Meningioma, mostly cured, occasionally deadly: Progress and challenges

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Meningioma: A frequent brain tumor…..

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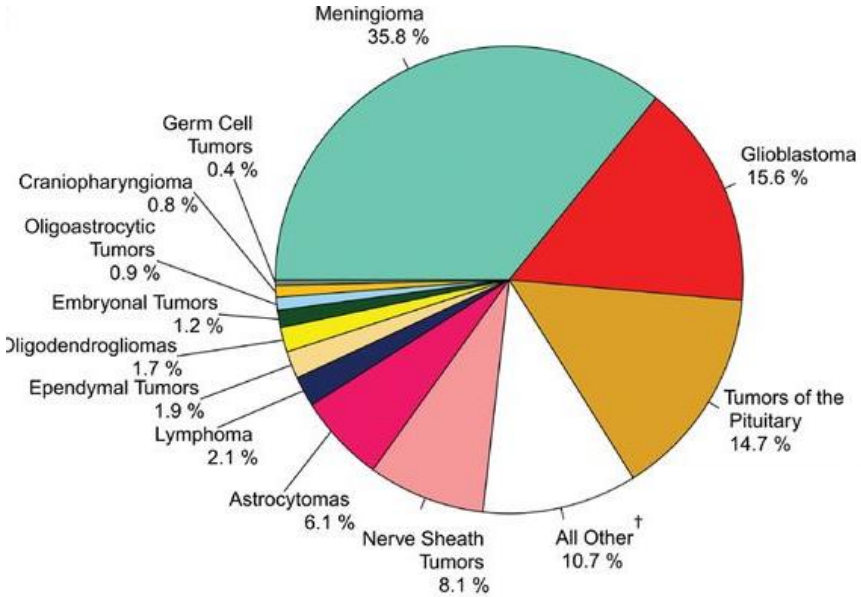
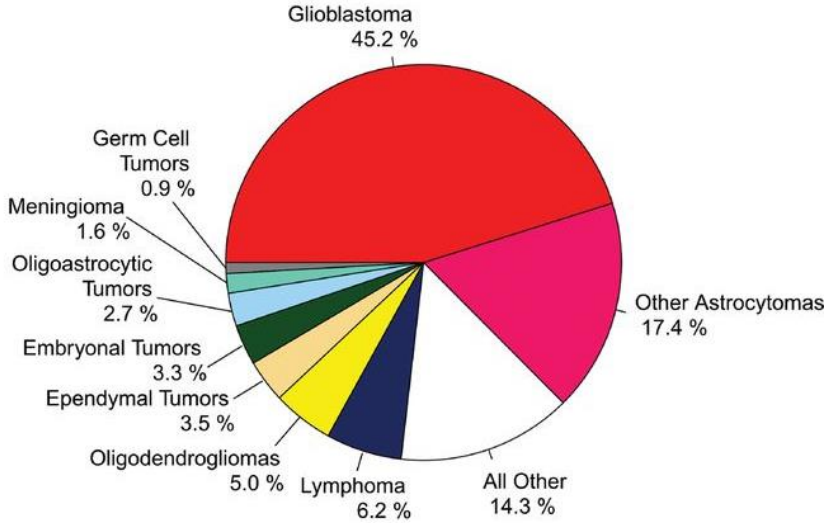
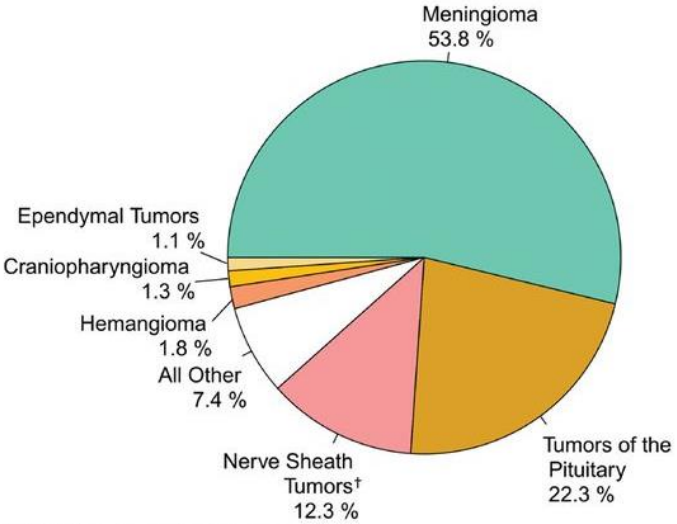
CBTRUS [Central Brain Tumor Registry US]

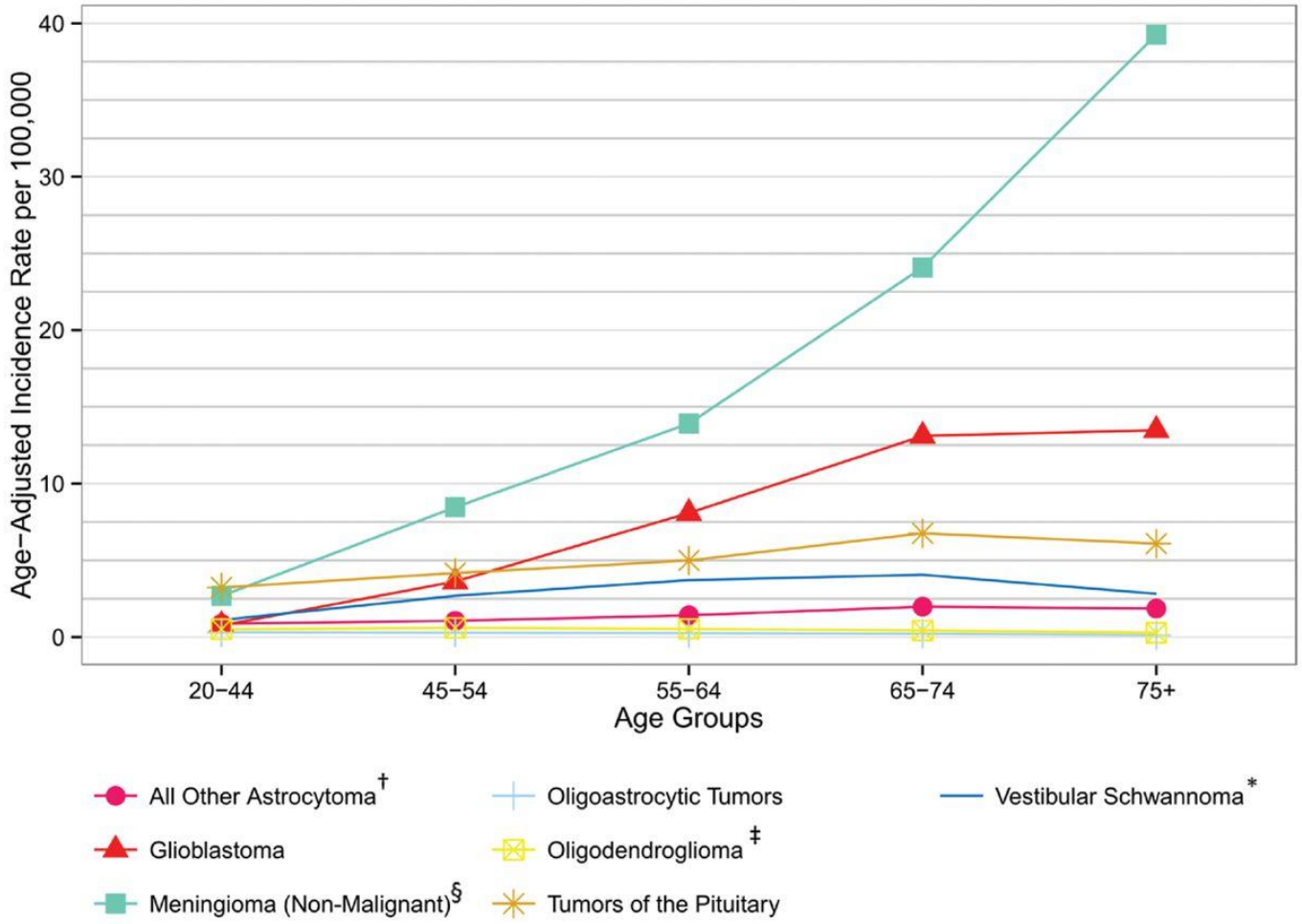






Ostrom et al., Neuro-Oncol 2013

……in older people



Ostrom et al., Neuro-Oncol 2013

Outline:

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- Meningioma pathology
- Classification und grading (new WHO)
- Molecular mechanisms of meningioma development and progression
- Recent treatment advances

…are reflected by histology

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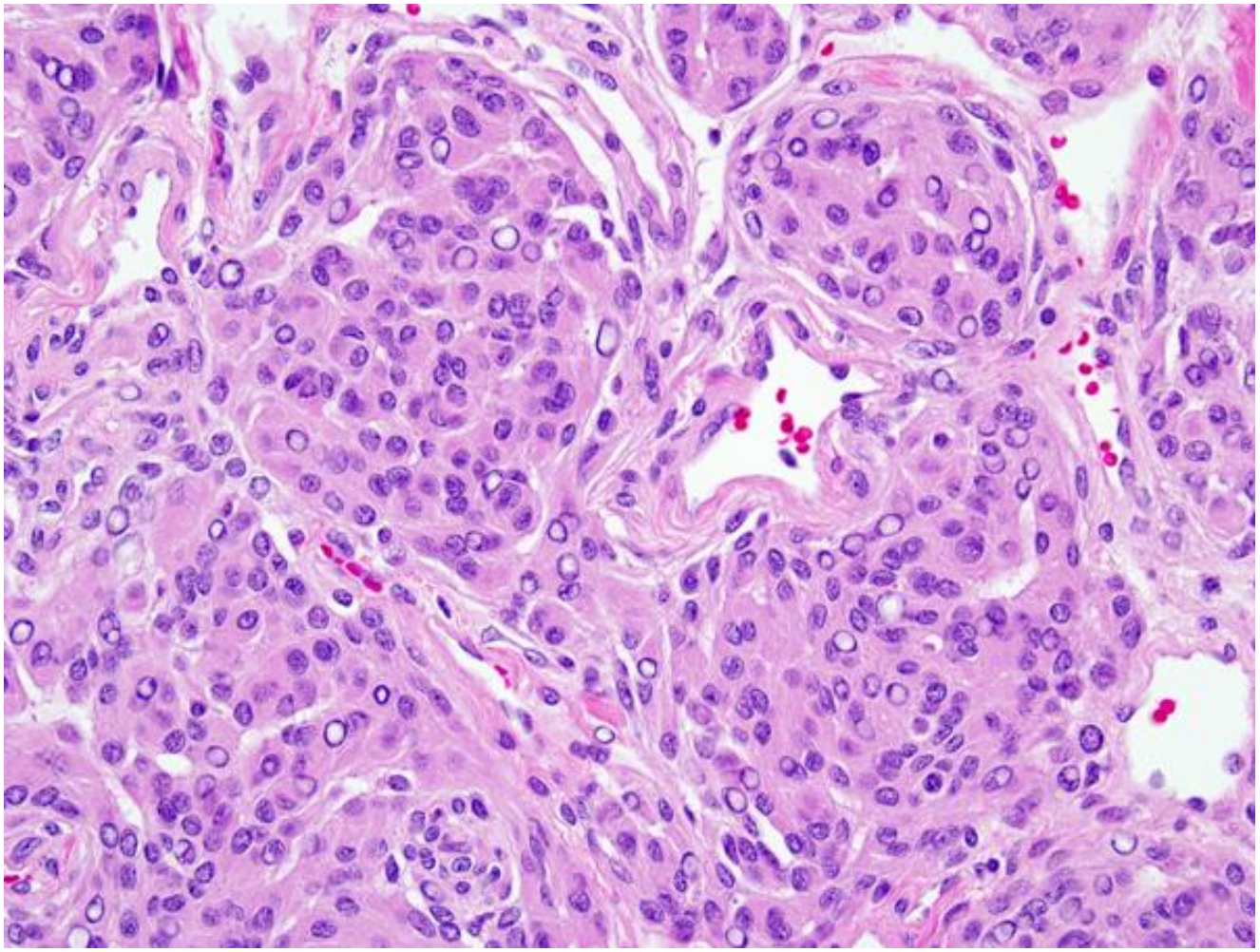
Histological subtype	WHO grade
Meningothelial meningioma	**I**
Fibrous (fibroblastic) meningioma	**I**
Transitional (mixed) meningioma	**I**
Psammomatous meningioma	I
Angiomatous meningioma	I
Microcystic meningioma	I
Secretory meningioma	I
Lymphoplasmacyte-rich meningioma	I
Metaplastic meningioma	I
Chordoid meningioma	II
Clear cell meningioma	II
Atypical meningioma	**II**
Brain invasive meningioma	**II**
Papillary meningioma	III
Rhabdoid meningioma	III
Anaplastic (malignant) meningioma	**III**

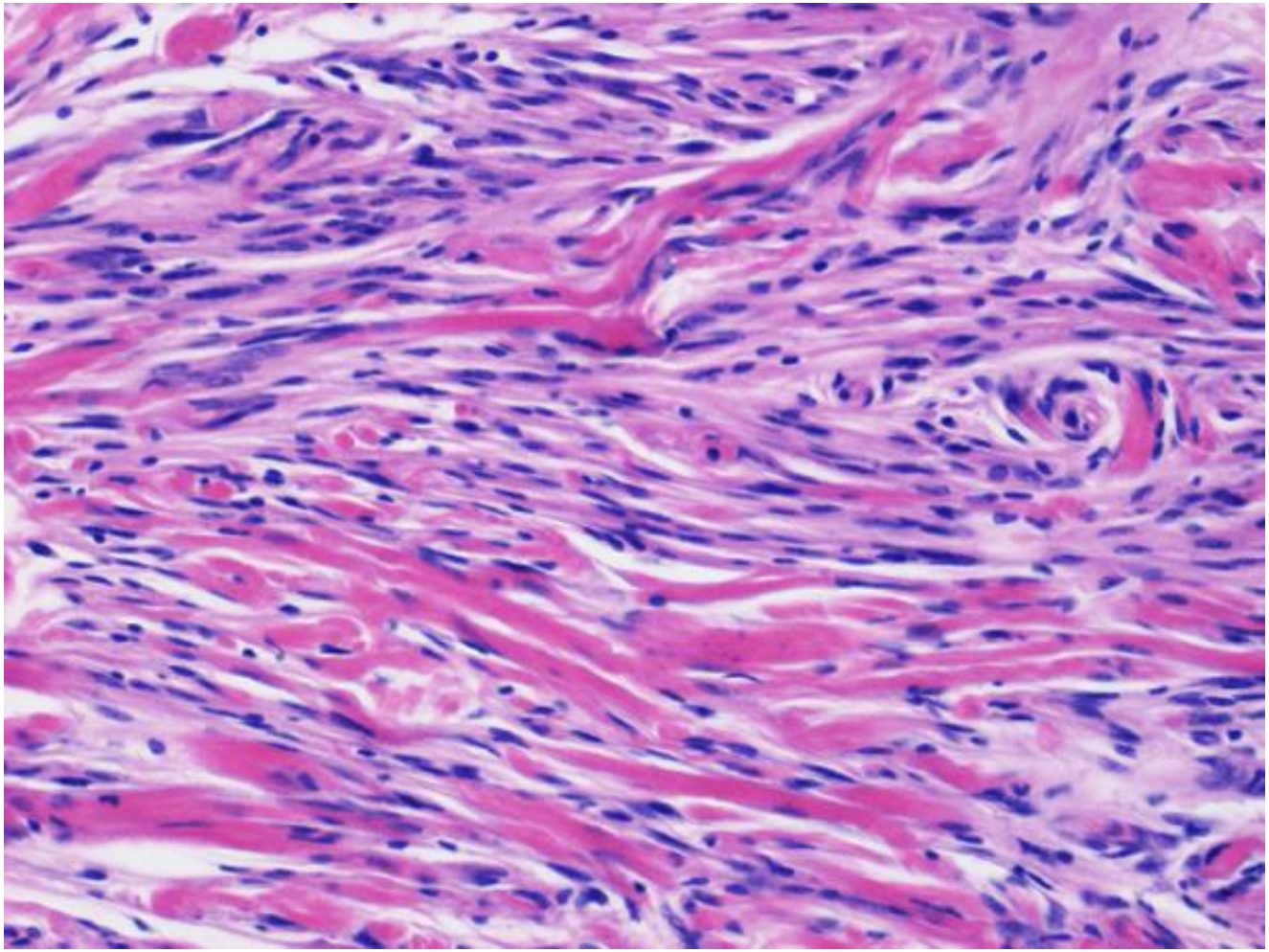
Mawrin C & Perry A, J Neuro-Oncol 2010

Meningothelial Meningioma Grade I



Epithelial phenotype

Fibroblastic meningioma Grade I



Mesenchymal phenotype

Long-term prognosis of WHO grade I meningioma

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Rate of 5 years progression free survival of patients with meningioma of WHO grade I

Authors	Year	No. of patients	Extent of surgery GTR/IR/IR+RT	% PFS after GTR	% PFS after IR	% total PFS GRT+IR
Adegbite	1983	114	88/26/–	~85%	48%	
Mirimanoff	1985	225	145/80/–	93%	63%	
Jääskelainen[a]	1986	657	657/–/–	81%		
Taylor[b]	1988	132		77%	18%	82%
Glaholm	1990	186	–/–/186			87%
Goldsmith	1994	117	–/–/117			89%
Mahmood	1994	276	199/77/–	97%	64%	
Condra	1997	250	137/92/21	93%	53%	90%
Stafford	1998	581	463/118/–	88%	61%	
Nutting	1999	82	–/–/82			92%
Ayerbe	1999	286	242/44/–	~90%	70%	
Debus	2001	113	–/–/113			97%

GTR. . . gross total resection = Simpson Grade I and II IR. . . incomplete resection = Simpson grade ≥III RT. . . radiotherapy.

[a] Follow-up of 20 years.

[b] Follow-up of 10 years.

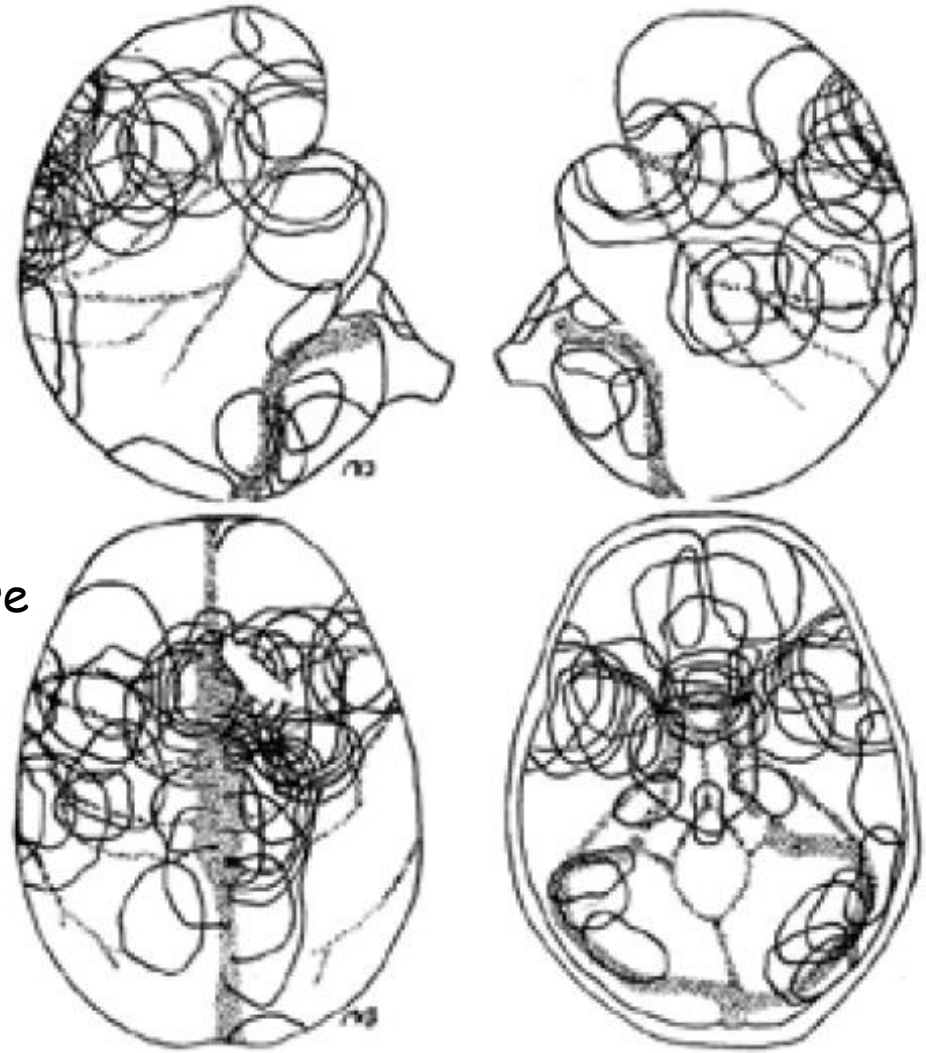
….mostly cured….

Marosi et al., Crit Rev Hem Oncol 2008

Intracranial meningioma: localisation

Convexity

- fibroblastic / transitional meningioma
- Grade II/III more frequent

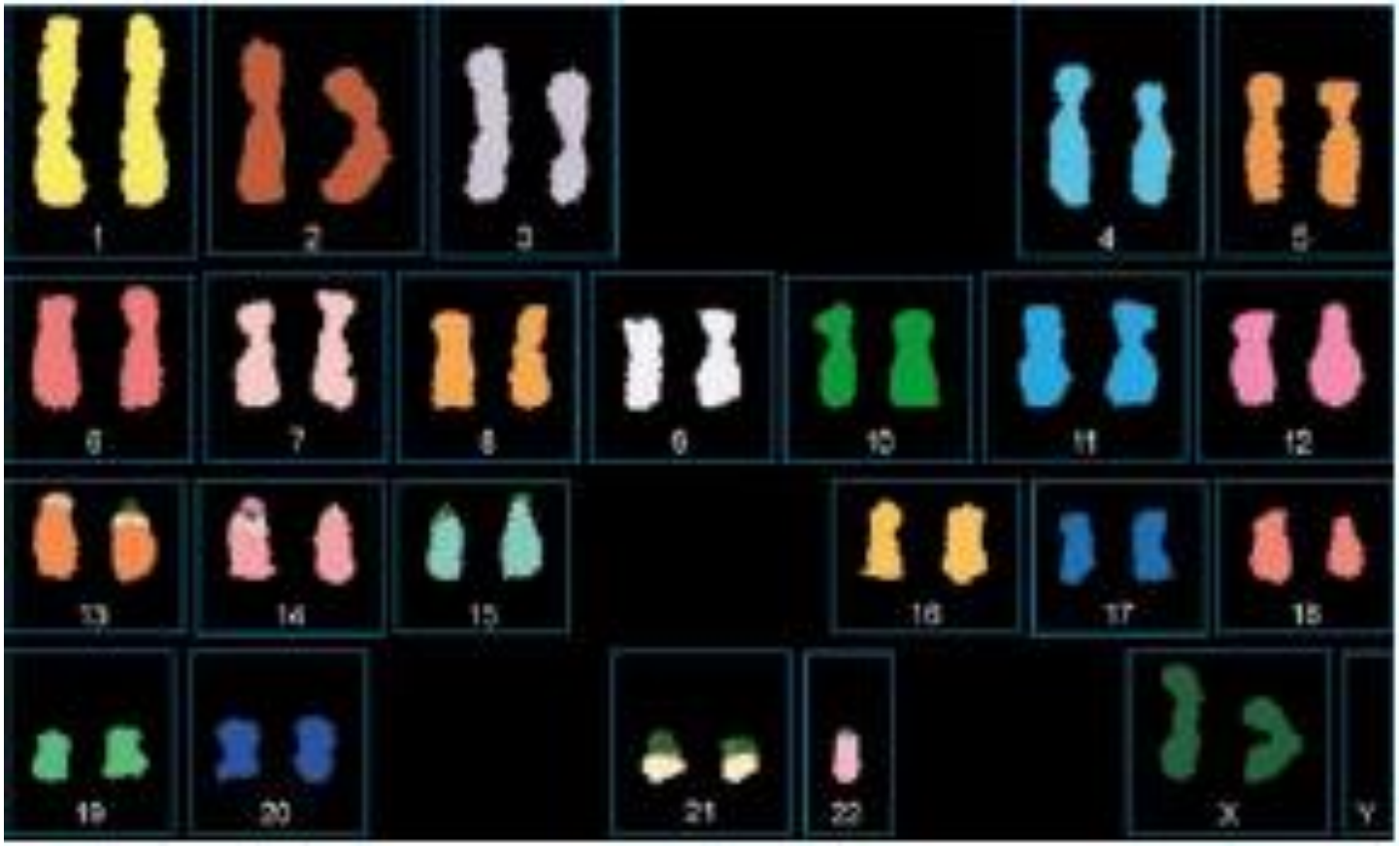


Skull base

- meningothelial meningioma
- Grade II/III uncommon

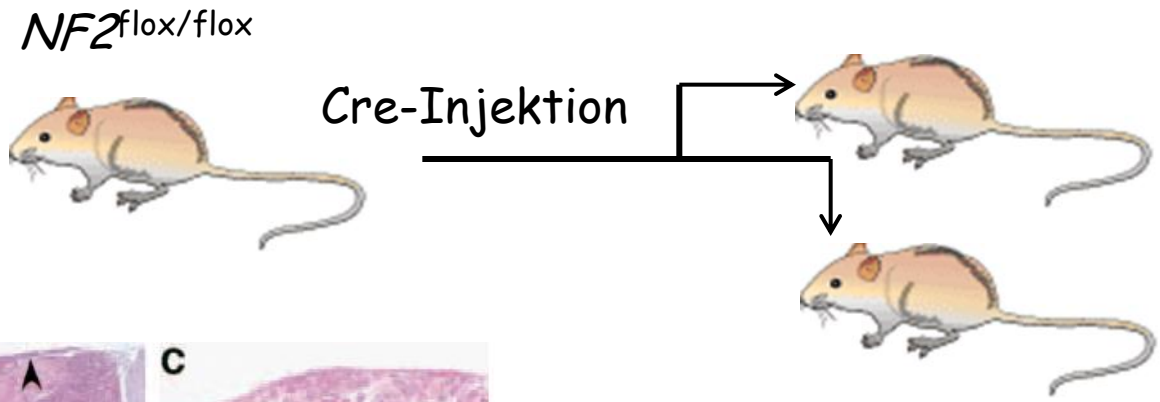
Bailey P 1948, Kros et al. 2001, Hansson et al. 2007, Ketter et al. 2008

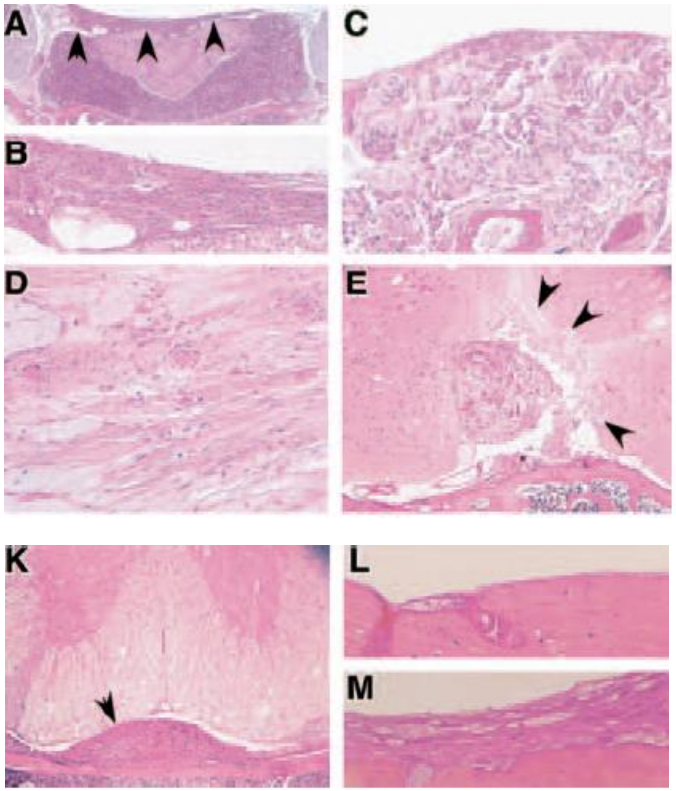
Loss of chromosome 22 in meningioma

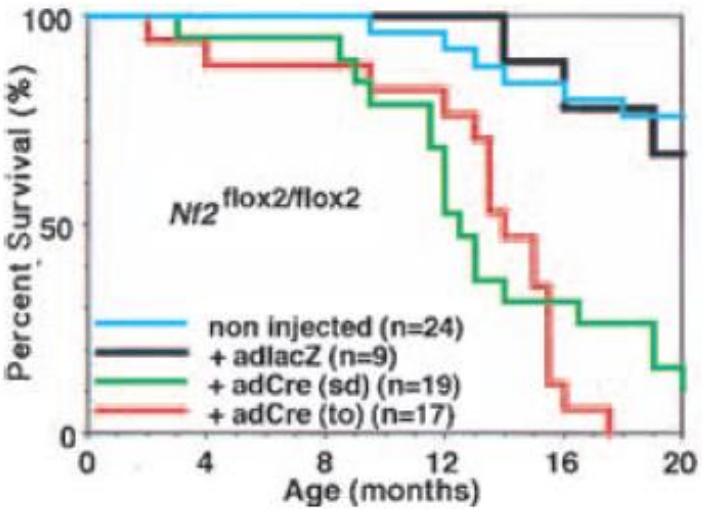


Zang & Singer, NATURE 1967, Zang Cytogen Cell Genet 2001

Meningioma development: Critical role of *NF2*







Kalamarides et al. Genes Dev 2002

Intracranial meningioma: localisation

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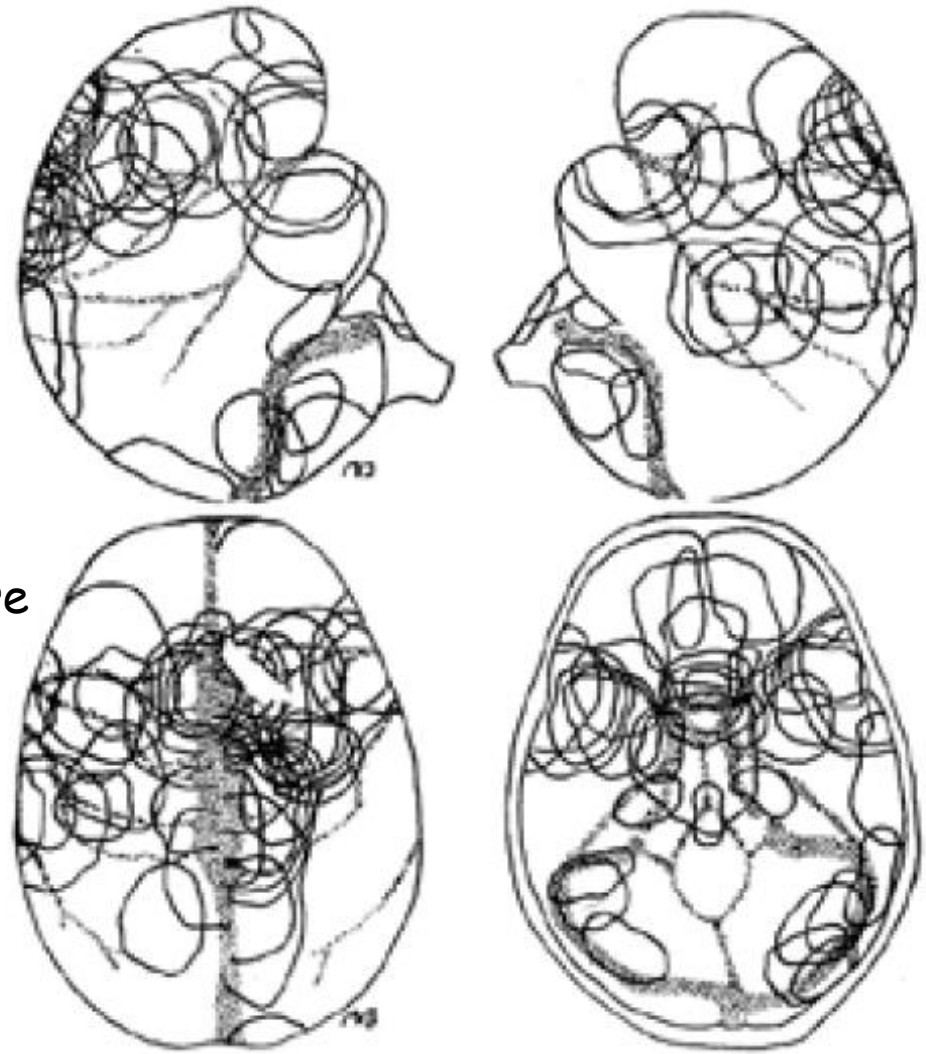
Convexity

- fibroblastic / transitional meningioma
- Grade II/III more frequent
- Frequent *NF2* alterations



Skull base

- meningothelial meningioma
- Grade II/III uncommon
- *NF2* wild-type

Bailey P 1948, Kros et al. 2001, Hansson et al. 2007, Ketter et al. 2008

Recurrence in meningiomas: Localisation matters !

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Table 3
Outcome and complications of resection of meningiomas "in difficult locations"

Author	Year	Characterization of meningioma	*n*	Rate of total resection in (%)	Diameter (cm)	Duration of follow-up in months	Rate of complications in %	Recurrence in %
Schick	2005	Tuberculum sellae	53	90	2.6		13	3.7
Sandalcioglu	2005	Spheno-orbital	16	69		68		56
Chandler	2005	Cranial base	29	83		34	55,100% cranial neuropathies	
Spector	2005	Olfactory groove	80	90	4.6	70	31	7
Tzortzidis	2005	Giant, anterior fossa	20	100	>4.5	3–10 years		10
Roser	2005	Sphenoid wing	82			66		30
Schick	2006	Sphenoid wing	67	60		30.5	15	10
Caroli	2006	Sinus sagittalis	328	59				38
Xu	2006	Sphenoidal ridge	56	19			25	
Bertalanffy	2006	Intraventricular	16	93	5		12.51 death	

Marosi et al., Crit Rev Hem Oncol 2008

Modeling meningioma pathology in mice

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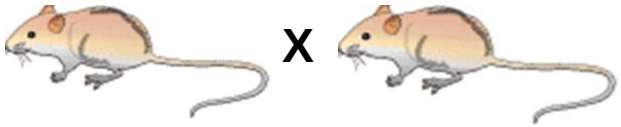
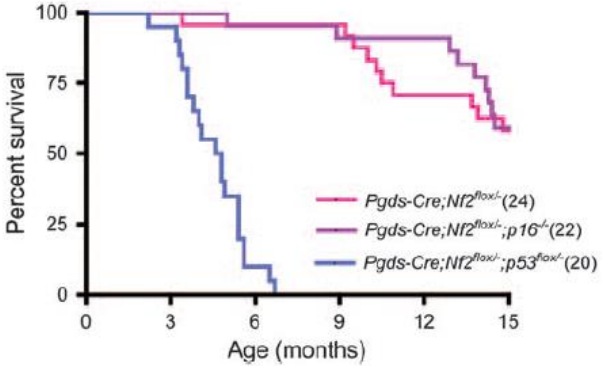
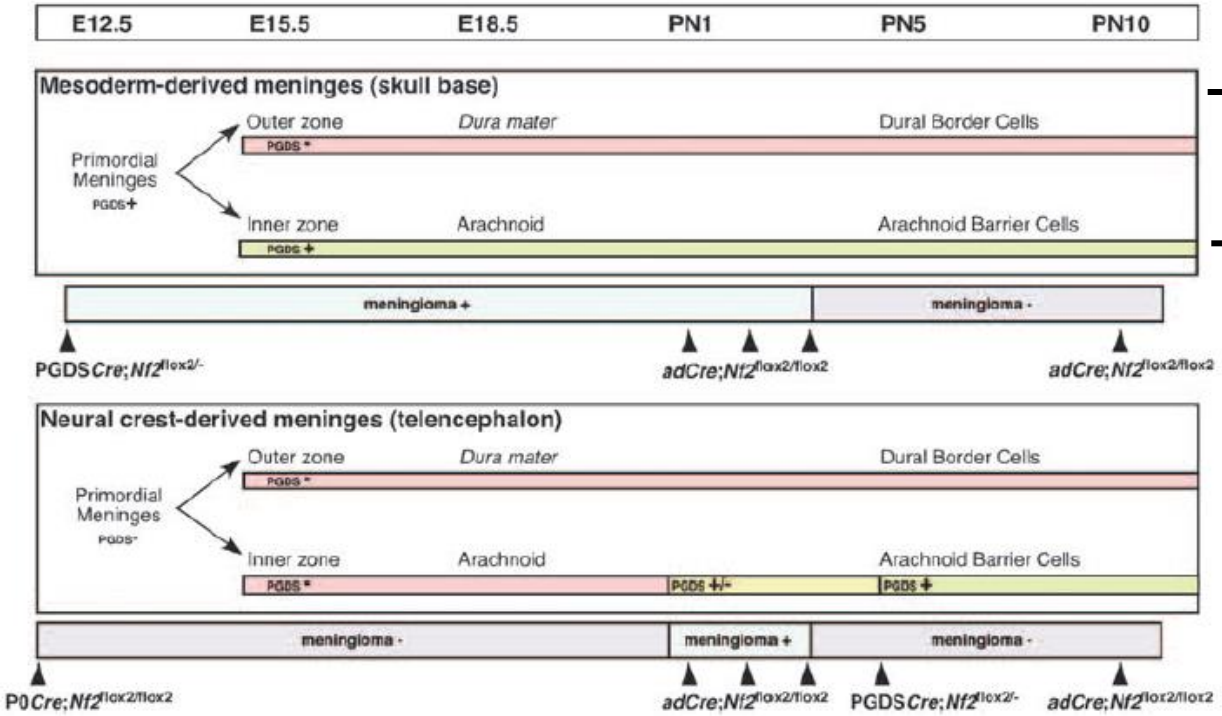
PGDS – prostaglandin D synthase gene = specific meningeal promoter

PGDS*Cre* X *NF2*$^{flox/flox}$

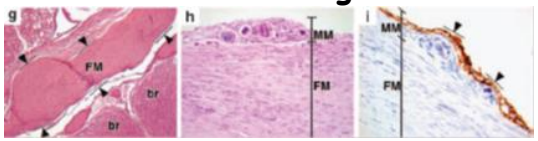


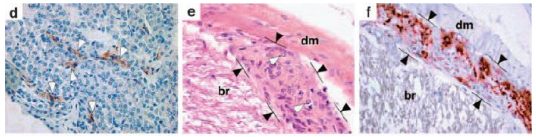


WHO Grade I meningioma of the skull base



Fibroblastic Meningioma



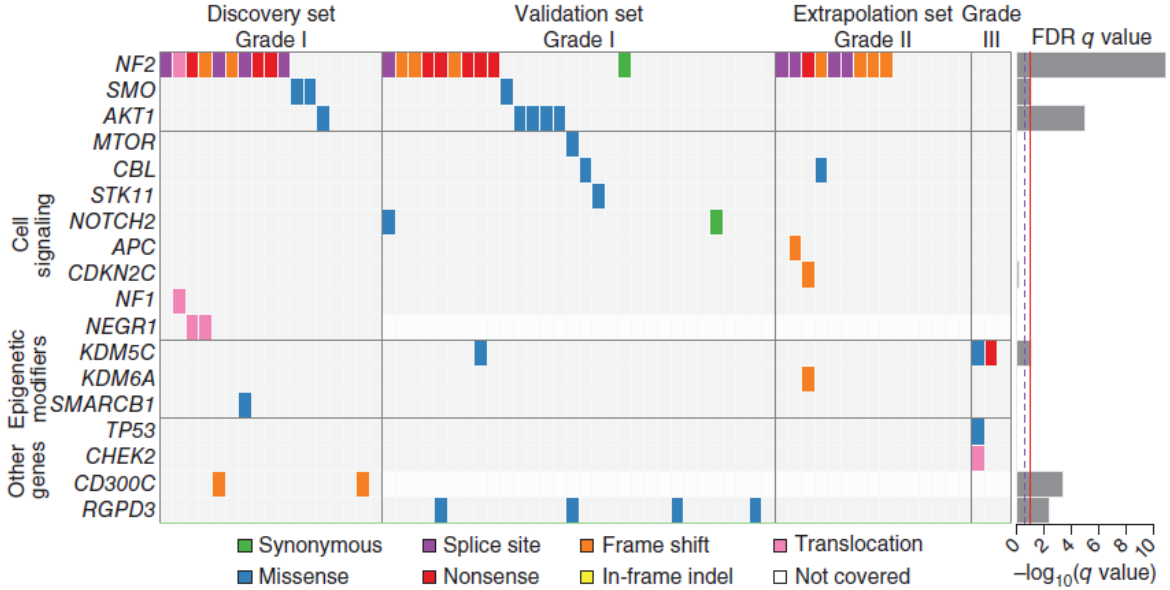


Meningothelial Meningioma

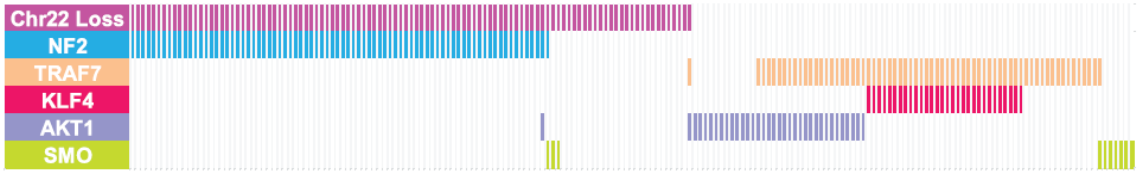
Kalamarides et al. Oncogene 2011

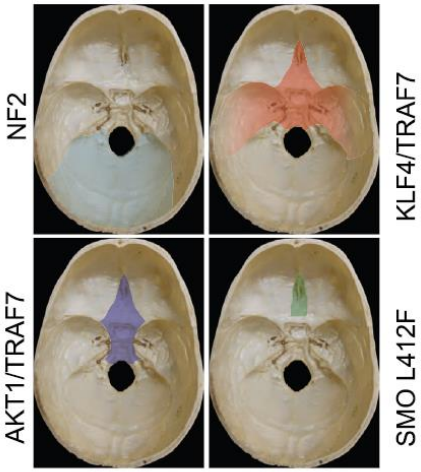
New molecular players in meningioma ?

- *AKT1*^{E17K} (~8%)
- *TRAF7/KLF4* (~25%)
- *Smo* (~5%)



Brastianos et al., Nat Genet. 2013

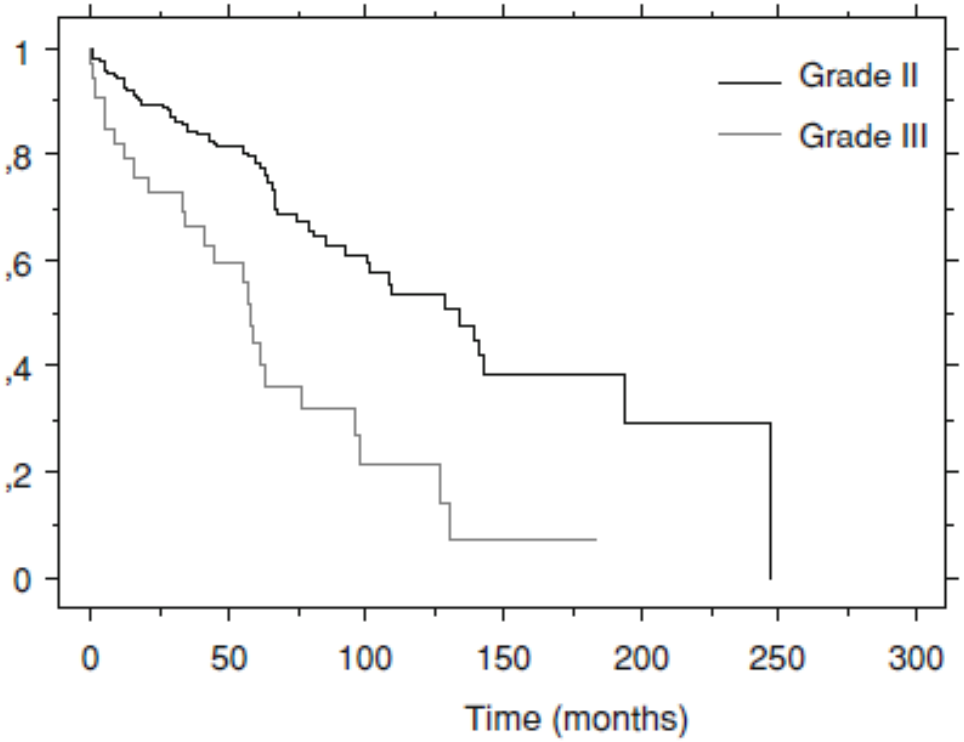


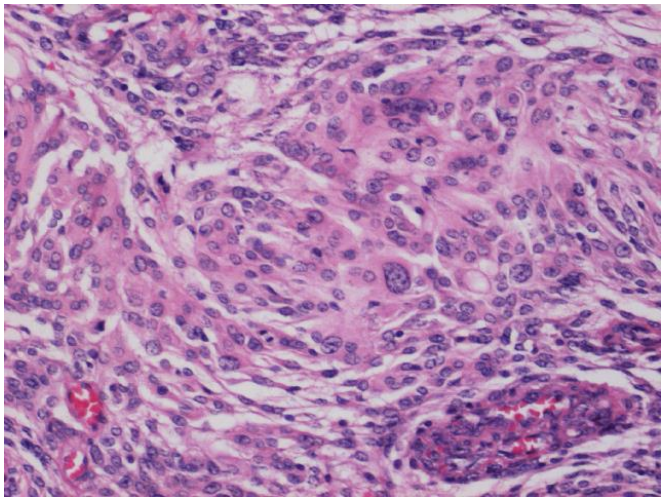


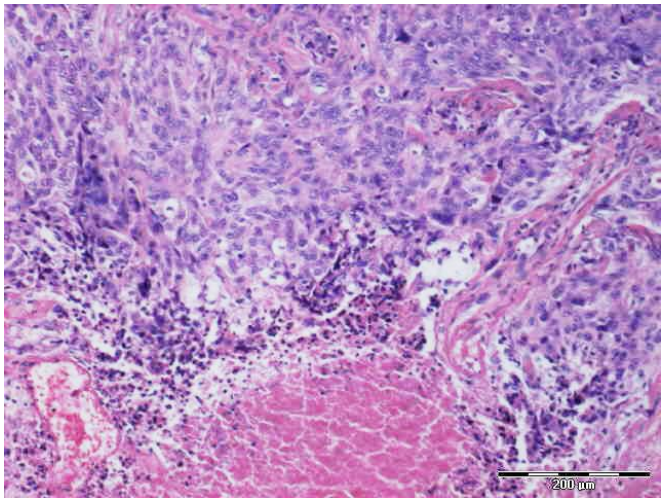
- occur in Grade I tumors !
- only wild-type *NF2* meningiomas

Clark et al., SCIENCE 2013; Reuss et al.; Acta Neuropathol 2013

Overall survival in high-grade meningiomas



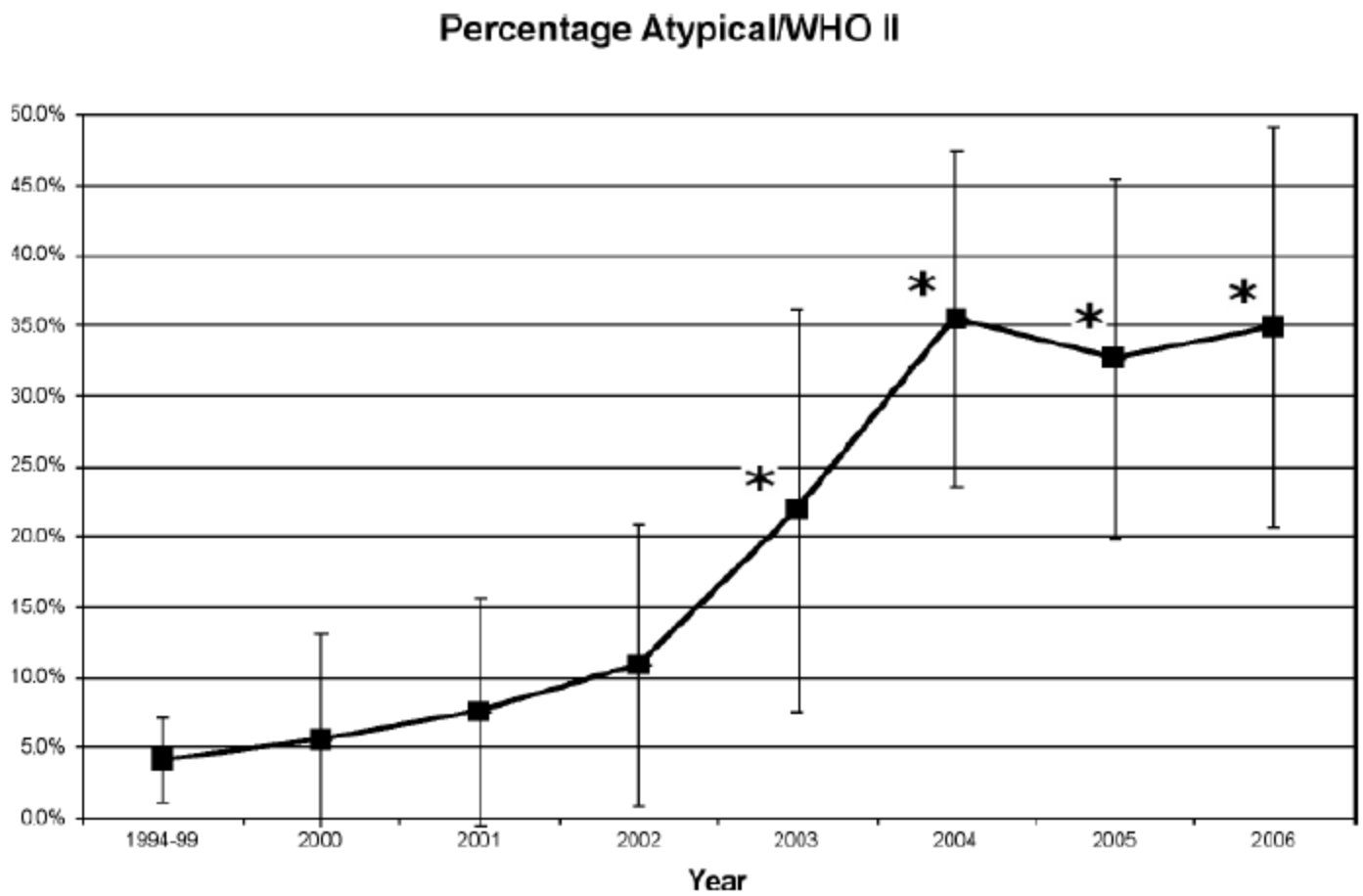




….occasionally deadly….

Durand et al., J Neuro-Oncol 2009

„Hitting a moving target…."



Pearson et al, Neurosurg Focus 2008

Brain invasion of meningiomas (WHO classification)

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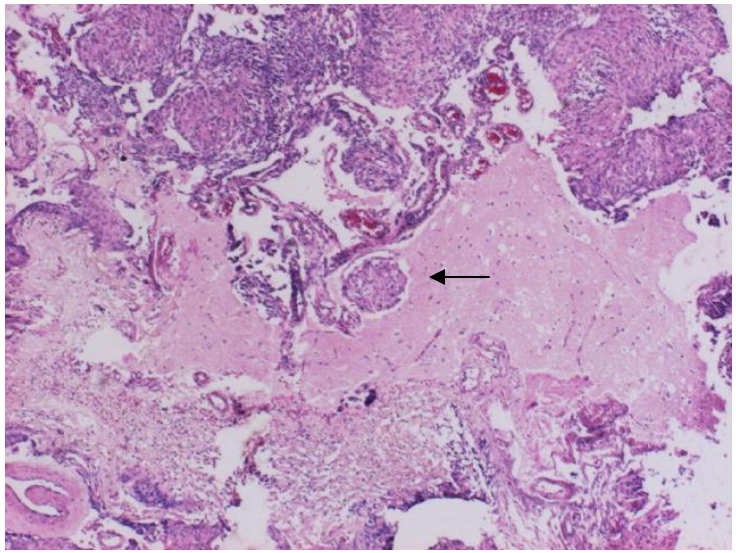
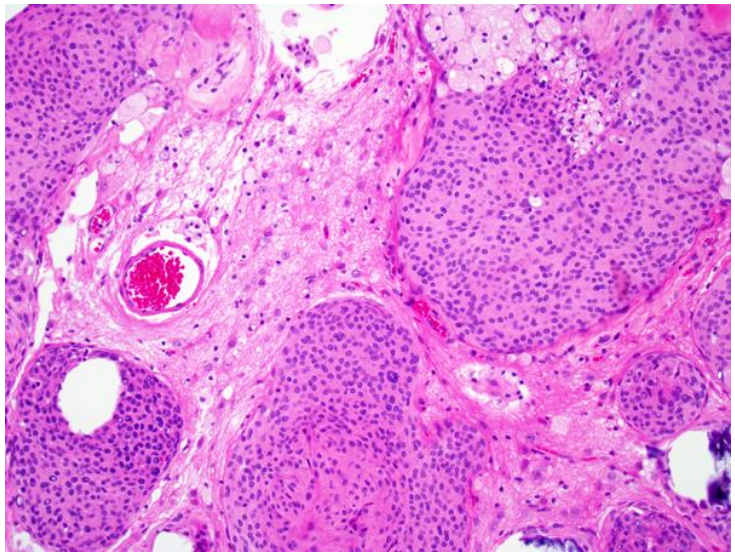
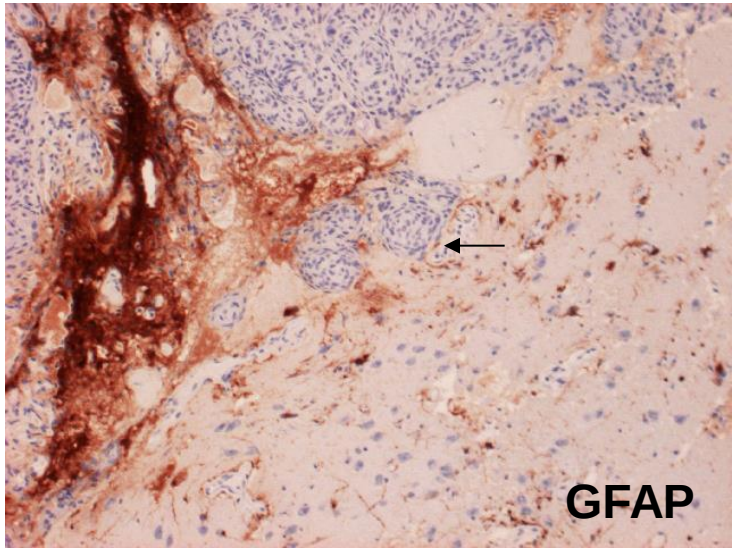
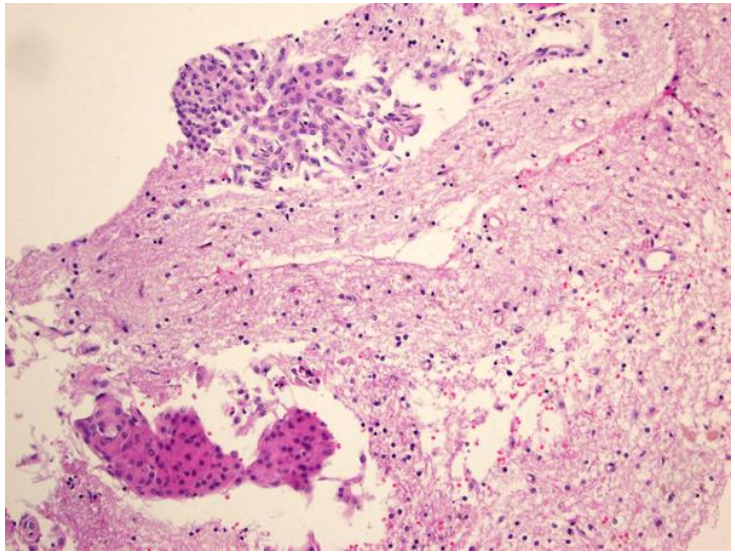
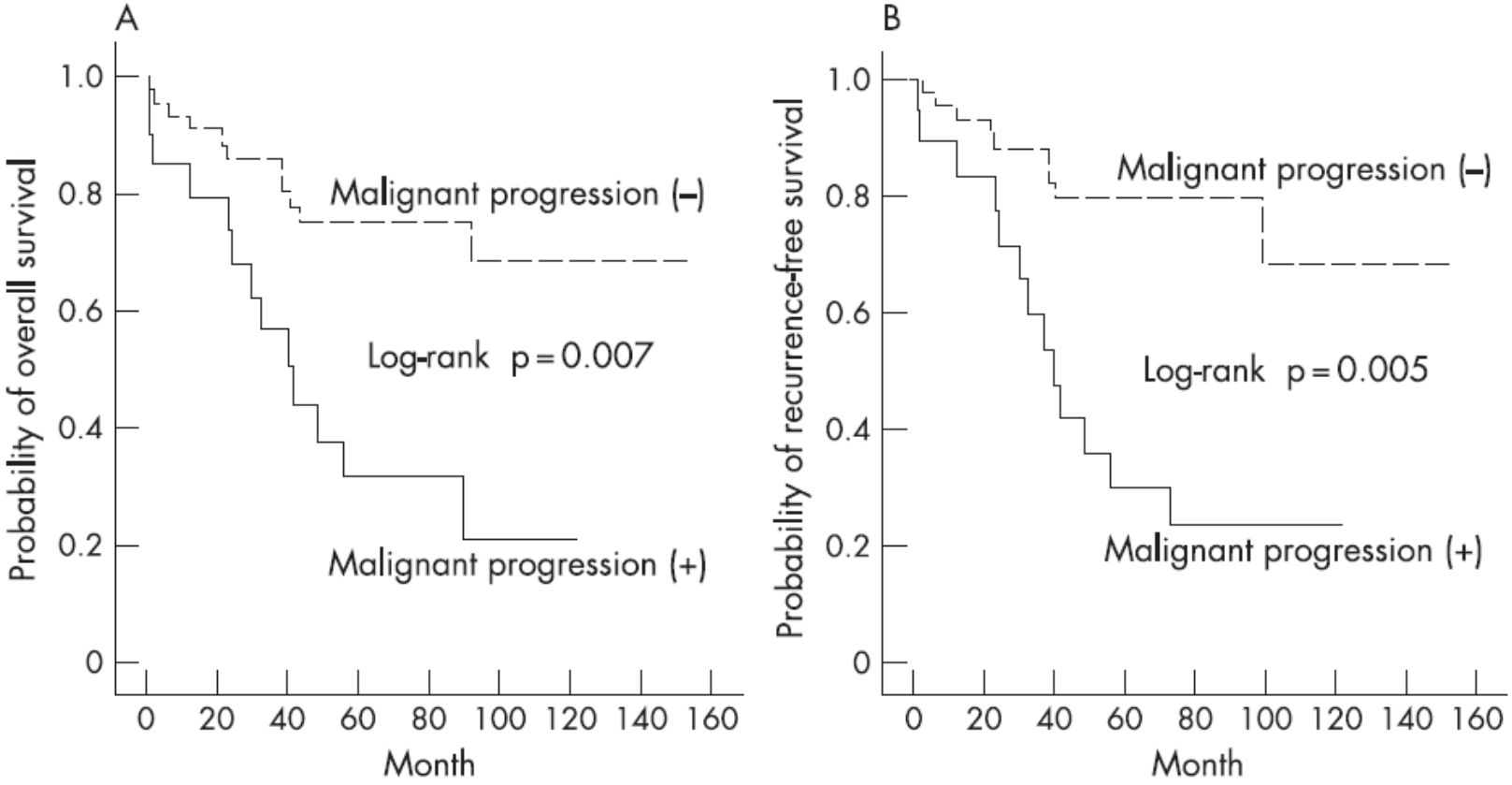








Malignant progression in meningioma



Yang et al., JNNP 2008

Molecular mechanisms of meningioma development

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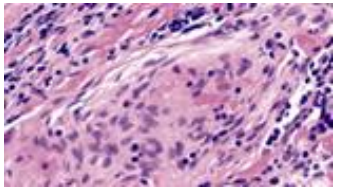
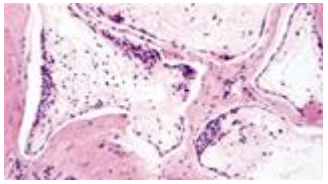
Meningothelial Hyperplasia

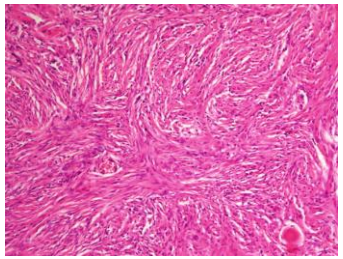


Gain of PR expression (65%)

Arachnoid Cap Cells

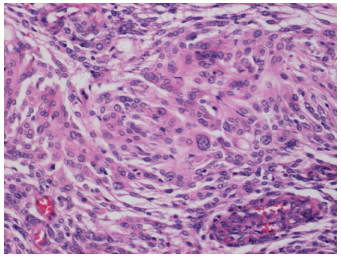


Meningioma Grade I



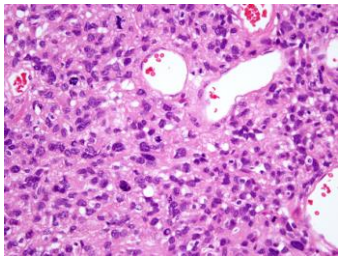
Chr. **22q loss** (40-70%)
NF2 mutations (30-60%)
PR expression gain (50-90%)
Loss of 4.1B expression (20-50%)
Loss of **TSLC1** xpression (30-50%)
Other 22q alterations: BAM22, BCR (breakpoint cluster region)

Atypical Meningioma



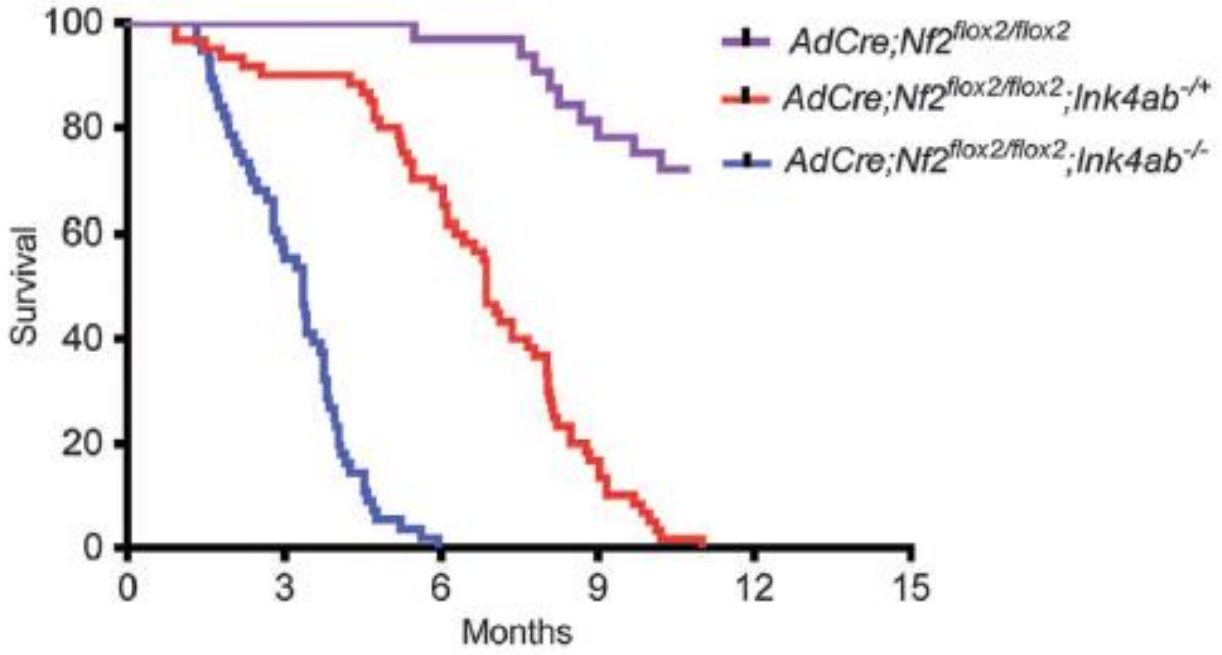
Chr. **1p loss** (40-75%)
Chr. **9p loss** (52 %)
Chr. **14q loss** (30-60%)
Chr. 18q loss (40%)
Chr. 10 loss (30-40%)
Chr. 6q loss (30%)
Chr. 22q: TIMP3 hypermeth.(22%)
Gains of 1q, 9q, 12q, 15q, 17q, 20q
Loss of **TSLC1** expression (70%)
Loss of PR expression (60-80%)
Telom./hTERT activation (60-95%)

Anaplastic Meningioma



Chr. **1p loss** (70-100%)
Chr. **9p loss** (74%)
Chr. **14q loss** (60-100%)
Chr. 18q loss (60-70%)
Chr. 10 loss (40-70%)
Chr. 6q loss (50%)
Loss of **TSLC1** expression (70%)
Loss of PR expression (80-90%)
Chr.**14q2**: NDRG2 hypermeth. (70%)
Chr. 22q: TIMP3 hypermeth.(67%)
17q23 amplification

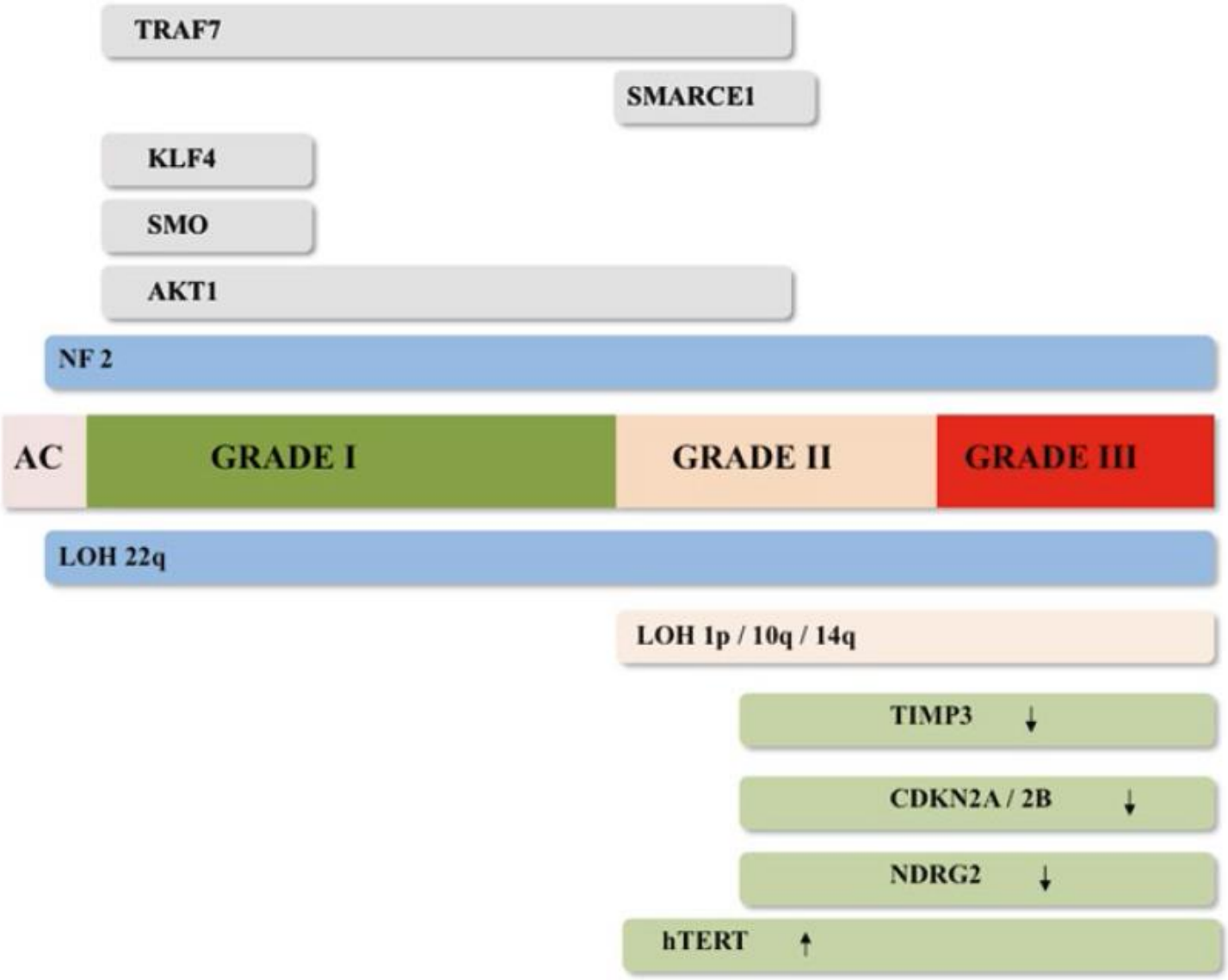
Malignancy in meningiomas: Mouse model support Cdkn2A



CDKN2A

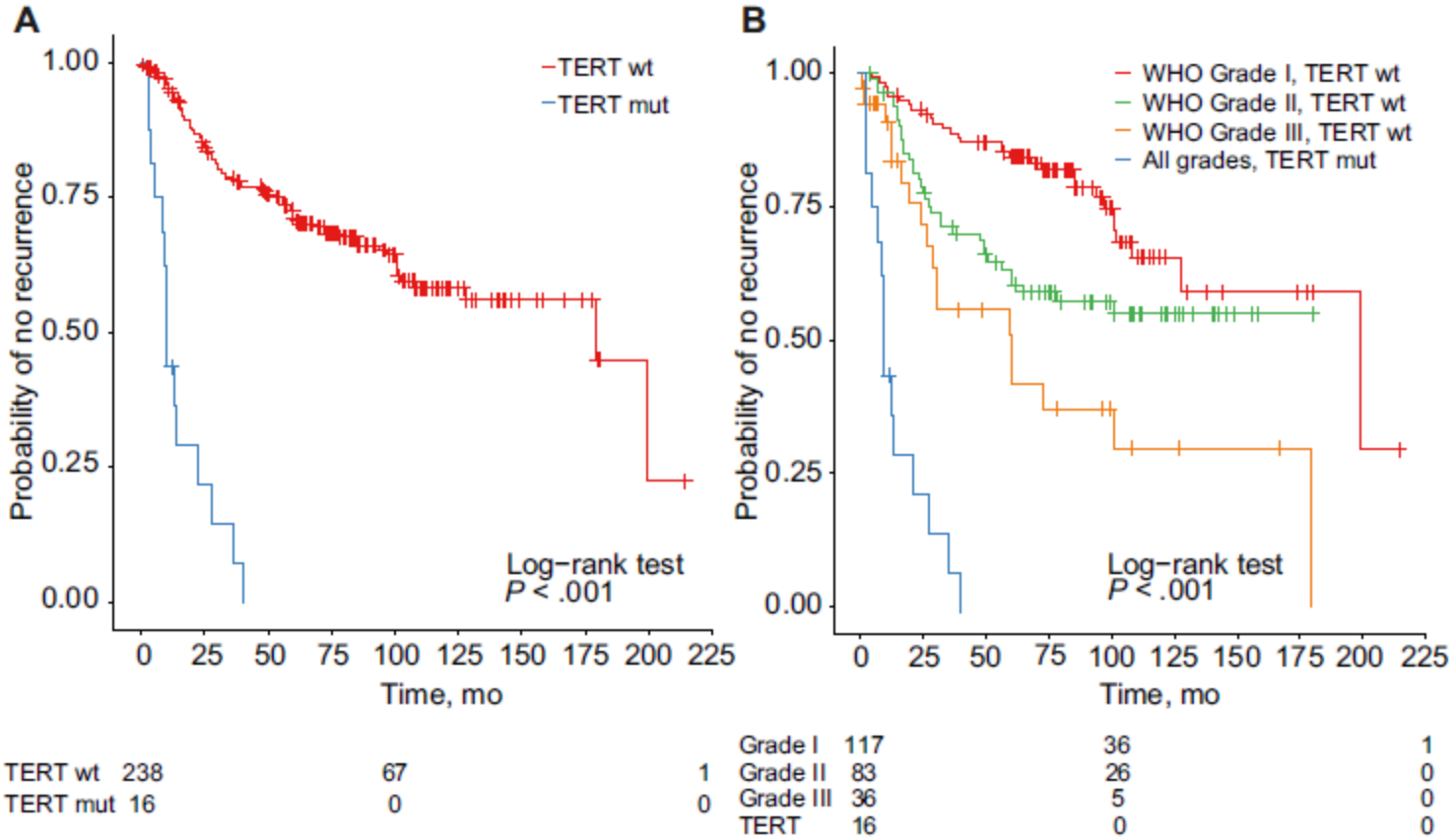
Peyre et al., Oncogene 2013

Molecular progression of meningiomas



from Mawrin C & Kalamarides M: Molecular Genetic Pathology of Meningiomas. Springer 2015

TERT promoter mutations define meningioma recurrence



Sahm et al. J Natl Cancer Inst 2015

Meningioma therapy - the major challenge…..

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Despite advances in surgery, radiation therapy and radiosurgery, there remain a small but important subset of patients with meningiomas who develop recurrent disease refractory to conventional therapies. To date, chemotherapies have shown minimal activity and hormonal therapies have proven to be largely ineffective. Progress in identifying alternative forms of therapy for these patients with recurrent meningiomas has been limited by poor understanding of the molecular pathogenesis of meningiomas and the critical molecular changes driving tumor growth, and by the lack of meningioma cell lines and tumor models for preclinical studies. Nonetheless, progress in cancer

Wen et al., J Neuro-Oncol 2010

Meningioma therapy: VEGF-R (PDGF-R) inhibition

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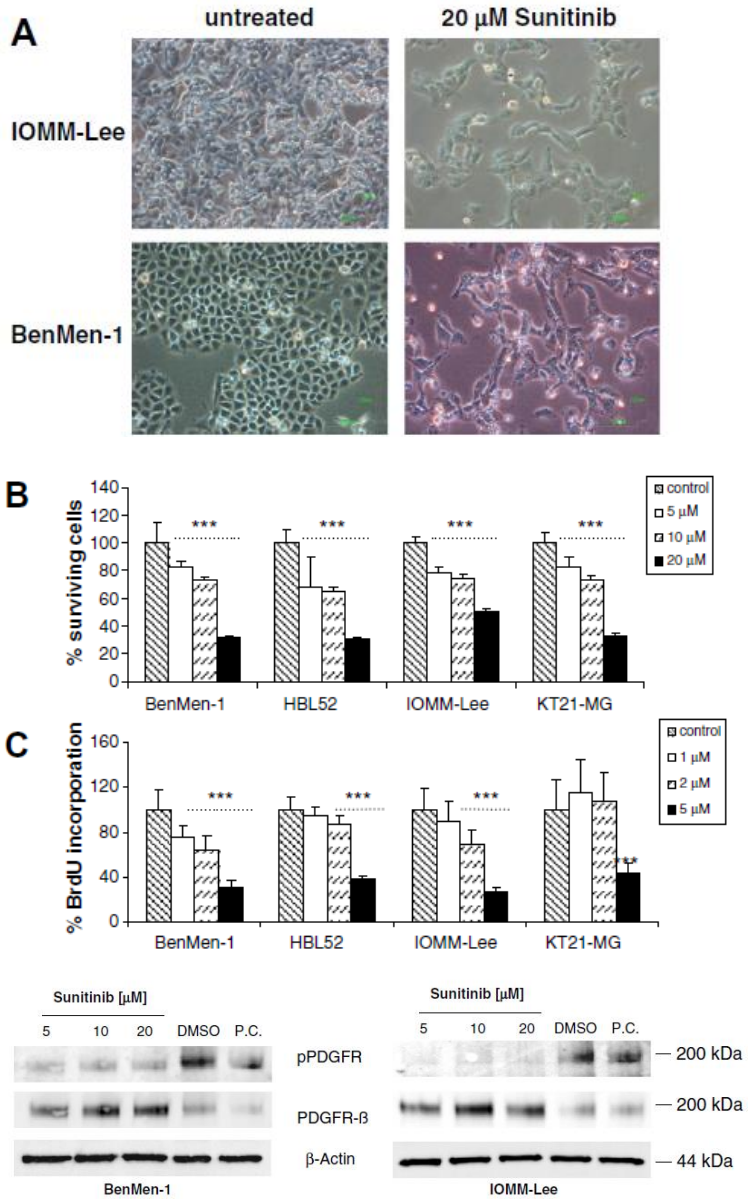
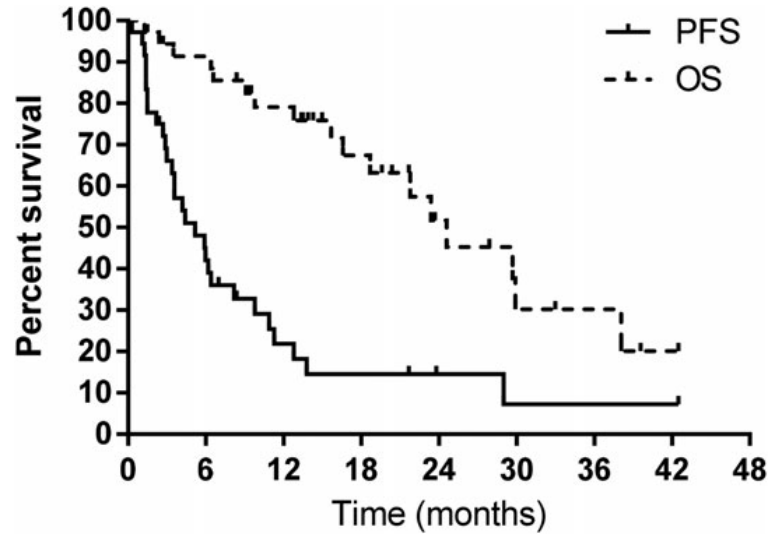
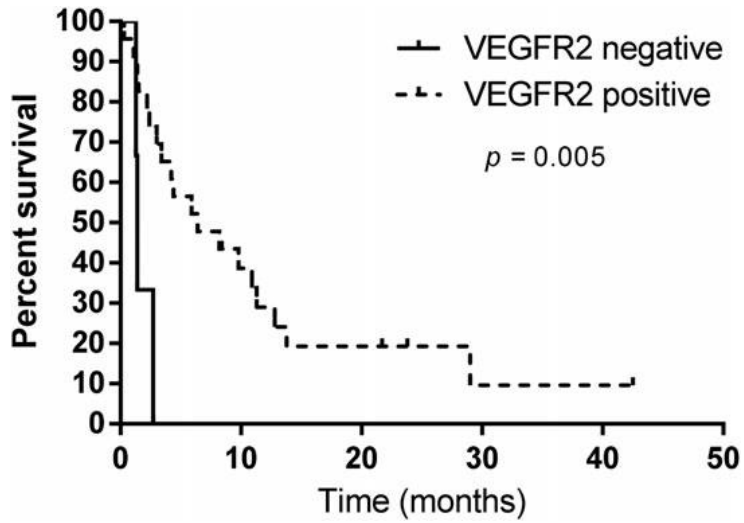
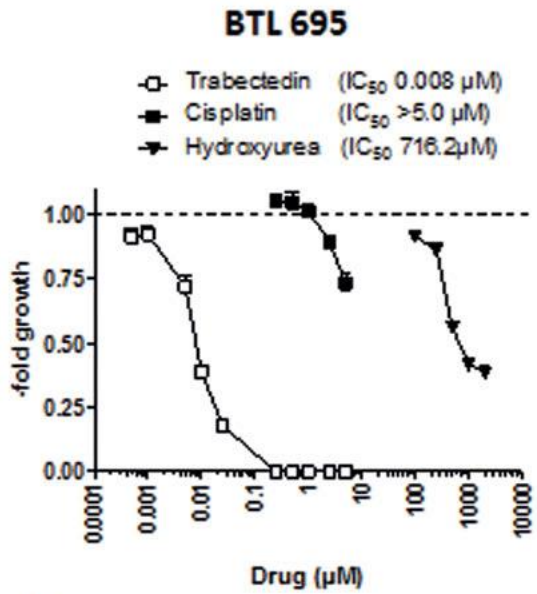


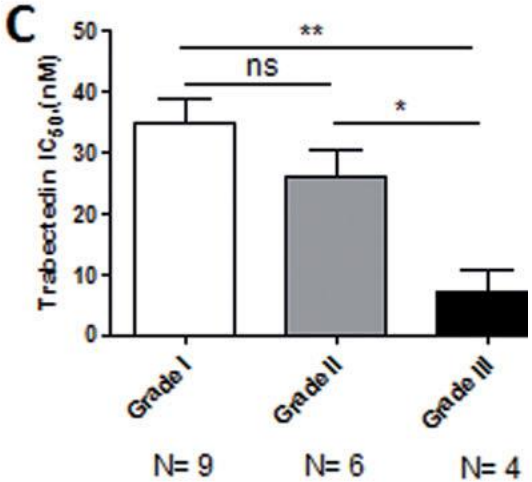


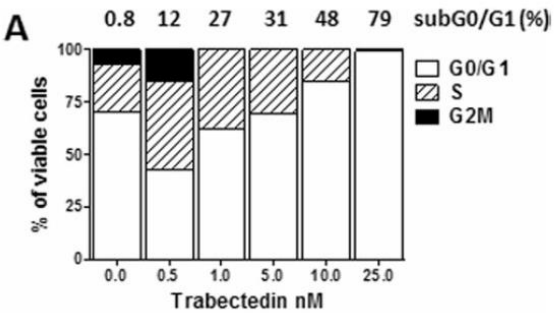


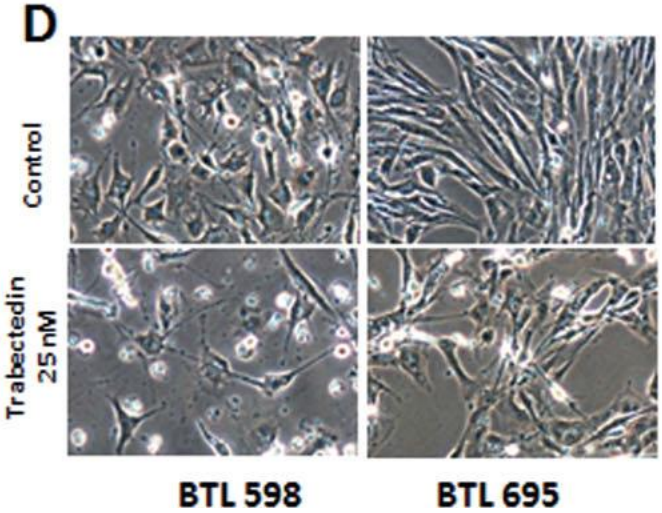
Andrae et al., Eur J Cancer 2012;Kaley et al., Neuro-Oncol 2014

Meningioma therapy: Trabectedin (EORTC-1320)









Trabectedin for Recurrent Grade II/III Meningioma
This study is currently recruiting participants. (see Contacts and Locations)
Verified December 2015 by European Organisation for Research and Treatment of Cancer - EORTC
Sponsor:
European Organisation for Research and Treatment of Cancer - EORTC
Information provided by (Responsible Party):
European Organisation for Research and Treatment of Cancer - EORTC
ClinicalTrials.gov Identifier:
NCT02234050
First received: August 7, 2014
Last updated: December 14, 2015
Last verified: December 2015
History of Changes

Preusser et al., Cancer 2012

Conclusion (and challenges):

- Broad histopathological spectrum (Challenge 1)
- Older patients (Challenge 2)
- Define the role of grade I molecular markers (Challenge 3)
- Find effective treatment options for aggressive/recurrent tumors (Challenge 4)