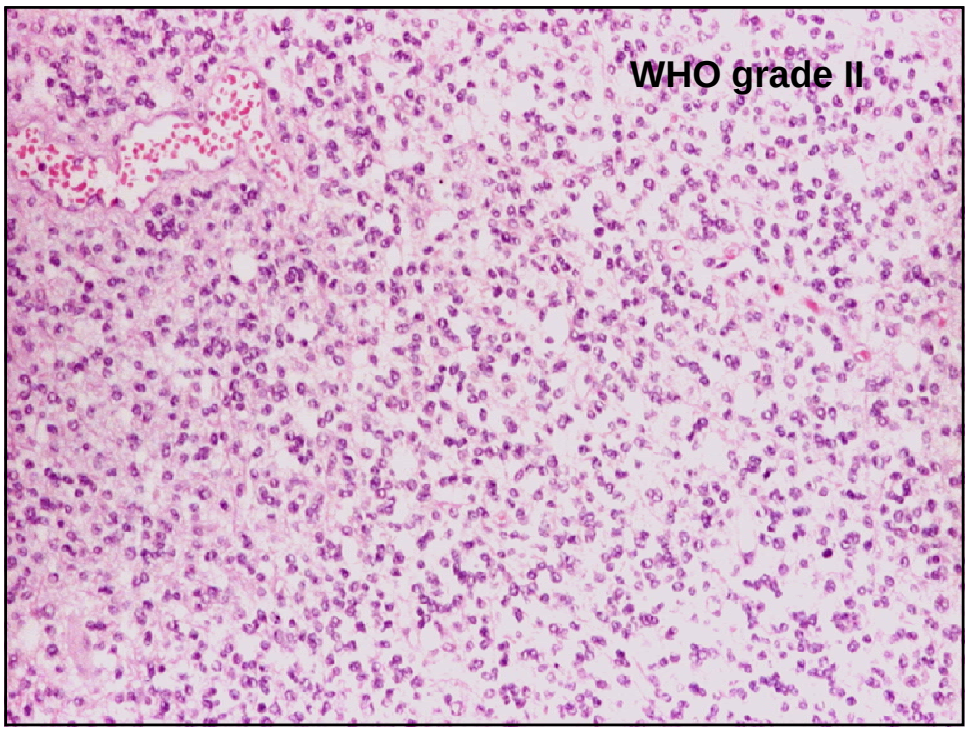
BACKGROUND. Small cell glioblastoma (GBM) is a variant with monomorphous, deceptively bland nuclei that often is misdiagnosed as anaplastic oligodendroglioma.
METHODS. To elucidate its clinicopathologic and genetic features, the authors studied 71 adult patients (median age, 57 years), including 22 patients who were

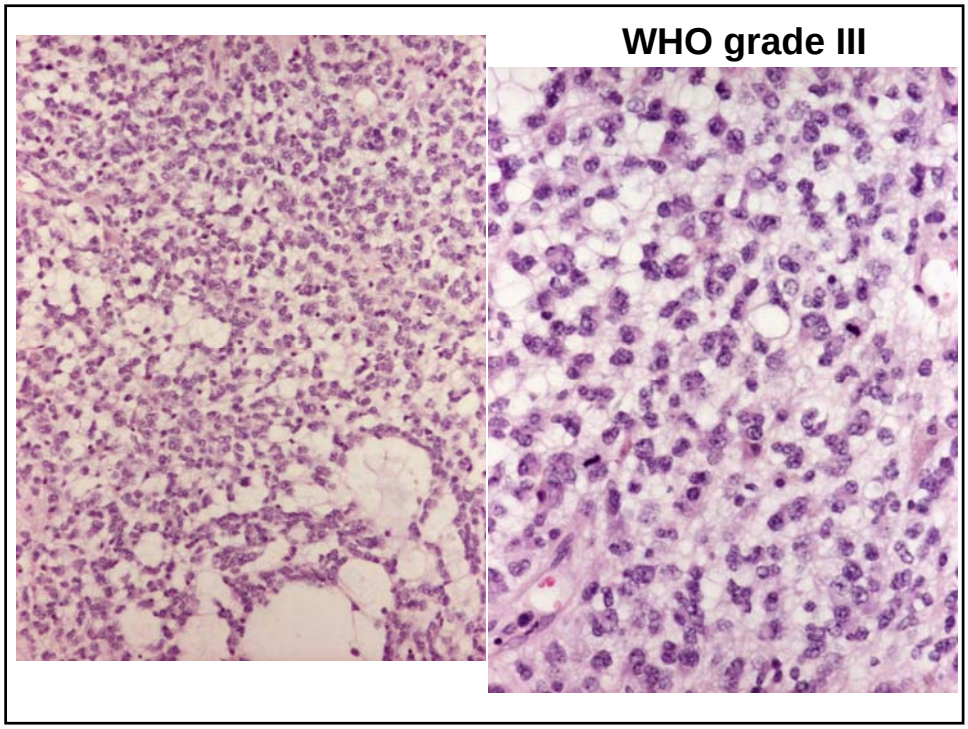
OLIGODENDROGLIOMA - GENERAL

- 5% of all primary brain tumours
- Involves cerebral hemispheres – frontal lobe in 50-60% of cases
- WHO grade II – anaplastic grade III – difficult grading
- Presents with long history of neurological signs – seizure is more frequent
- Neuroimaging: well-demarcated, extends to grey matter, no or patchy contrast enhancement, 30% contain calcification, sometime cystic
- Surgery is the treatment of choice – chemosensitive

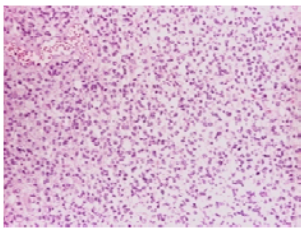
- **Better prognosis than astrocytomas – resection is important**



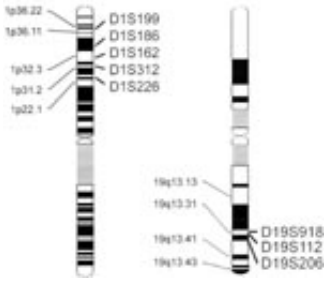

WHO grade II

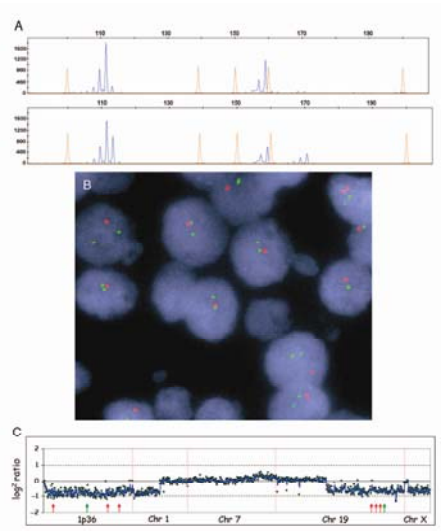

WHO grade III

Loss of heterozygosity 1p19q in oligodendrogliomas



Chromosome 1 Chromosome 19





Acta Neuropathol (2010) 120:567–584
DOI 10.1007/s00401-010-0736-4

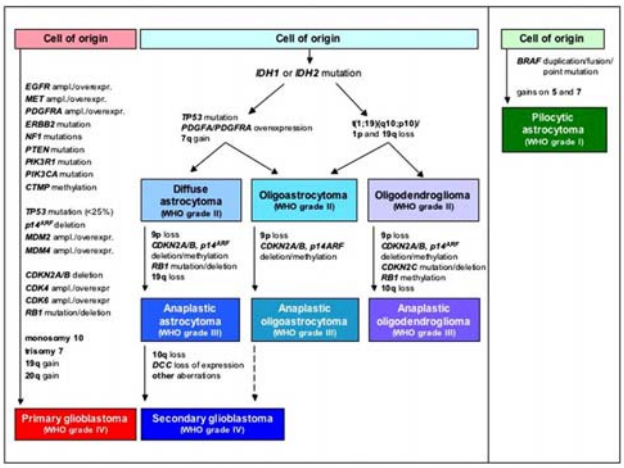
REVIEW

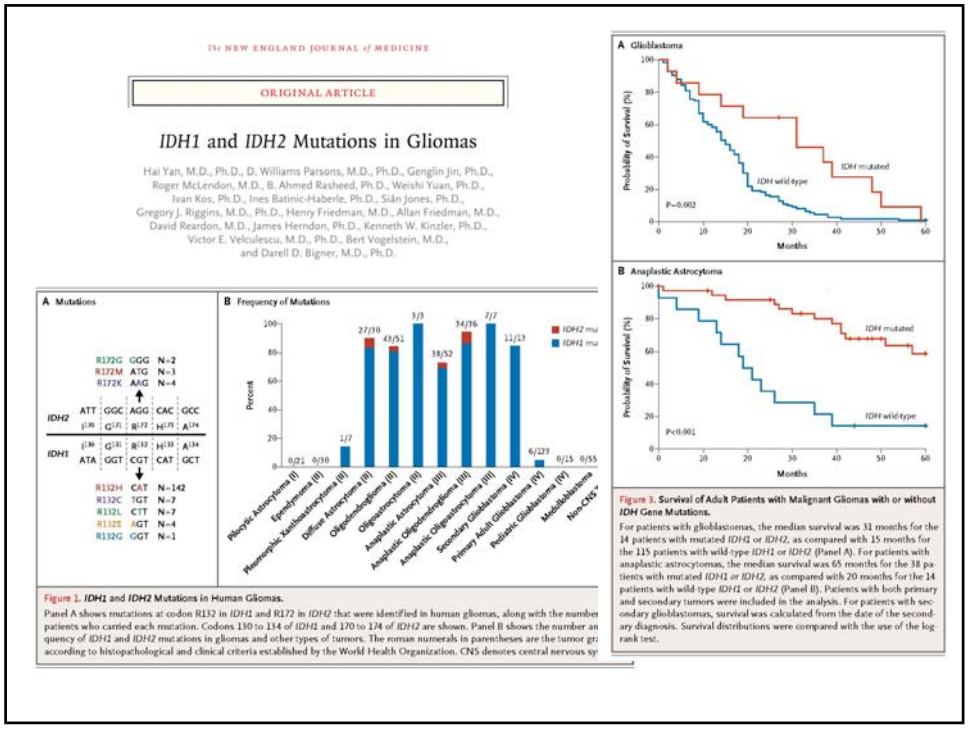
Molecular diagnostics of gliomas: state of the art

Markus J. Riemenschneider · Judith W. M. Jeuken · Pieter Wesseling · Guido Reifenberger

The neurobiology of gliomas: from cell biology to the development of therapeutic approaches

Manfred Westphal and Katrin Lamszus





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

IDH1 and *IDH2* Mutations in Gliomas

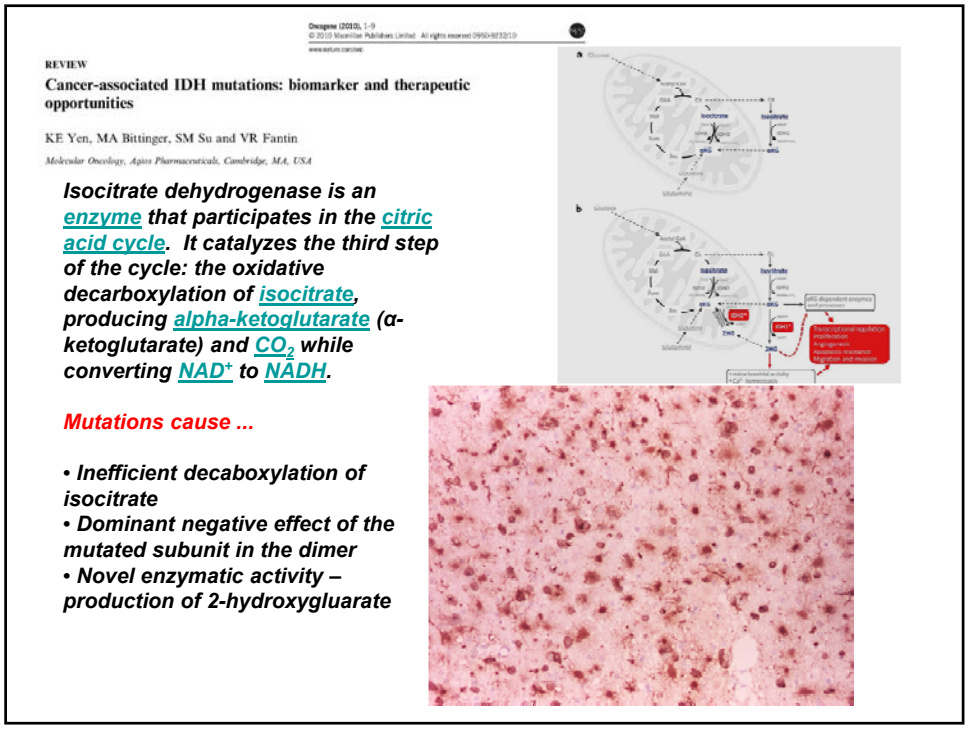
Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

Figure 1. *IDH1* and *IDH2* Mutations in Human Gliomas.

Panel A shows mutations at codon R132 in *IDH1* and R172 in *IDH2* that were identified in human gliomas, along with the number patients who carried each mutation. Codons 130 to 134 of *IDH1* and 170 to 174 of *IDH2* are shown. Panel B shows the number an quency of *IDH1* and *IDH2* mutations in gliomas and other types of tumors. The roman numerals in parentheses are the tumor gr according to histopathological and clinical criteria established by the World Health Organization. CNS denotes central nervous sy

Figure 3. Survival of Adult Patients with Malignant Gliomas with or without *IDH* Gene Mutations.

For patients with glioblastomas, the median survival was 31 months for the 14 patients with mutated *IDH1* or *IDH2*, as compared with 15 months for the 115 patients with wild-type *IDH1* or *IDH2* (Panel A). For patients with anaplastic astrocytomas, the median survival was 65 months for the 38 patients with mutated *IDH1* or *IDH2*, as compared with 20 months for the 14 patients with wild-type *IDH1* or *IDH2* (Panel B). Patients with both primary and secondary tumors were included in the analysis. For patients with secondary glioblastomas, survival was calculated from the date of the second-ary diagnosis. Survival distributions were compared with the use of the log-rank test.



Oncogene (2010), 1–9

REVIEW

Cancer-associated IDH mutations: biomarker and therapeutic opportunities

KE Yen, MA Bittinger, SM Su and VR Fantin

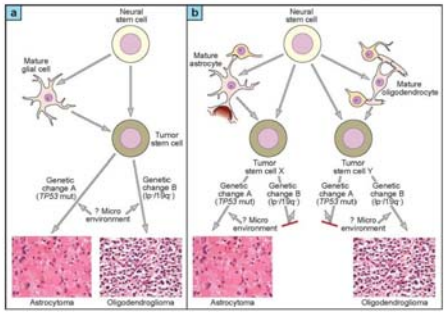
Molecular Oncology, Agios Pharmaceuticals, Cambridge, MA, USA

Isocitrate dehydrogenase is an enzyme that participates in the citric acid cycle. It catalyzes the third step of the cycle: the oxidative decarboxylation of isocitrate, producing alpha-ketoglutarate (α-ketoglutarate) and CO_2 while converting NAD^+ to NADH.

Mutations cause ...

• Inefficient decaboxylation of isocitrate
• Dominant negative effect of the mutated subunit in the dimer
• Novel enzymatic activity – production of 2-hydroxygluarate

The controversy of stem cells in CNS cancer



Cancer initiating cells – functional definition – (CD133+ and -)

Self-renew
Differentiate
Proliferate
Chemoresistant

Cell PRESS

Cancer Cell
Article

Asymmetry-Defective Oligodendrocyte Progenitors Are Glioma Precursors

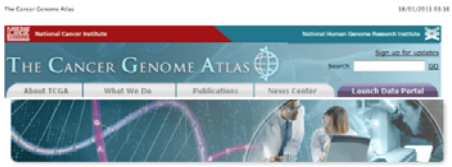
Brain Pathology ISSN 1015-6305

REVIEW ARTICLE

Array-Based Genomics in Glioma Research

Ahmed Idbaih[1,2,3]; Emmanuelle Crinière[1,2]; Keith L. Ligon[4,5,6]; Olivier Delattre[7]; Jean-Yves Delattre[1,2,3]

[1] INSERM, Unité 711, Paris, France.
[2] Université Pierre et Marie Curie-Paris6, Laboratoire Biologie des Interactions Neurone-Glie, Groupe hospitalier Pitié-Salpêtrière, Paris, France.
[3] AP-HP, Groupe hospitalier Pitié-Salpêtrière, Service de neurologie Mazarin, Paris, France.
[4] Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Ma.
[5] Center for Molecular Oncologic Pathology, Dana-Farber Cancer Institute, Boston, Ma.
[6] Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Ma.
[7] INSERM U830, Institut Curie, Section Recherche, Laboratoire Pathologie Moléculaire des Cancers, Paris, France.



Search for new classifiers … the age of " omics"

Review

The DNA methylome of glioblastoma multiforme

Ramon Martinez [a,*], Manel Esteller [b,c,*]

Brain Pathology ISSN 1015-6305

REVIEW ARTICLE

Glioma Pathophysiology: Insights Emerging from Proteomics

Ruth F. Deighton*; Richard McGregor*; Jocelyn Kemp; James McCulloch; Ian R. Whittle

Department of Clinical Neurosciences, Western General Hospital; and Centre for Cognitive and Neural Systems, University of Edinburgh, Scotland, UK

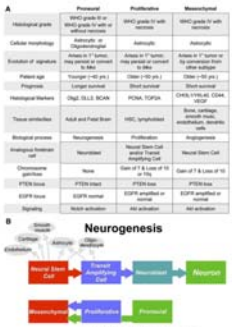
ARTICLE

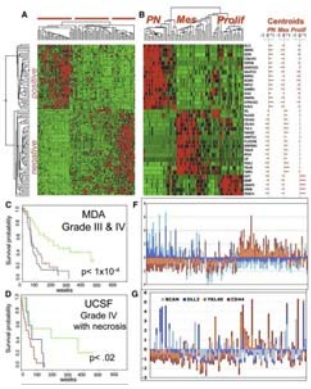
Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis

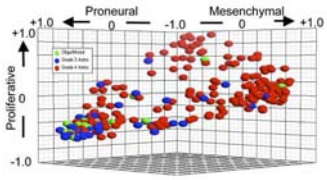
Heidi S. Phillips,[1,*] Samir Kharbanda,[1] Ruihuan Chen,[1] William F. Forrest,[2] Robert H. Soriano,[3] Thomas D. Wu,[4] Anjan Misra,[1] Janice M. Nigro,[1] Howard Colman,[4] Liliana Soroceanu,[1] P. Mickey Williams,[2] Zora Modrusan,[1] Burt G. Feuerstein,[1] and Ken Aldape[1]

Subclassification based on molecular signature

Proneural
Mesenchymal
Proliferative
Stem cell







HIGH-THROUGHPUT TECHNIQUES can be misleading

Disillusion between scientists

Difference between driver and passenger genes

Review

Cancer Research

Heterogeneity Maintenance in Glioblastoma: A Social Network

Rudy Bonavia[1], Maria-del-Mar Inda[4], Webster K. Cavenee[2,3,4], and Frank B. Furnari[2,3,4]

Perspectives in Cancer Research

Sample Type Bias in the Analysis of Cancer Genomes

David A. Solomon,[1] Jung-Sik Kim,[1] Habtom W. Ressom,[1] Zita Sibenaller,[3] Timothy Ryken,[3] Walter Jean,[3] Darell Bigner,[4] Hai Yan,[4] and Todd Waldman[1]

There can be difference in gene/protein expression

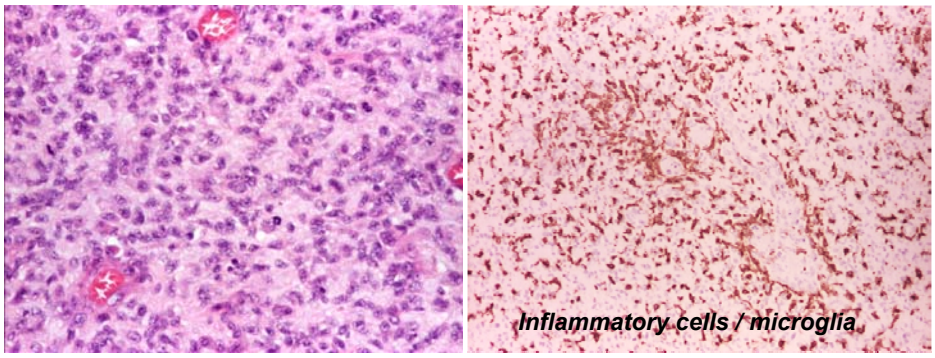
Primary tumour
Ex vivo culture
Xenografts
Established cell lines

GLIA

GLIA 59:1169–1180 (2011)

The Brain Tumor Microenvironment

NIKKI A. CHARLES,[1]* ERIC C. HOLLAND,[1] RICHARD GILBERTSON,[2] RAINER GLASS,[3] AND HELMUT KETTENMANN[4]



GLIA

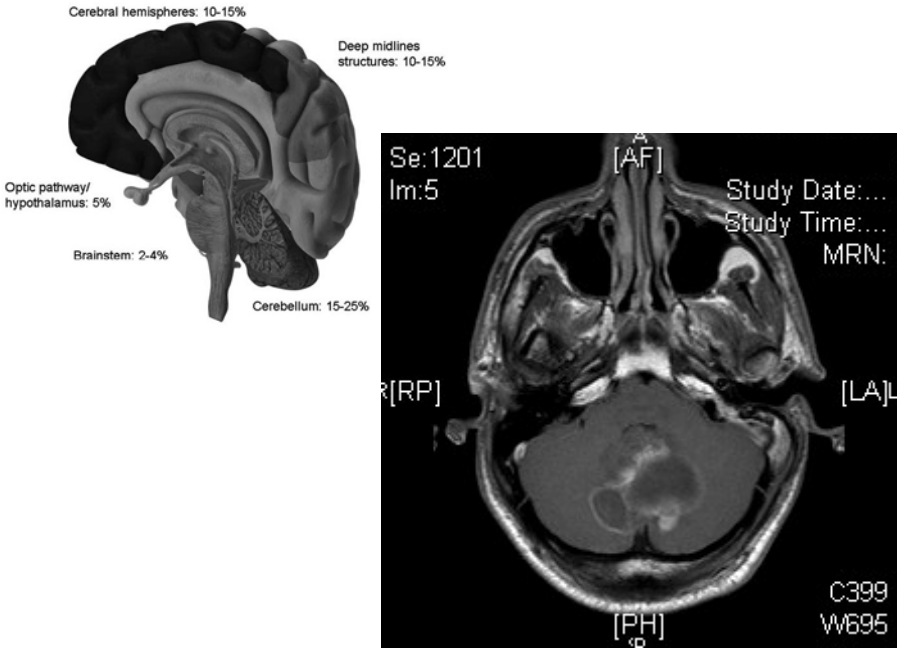
GLIA 59:472–485 (2011)

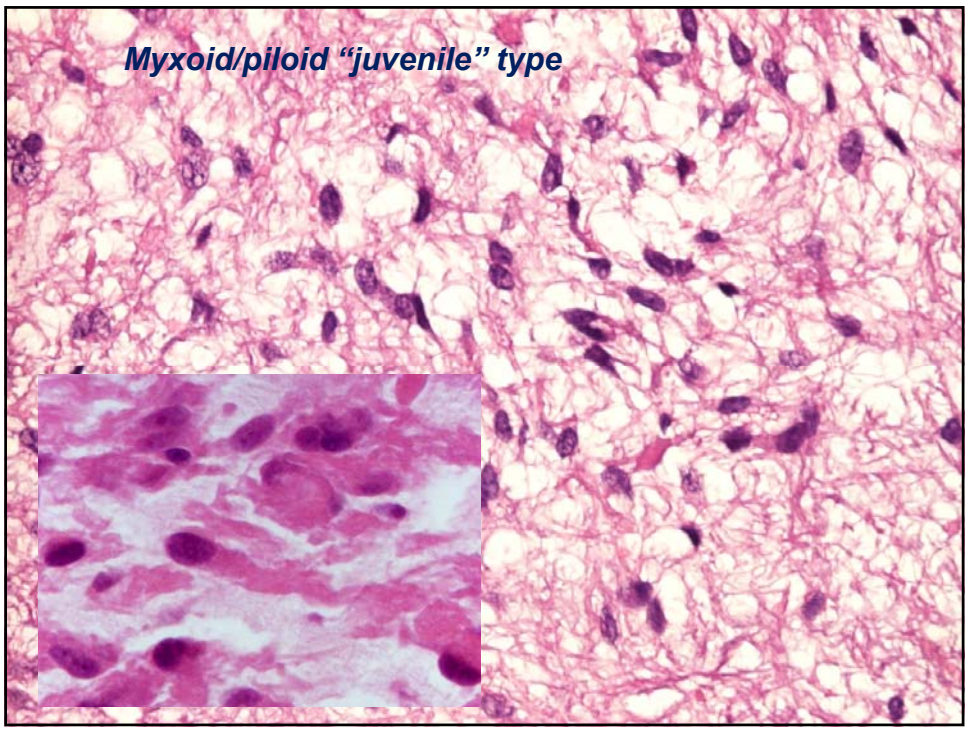
Microglia/Macrophages Promote Glioma Progression

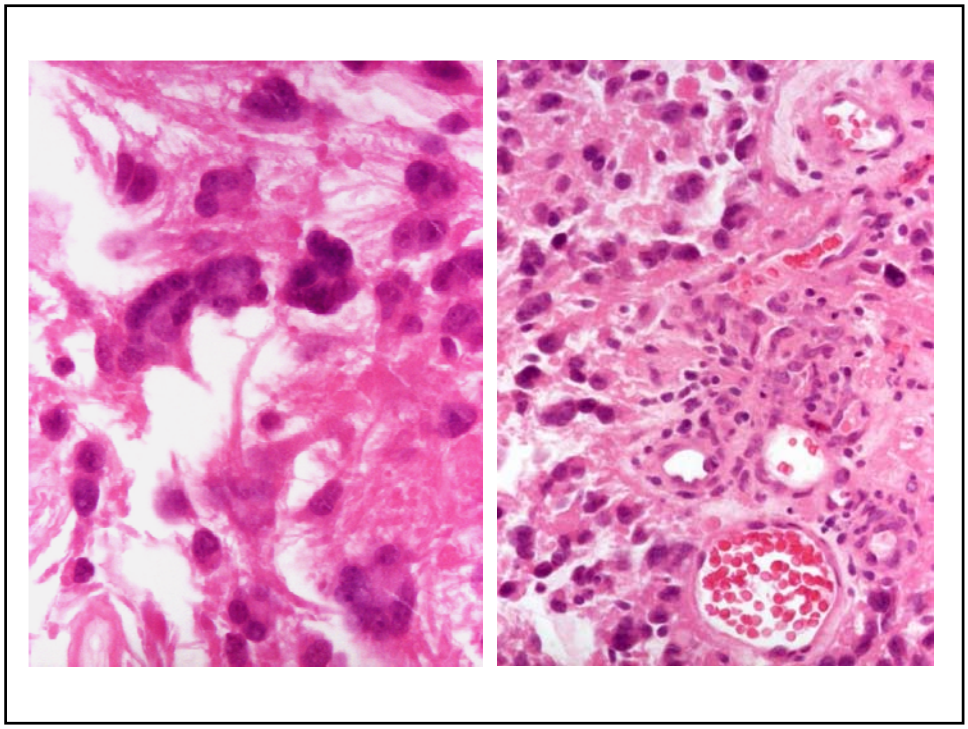
HAIYAN ZHAI,[1,2] FRANK L. HEPPNER,[2] AND STELLA E. TSIRKA[1,2]*

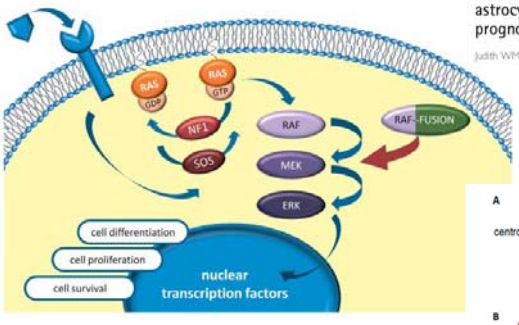
PILOCYTIC ASTROCYTOMA - GENERAL FEATURES

- **WHO grade I**
- **Usually 1st and 2nd decade - 20% of CNS tumours below 14 years and 15% between 14-18 years**
- **Often cerebellar, optic-hypothalamic, brain stem**
- **Often cystic. Always contrast enhancement**
- **They can disseminate in the subarachnoid space (es: follow nerve roots)**
- **Compressive margins (never diffuse infiltration)**
- **Variable histological features**
- **Always show marked nuclear atypia and vascular/endothelial proliferation**
- **Very often Rosenthal fibres and granular bodies**
- **Hallmark: Piloid "hairy" cell**




Myxoid/piloid “juvenile” type



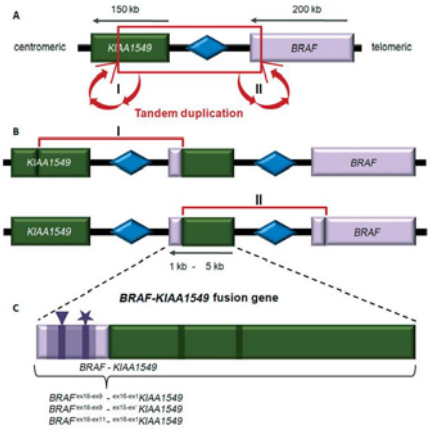


Journal of Pathology
J Pathol 2010; 222: 324–328
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.2780

INVITED COMMENTARY

MAPK pathway activation through *BRAF* gene fusion in pilocytic astrocytomas; a novel oncogenic fusion gene with diagnostic, prognostic, and therapeutic potential

Judith WM Jeuken* and Pieter Wesseling†‡

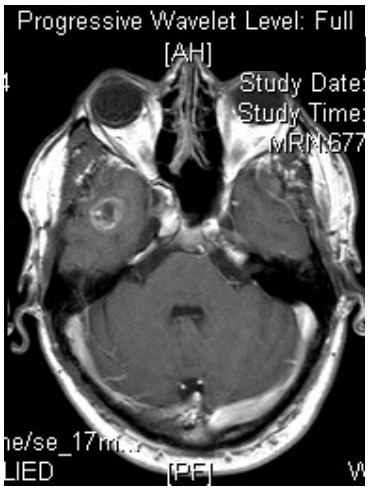


Fusion present in about 80% of juvenile pilocytic astrocytomas

Supratentorial Pilocytic Astrocytomas

A Clinicopathologic, Prognostic, and Flow Cytometric Study of 51 Patients

Peter A. Forsyth, M.D., Edward G. Shaw, M.D.,† Bernd W. Scheithauer, M.D.,‡ Judith R. O'Fallon, Ph.D.,§ Donald D. Layton, Jr., M.D.,* and Jerry A. Katzmann, Ph.D.‖*

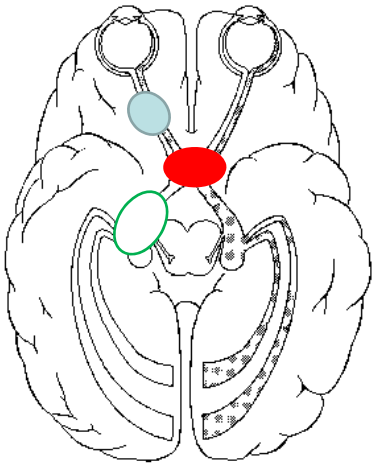


Neurosurg Focus 23 (5):E2, 2007

Optic pathway gliomas: a review

MANDY J. BINNING, M.D.,[1] JAMES K. LIU, M.D.,[2] JOHN R. W. KESTLE, M.D.,[1] DOUGLAS L. BROCKMEYER, M.D.,[1] AND MARION L. WALKER, M.D.[1]

[1]Department of Neurosurgery and Primary Children's Medical Center, University of Utah School of Medicine, Salt Lake City, Utah; and [2]Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, Evanston Northwestern Healthcare, Evanston, Illinois



Interior view of central pathway

MEDULLOBLASTOMA

- Rare (0.5 per 100,000 year, in children)
- 75% arise in the vermis in children and hemispheric in adults
- Present with cerebellar signs, cranial hypertension

- WHO DEFINITION: A malignant, invasive embryonal tumour of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation, and an inherent tendency to metastasize via CSF pathway

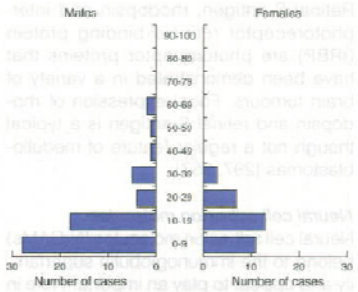
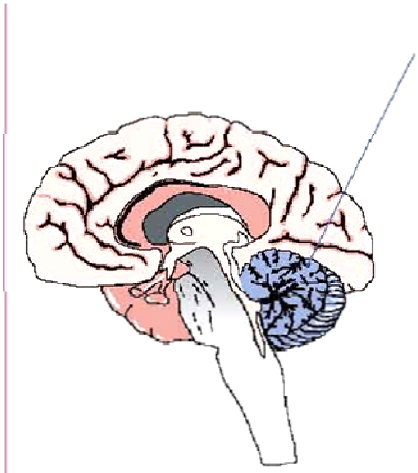


Fig. 8.5 Age and sex distribution of medulloblastoma, based on 89 cases treated at the University Hospital, Zurich.

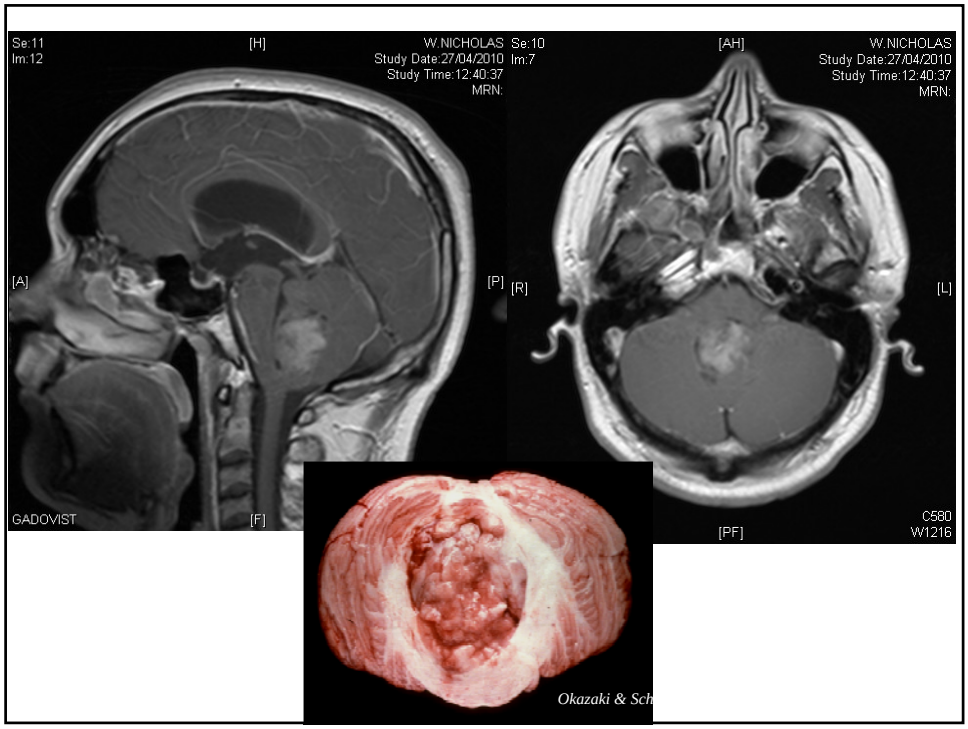
- WHO GRADE IV

Outcome considerably improved with radio-chemotherapy



Posterior fossa tumours:

- Nausea and vomiting* 75%
- Headache* 67%
- Abnormal gait and coordination difficulties 60%
- Papilloedema* 34%
- Abnormal eye movements 20%
- Lethargy 13%
- Nausea without vomiting* 10%
- Unspecified symptoms and signs of raised ICP* 9%
- Weight loss 9%
- Focal motor weakness 9%
- Macrocephaly* 7%
- Impaired consciousness 7%
- Vertigo or auditory symptoms 7%
- Squint 6%
- Stiff neck 6%
- Head tilt
- Accidental head injury 5%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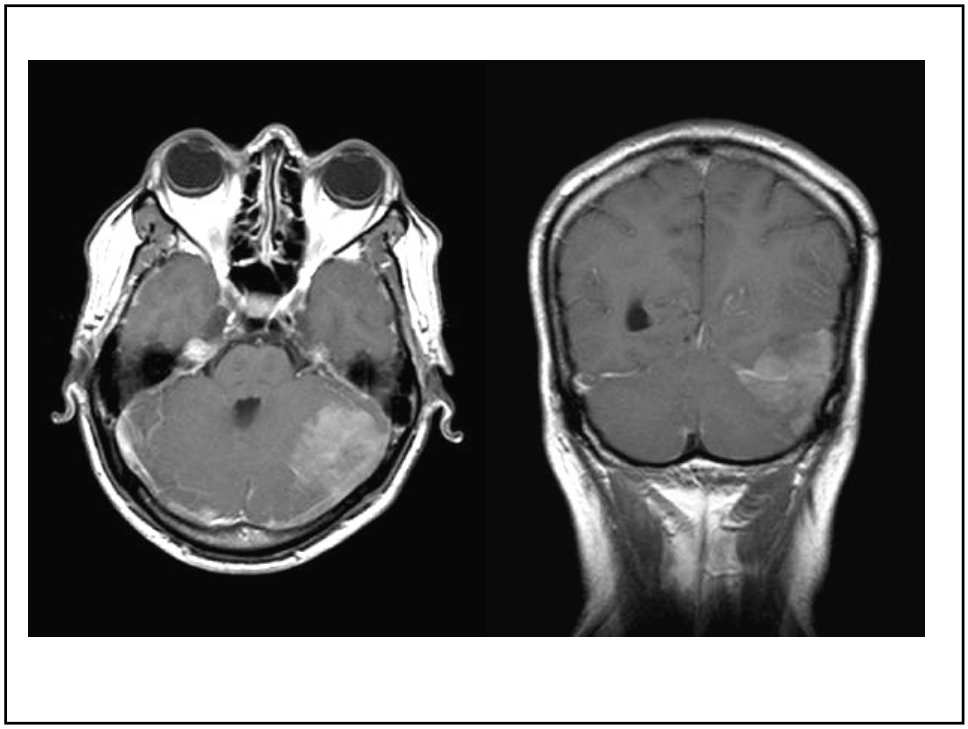
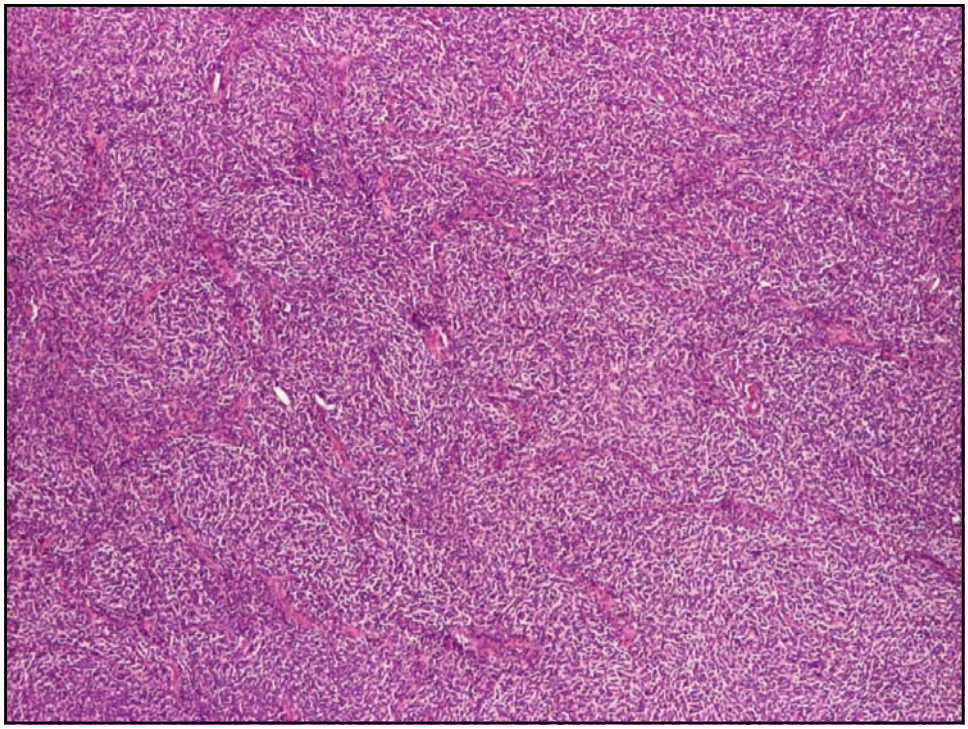
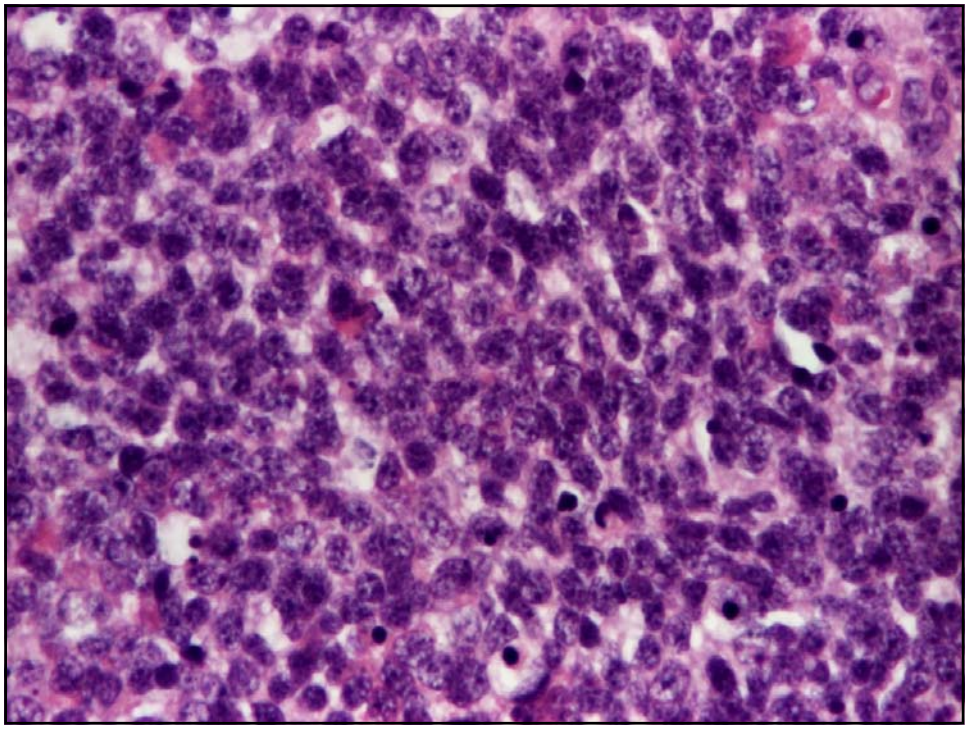
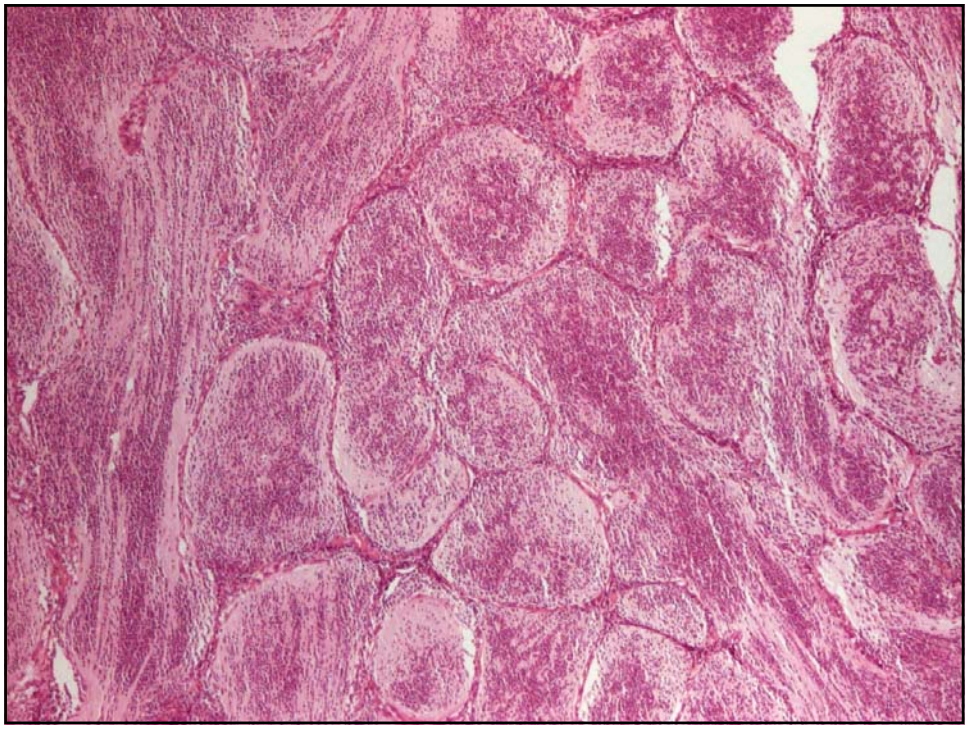
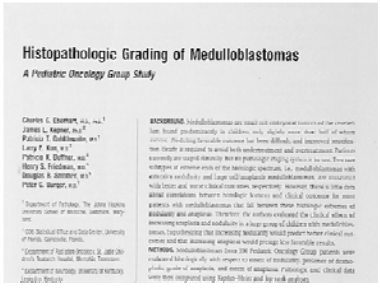










Histopathologic Grading of Medulloblastomas

A Pediatric Oncology Group Study

- **Amount of nodularity (5 groups)**
- **Desmoplasia (presence/absence of collagen)**
- **Anaplasia (nuclear size and shape, mitoses, apoptosis, nucleoli)**
- **Extent of anaplasia (slight, moderate, severe)**

Grade and extent of anaplasia correlate with prognosis

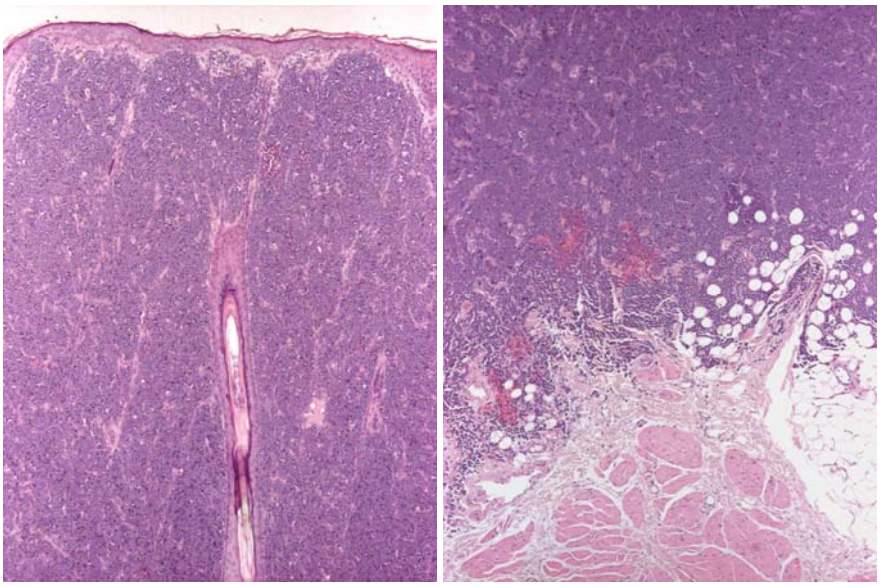
Outcome

Aggressive – usually disseminated in the CSF

Prognostic factors: age (<3 yrs), seeding, histology (nodular vs anaplastic)

Requires surgery, Rx therapy and chemotherapy

They can spread outside the CNS



Acta Neuropathol (2010) 120:553–566
DOI 10.1007/s00401-010-0751-5

REVIEW

Molecular diagnostics of CNS embryonal tumors

Stefan M. Pfister · Andrey Korshunov · Marcel Kool · Martin Hasselblatt · Charles Eberhart · Michael D. Taylor

Medulloblastoma

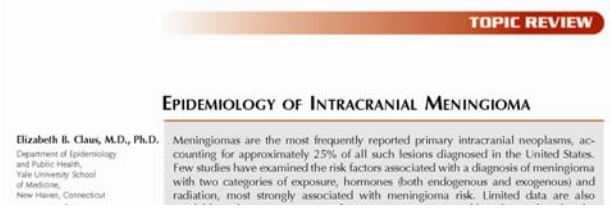
Subtype *Kool* *Northcott*	A WNT	B SHH	E Group C	CD Group D
Expression characteristics	WNT / TGF signaling NOTCH / PDGF signaling Cell cycle proteins ↑	SHH signaling NOTCH / PDGF signaling Cell cycle proteins ↑	Photoreceptor markers Cell cycle proteins ↑	Neuronal and photoreceptor markers
Genetic characteristics	- 6 *CTNNB1* mutations	- 9q *MYCN* ampl. *PTCH* / *SMO* / *SUFU* mutations	i(17q), -X, +18 *MYC* ampl.	i(17q), - 8, -X, +18 *MYCN* ampl.
Histology	Classic	Desmoplastic/classic	Classic/LCA	Classic/LCA
Clinical characteristics	Rarely metastatic	Rarely metastatic	Frequently metastatic	Frequently metastatic
Age groups	Older children	Infants and adults	Young children	Children
Prognosis	Very good	Infants good Others intermediate	Poor	Intermediate

MENINGIOMA

- 24-30% primary intracranial tumours
- Incidental in up to 10% of post-mortem
- Usually adults – rare in patients younger than 40 (more aggressive)
- Focal symptoms (seizure, compression)
- Any site of craniospinal axis

Studies in PubMed – 2 Dec 2010

- Alzheimer's disease - 74,339
- Glioma - 53,548
- Encephalitis - 47,775
- Mutiple sclerosis - 47,269
- Meningioma - 16,189
- Brain metastases - 12,388

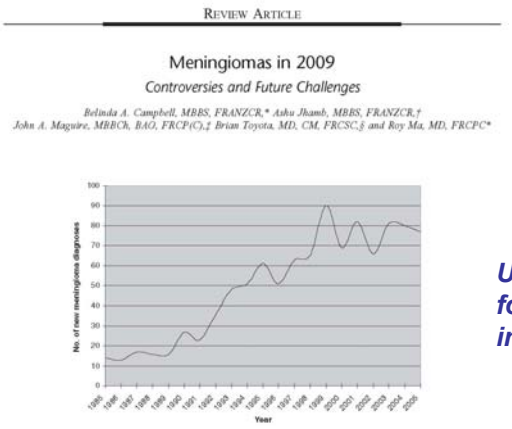


TOPIC REVIEW

EPIDEMIOLOGY OF INTRACRANIAL MENINGIOMA

Elizabeth B. Claus, M.D., Ph.D.
Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut

Meningiomas are the most frequently reported primary intracranial neoplasms, accounting for approximately 25% of all such lesions diagnosed in the United States. Few studies have examined the risk factors associated with a diagnosis of meningioma with two categories of exposure, hormones (both endogenous and exogenous) and radiation, most strongly associated with meningioma risk. Limited data are also



REVIEW ARTICLE

Meningiomas in 2009

Controversies and Future Challenges

Belinda A. Campbell, MBBS, FRANZCR, Ashu Jhamb, MBBS, FRANZCR,† John A. Maguire, MBBCh, BAO, FRCP(C),‡ Brian Toyota, MD, CM, FRCSC,§ and Roy Ma, MD, FRCPC**

US Government Legislation for register benign brain tumours including meningiomas

Discuss the morbidity of meningiomas – quality of life of patients with meningioma related to treatment

Histology and grading

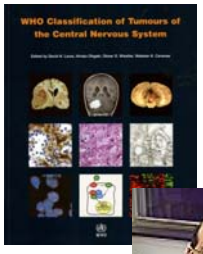


Table 11.1
Meningiomas grouped by likelihood of recurrence and grade.

Meningiomas with low risk of recurrence and aggressive growth:	
Meningothelial meningioma	WHO grade I
Fibrous (fibroblastic) meningioma	WHO grade I
Transitional (mixed) meningioma	WHO grade I
Psammomatous meningioma	WHO grade I
Angiomatous meningioma	WHO grade I
Microcystic meningioma	WHO grade I
Secretory meningioma	WHO grade I
Lymphoplasmacyte-rich meningioma	WHO grade I
Metaplastic meningioma	WHO grade I
Meningiomas with greater likelihood of recurrence and/or aggressive behaviour:	
Atypical meningioma	WHO grade II
Clear cell meningioma (intracranial)	WHO grade II
Chordoid meningioma	WHO grade II
Rhabdoid meningioma	WHO grade III
Papillary meningioma	WHO grade III
Anaplastic (malignant) meningioma	WHO grade III
Meningiomas of any subtype or grade with high proliferation index and/or brain invasion	

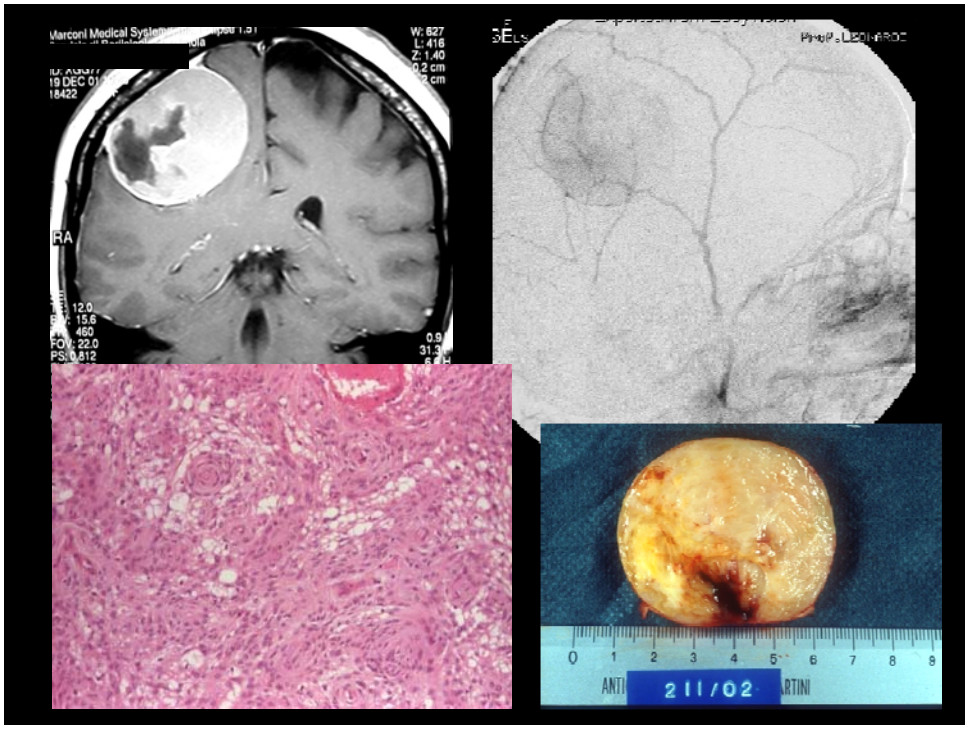
- **Based on pathology**
- **Proliferation and architecture**
- **Grade I – benign**
- **Grade II (atypical) – 20% of meningiomas; 40% recurrence**
- **Grade III (anaplastic) – 1% of meningiomas; often lethal in 1 year**

From: WHO 2000

OUTCOME OF MENINGIOMAS DEPENDS MOSTLY ON

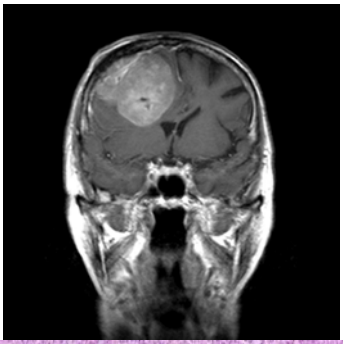
EXTENT OF SURGICAL RESECTION (often related to site)

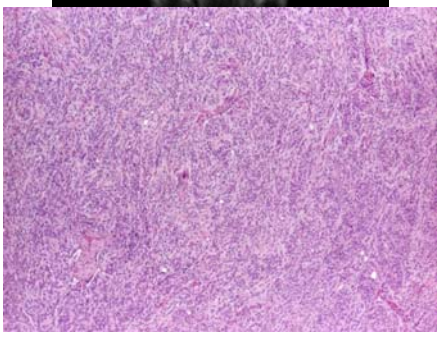
& HISTOLOGICAL FEATURES



ATYPICAL MENINGIOMA

- GRADE II, WHO 2007
- 20% of meningioma
- High recurrence rate
- Close follow-up (radiotherapy?)
- Mitoses > 4x10 HPF (count at least 100 fields in different areas)
- Three of these features: small cells, cellularity, sheet-like architecture, macronucleoli, necrosis

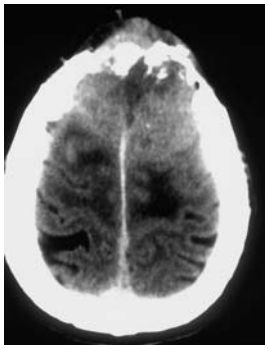


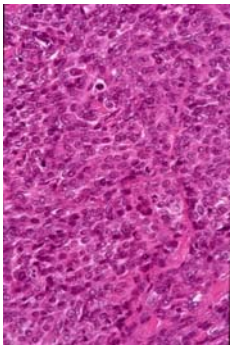


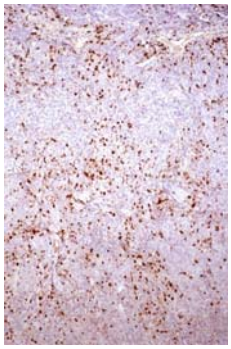
ANAPLASTIC MENINGIOMA

- GRADE III, WHO 2000
- 1% meningiomas
- Very aggressive
- Surgery and radiotherapy

- More than 20 mitoses x 10 HPF
- Meningeal tumour resembling carcinoma, melanoma, sarcoma.
- Diagnosis difficult, often require EM

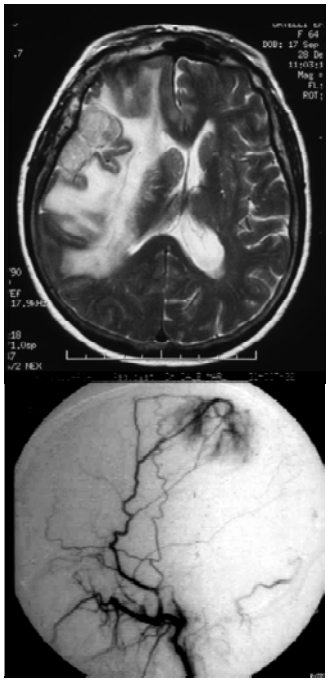






BRAIN INVASION

- Neoplastic tissue in the cortex without connection with the tumour
- Seen in benign meningiomas – does not mean “malignant” but now proposed as criterion for grade II
- Higher recurrence rate



Any questions?

Thank you