MOLECULAR DIAGNOSTICS OF GLIOMAS

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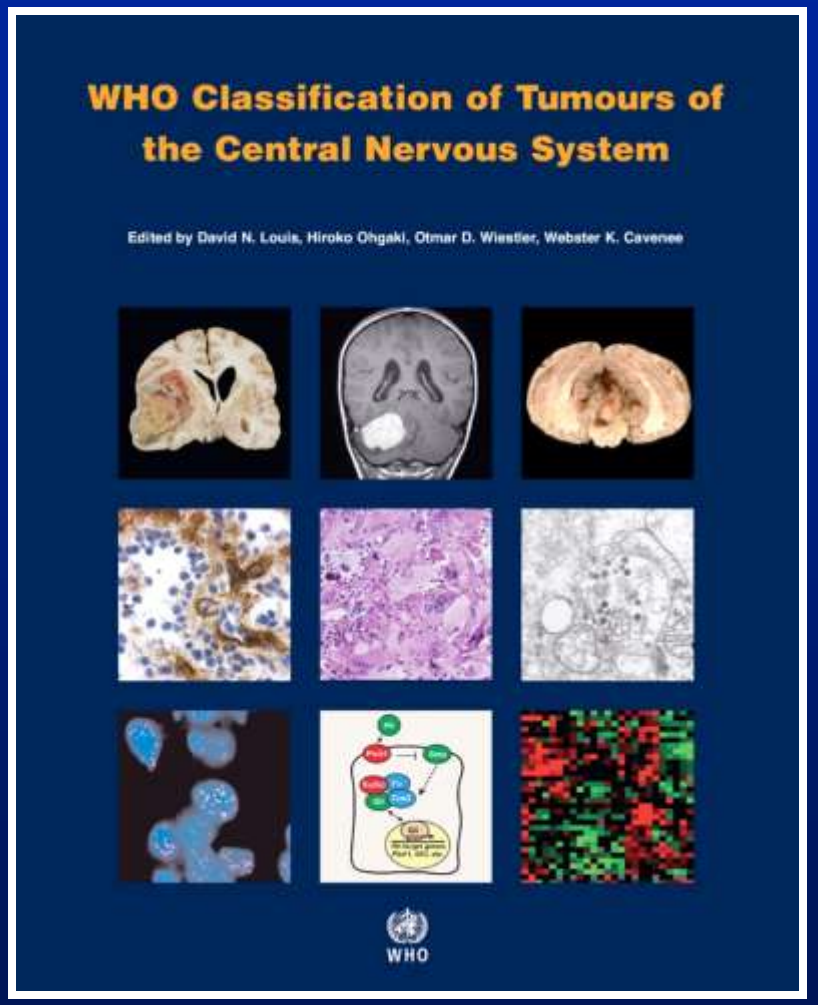
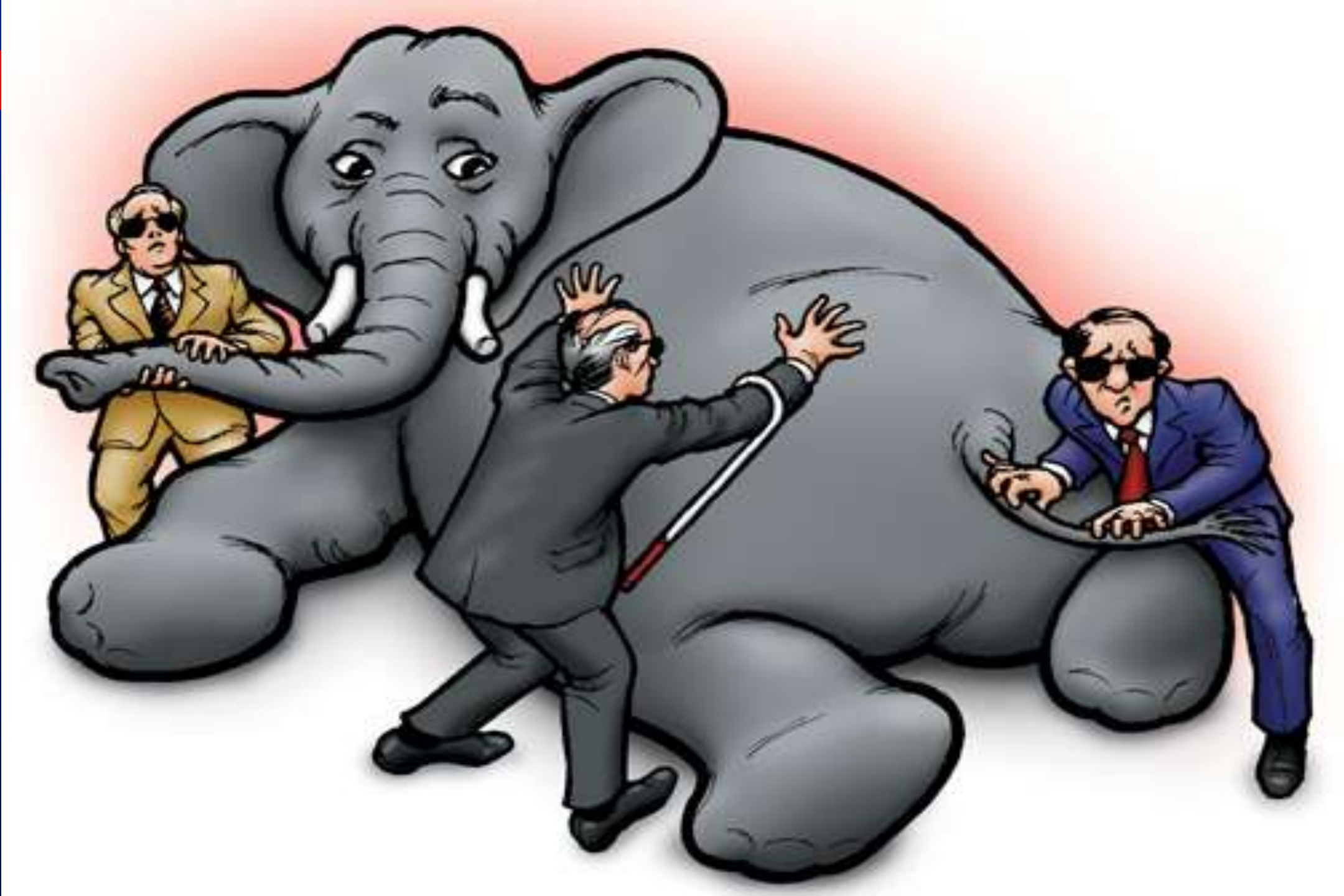
DIFFUSE GLIOMAS

- Cell types
  - Astrocytomas (A)
  - Oligodendrogliomas (O)
  - Mixed oligoastrocytoma (MOA)
- Three WHO grades: II, III, IV

GLIOMA GRADING: WHO 2007

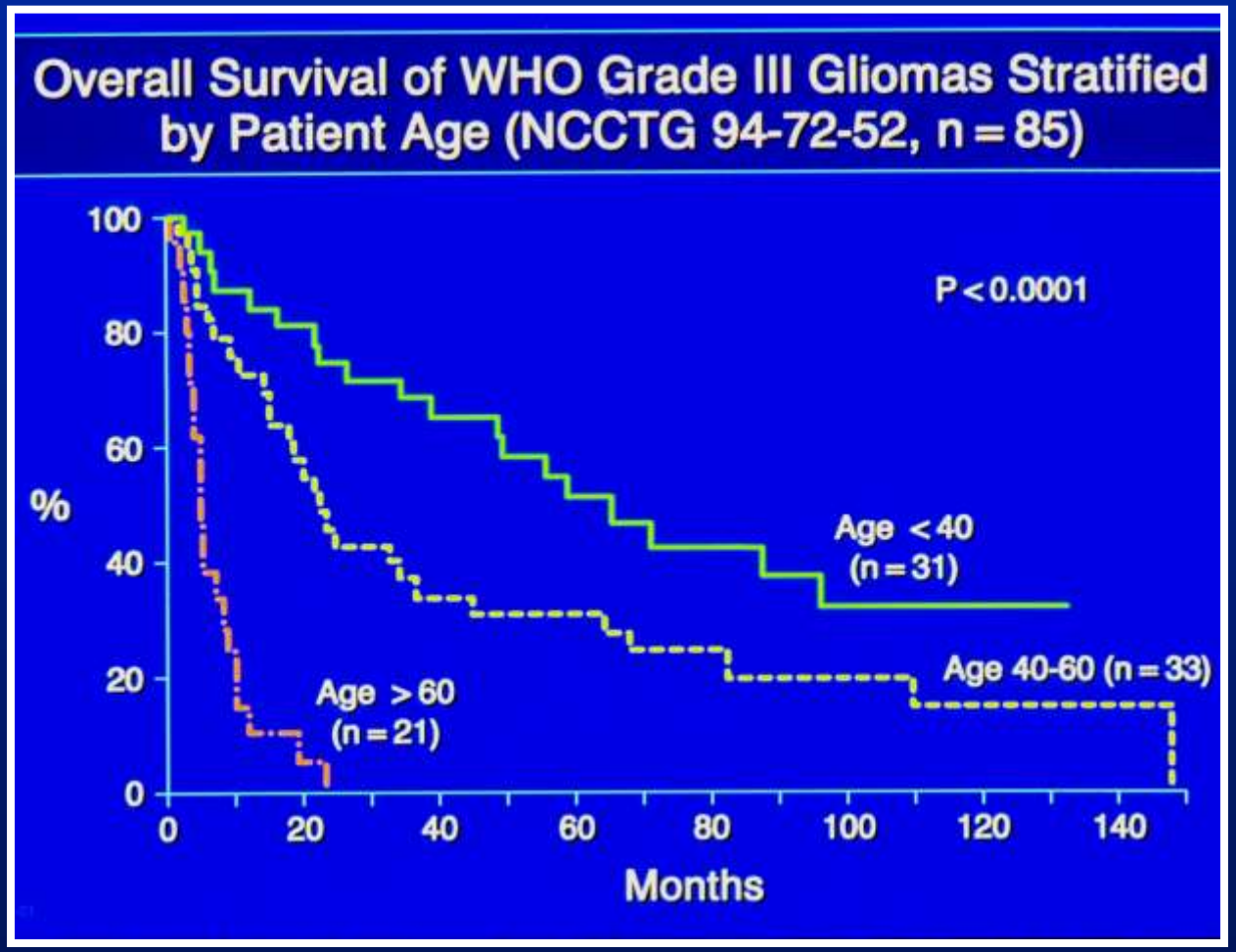
- Grade I = Benign
- Grade II = Low-grade
- Grade III = Anaplastic
- Grade IV = “GBM”



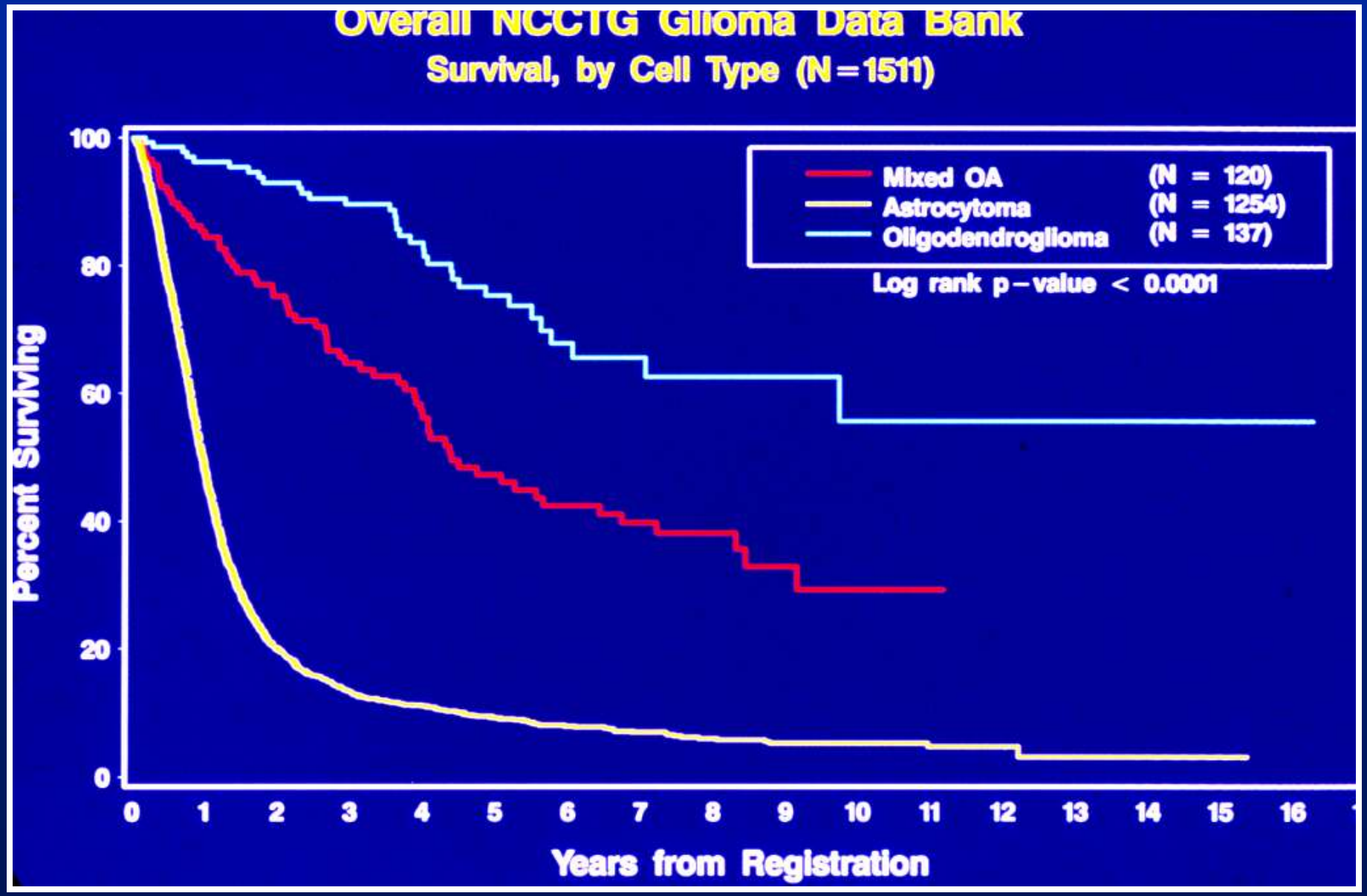


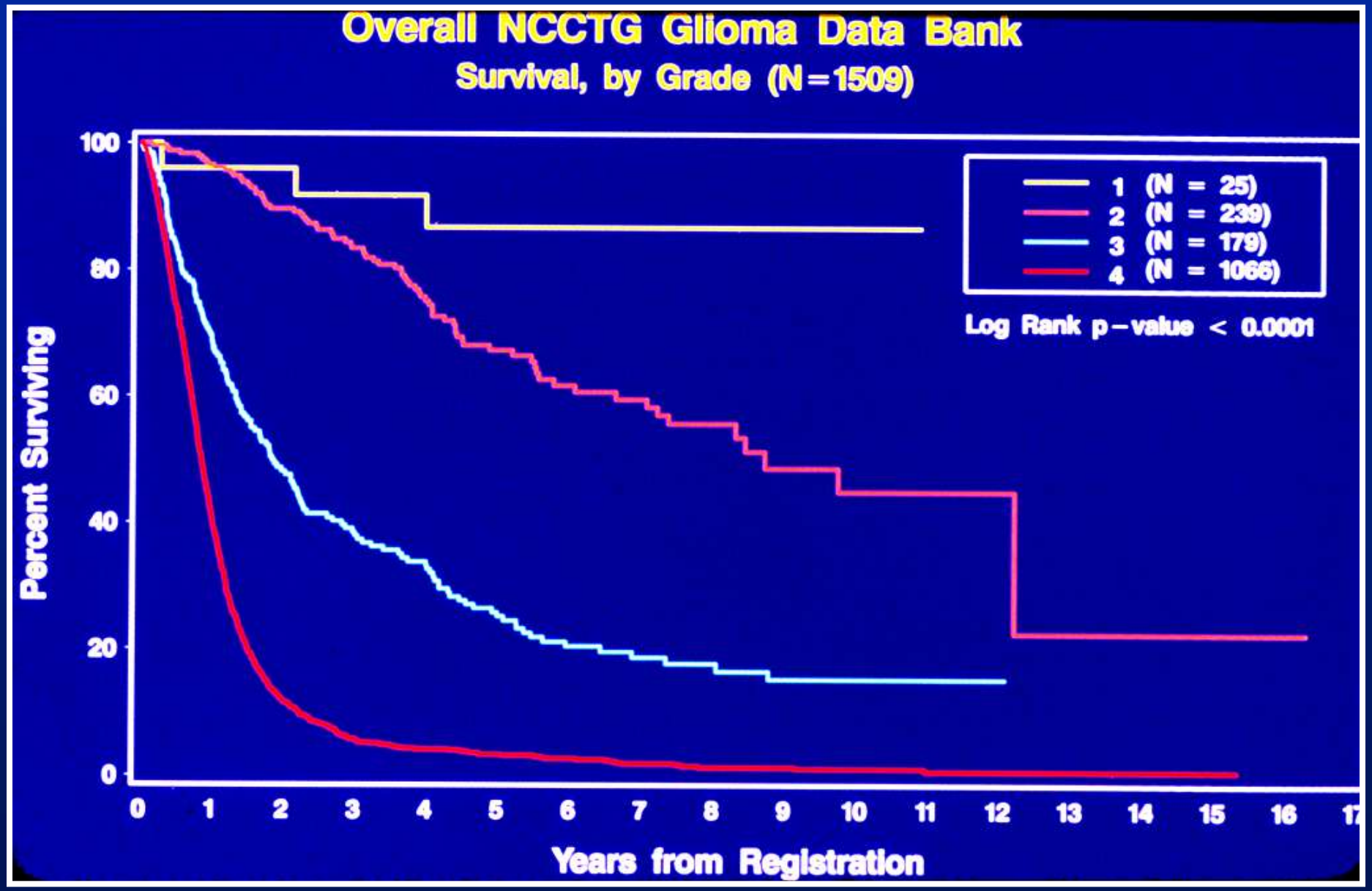
PROGNOSTIC VARIABLES

- Patient Age
- Histology
- KPS
- EOR
- Rx Response by Radiology
- Genetics



From: Perry A et al., Cancer 86:672-83, 1999

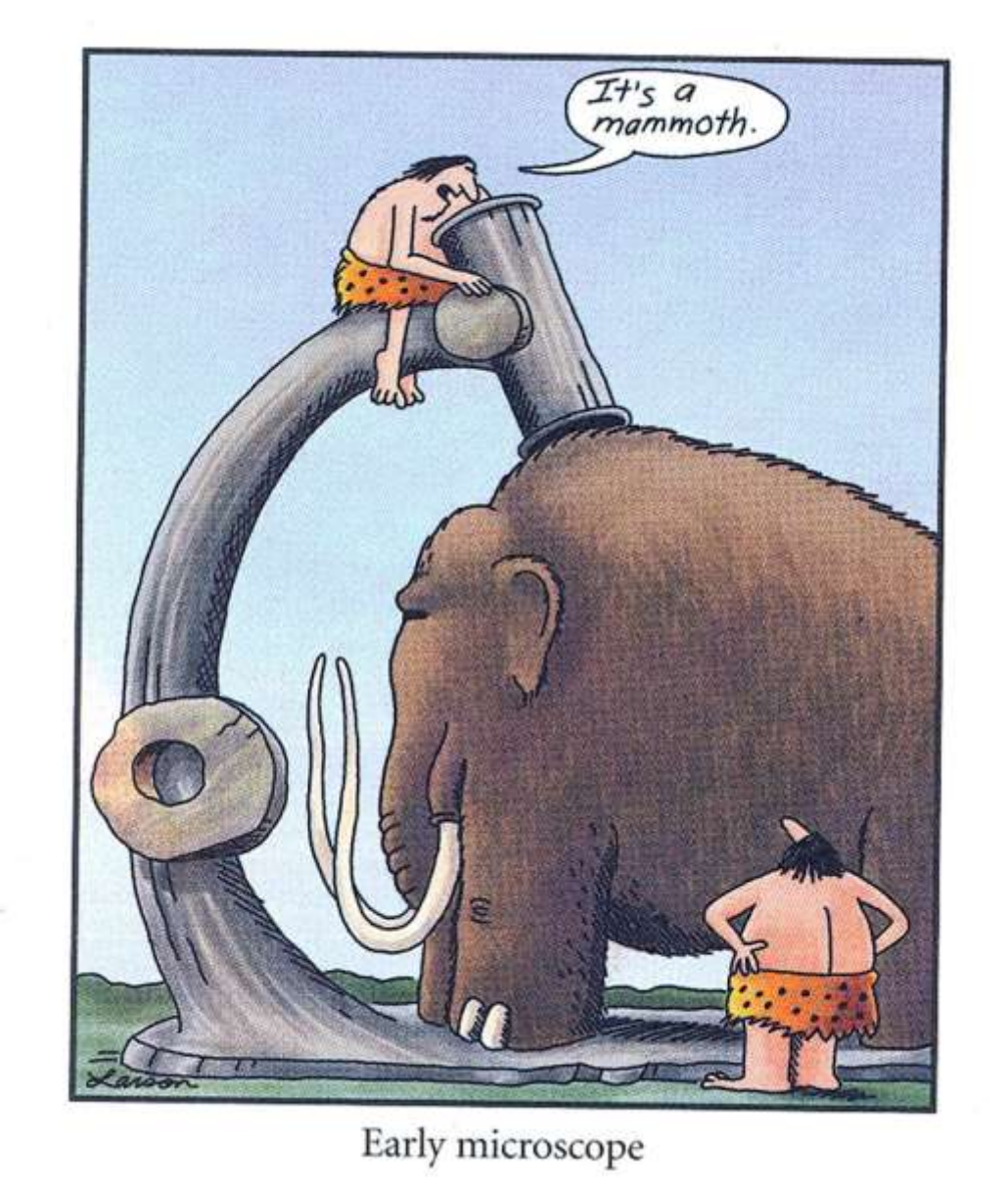

Overall NCCTG Glioma Data Bank
Survival, by Cell Type (N=1511)
Mixed OA (N = 120)
Astrocytoma (N = 1254)
Oligodendroglioma (N = 137)
Log rank p−value < 0.0001
Percent Surviving
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Years from Registration


Overall NCCTG Glioma Data Bank
Survival, by Grade (N=1509)
Percent Surviving
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Years from Registration
1 (N = 25)
2 (N = 239)
3 (N = 179)
4 (N = 1066)
Log Rank p-value < 0.0001

PATTERN RECOGNITION

HETEROGENEITY ISSUES

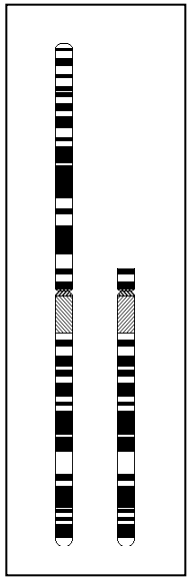
SAMPLING ERRORS



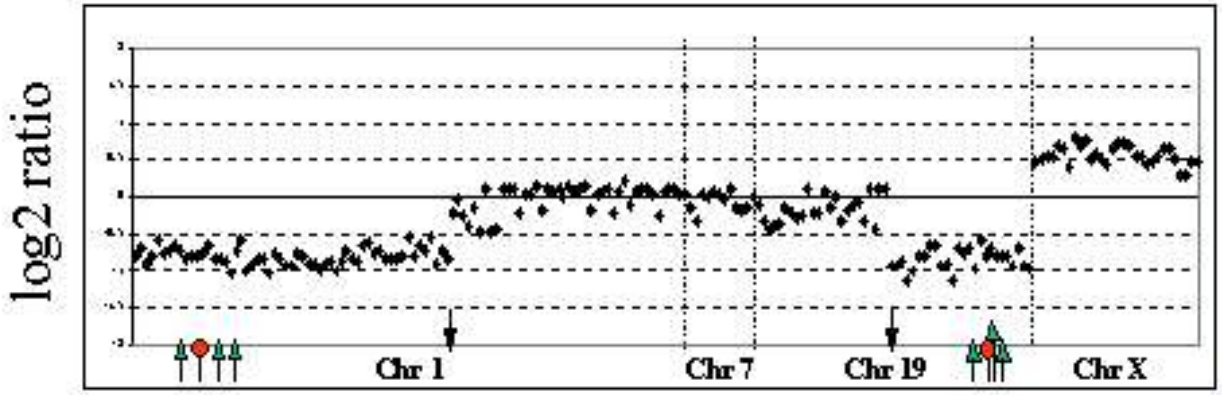
Early microscope

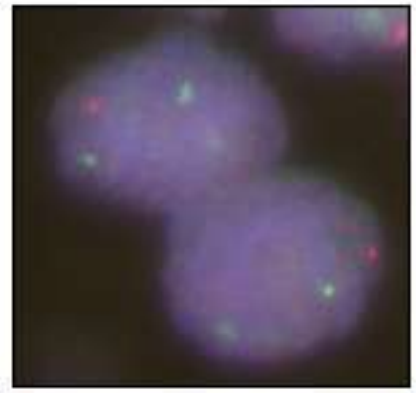
Molecular Diagnostics?

1p/19q loss assessed by aCGH, FISH or LOH



aCGH **FISH** **LOH**





Slide provide by Dr. David Louis, MGH

Mohapatra et al, J Molec Diagnostics 2006

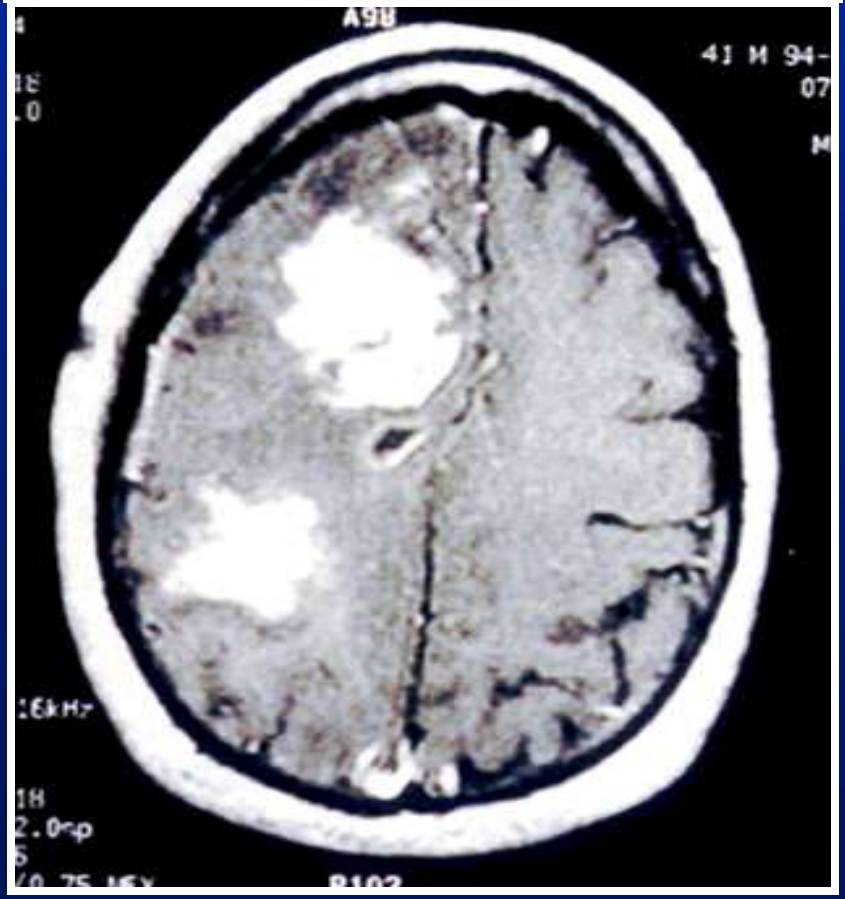
OLIGODENDROGLIOMA (II-III)

- Age 30-40 years
- Corticotropism / seizures common
- Cerebral, especially frontal lobe
- Slow progression
- Survival ~10 years for grade II, 2-5 years for grade III, but higher for the "genetically favorable" (1p/19q deleted)
- 15-25% of diffuse gliomas

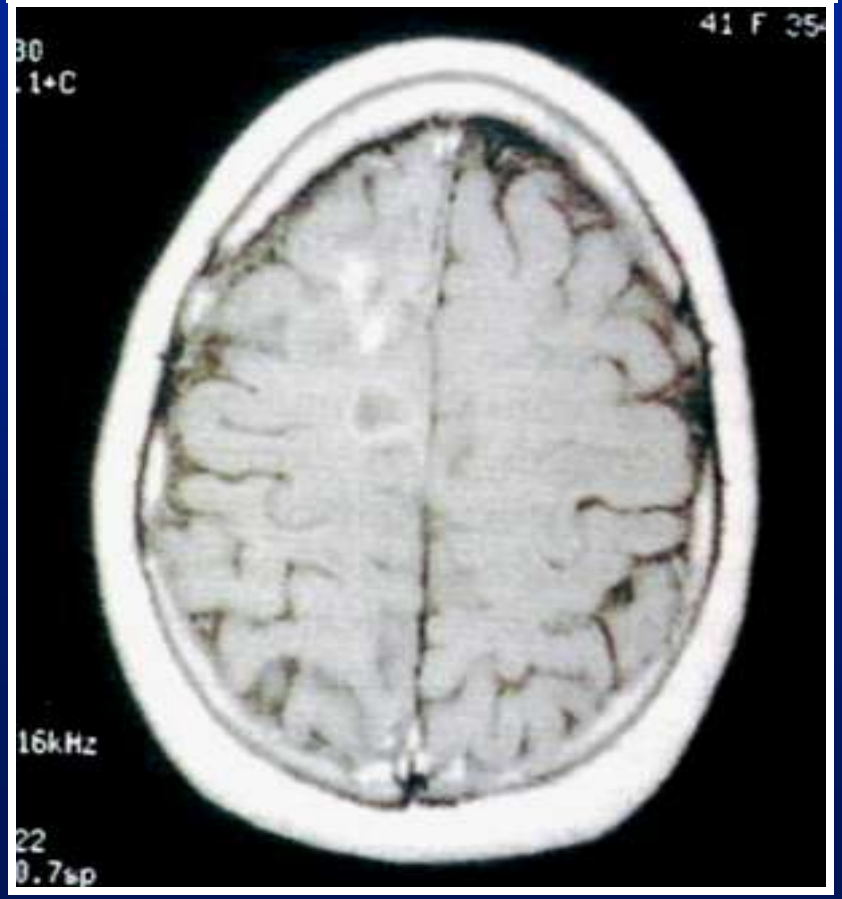
ANAPLASTIC OLIGODENDROGLIOMA

Paleologos N and Cairncross JG Neuro-Oncology 1:63,1999

Pre-PCV

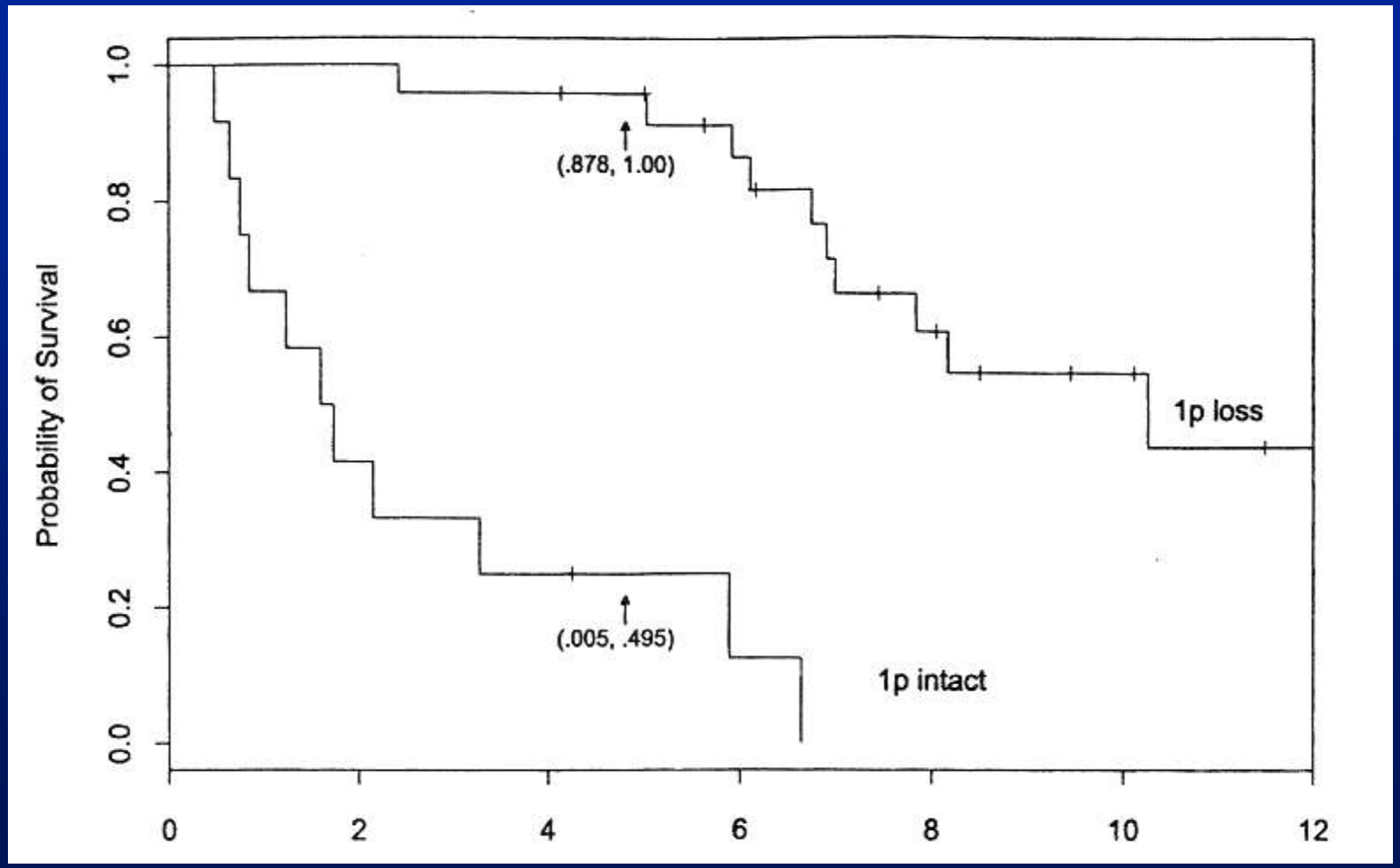


Post-PCV



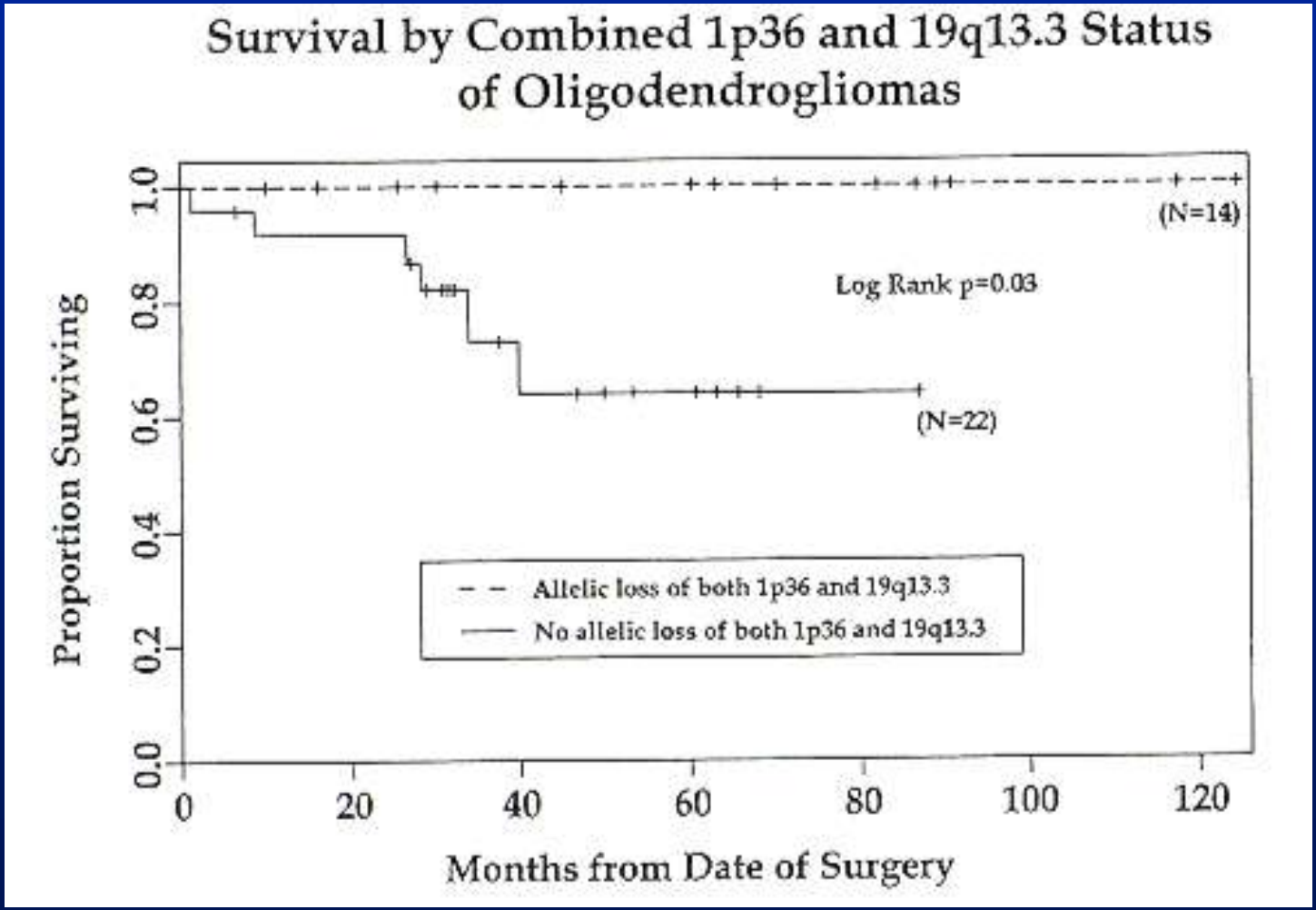
AO PATIENT SURVIVAL

Cairncross JG et al. JNCI 90:1473, 1998

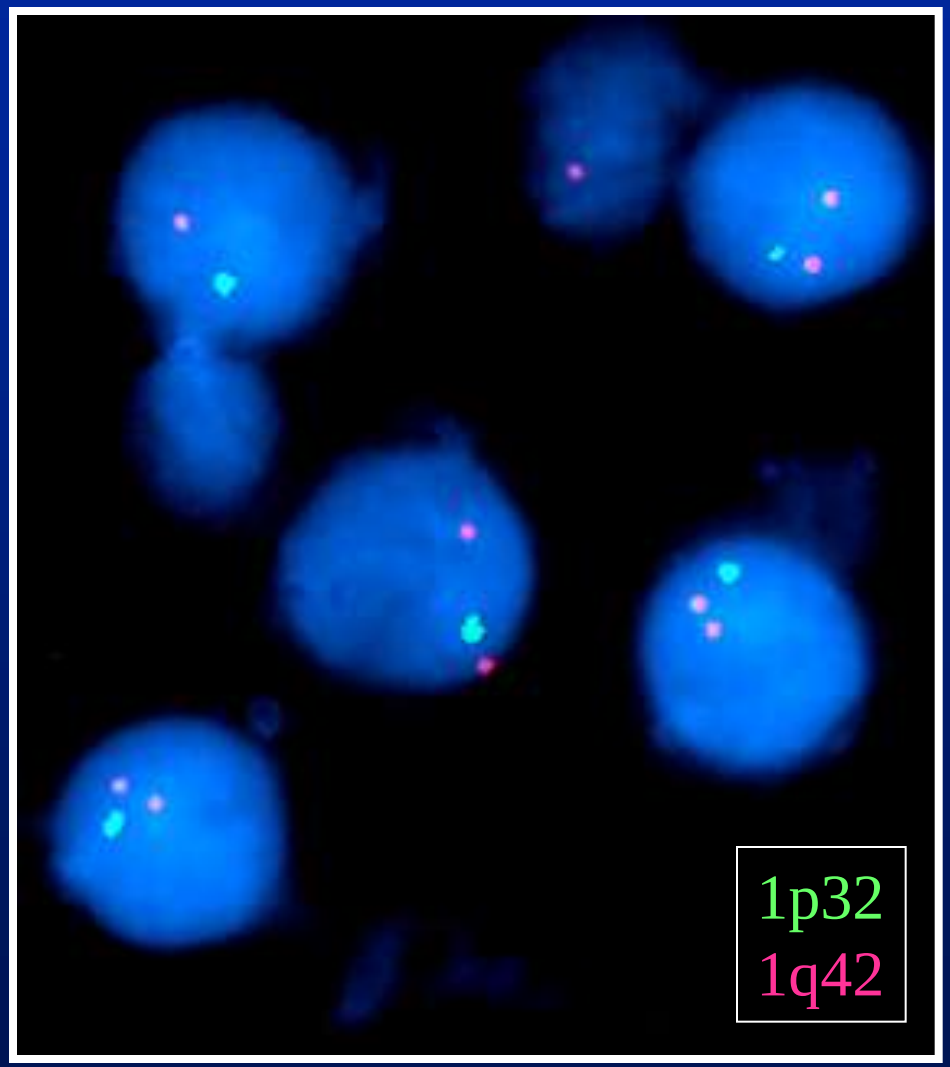


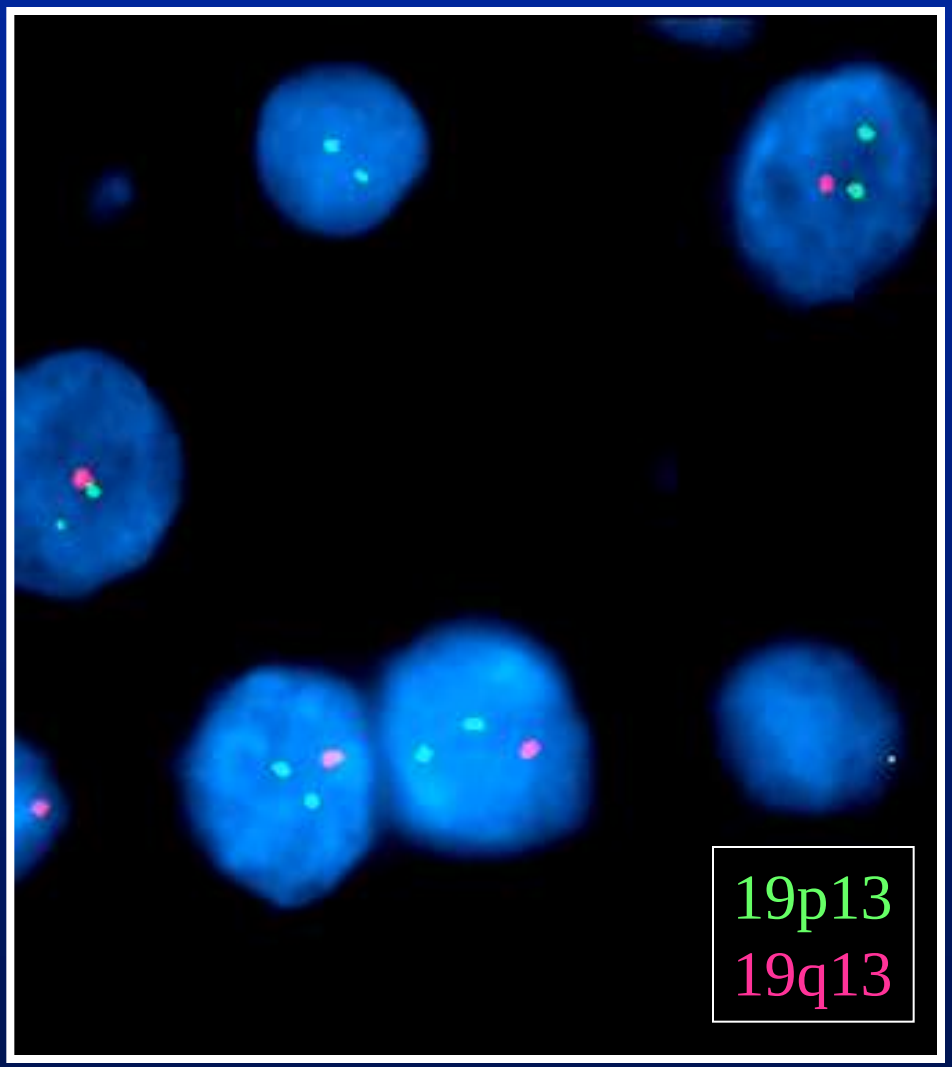
OLIGO SURVIVAL BY 1p/19q FISH

Smith JS, Perry A et al. JCO 18:636, 2000

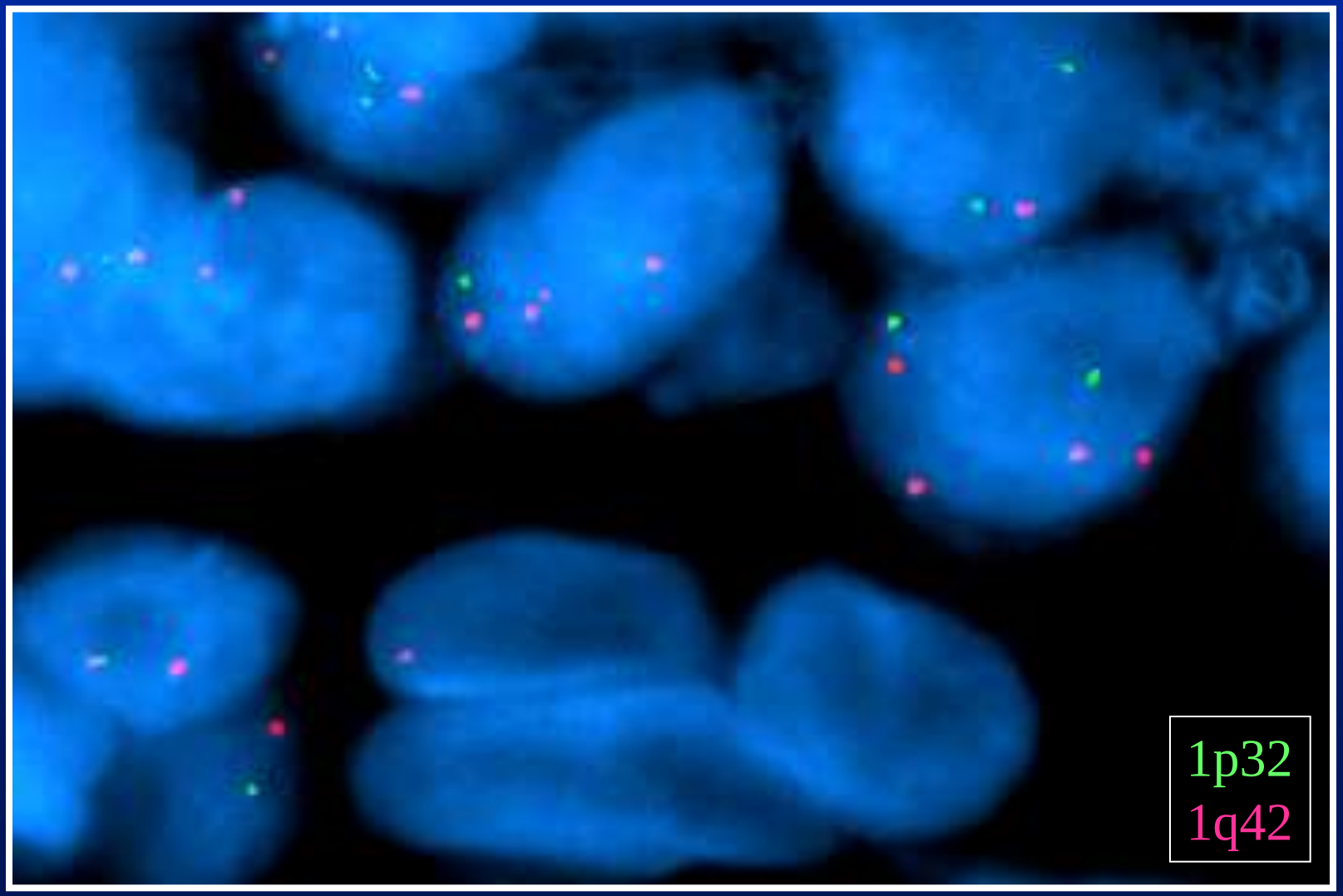


ANAPLASTIC OLIGODENDROGLIOMA





RELATIVE DELETION



FISH TESTING 1999-2009: N=2559

Glioma	1p/19q	19q only	Gains	Normal
Oligo (983)	86%	1%	23%	6%
MOA (1006)	17%	18%	60%	18%
Astro (452)	<1%	9%	69%	23%
P-value	<0.001	<0.001	<0.001	<0.001

Modified from: Perry A et al., Frontiers Biosci 8:a1-9, 2003

CONSULT SERVICE VS REFERENCE LAB

- Change in diagnosis: ~20%
- Diagnoses other than diffuse glioma: N=116; 5%
  - DNET or favor DNET: N=36
  - PNET/high grade glioneuronal tumor: N=19
  - GG/low grade glioneuronal tumor: N=17
  - Pilocytic astrocytoma, N=12
  - Reactive process/atypical gliosis, N=14
  - Clear cell ependymoma: N=6
  - Neurocytic neoplasms: N=6
  - Astroblastoma: N=2
  - Uncertain: N=4
- SC GBM: N=218; 9%

TIMING OF 1p/19q LOSS

- Early genetic alteration, but not the earliest
- Different regions of the same tumor discordant in only 1 case
- Discordant over multiple resections from same patient in 6 of 94 patients (6%)
  - 2 different gliomas
  - 2 different clones of same glioma
- IDH1 mutations earlier (discussed later)

CLINICAL FOLLOWUP COHORT

- FU until death or at least 5 years in 833 pts
- Death in 524 (63%), 0-28.5 years after dx
- WUSM=20%; consults=80%
- Age at diagnosis=4-90 (mean: 45.5) years
- Pediatric (≤18 years)=2%; Adults=98%
- O=34%, MOA=39%, A=27%
- Gr. II=32%, Gr. III=42%, Gr. IV=26%

LONG SURVIVAL

- Survival >5 years in 466 patients
  - 1p/19q del = 51%
  - 51% O, 44% MOA, 5% A
- Survival >10 years in 179 patients
  - 1p/19q del = 58%
  - 60% O, 36% MOA, 3% A
- Survival >15 years in 51 patients
  - 1p/19q del = 69%
  - 63% O, 31% MOA, 6% A
- Longest Survivor: 28.5 years

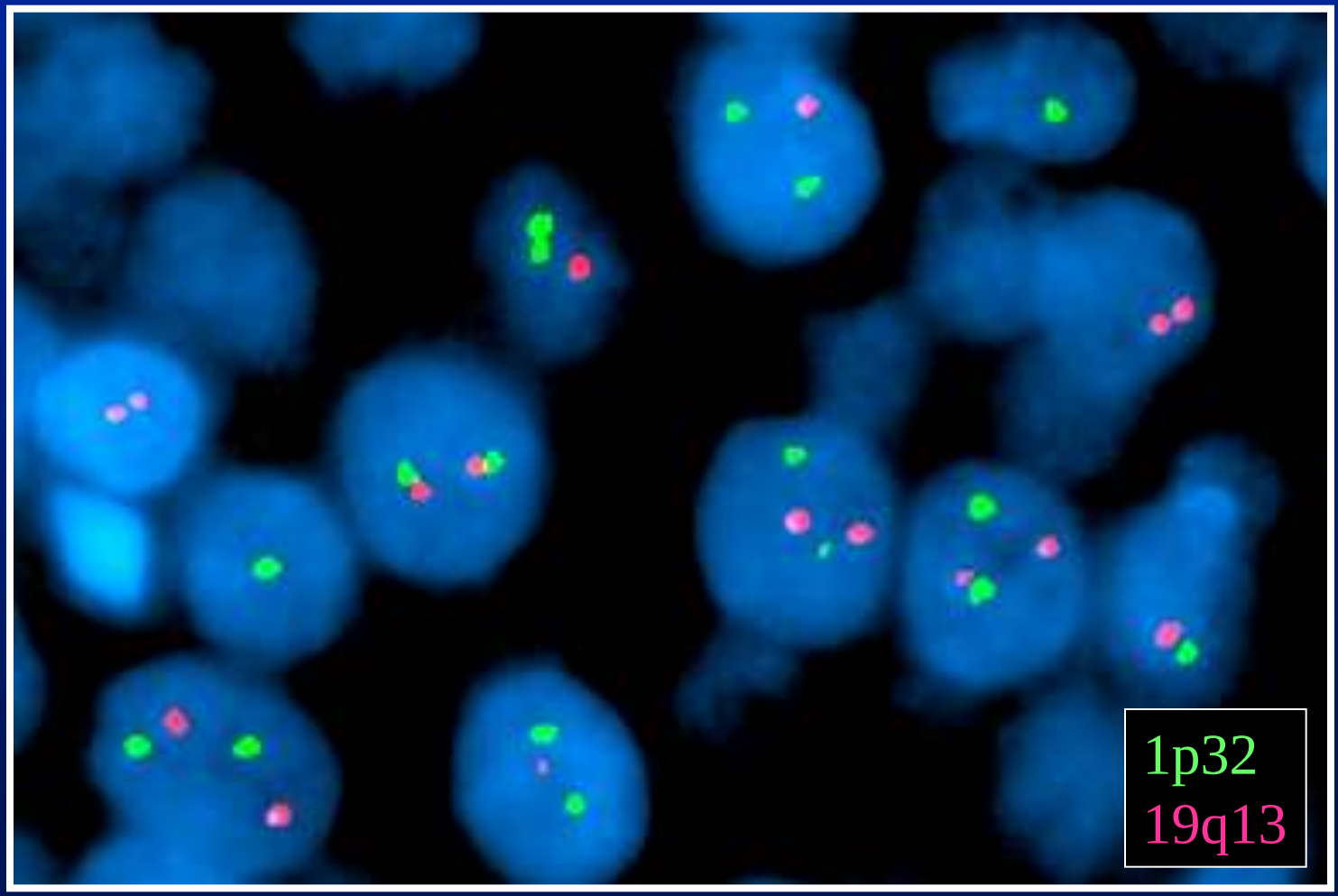
SHORT SURVIVAL (<2 YEARS)

- N=242; 1/19q co-deletions in 14%
  - Ages 21-75, median 52
  - 8 grade II, 20 grade III, 6 grade IV
  - Large and enhancing/ring-enhancing
  - Intracranial hemorrhage?
  - Peri-operative deaths?
  - Diagnosed late in course?
- Of 1p/19q co-deleted cases (N=976), 3.5% died <2 years

IMPERSONATORS

SPECIFICITY: DNT, CN, EVN, CCE

Perry A et al., Frontiers Biosci 8:a1-9, 2003



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pp. 947–955

Oligodendrogliomas with Neurocytic Differentiation. A Report of 4 Cases with Diagnostic and Histogenetic Implications

ARIE PERRY, MD, BERND W. SCHEITHAUER, MD, ROBERT J. B. MACAULAY, MD, COREY RAFFEL, MD, PHD, KEVIN A. ROTH, MD, PHD, AND JOHAN M. KROS, MD, PHD

Abstract. Oligodendroglioma represents a distinct type of diffuse glioma with a relatively favorable prognosis. Although an O2A-like glial progenitor cell of origin has been suggested, a neuronal-oligodendroglial progenitor cell is also of interest, particularly because variable degrees of neuronal marker expression have been reported in typical oligodendrogliomas. We present 2 female and 2 male patients (ages 34–54) with frontal lobe oligodendrogliomas containing a) morphologically distinct collections of small round cells with hyperchromatic nuclei, b) well-formed Homer Wright-like and perivascular rosettes, and c) demonstrable neuronal differentiation by immunohistochemistry and/or electron microscopy in the rosette-associated regions. Unlike extraventricular neurocytomas, these cases featured an infiltrative growth pattern and a classic oligodendroglioma immunophenotype in non-rosette bearing portions of each tumor. FISH analysis demonstrated chromosome 1p and 19q codeletions in 3 (75%) cases, both in regions with and without rosettes. Recurrences were common, although all patients are currently alive 4 months to 13 yr from initial diagnosis. Based on clinicopathologic and genetic features, we diagnosed these tumors as oligodendrogliomas with neurocytic differentiation. However, it is unclear whether they represent a) gliomas with divergent neuronal differentiation, b) a distinctive form of glioneuronal neoplasm, or c) a reflection of glioneuronal histogenesis in oligodendrogliomas in general. In any case, their occurrence suggests a histogenetic overlap between oligodendroglioma and extraventricular neurocytoma not previously recognized.

Key Words: Fluorescence in situ hybridization (FISH); Glial progenitor cell; Neurocytic differentiation; Oligodendroglioma.

Acta Neuropathol (2010) 120:237–252
DOI 10.1007/s00401-010-0695-9

ORIGINAL PAPER

Oligodendroglial neoplasms with ganglioglioma-like maturation: a diagnostic pitfall

Arie Perry · Stephanie S. Burton · Gregory N. Fuller · Christopher A. Robinson · Cheryl A. Palmer · Lothar Resch · Eileen H. Bigio · Meena Gujrati · Marc K. Rosenblum

Received: 19 April 2010 / Revised: 4 May 2010 / Accepted: 4 May 2010 / Published online: 13 May 2010

Abstract Although oligodendroglial neoplasms are traditionally considered purely glial, increasing evidence suggests that they are capable of neuronal or neurocytic differentiation. Nevertheless, ganglioglioma-like foci (GGLF) have not been previously described. Herein, we report seven examples where the primary differential diagnosis was a ganglioglioma with an oligodendroglial component. These five male and two female patients ranged in age from 29 to 63 (median 44) years at initial presentation and neuroimaging features were those of diffuse gliomas in general. At presentation, the glial component was oligodendroglioma in six and oligoastrocytoma in one; one was low-grade and six were anaplastic. A sharp demarcation from adjacent GGLF was common, although some intermingling was always present. The GGLF included enlarged dysmorphic and occasionally binucleate ganglion cells, Nissl substance, expression of neuronal antigens, GFAP-positive astrocytic elements, and low Ki-67 labeling indices. In contrast to classic ganglioglioma, however, cases lacked eosinophilic granular bodies and CD34-positive tumor cells. Scattered bizarre astrocytes were also common and one case had focal neurocytic dif-

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

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

[1] Division of Neuropathology, Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri.

[2] Division of Neuropathology, Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

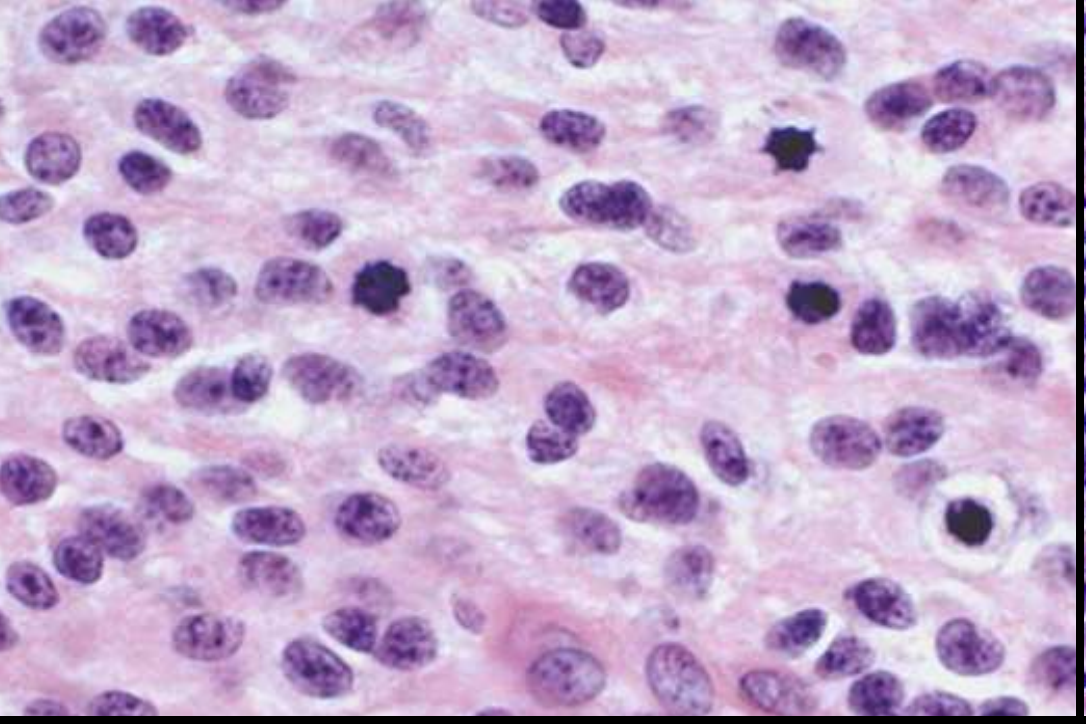
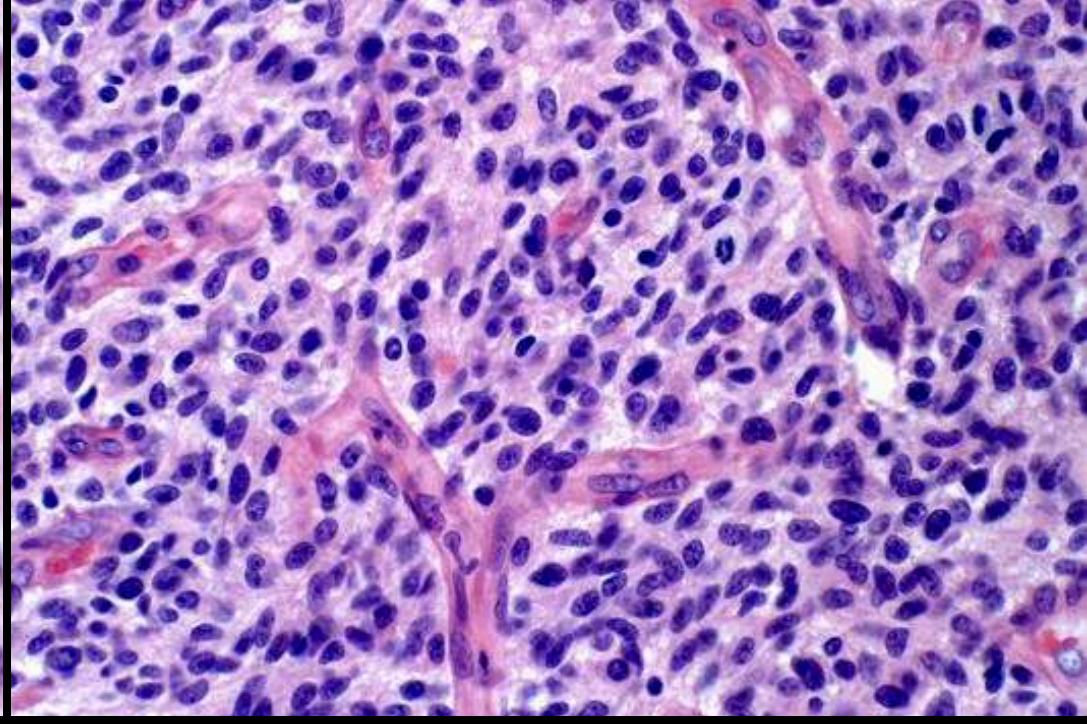
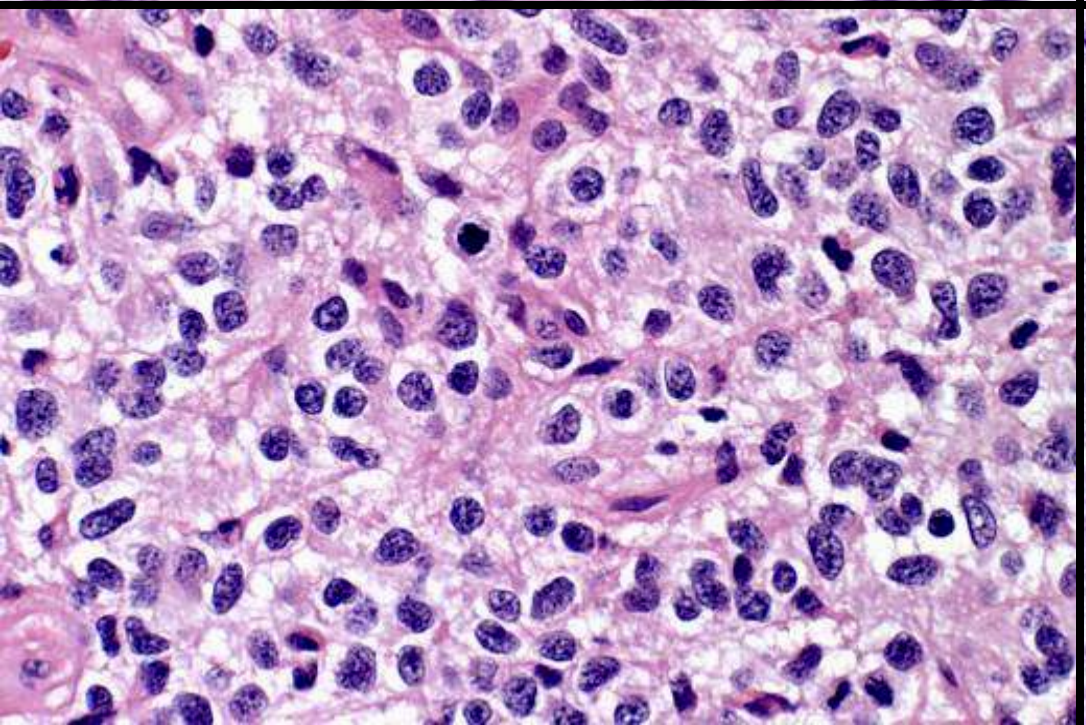
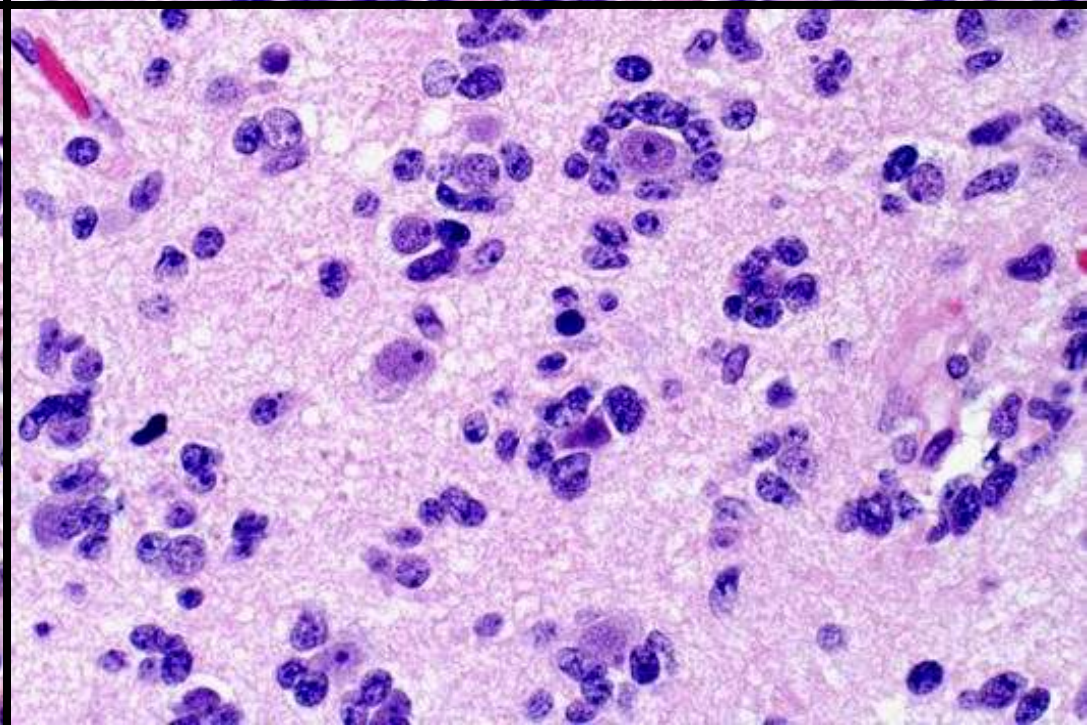
[3] Division of Neuropathology, Foothills Medical Center, Calgary, Alberta, Canada.

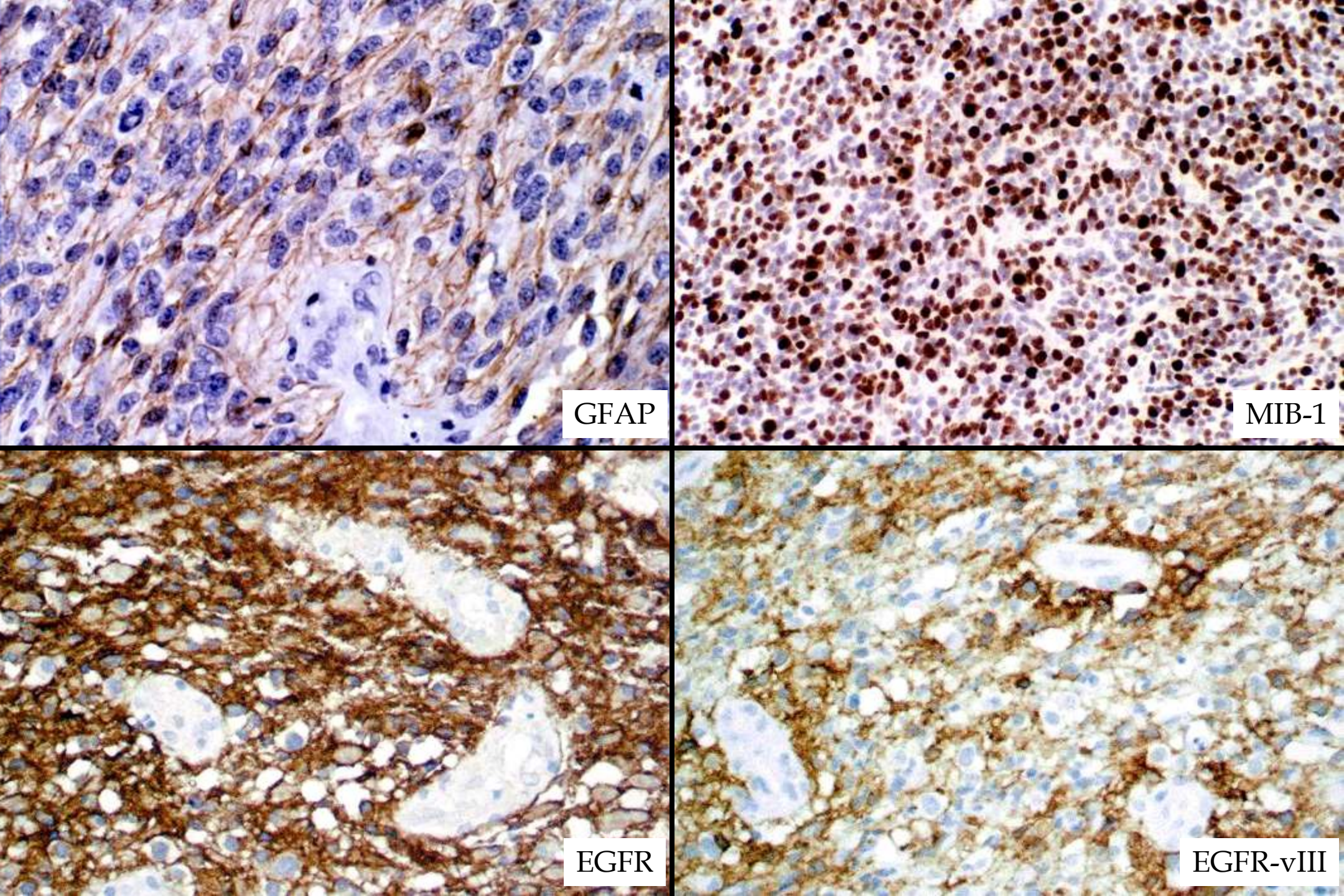
[4] Division of Neuropathology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

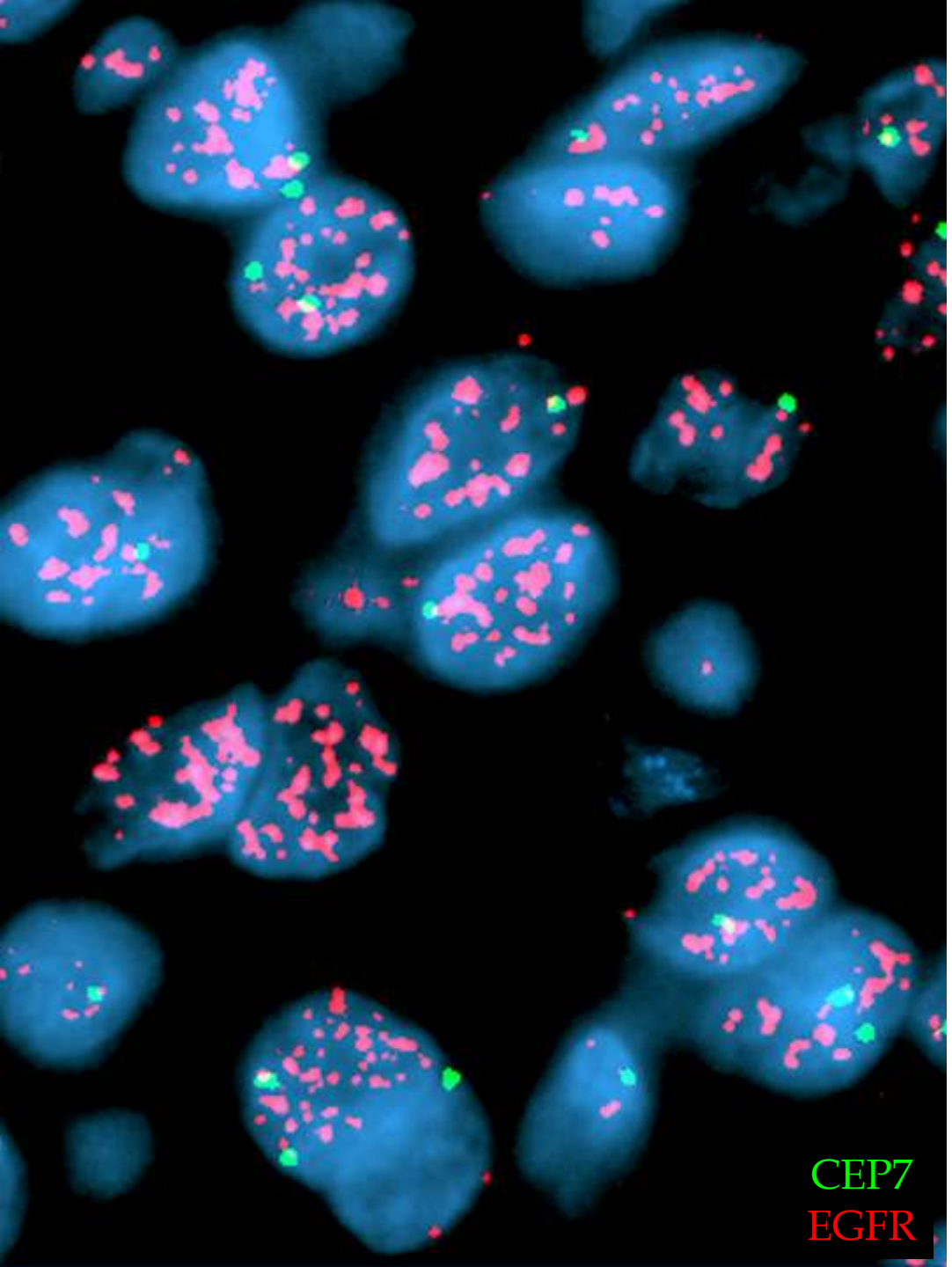
BACKGROUND. Small cell glioblastoma (GBM) is a variant with monomorphous, deceptively bland nuclei that often is misdiagnosed as anaplastic oligodendroglioma.

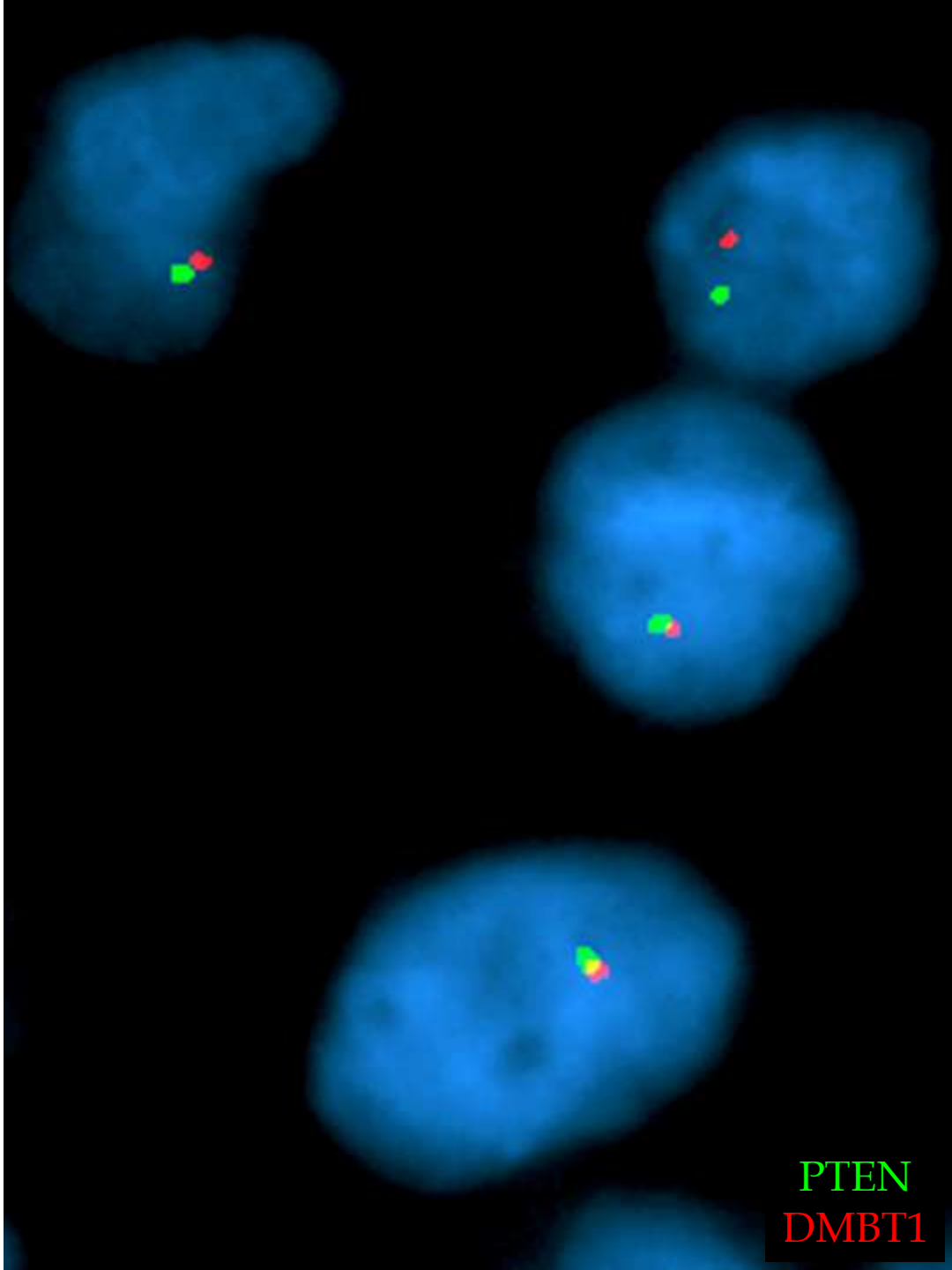
METHODS. To elucidate its clinicopathologic and genetic features, the authors studied 71 adult patients (median age, 57 years), including 22 patients who were identified from a set of 229 GBMs (10%) that had been characterized previously by epidermal growth factor receptor (EGFR)/EGFR-vIII variant immunohistochemistry. Tumors also were analyzed by fluorescence in situ hybridization for 1p, 19q, 10q, and EGFR copy numbers.

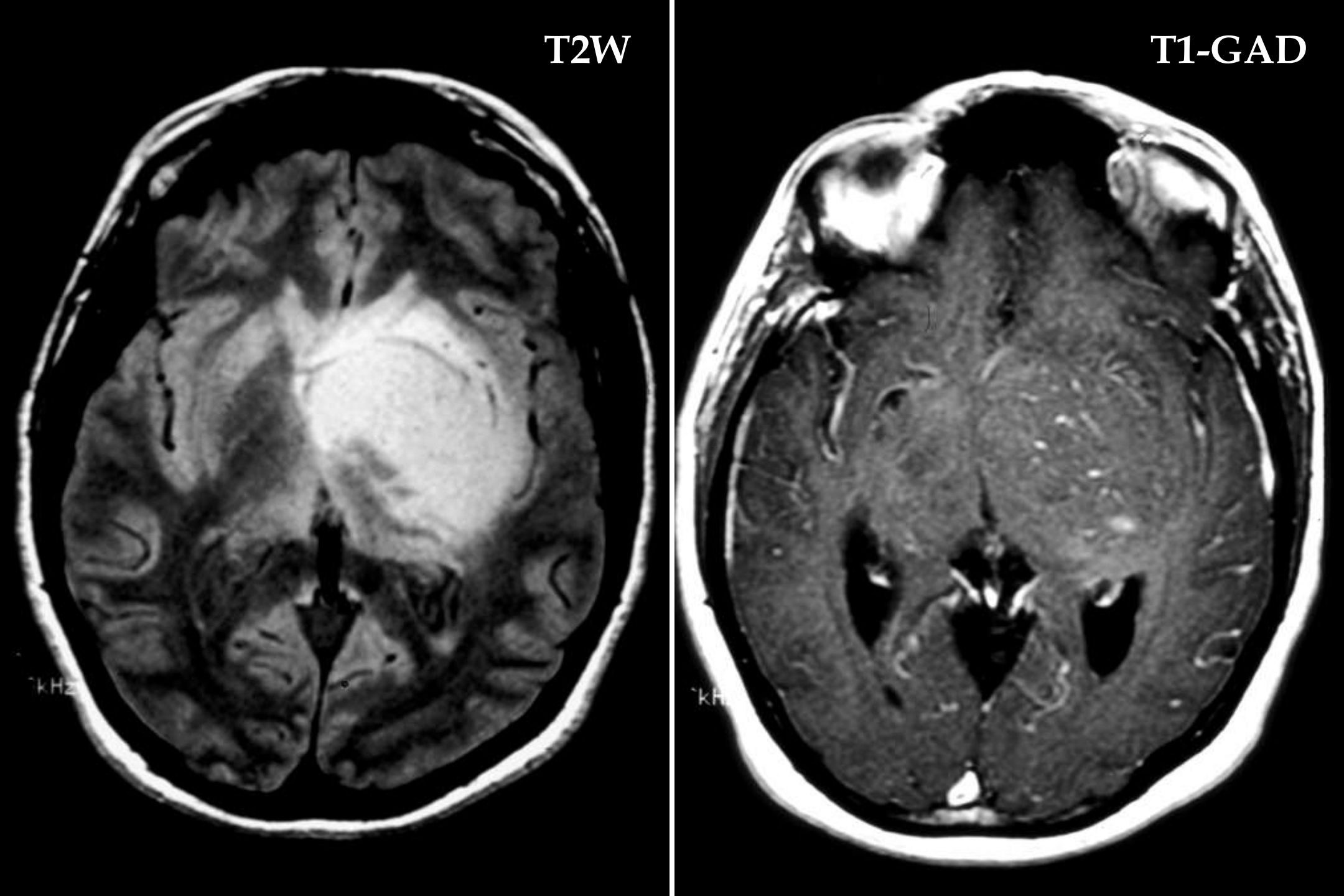
RESULTS. Radiologically, 37% of tumors that were not selected for grade showed minimal to no enhancement. Similarly, 33% of tumors had no endothelial hyperplasia or necrosis histologically, qualifying only as anaplastic astrocytoma (Grade 3) using World Health Organization criteria. Nevertheless, such tumors progressed rapidly, with mortality rates that were indistinguishable from their Grade 4 counterparts. The median survival for 37 patients who were followed until death was 11 months. Oligodendroglioma-like histology included chicken-wire vasculature (86%), haloes (73%), perineuronal satellitosis (58%), and microcalcifications (45%), although mucin-filled microcystic spaces were lacking. No small cell astrocytomas


GFAP
MIB-1
EGFR
EGFR-vIII


CEP7
EGFR


PTEN
DMBT1


T2W
T1-GAD

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pp. 530–537

Pediatric Oligodendrogliomas: A Study of Molecular Alterations on 1p and 19q Using Fluorescence In Situ Hybridization

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Abstract. Oligodendrogliomas (OGs) are rare in children and have not been well characterized from a molecular viewpoint. In adults, losses on chromosomes 1p and/or 19q are common in "oligodendroglial" neoplasms and are highly associated with chemosensitivity and greater length of survival, especially in the anaplastic category. We have analyzed the 1p/19q status of pediatric OGs and compared it with similar alterations in adult OGs. Paraffin sections from 26 pediatric OGs (21 WHO Grade II OGs; 2 anaplastic oligodendrogliomas [AOGs]; and 3 mixed oligo-astrocytomas [MOA]) were retrieved. Fluorescence in situ hybridization (FISH) was performed using probes spanning the 1p32 and 19q13 regions. In tumors from children 0 to 9 years of age (n =15), none had any deletions on 1p or 19q, but 2 had polysomies for 1p and/or 19q. All are alive and 4 have had recurrences. In tumors from children >9 years, losses were identified on chromosomes 1p (5/11; 45%) and/or 19q (3/11; 27%), but to a much lesser extent than that observed in adult OGs. Tumors from 6 older patients also had polysomies for 1p and/or 19q. Although the majority of the older children are alive, 4 had recurrences. Curiously, 2 of the older children with AOGs had combined losses and polysomies on 1p and 19q, but responded poorly to treatment and died within a year. We conclude that alterations on 1p or 19q are infrequent in pediatric compared to adult OGs and are virtually absent in OGs presenting in the first decade of life. Compared to adults therefore, different genetic pathways are likely involved in the pathogenesis of most pediatric OGs. Genomic screening on a larger series is clearly indicated to delineate the unique molecular characteristics of these rare pediatric tumors.

Key Words: Chromosome 1p; Chromosome 19q; Fluorescence in situ hybridization (FISH); Molecular genetics; Pediatric oligodendroglioma.

Raghavan et al. JNEN 62:530, 2003

TABLE 2
Deletions in Predominantly Adult Oligodendroglial Tumors from Studies Using FISH as an Analysis Tool: Comparison with Data from Pediatric OGs

	1p Del	19q Del
Burger et al (23)		
Present	8 (100%)	8 (100%)
Absent	0	0
Total	8	8
Smith et al (6)		
Present	24 (72%)	24 (72%)
Absent	9	9
Total	33	33
Perry et al (21)		
Present	74 (74%)	76 (76%)
Absent	27	25
Total	101	101
Raghavan et al (current study)		
Present	5 (20%)	3 (12%)
Absent	21	22
Total	26	25

Acta Neuropathol
DOI 10.1007/s00401-010-0770-2

ORIGINAL PAPER

Mutation-specific IDH1 antibody differentiates oligodendrogliomas and oligoastrocytomas from other brain tumors with oligodendroglioma-like morphology

David Capper · David Reuss · Jens Schittenhelm · Christian Hartmann · Juliane Bremer · Felix Sahm · Patrick N. Harter · Astrid Jeibmann · Andreas von Deimling

Received: 31 August 2010 / Revised: 26 October 2010 / Accepted: 26 October 2010

Abstract Isocitrate dehydrogenase 1 (*IDH1*) mutations are frequent in astrocytomas, oligoastrocytomas and oligodendrogliomas. We previously reported the generation of a mutation-specific antibody that specifically detects R132H mutated IDH1 protein (clone H09). Here, we investigate the feasibility of H09 immunohistochemistry to differentiate between oligodendrogliomas/oligoastrocytomas and other tumors with similar morphology. A total of 274 brain tumors presenting with focal or extensive clear cell morphology were investigated. High numbers of H09-positive cases were observed in adult grade II oligodendrogliomas (67 of 74, 91%), grade II oligoastrocytomas (11 of 14, 79%) and grade III oligoastrocytomas (10 of 11, 91%). All cases of pediatric oligodendrogliomas ($n = 7$), neurocytomas ($n = 41$, 35 central, 4 extraventricular, 2 cerebellar liponeurocytomas), dysembryoplastic neuroepithelial tumors ($n = 21$), clear cell ependymomas ($n = 8$), clear cell meningiomas ($n = 9$) as well as 12 primary glioblastomas with oligodendroglial differentiation and 5 pilocytic astrocytomas with oligodendroglial-like differentiation were negative for H09 immunohistochemistry. Three oligodendrogliomas with neurocytic differentiation had evidence of *IDH1*/*IDH2*

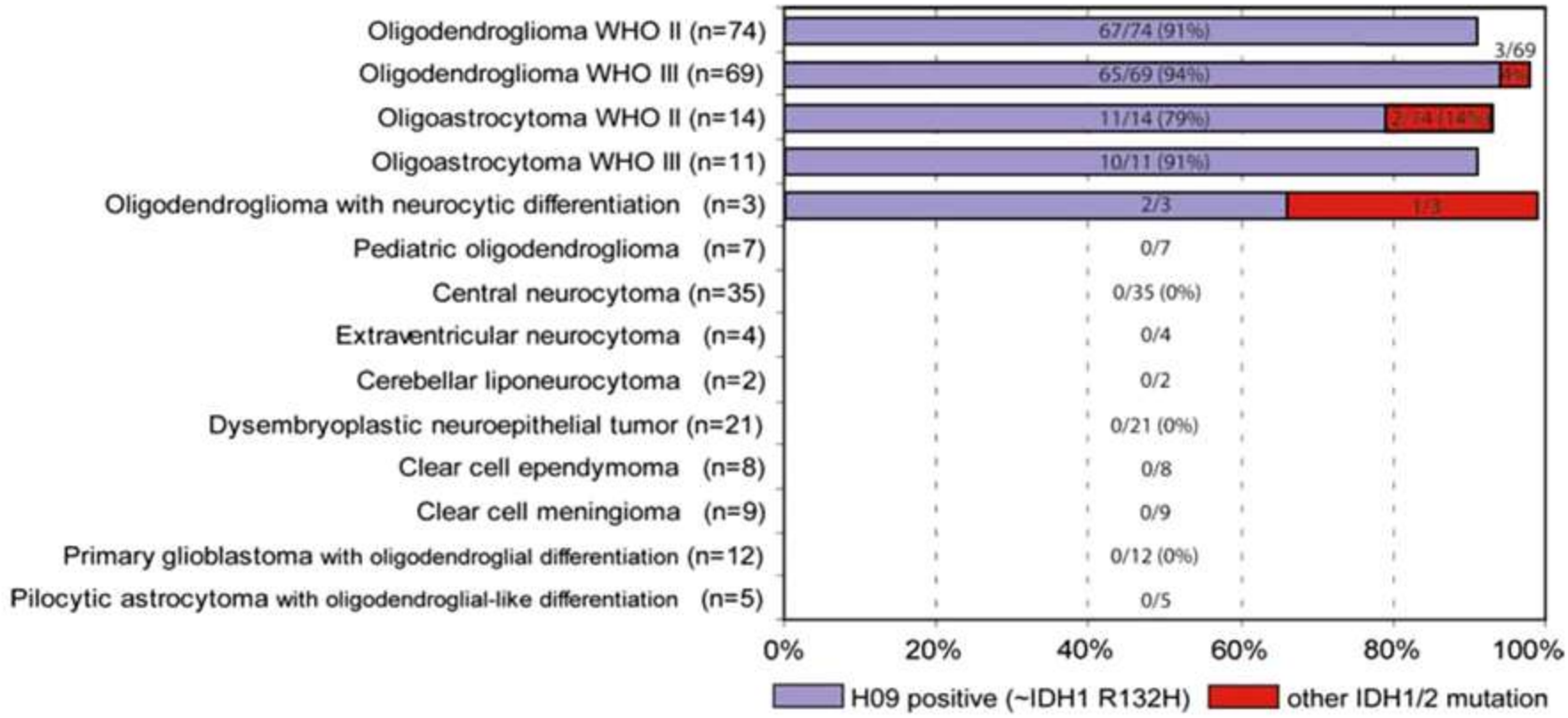
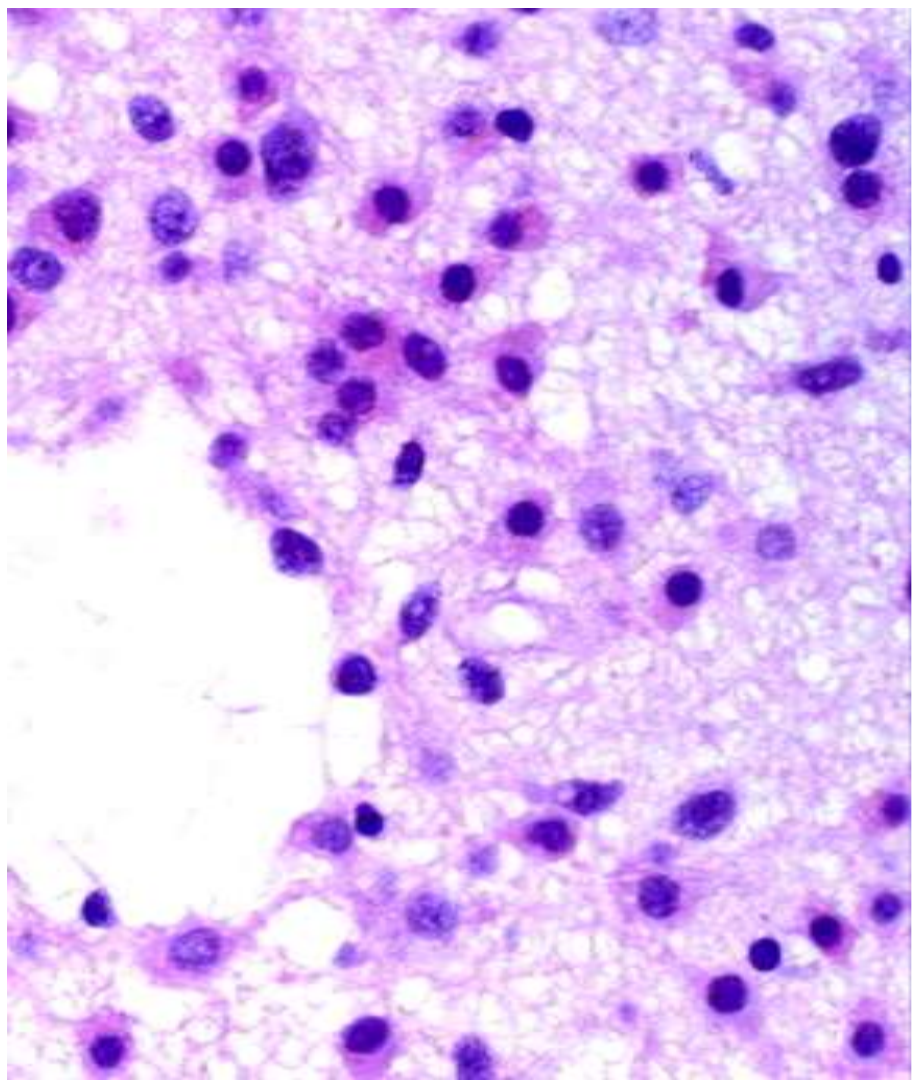


Fig. 1 H09 immunohistochemistry and IDH1/2 sequencing of clear cell brain tumors. All cases were analyzed by IDH1 R132H mutation-specific antibody H09. In tumor types with at least one H09-positive case, all negative tumors were sequenced for other mutations of IDH1 or IDH2 (for details of mutations see Tables 2 and 3). Percentages are given for tumor types with at least 10 analyzed cases

MOA, WHO II-III



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Clinical Utility of Fluorescence In Situ Hybridization (FISH) in Morphologically Ambiguous Gliomas with Hybrid Oligodendroglial/Astrocytic Features

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Abstract. Gliomas with hybrid oligodendroglial/astrocytic features are diagnostically problematic, and our ability to predict tumor behavior is limited. Some likely represent intermingled mixed oligoastrocytomas (MOAs), though precise diagnostic criteria and specific markers for this lesion are lacking. From the files at Washington University (1987–2000), 155 "ambiguous" glioma/intermingled MOA candidates were independently classified and graded by 5 neuropathologists, with consensus-derived pure oligodendrogliomas and astrocytomas excluded from further study. The 90 remaining cases (grades II = 29, III = 44, IV = 17) were analyzed by FISH on formalin-fixed, paraffin-embedded sections. Detectable deletions included combined 1p/19q (9%), solitary 19q (22%), *PTEN/DMBT1* (26%), and *p16* (32%). *EGFR* amplification was found in 11%. Patients were followed until death (47%) or a median of 3.3 years. Similar to prior glioma series, patient age ($p < 0.0001$) and tumor grade ($p < 0.0001$) were strongly associated with survival times. *EGFR* amplification ($p = 0.0007$) and deletions of *PTEN/DMBT1* ($p = 0.016$) or *p16* ($p = 0.014$), either individually or as a group ($p = 0.04$), portended a shorter median survival compared with tumors lacking these alterations. We conclude that 1) distinct genetic subsets are identifiable by FISH in morphologically ambiguous gliomas, and 2) both histological grading and molecular analysis yield prognostically useful information.

Key Words: Chromosome 1; Chromosome 19; *EGFR;* In situ hybridization; Oligoastrocytoma; *p16*; *PTEN.*

INTRODUCTION

Three distinct subtypes of diffuse glioma are recognized in the current WHO classification of tumors of the nervous system: astrocytoma, oligodendroglioma, and mixed oligoastrocytoma (MOA) (1). Accurate identifi-

morphologic criteria, there has been considerable inter-observer variability and low diagnostic reproducibility among neuropathologists asked to classify such lesions, particularly the intermingled subtype (8). Not surprisingly, these tumors vary greatly in terms of biologic behavior, likely representing a heterogeneous group of "inde-

STUDY DESIGN

- Washington Univ, St Louis (1987-2000)
  - "MOA"
  - "mixed glioma"
  - "glioma NOS"
  - "GBM with oligo features"
- 155 cases

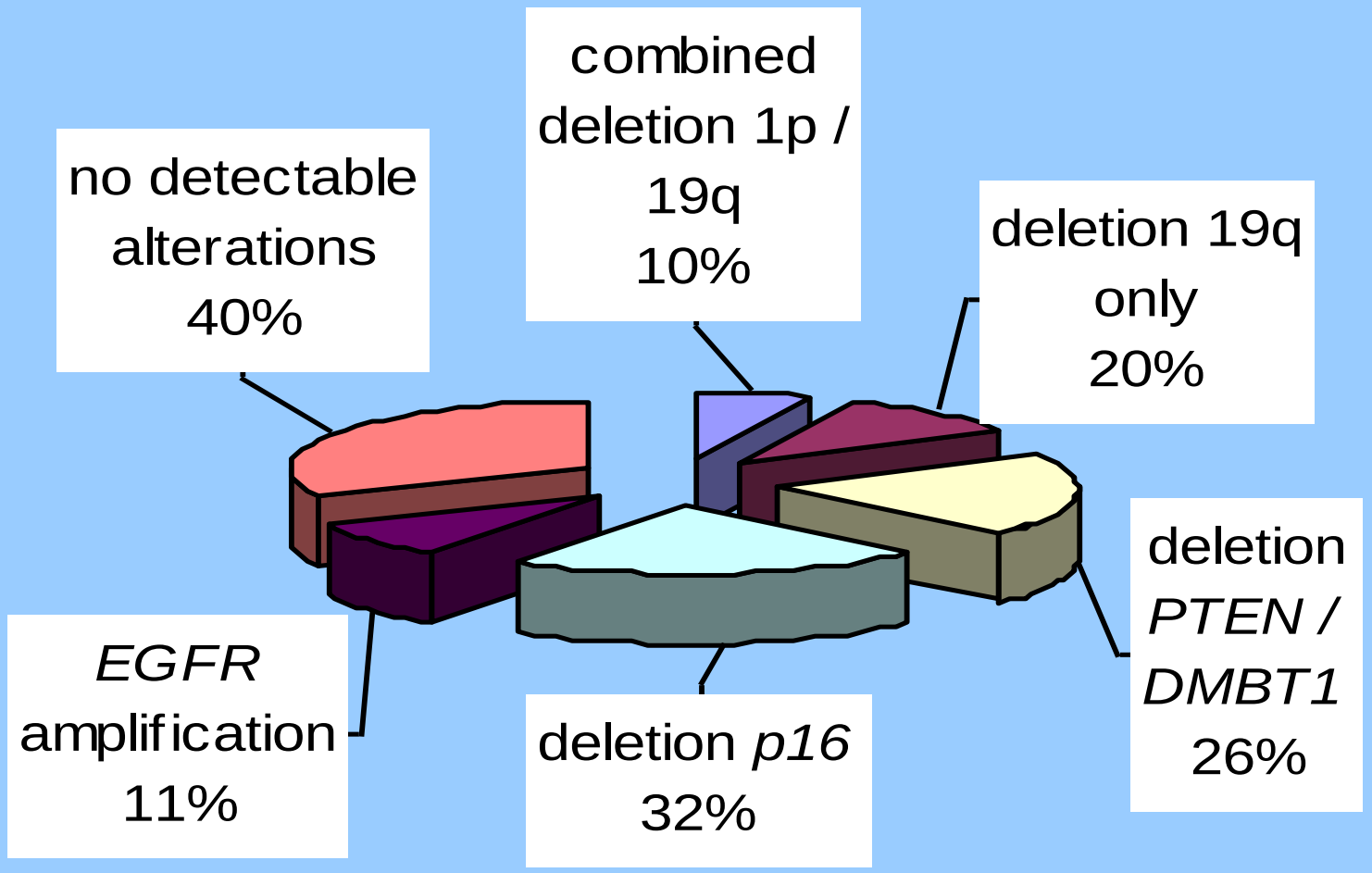
PATHOLOGY REVIEW

- 5 experienced neuropathologists
  - Classification: oligo, astro, MOA, glioma NOS
  - Grade: II, III, IV, indeterminate

- Criteria for Inclusion in Study
  - consensus diagnosis of MOA or glioma NOS
  - no consensus between pathologists

(consensus = 3 of 5 pathologists in diagnostic agreement)

Summary of Molecular Alterations



OVERALL SURVIVAL

- Deletion 1p and/or 19q
  Median 100.0 months
- No Alterations Detected
  Median 85.0 months
- Amp EGFR or Del 10q or Del p16
  Median 16 months

MULTIVARIATE ANALYSIS

- Always included age and tumor grade as the most powerful prognostic variables
- Models using genetic alterations may add additional independent prognostic information

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Prognostic Value of 1p, 19q, 9p, 10q, and EGFR-FISH Analyses in Recurrent Oligodendrogliomas

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Abstract. Although 1p/19q codeletions define "genetically favorable" oligodendrogliomas, eventual tumor progression and patient death remain constant. Genetic testing is often performed at the time of recurrence, though it is unclear whether these or other genetic alterations provide useful prognostic information. We characterized 138 of 189 (73%) available primary and recurrent oligodendroglial neoplasms from 80 patients, utilizing paired FISH probes for 1p32/1q42, 19p13/19q13, CEP7/EGFR, CEP9/p16, and PTEN/DMBT1. Patients were followed until death (49%), or a median follow-up of 8.9 years. Patients with 1p/19q codeleted tumors (71%) had an estimated overall median survival of 14.9 years with an estimated 3.9 years from first recurrence. In contrast, those lacking deletions had significantly lower estimated overall median survivals of 4.7 years and 1.0 year after first recurrence (both $p < 0.001$). This increased survival in patients with 1p/19q codeleted tumors remained significant when adjustments were made for age, tumor grade, type of surgical procedure, and treatment with radiation or chemotherapy. Only 1 recurrence showed focal EGFR amplification, while 5 developed 10q deletions, mostly in high-grade mixed oligoastrocytomas lacking 1p/19q deletions. In contrast, p16 (9p21) deletions were common and associated with both high grade ($p < 0.001$) and recurrence ($p = 0.002$). Our data suggest that in classic oligodendrogliomas: 1) 1p/19q tumor status is a powerful predictor of patient survival, even after recurrence; 2) p16 deletions are common progression-associated alterations; and 3) 10q deletions and EGFR amplifications are sufficiently rare to suggest the possibility of alternate diagnoses.

Key Words: Fluorescence in situ hybridization (FISH); Gene amplification; Gene deletion; Oligodendroglioma; Recurrence; Survival; Tumor genetics.

INTRODUCTION

Oligodendrogliomas are primary central nervous system (CNS) neoplasms that have long been recognized to

toxic forms of chemotherapy as well, such as temozolomide (4). However, the prolonged survival times previously reported have mostly been measured from the time of

MATERIALS/METHODS

- 138/189 (73%) classic oligodendroglial tumor specimens from 80 patients
- Dual color FISH
  - 1p32/1q42
  - 19p13/19q13
  - CEP7/7p12 (*EGFR*)
  - CEP9/9p21 (*p16*)
  - 10q23 (*PTEN*)/10q25-26 (*DMBT1*)
- Followup until death (49%) or median of 8.6 yr

GENETICS VS. CELL TYPE

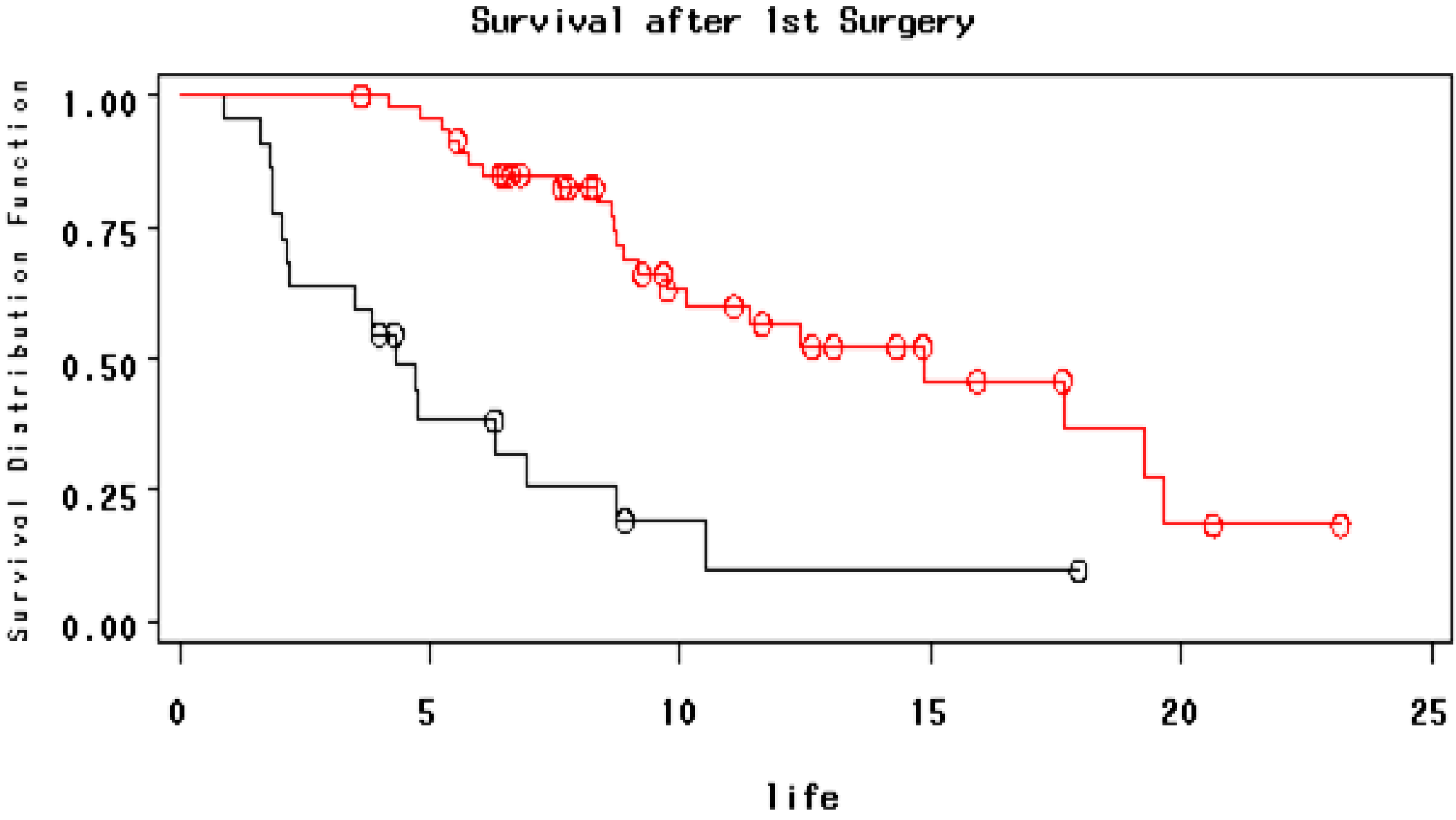
	-1p/19q	-19q	-p16	-10q	EGFR	Poly
O (85%)	80%	1%	31%	1%	0	39%
MOA (15%)	39%	29%	48%	15%	4%	54%

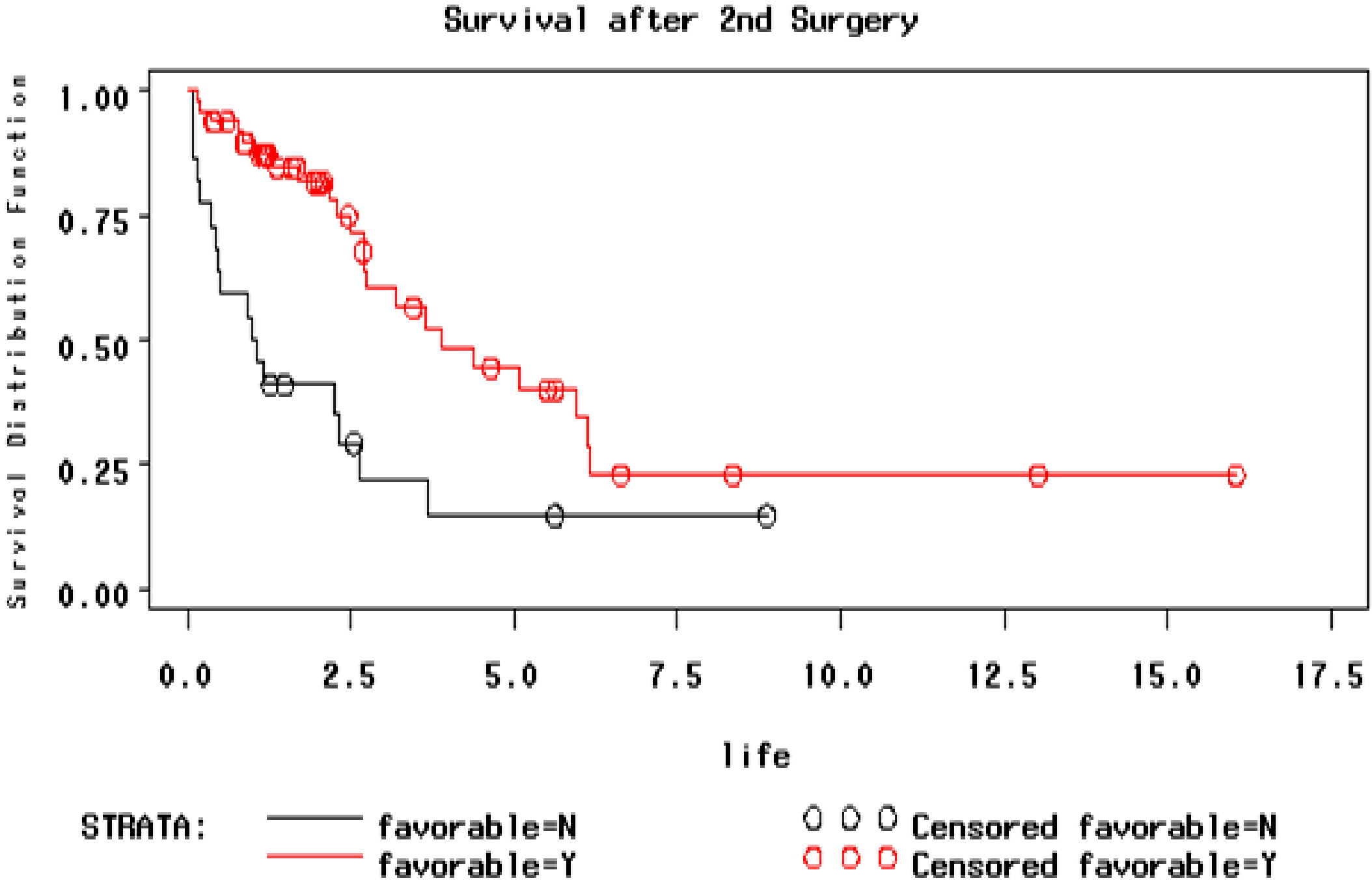
GENETICS VS. GRADE

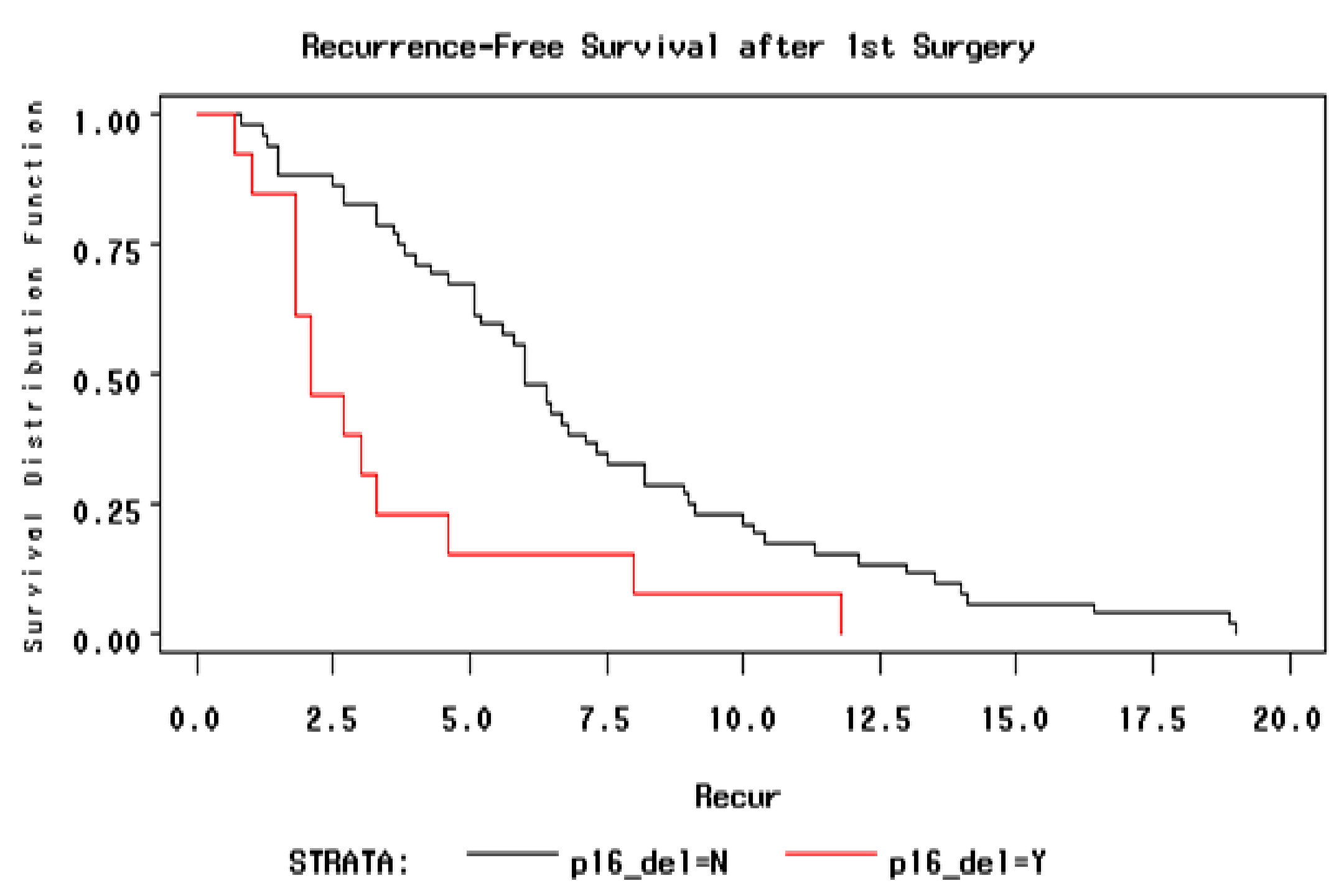
	-1p/19q	-19q	-p16	-10q	EGFR	Poly
II (43%)	63%	6%	11%	0	0	20%
III (51%)	83%	4%	47%	5%	1%	54%
IV (5%)	70%	0	60%	10%	0	70%

GENETICS IN PRIMARY VS. RECURRENCE

	-1p/19q	-19q	-p16	-10q	EGFR	Poly
P (41%)	71%	5%	18%	1%	0	16%
R (59%)	75%	6%	43%	5%	1%	54%


Survival after 1st Surgery
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
life
STRATA:
favorable=N
favorable=Y
Censored favorable=N
Censored favorable=Y


Survival after 2nd Surgery
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
life
STRATA:
favorable=N
favorable=Y
Censored favorable=N
Censored favorable=Y


Recurrence-Free Survival after 1st Surgery
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
Recur
STRATA:
p16_del=N
p16_del=Y

GLIOBLASTOMA VARIANTS

- Fibrillary
- Gemistocytic
- Giant Cell
- Gliosarcoma
- Adenoid
- Granular Cell
- Small Cell
- GBM with oligodendroglial features
- GBM with neuroblastic (PNET-like) features

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ORIGINAL REPORT

Significance of Necrosis in Grading of Oligodendroglial Neoplasms: A Clinicopathologic and Genetic Study of Newly Diagnosed High-Grade Gliomas

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2434-5419/$20.00

ABSTRACT

Purpose
High-grade gliomas (HGGs; WHO grades 3-4) are highly diverse, with survival times ranging from months to years. WHO 2000 grading criteria for high-grade oligodendroglial neoplasms [anaplastic oligoastrocytoma (AOA) and anaplastic oligodendroglioma (AO)] remain subjective, and the existence of grade 4 variants is controversial.

Patients and Methods
Overall survival (OS) of 1,093 adult patients with a cerebral HGG newly diagnosed between 1990 and 2005 was analyzed by univariate and multivariate models for significance of the following factors: patient age, surgery type, year of diagnosis, endothelial proliferation, necrosis, oligodendroglial histology, treatment center, and chromosome 1p, 19q, 7p (*EGFR*), and 10q (*PTEN*) abnormalities by fluorescence in situ hybridization (FISH).

Results
Necrosis was a statistically significant predictor of poor OS on univariate and multivariate analyses in AOA but not in AO. Median OS for patients with necrotic AOA (22.8 months) was significantly worse than for patients with non-necrotic AOA (86.9 months; $P < .0001$) but was better than conventional glioblastomas (9.8 months; $P < .0001$). In addition to patient age, the following were significant independent prognostic factors ($P \leq .001$): grade and surgery type for the entire HGG cohort; modified grade for AOA (3 *v* 4); and modified grade, 1p/19q codeletion status, and oligodendroglial histology for the 586 HGGs analyzed by FISH.

Conclusion
Stratification of AOA, but not of pure AO, into grades 3 and 4 on the basis of necrosis is prognostically justified and is more powerful than the current approach. Both routine histology and genetic testing provide independent, prognostically useful information.

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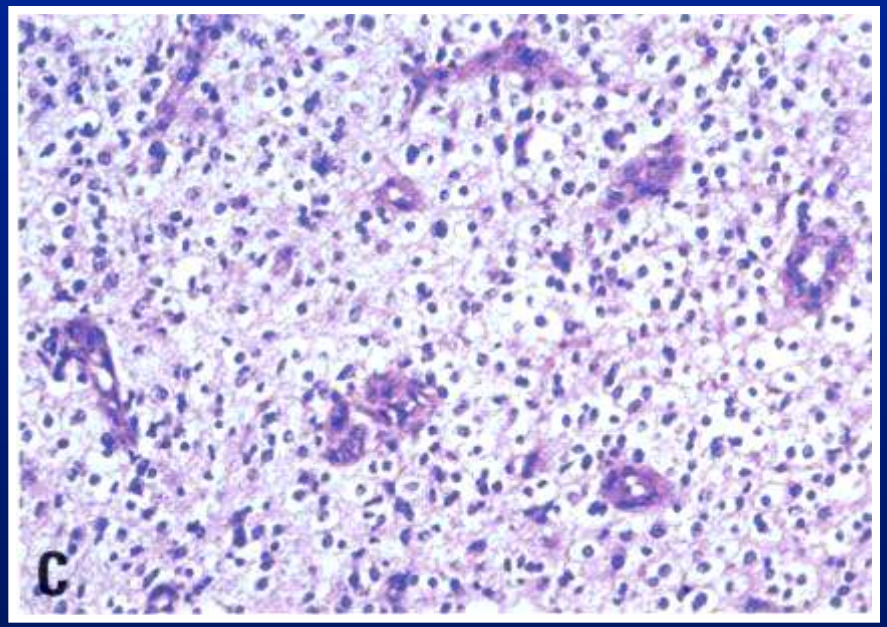
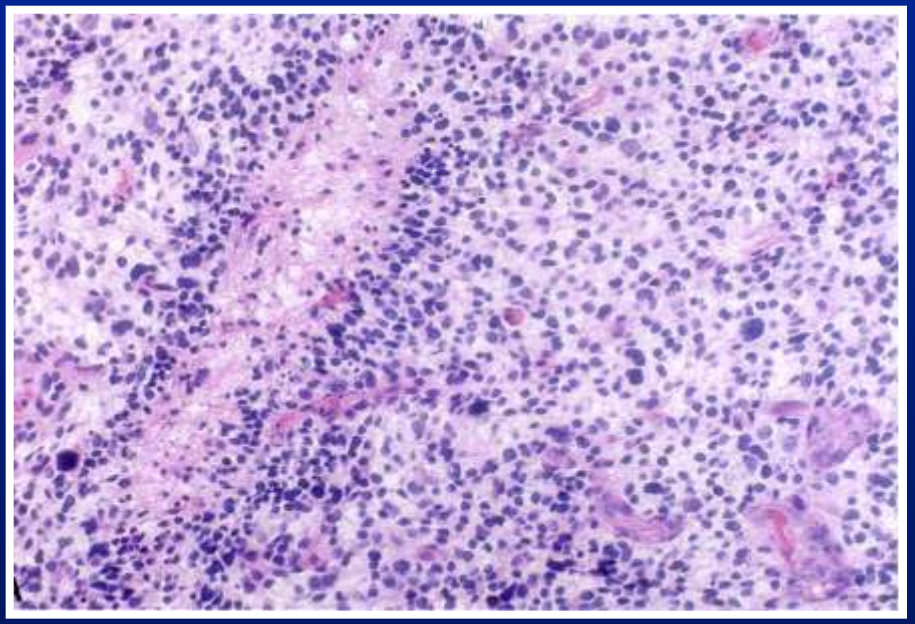
WHO 2000 Classification



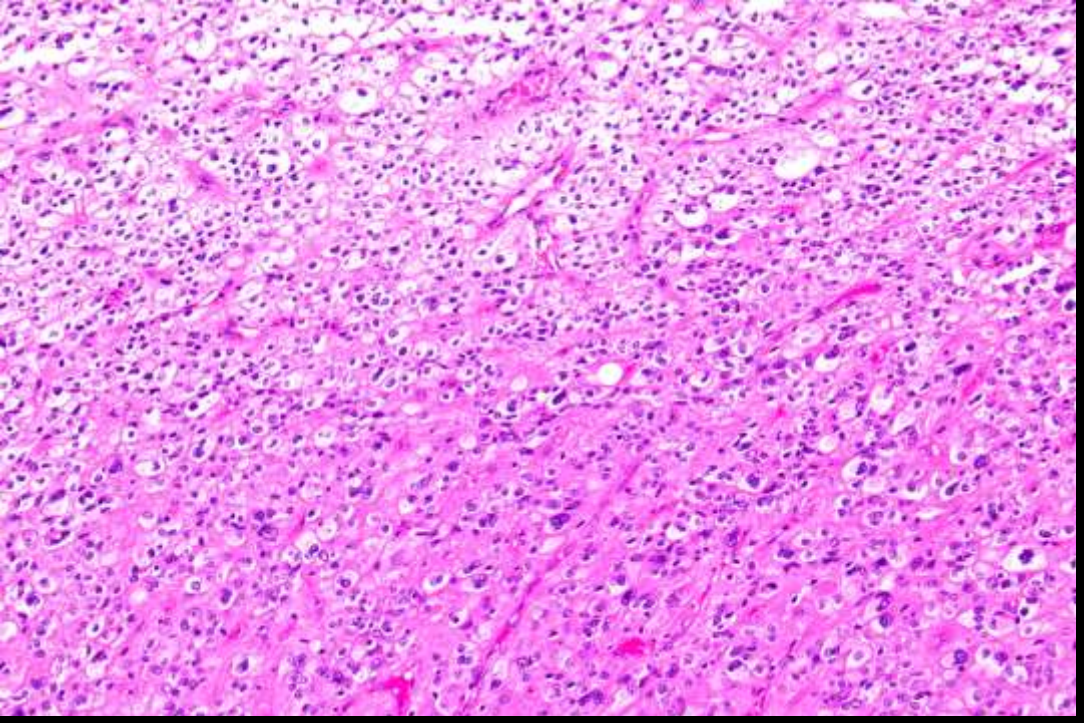
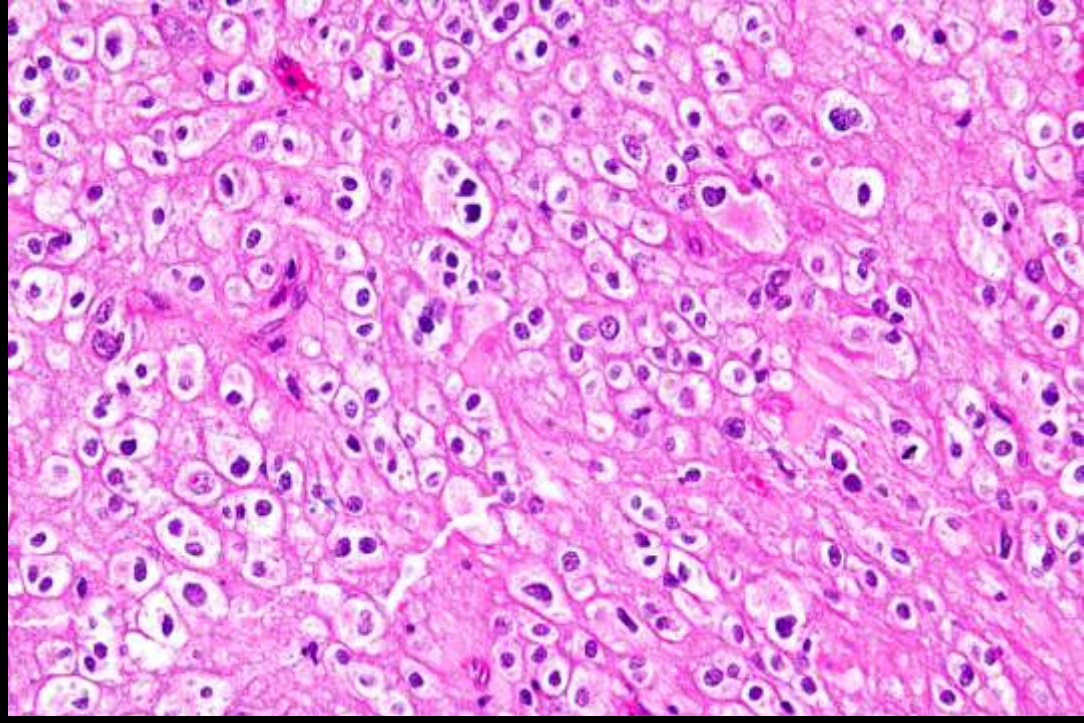
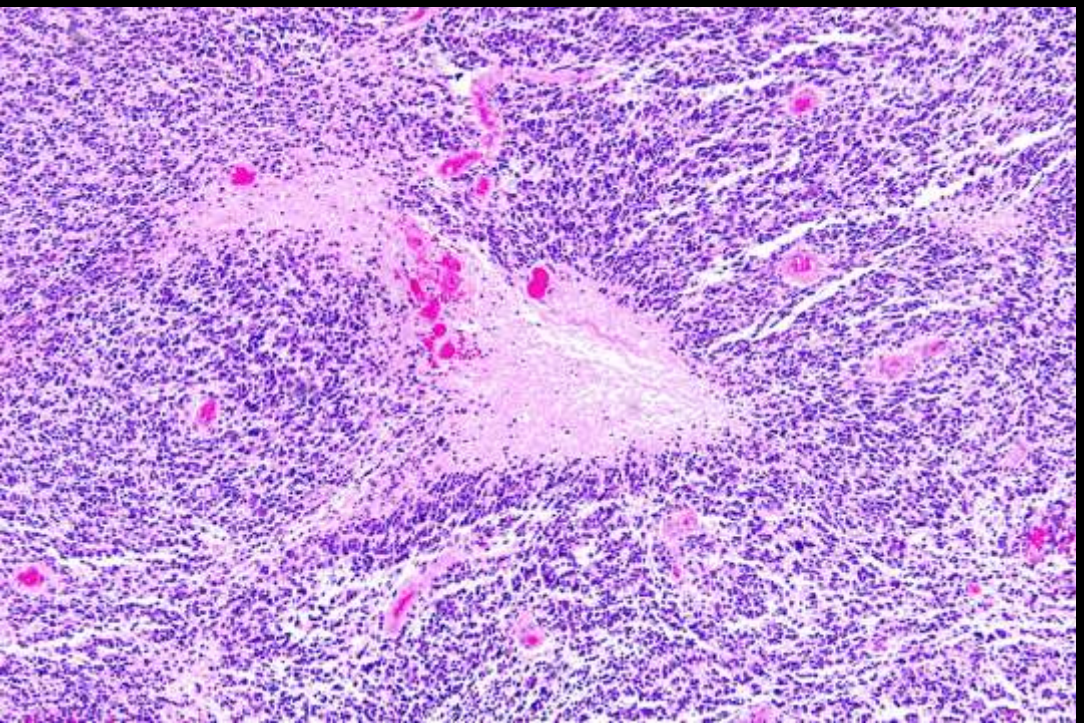
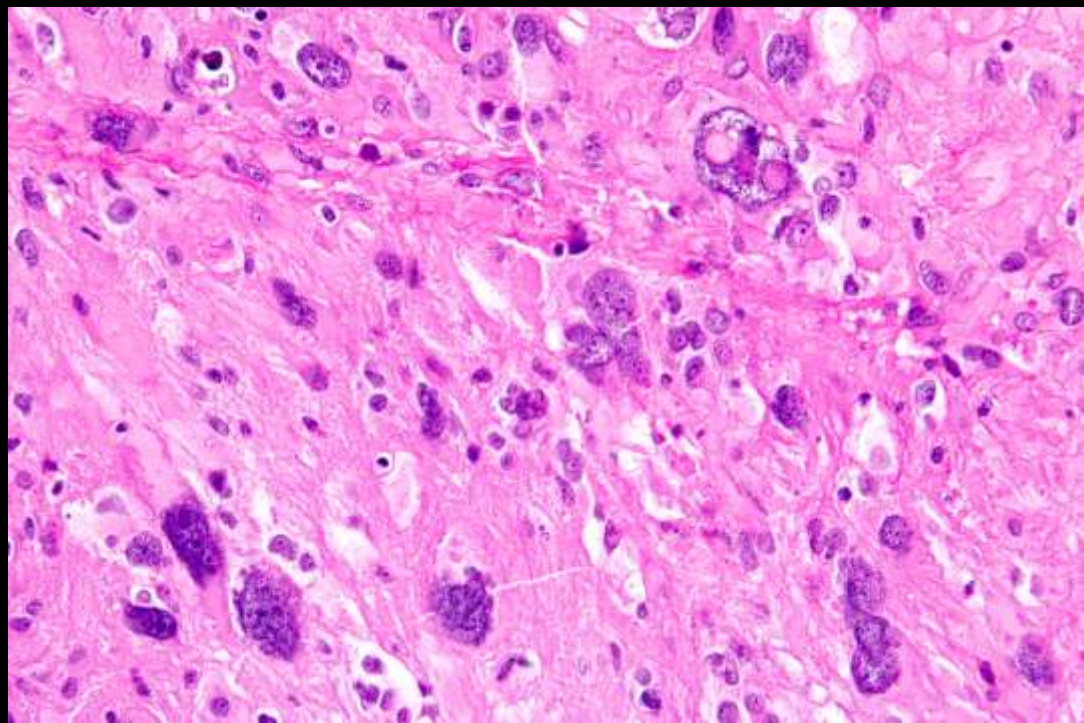
GBM-O
Fig. 1.26 C (p 33)

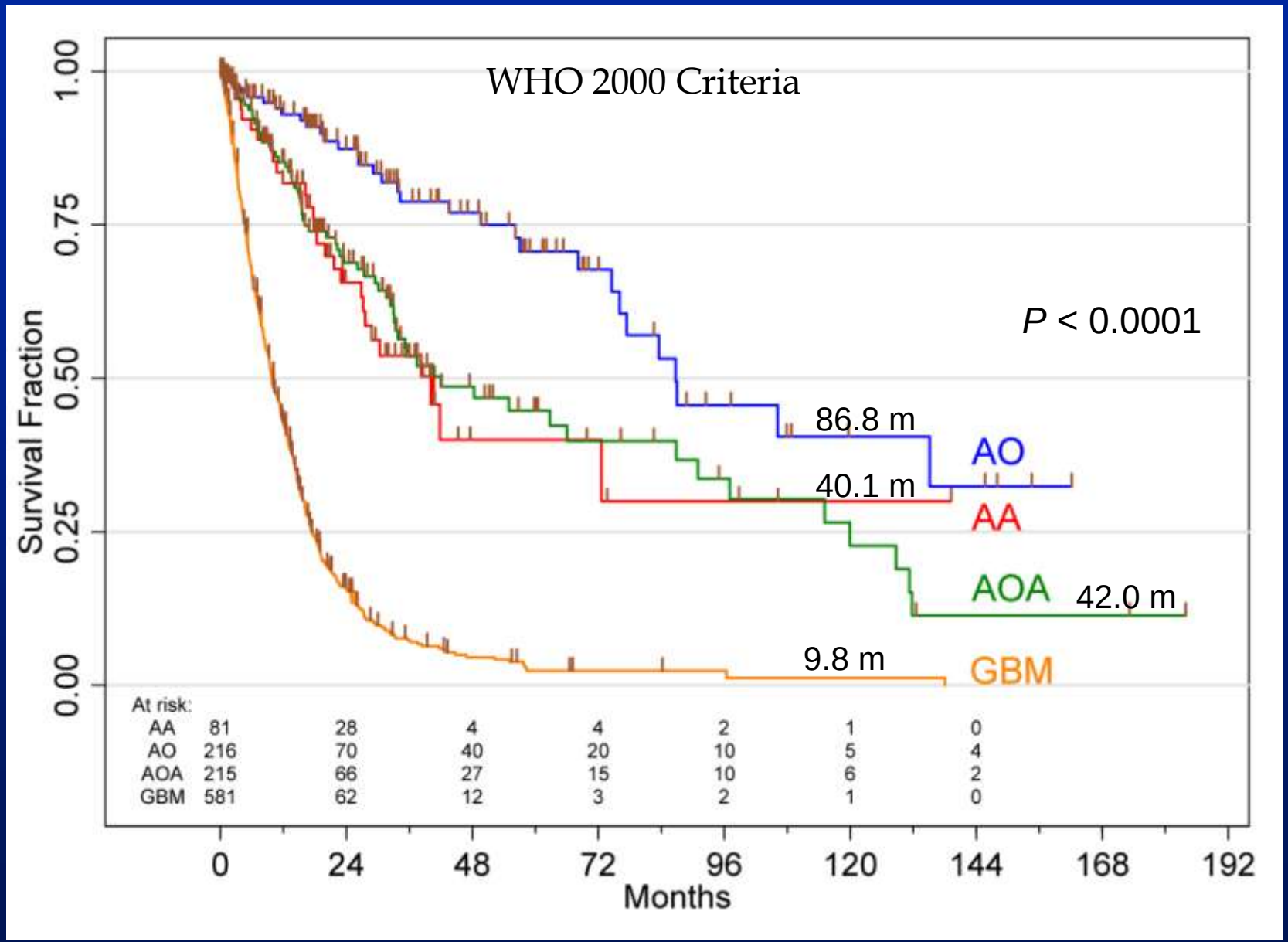


O3 with PPN
Fig. 2.10 A (p 62)

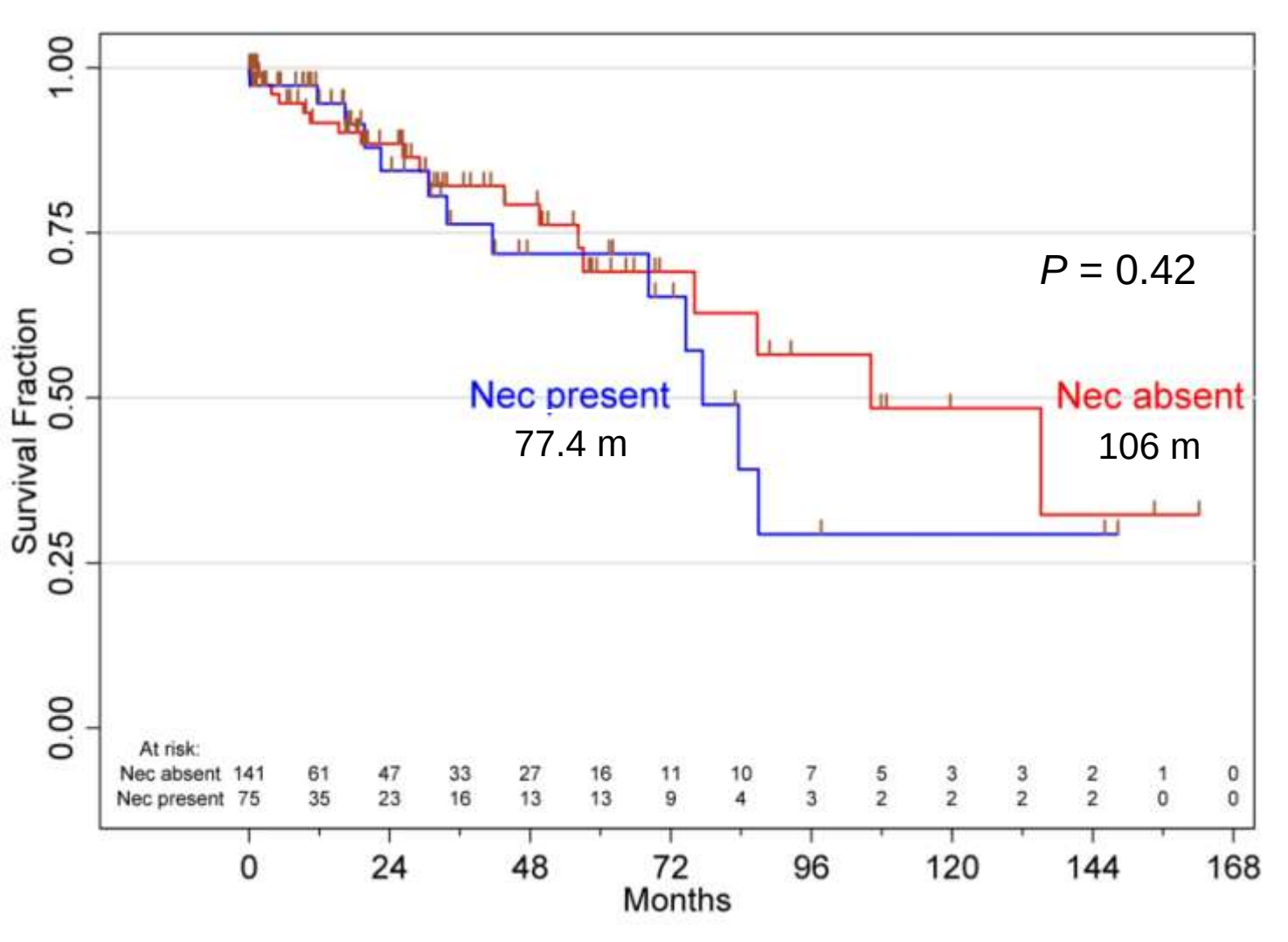
High-Grade Gliomas

- 1093 adults with primary cerebral HGG
  - GBM = 581, AO = 216, AOA = 215, AA = 81
  - WUSM ~50%, Consults ~50%
  - Age: 21-90 years (Mean 52)
  - M:F = 1.4
  - Resection = 78%, Biopsy = 22%
- F/U until death (54%); mean: 1.5 years in rest
- Necrosis in 59%, MVP in 73%
- -1p/19q in 37% (of 570), EGFR amp in 33% (of 239), -10q in 61% (of 222)

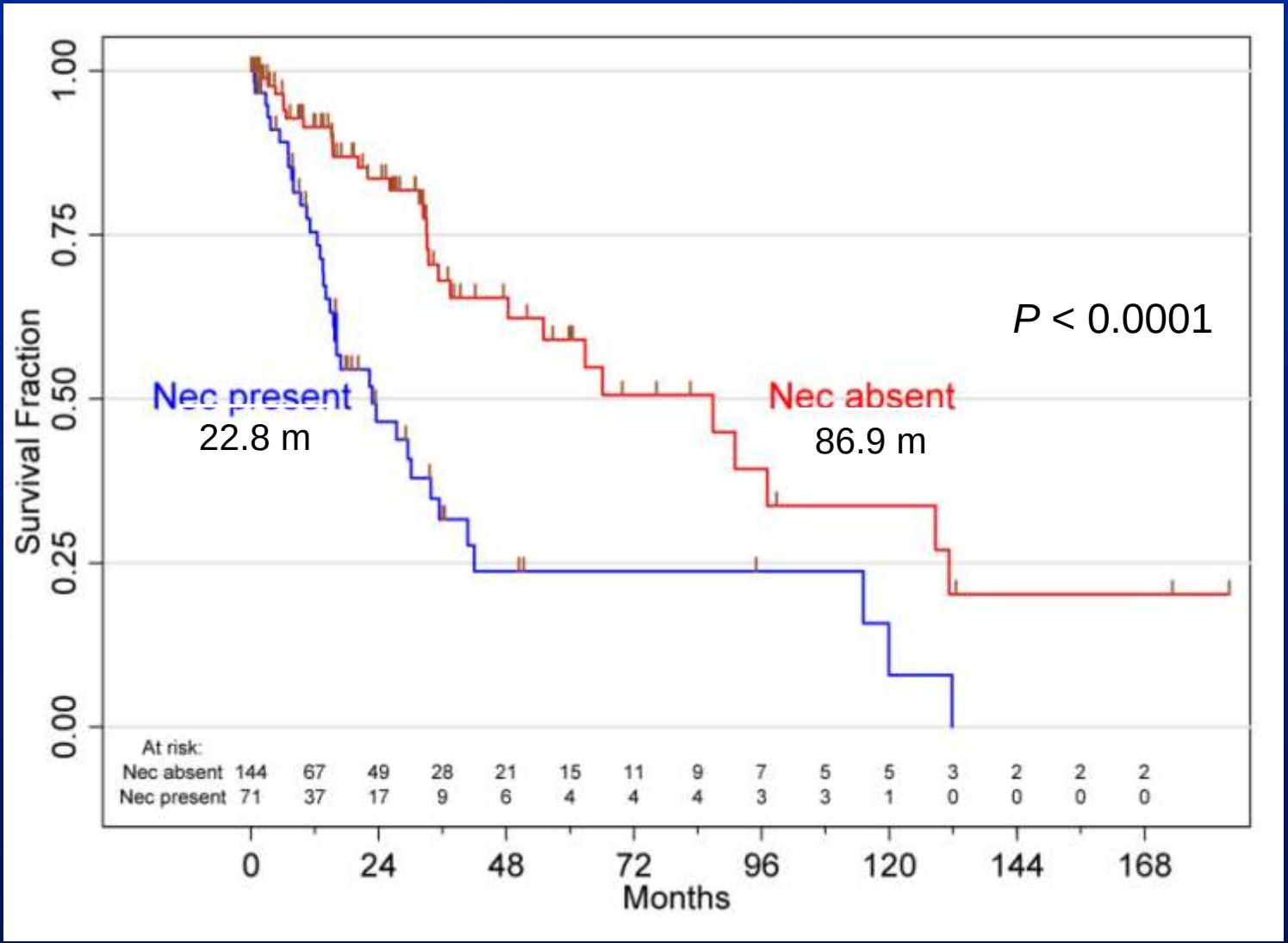





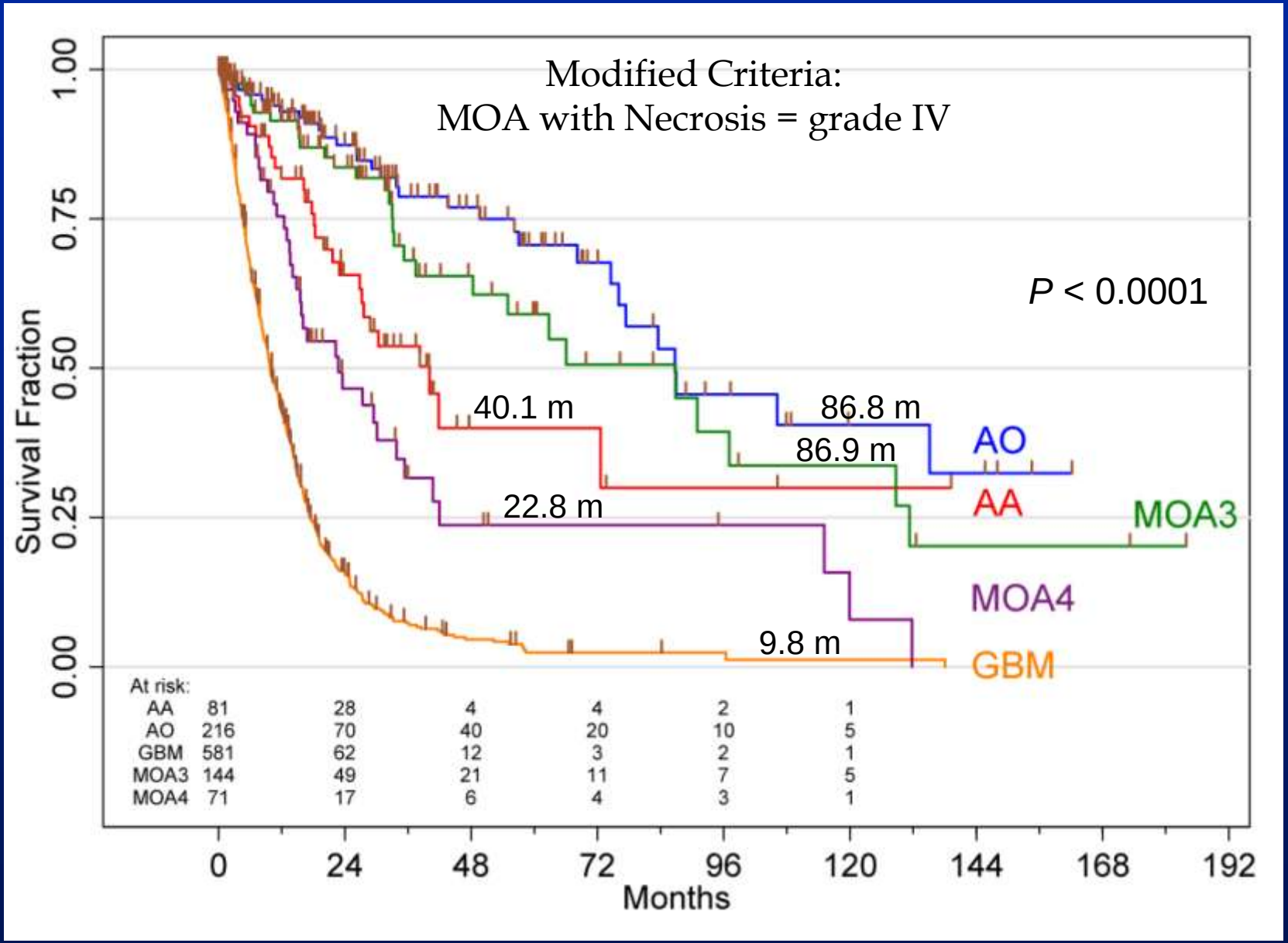

WHO 2000 Criteria
Survival Fraction
1.00
0.75
0.50
0.25
0.00
P < 0.0001
86.8 m
AO
40.1 m
AA
AOA
42.0 m
9.8 m
GBM
At risk:
AA 81 28 4 4 2 1 0
AO 216 70 40 20 10 5 4
AOA 215 66 27 15 10 6 2
GBM 581 62 12 3 2 1 0
0 24 48 72 96 120 144 168 192
Months

Anaplastic Oligodendrogliomas (AO)

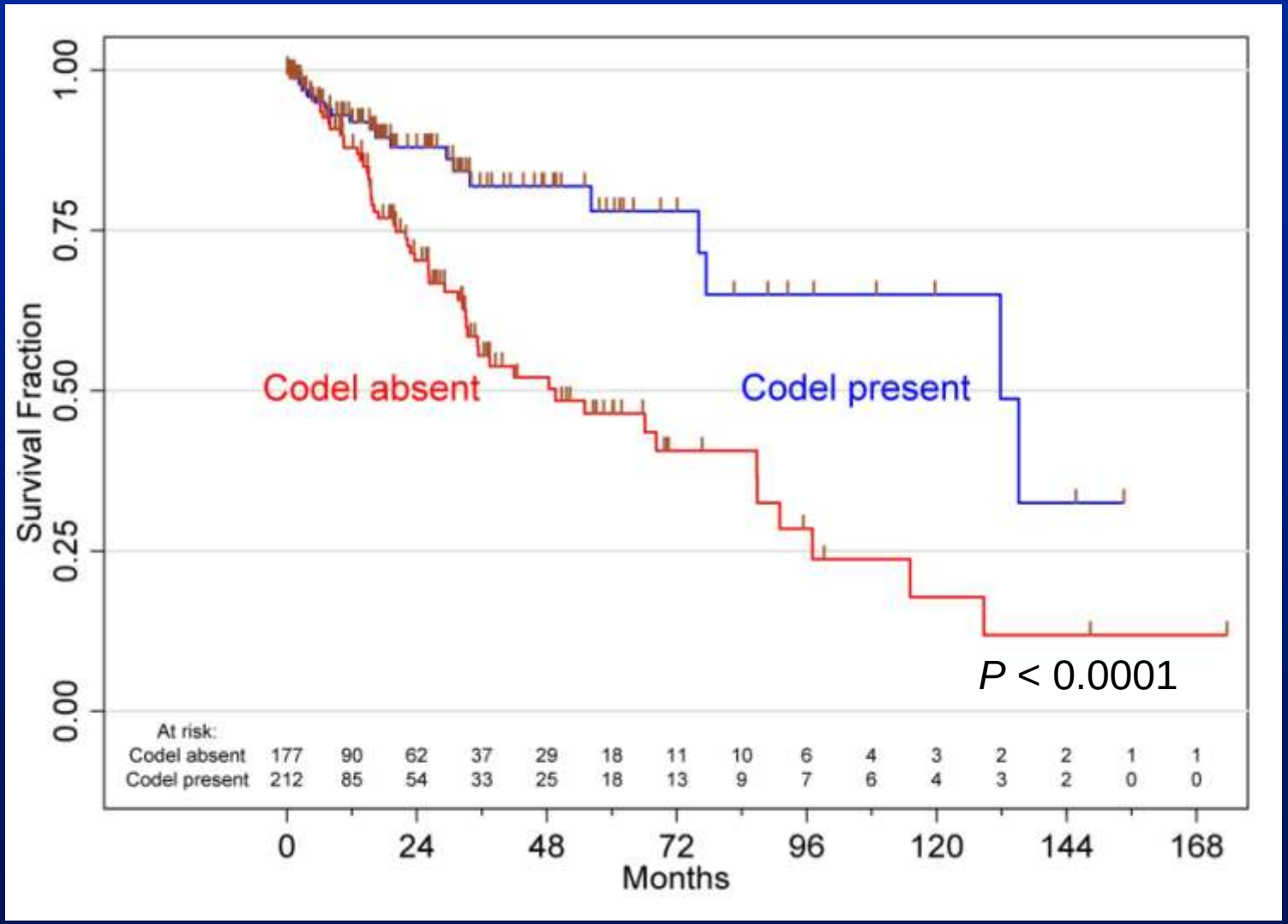


Anaplastic Oligoastrocytomas (AOA)



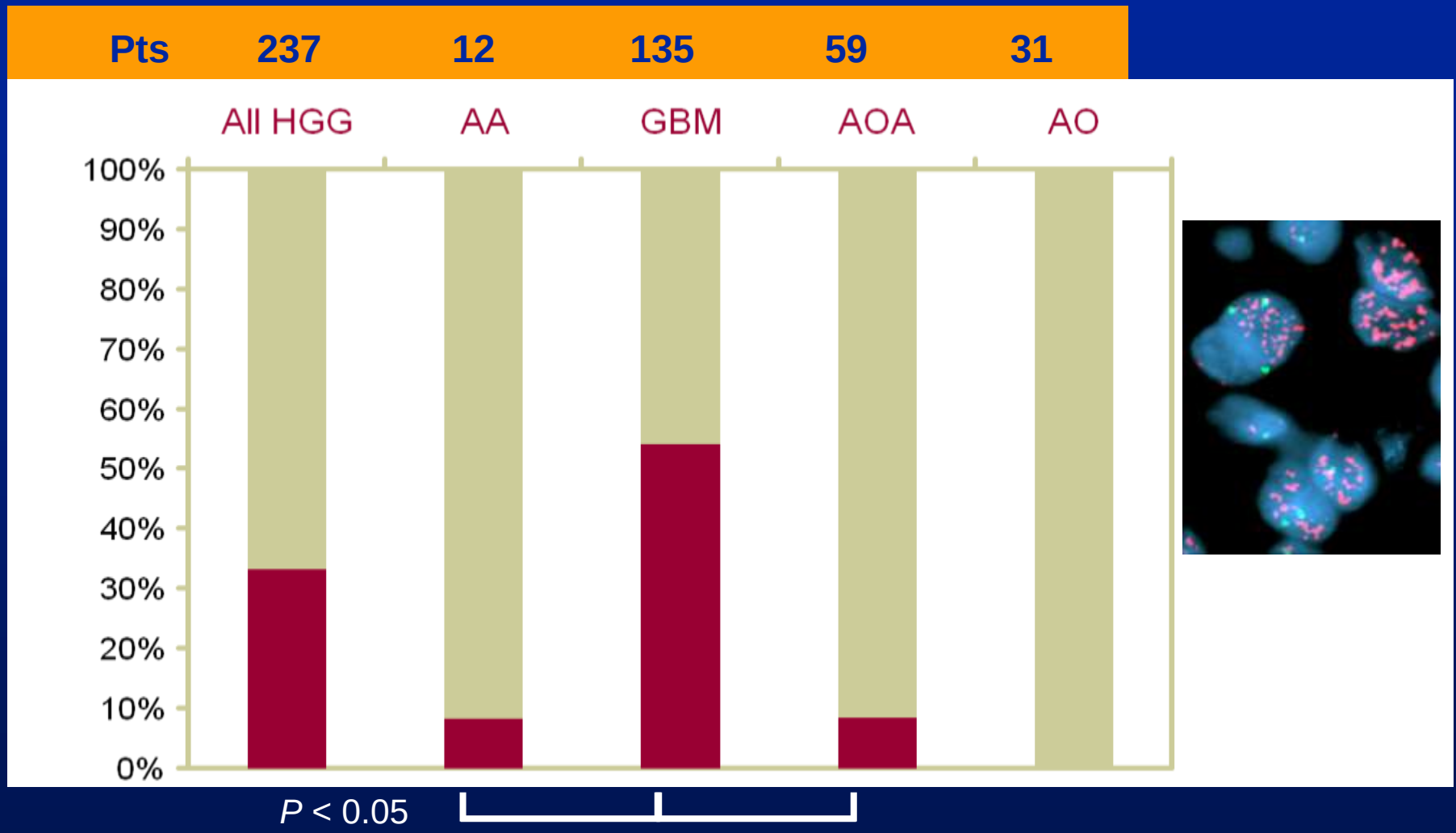

Modified Criteria:
MOA with Necrosis = grade IV
P < 0.0001
Survival Fraction
1.00
0.75
0.50
0.25
0.00
40.1 m
86.8 m
86.9 m
22.8 m
9.8 m
AO
AA
MOA3
MOA4
GBM
At risk:
AA 81 28 4 4 2 1
AO 216 70 40 20 10 5
GBM 581 62 12 3 2 1
MOA3 144 49 21 11 7 5
MOA4 71 17 6 4 3 1
0 24 48 72 96 120 144 168 192
Months

1p/19q Status: HGOs



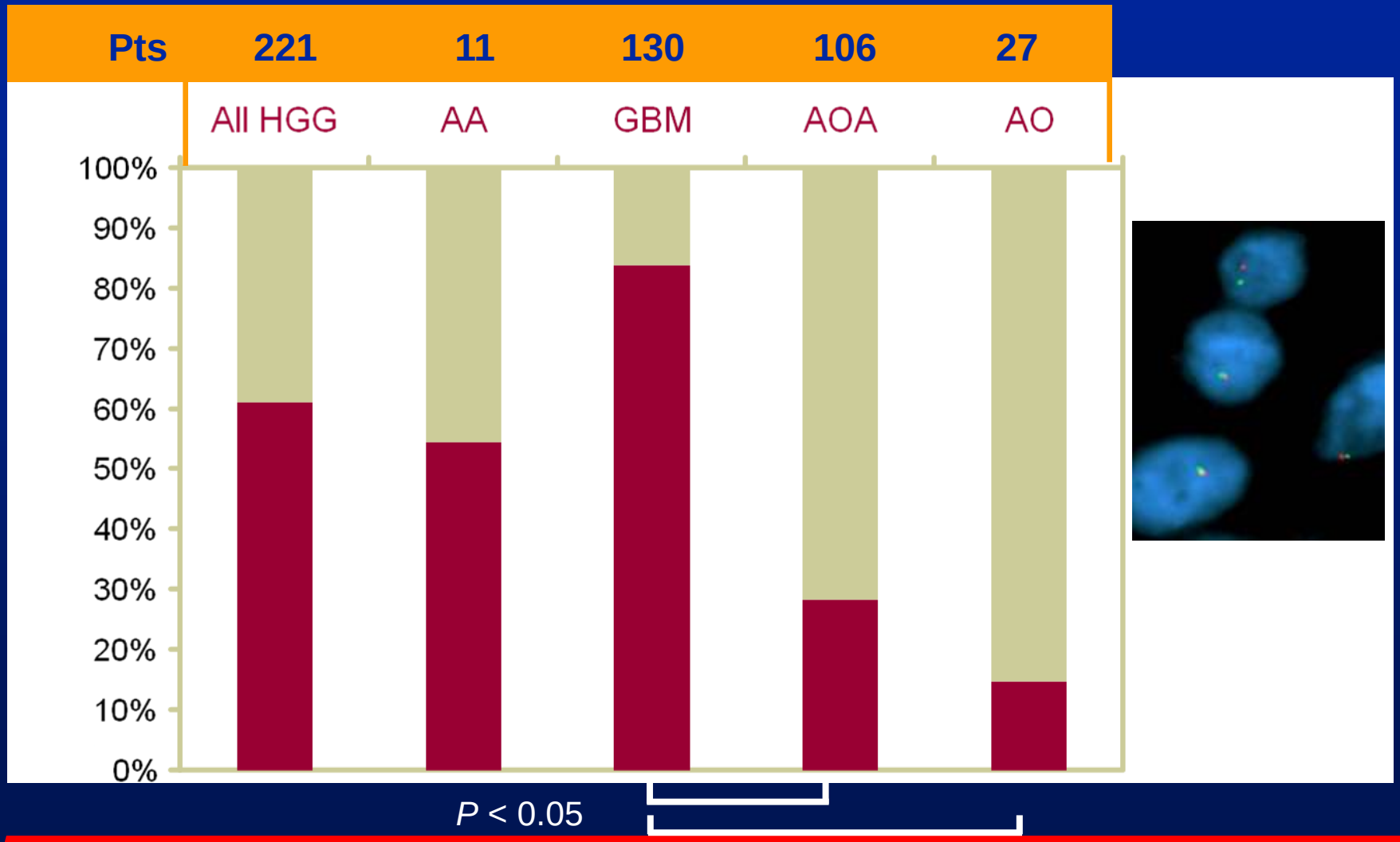
Genetic Characteristics

EGFR Amplification



Genetic Characteristics

Chromosome 10q (PTEN) Deletion



Multivariable (Cox Proportional Hazards) Analysis After Modified Grading of High Grade Gliomas

	HR	*P*
Age	2.2	0.001
Grade	2.1	0.001
1p & 19q codeletion	0.41	0.001
Oligo cytology	0.60	0.026
C index	0.783	
Explained variation	52%	

CONCLUSIONS

- Whole arm 1p/19q codeletion is relatively specific to "genetically favorable" oligodendrogliomas in adults
- The relevant 1p/19q genes have yet to be identified
  - Haploinsufficiency of multiple genes?
  - Epigenetic mechanisms?
  - Non-balanced translocation?
- 1p/19q codeletion is a very early, but not the earliest genetic event. IDH1 probably earlier.
- Pediatric oligodendrogliomas likely utilize a different mechanism of tumorigenesis

CONCLUSIONS

- EGFR amplifications and 10q losses are sufficiently rare in oligos to consider other diagnoses (SC GBM).
- Other alterations likely play a role in the malignant progression of oligos and in the tumorigenesis of favorable MOAs.
- The combination of light microscopy and molecular diagnostics will be more accurate than either one alone.

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ORIGINAL ARTICLE

Identification of der(1;19)(q10;p10) in Five Oligodendrogliomas Suggests Mechanism of Concurrent 1p and 19q Loss

Constance A. Griffin, MD, Peter Burger, MD, Laura Morsberger, BA, Raluca Yonescu, MD, Sharon Swierczynski, MD, PhD, Jon D. Weingart, MD, and Kathleen M. Murphy, PhD

Abstract

Deletions of portions of chromosomes 1p and 19q are closely associated with the oligodendroglioma histologic phenotype. In most cases, 1p and 19q are codeleted, yet the mechanism of dual loss is unexplained. We report 5 cases (World Health Organization grade III) in which metaphase cytogenetics identified a derivative chromosome consisting of what appears to be the whole arms of 1q and 19p forming a der(1;19)(q10;p10). Metaphase fluorescent in situ hybridization (FISH) confirmed the derivative chromosome was composed of 1q and 19p material in 3 cases; in 2 cases with few metaphases, FISH confirmed 19p material on the derivative chromosome. In all cases, interphase FISH showed net loss of 1p and 19q in 77% to 92% of cells, and microsatellite studies were consistent with 1p and 19q loss. We hypothesize the following: occurrence of a balanced whole-arm translocation between chromosomes 1 and 19 forming 2 derivative chromosomes, one composed of 1q and 19p, the other of 1p and 19q. Subsequent loss of the der(1;19)(p10;q10) then results in the simultaneous 1p and

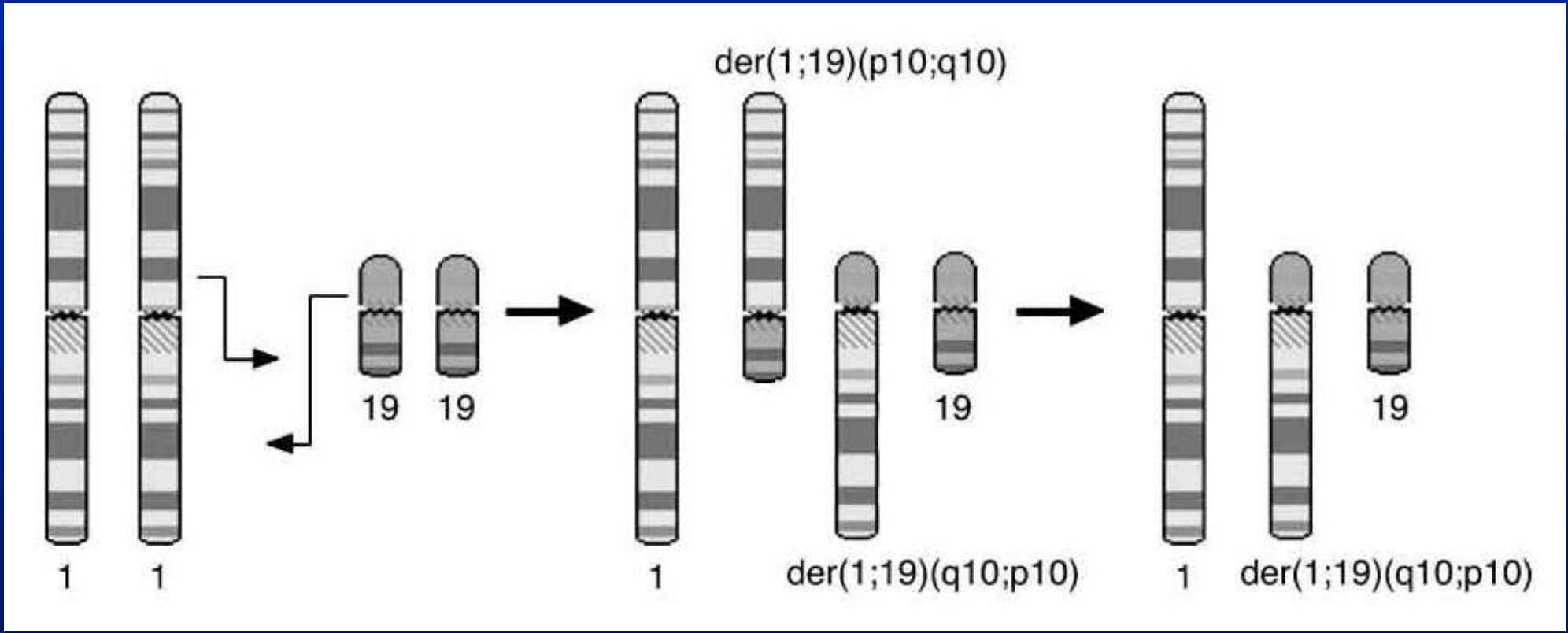
(CGH), and allelic loss as measured by loss of heterozygosity (LOH). The loss of 1p and 19q is assessed on clinical specimens because such loss is associated with a better response to chemotherapy than is seen in other types of infiltrating gliomas (2–4), although how such loss confers the observed sensitivity to therapy has not been reported. The mechanism of concurrent loss of 2 large unlinked genomic regions has not been elucidated. In 2005, we reported an oligodendroglioma in which the karyotype suggested one possible explanation (5). Since then, we have found 4 additional cases, providing additional evidence to the possibility that this is a common mechanism for loss of both 1p and 19q.

MATERIALS AND METHODS

Case 1

A 26-year-old woman presented with neurologic symptoms and was found to have a 6.0 × 6.8 × 15.0-cm mass in the right temporal region. Craniotomy and subtotal

MECHANISM OF 1p/19q CODELETION



A t(1;19)(q10;p10) Mediates the Combined Deletions of 1p and 19q and Predicts a Better Prognosis of Patients with Oligodendroglioma

Robert B. Jenkins,[1] Hilary Blair,[1] Karla V. Ballman,[1] Caterina Giannini,[1] Robert M. Arusell,[2] Mark Law,[1] Heather Flynn,[1] Sandra Passe,[1] Sara Felten,[1] Paul D. Brown,[1] Edward G. Shaw,[3] and Jan C. Buckner[1]

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Abstract

**Combined deletion of chromosomes 1p and 19q is associated with improved prognosis and responsiveness to therapy in patients with anaplastic oligodendroglioma. The deletions usually involve whole chromosome arms, suggesting a t(1;19)(q10;p10). Using stem cell medium, we cultured a few tumors. Paraffin-embedded tissue was obtained from 21 Mayo Clinic patients and 98 patients enrolled in 2 North Central Cancer Treatment Group (NCCTG) low-grade glioma trials. Interphase fusion of CEP1 and 19p12 probes detected the t(1;19). 1p/19q deletions were evaluated by fluorescence *in situ* hybridization. Upon culture, one oligodendroglioma contained an unbalanced 45,XX,t(1;19)(q10;p10). CEP1/19p12 fusion was observed in all metaphases and 74% of interphase nuclei. Among Mayo Clinic oligodendrogliomas, the prevalence of fusion was 81%. Among NCCTG patients, CEP1/19p12 fusion prevalence was 55%, 47%, and 0% among the oligodendrogliomas, mixed oligoastrocytomas, and astrocytomas and 50% of mixed oligoastrocytomas (3–5). The prevalence of deletions is similar in both low-grade (WHO grade 1) and anaplastic (WHO grade 3) oligodendroglial tumors (3–6). In addition to their diagnostic relevance, deletions of 1p and 19q have been associated with a prolonged survival in patients with anaplastic oligodendrogliomas and mixed oligoastrocytomas using retrospectively collected cohorts (3–5, 7–9). The prognostic relevance of the deletions has been validated recently by two prospective clinical trials, one led by the Radiation Therapy Oncology Group (RTOG) and another led by the European Organization for Research and Treatment of Cancer (EORTC; refs. 10, 11). Both retrospective and prospective data also suggest that 1p and 19q deletion also predict the responsiveness of anaplastic oligodendroglial tumors to combined radiation therapy (RT) and chemotherapy (7, 10, 11).

Whereas the prognostic relevance of 1p and 19q deletions is well established for anaplastic oligodendrogliomas and mixed oligoastrocytomas, the prognostic relevance of the deletions for low-grade gliomas is more controversial. In this report, using

groups (i.e., those with deletion versus those without deletion, those with fusion and those without fusion) were compared with a Wilcoxon test. Univariable and multivariable analyses of time-to-event data were conducted using Cox proportional hazards modeling. The following variables were included in the modeling: age, gender, histologic type, mini-mental status exam (MMSE) status, 1p/19q deletion status, and CEP1/19p12 fusion status. The intent of the multivariable models was to ascertain whether the univariable association between deletion status and fusion and the time-to-event end points (survival and PFS) remained after adjusting for known prognostic factors.

Results

Identification of a t(1;19)(q10;p10) in an oligodendroglioma. Using modifications of various stem cell medium, we have been able to do short-term culture and recovery of metaphases from a few oligodendrogliomas. In one oligodendroglioma, we observed an unbalanced 45,XX,der(1;19)(q10;p10) karyotype in all abnormal metaphases (Fig. 1*A*). Other nonclonal abnormalities, such as an extra chromosome 7 (see Fig. 1*A*), were also observed in single metaphases. Initially, the translocation was verified in metaphases using WCP probes for chromosomes 1 and 19 (Fig. 1*B*). We then developed a BAC contig FISH probe for proximal 19p12 in green and combined it with CEP1 in orange. Using a single-fusion strategy, this probe mixture was applied to metaphase cells and interphase nuclei from this glioma (Fig. 1*C* and *D*). Fusion of the CEP1 and 19p12 probes was observed in all abnormal metaphases as well as 74% of interphase nuclei.

Initial validation of the CEP1/19p12 FISH fusion probe set. The translocation probe was then applied to 4 nontumor gliosis specimens, 5 oligodendroglioma paraffin specimens with (3) and without (2) 1p and 19q deletion, and a tissue microarray containing core biopsies from paraffin blocks from 16 oligodendrogliomas

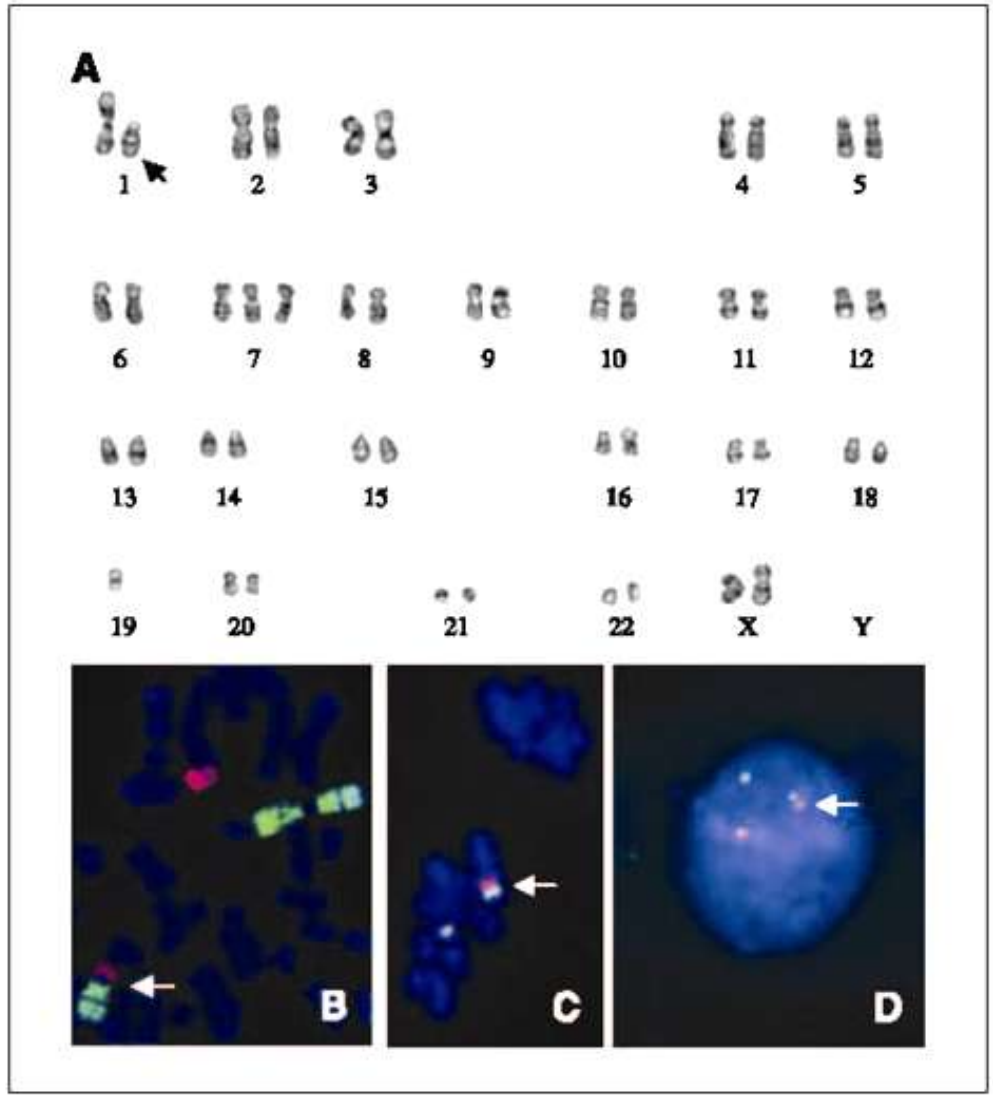


Figure 1. *A*, karyotype of oligodendroglioma patient. *Arrow*, t(1;19)(q10;p10). *B*, metaphase FISH using whole chromosome painting probes. *Arrow*, t(1;19). Spectrum Green = 1 WCP, Spectrum Orange = 19 WCP. *C*, metaphase FISH using 1CEP in Spectrum Orange and a BAC contig for 19p12 in Spectrum Green. *Arrow*, fusion of the probes at the translocation site. *D*, interphase FISH using 1CEP in Spectrum Orange and a BAC contig for 19p12 in Spectrum Green. *Arrow*, fusion signal.

OTHER BIOMARKERS

- MGMT inactivation by methylation of CpG islands in promoter region
- IDH1 mutations
- Array based stratifiers
- Paradigm of targeted therapies

Hegi ME et al.,
NEJM 352;10:997, 2005

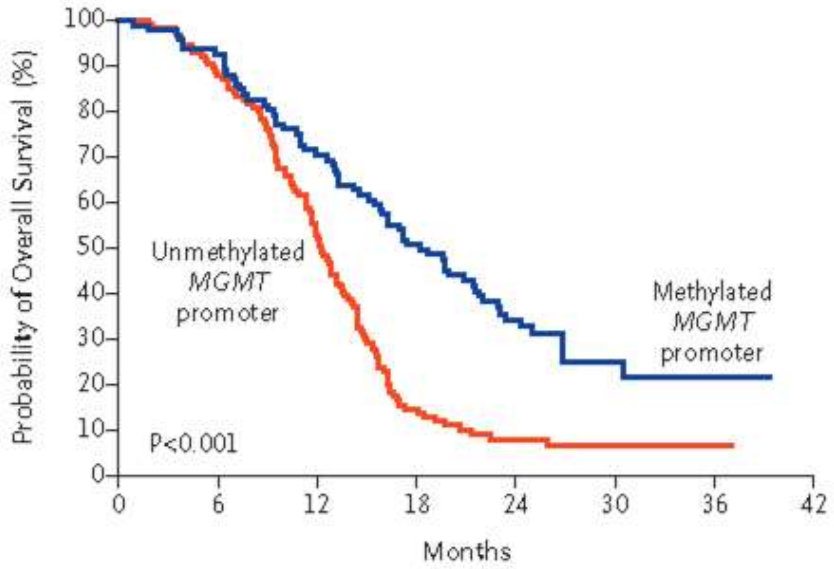
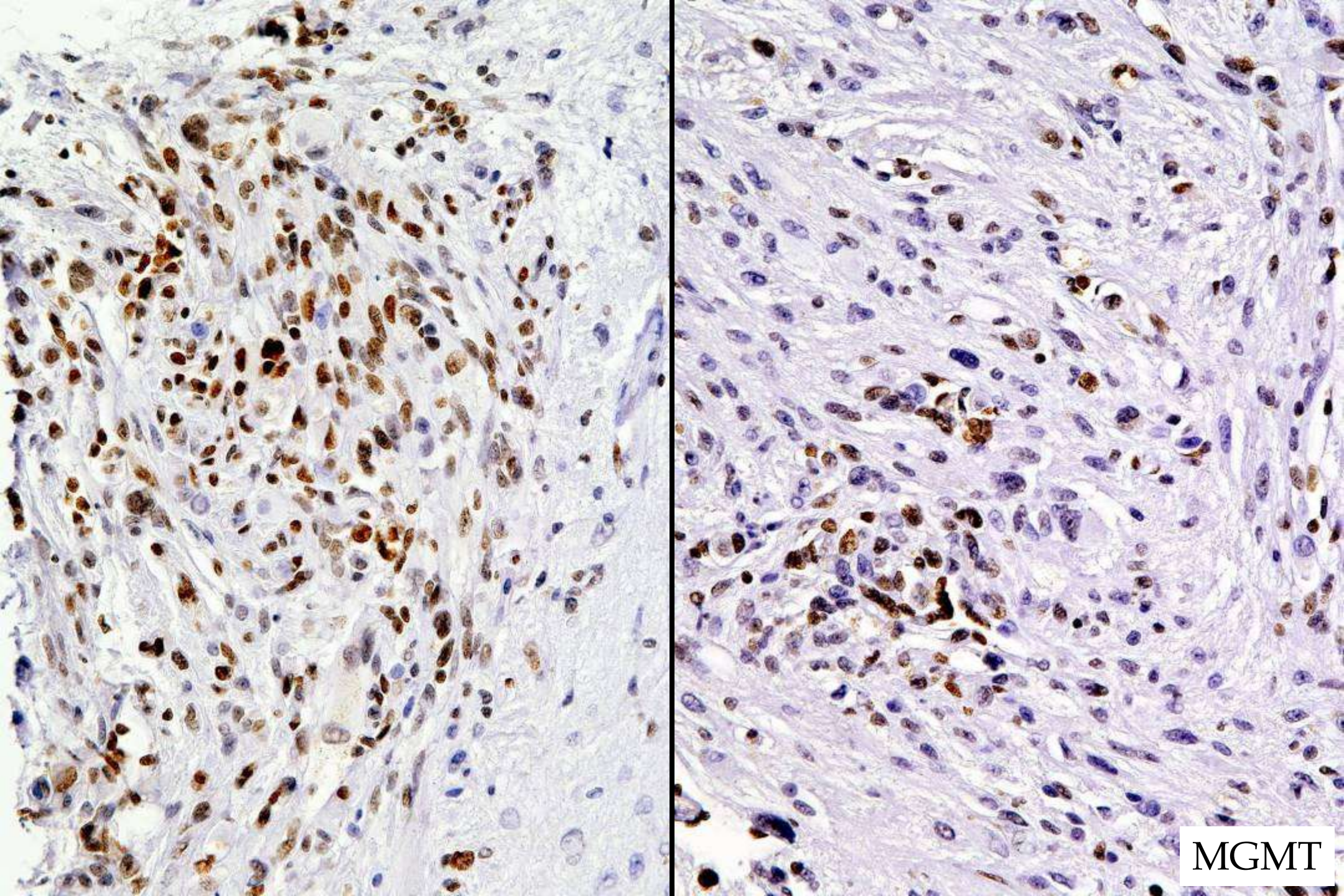


Figure 2. Kaplan–Meier Estimates of Overall Survival, According to *MGMT* Promoter Methylation Status.

The difference in survival between patients with a methylated *MGMT* promoter (92 patients, 65 of whom died) and those with an unmethylated *MGMT* promoter (114 patients, 105 of whom died) was highly significant ($P<0.001$ by the log-rank test), indicating that the *MGMT* methylation status has prognostic value. In the group of patients with a methylated *MGMT* promoter, there was a risk reduction of 55 percent (hazard ratio for death, 0.45; 95 percent confidence interval, 0.32 to 0.61), as compared with the group with an unmethylated *MGMT* promoter.


MGMT

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

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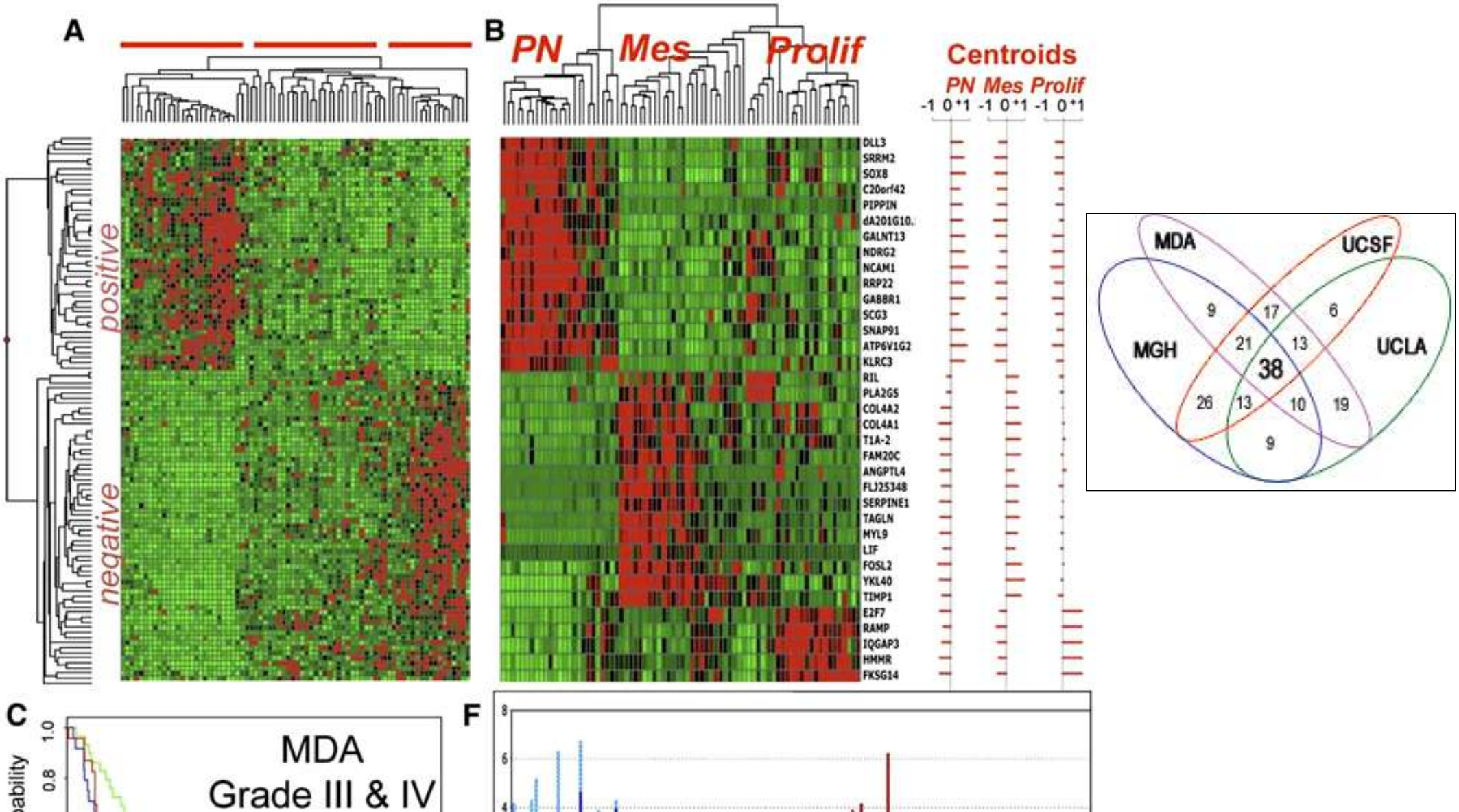
Cancer Cell 9:157-173, 2006

Summary

Previously undescribed prognostic subclasses of high-grade astrocytoma are identified and discovered to resemble stages in neurogenesis. One tumor class displaying neuronal lineage markers shows longer survival, while two tumor classes enriched for neural stem cell markers display equally short survival. Poor prognosis subclasses exhibit markers either of proliferation or of angiogenesis and mesenchyme. Upon recurrence, tumors frequently shift toward the mesenchymal subclass. Chromosomal locations of genes distinguishing tumor subclass parallel DNA copy number differences between subclasses. Functional relevance of tumor subtype molecular signatures is suggested by the ability of cell line signatures to predict neurosphere growth. A robust two-gene prognostic model utilizing PTEN and DLL3 expression suggests that Akt and Notch signaling are hallmarks of poor prognosis versus better prognosis gliomas, respectively.


A
B
PN
Mes
Prolif
Centroids
PN Mes Prolif
-1 0 +1 -1 0 +1 -1 0 +1
positive
negative
DLL3
SRRM2
SOX8
C20orf42
PIPPIN
dA201G10.
GALNT13
NDRG2
NCAM1
RRP22
GABBR1
SCG3
SNAP91
ATP6V1G2
KLRC3
RIL
PLA2G5
COL4A2
COL4A1
T1A-2
FAM20C
ANGPTL4
FLJ25348
SERPINE1
TAGLN
MYL9
LIF
FOSL2
YKL40
TIMP1
E2F7
RAMP
IQGAP3
HMMR
FKSG14
MDA
UCSF
MGH
UCLA
9
17
6
21
13
38
26
13
10
19
9
C
MDA
Grade III & IV
1.0
0.8
F
8
6

Cancer Cell 17, 98–110, January 19, 2010

Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in *PDGFRA*, *IDH1*, *EGFR*, and *NF1*

Roel G.W. Verhaak,[1,2,17] Katherine A. Hoadley,[3,4,17] Elizabeth Purdom,[7] Victoria Wang,[8] Yuan Qi,[4,5] Matthew D. Wilkerson,[4,5] C. Ryan Miller,[4,6] Li Ding,[9] Todd Golub,[1,10] Jill P. Mesirov,[1] Gabriele Alexe,[1] Michael Lawrence,[1,2] Michael O'Kelly,[1,2] Pablo Tamayo,[1] Barbara A. Weir,[1,2] Stacey Gabriel,[1] Wendy Winckler,[1,2] Supriya Gupta,[1] Lakshmi Jakkula,[11] Heidi S. Feiler,[11] J. Graeme Hodgson,[12] C. David James,[12] Jann N. Sarkaria,[13] Cameron Brennan,[14] Ari Kahn,[15] Paul T. Spellman,[11] Richard K. Wilson,[9] Terence P. Speed,[7,16] Joe W. Gray,[11] Matthew Meyerson,[1,2] Gad Getz,[1] Charles M. Perou,[3,4,8] D. Neil Hayes,[4,5,*] and The Cancer Genome Atlas Research Network

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[17]These authors contributed equally to the work
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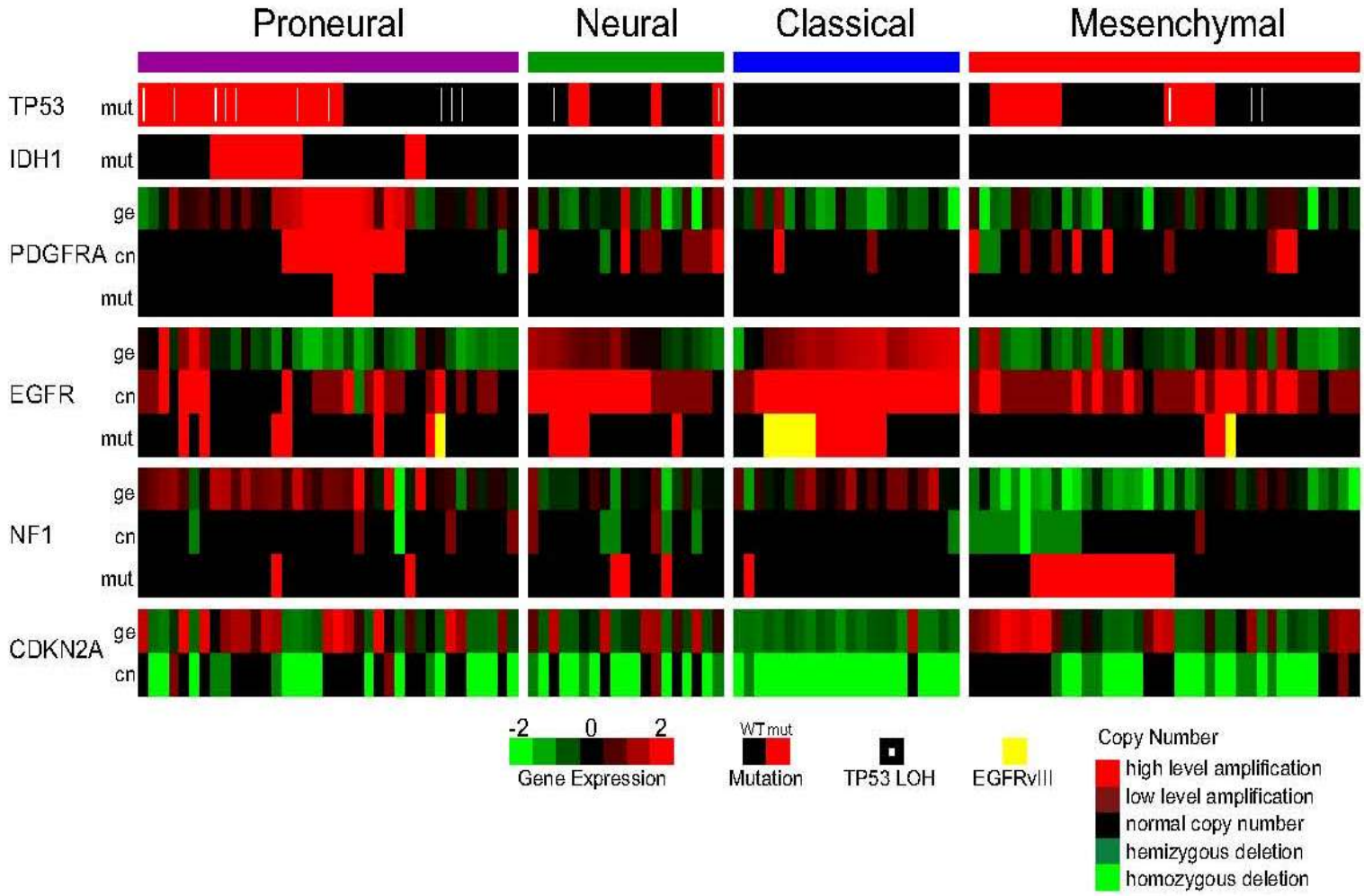

Figure 3. Integrated View of Gene Expression and Genomic Alterations across Glioblastoma Subtypes

Gene expression data (ge) were standardized (mean equal to zero, standard deviation equal to 1) across the 202 data set; data are shown for the 116 samples with both mutation and copy number data. Mutations (mut) are indicated by a red cell, a white pipe indicates loss of heterozygosity, and a yellow cell indicates the presence of an EGFRvIII mutation. Copy number events (cn) are illustrated by bright green for homozygous deletions, green for hemizygous deletions, black for copy number neutral, red for low-level amplification, and bright red for high-level amplifications. A black cell indicates no detected alteration.

Neuro-Oncology 12(1):49–57, 2010.
doi:10.1093/neuonc/nop007
Advance Access publication October 20, 2009

NEURO-ONCOLOGY

A multigene predictor of outcome in glioblastoma

Howard Colman, Li Zhang, Erik P. Sulman, J. Matthew McDonald, Nasrin Latif Shooshtari, Andreana Rivera, Sonya Popoff, Catherine L. Nutt, David N. Louis, J. Gregory Cairncross, Mark R. Gilbert, Heidi S. Phillips, Minesh P. Mehta, Arnab Chakravarti, Christopher E. Pelloski, Krishna Bhat, Burt G. Feuerstein, Robert B. Jenkins, and Ken Aldape

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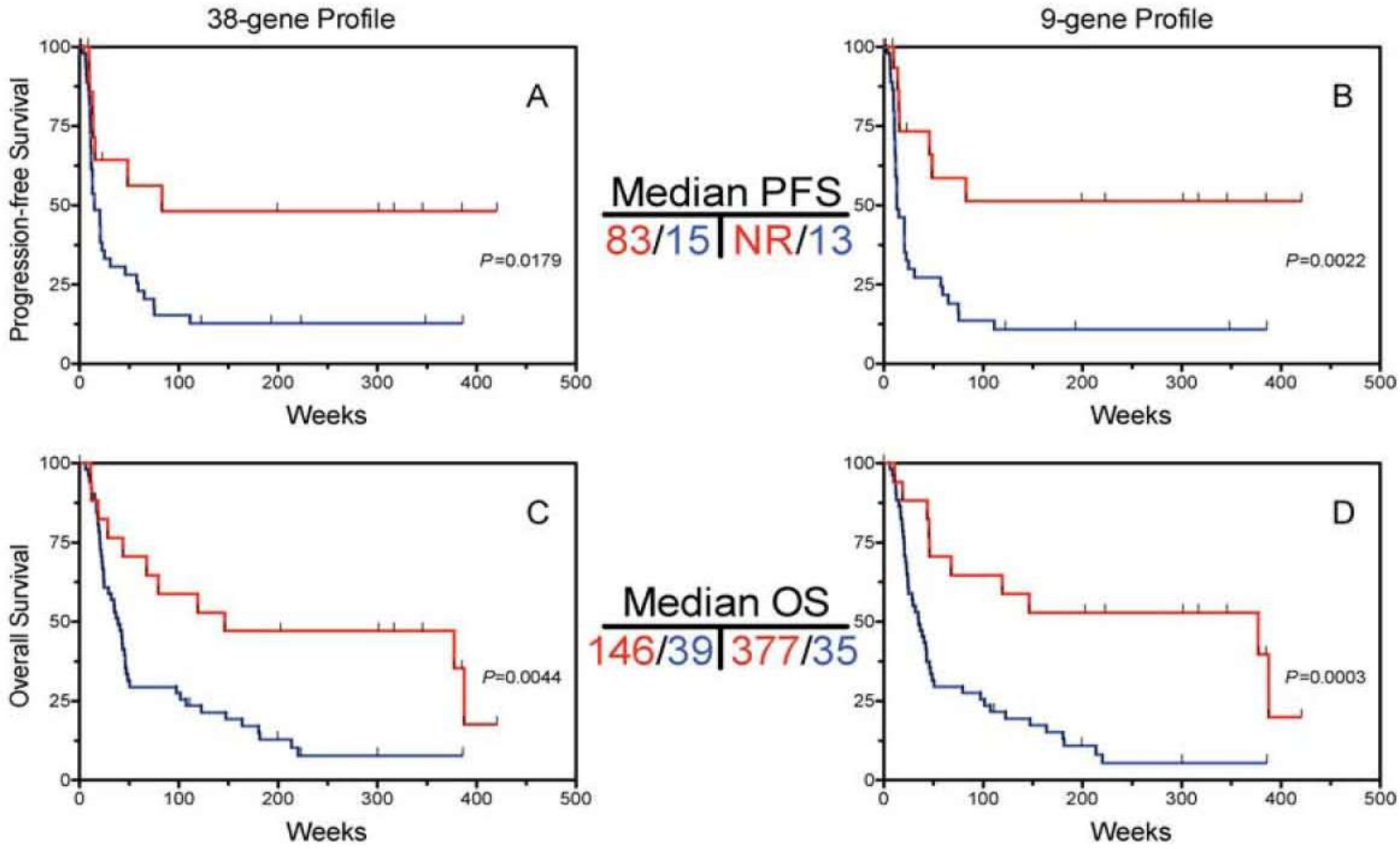

Fig. 2. Validation of multigene predictor for overall survival in an independent sample set. A set of 68 formalin-fixed, paraffin-embedded glioblastoma samples was subject to qRT-PCR for the 38 gene set identified in Fig. 1. A metagene score was calculated as in Fig. 1 and the samples were ranked by metagene score. Patients were dichotomized into 2 groups based on metagene score using proportions identical to those in Fig. 1. Survival is shown for the lower metagene scores (red) vs the higher metagene scores (blue). Analyses were performed for the entire 38-gene set as well as a smaller 9-gene profile composed of those genes that had the highest individual survival association in the tumors and showed high technical feasibility in paraffin tissues. (A) and (B) Progression-free survival (PFS) according to the entire 38-gene set (A) as well as the 9 gene-profile (B). (C) and (D) Overall survival (OS) according to the 38-gene set (C) and 9-gene set (D). NR, median not reached.

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GBM DECISIONDx

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The tabs at the top of this home page link you to information for **Patients and Caregivers**, **Healthcare Professionals** and **Ordering information**.

Glioblastoma Multiforme (GBM)...

Glioblastoma multiforme is the most prevalent and aggressive form of primary brain cancer in adults, affecting over 15,000 patients per year in the US alone.

Today's treatment starts with surgical removal as much of the tumor as possible. Following a brief recovery period, patients are typically placed on the standard of care, first line treatment of radiation plus concurrent and adjuvant temozolomide. Periodic imaging is ordered to monitor tumor status. Upon progression, a number of second-line treatment options may be pursued, including protocol driven or investigational approaches. Some centers are also incorporating additional treatments into first line care.

The Need for DecisionDx-GBM...

Today, GBM is diagnosed using traditional histo-pathology techniques. However, tissue staining and microscopic visualization does not discern prognosis of an individual patient.

It is known that some GBM tumors exhibit a good, sustained response to first line treatment while others appear refractory. However, diagnosis of GBM itself does not enable prospective risk-stratification.

The **DecisionDx-GBM** assay was developed to fulfill this need. Prospective risk-stratification allows for more individualized treatment options to be considered early on in diagnosis.

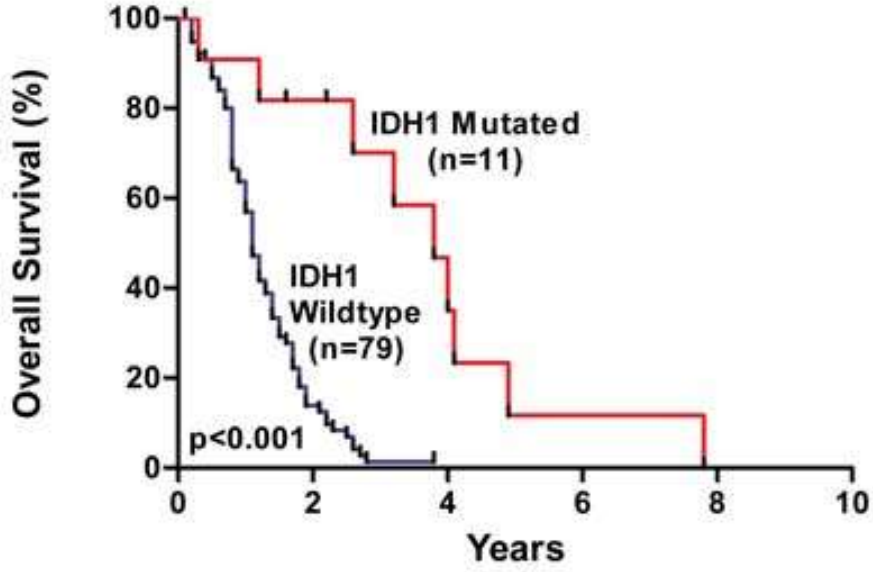
It is our hope that the additional information provided from **DecisionDx-GBM**, in concert with other clinical information, will become a valuable component of the comprehensive baseline evaluation.

Sciencexpress Research Article

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

D. Williams Parsons,[1,2*] Siân Jones,[1*] Xiaosong Zhang,[1*] Jimmy Cheng-Ho Lin,[1*] Rebecca J. Leary,[1*] Philipp Angenendt,[1*] Parminder Mankoo,[3] Hannah Carter,[3] I-Mei Siu,[4] Gary L. Gallia,[4] Alessandro Olivi,[4] Roger McLendon,[5] B. Ahmed Rasheed,[5] Stephen Keir,[5] Tatiana Nikolskaya,[6] Yuri Nikolsky,[7] Dana A. Busam,[8] Hanna Tekleab,[8] Luis A. Diaz Jr.,[1] James Hartigan,[9] Doug R. Smith,[9] Robert L. Strausberg,[8] Suely Kazue Nagahashi Marie,[10] Sueli Mieko Oba Shinjo,[10] Hai Yan,[5] Gregory J. Riggins,[4] Darell D. Bigner,[5] Rachel Karchin,[3] Nick Papadopoulos,[1] Giovanni Parmigiani,[1] Bert Vogelstein,[1†] Victor E. Velculescu,[1†] Kenneth W. Kinzler[1†]

321(5897):1807-12, 2008



The American Journal of Pathology, Vol. 174, No. 4, April 2009

DOI: 10.2353/ajpath.2009.080958

Short Communication

IDH1 Mutations Are Early Events in the Development of Astrocytomas and Oligodendrogliomas

Takuya Watanabe,* Sumihito Nobusawa,* Paul Kleihues,† and Hiroko Ohgaki*

From the International Agency for Research on Cancer, Lyon, France; and the Department of Pathology,† University Hospital Zurich, Zurich, Switzerland*

***IDH1* encodes isocitrate dehydrogenase 1, which participates in the citric acid cycle and was recently reported to be mutated in 12% of glioblastomas. We assessed *IDH1* mutations in 321 gliomas of various histological types and biological behaviors. A total of 130 *IDH1* mutations was detected, and all were located at amino acid residue 132. Of these, 91% were**

(World Health Organization [WHO]grade IV), the most frequent and most malignant glioma, may develop rapidly after a short clinical history and without evidence of a less malignant precursor lesion (primary or *de novo* glioblastoma), or slowly through progression from low-grade diffuse or anaplastic astrocytoma (secondary glioblastoma).[1–3] Both glioblastoma subtypes show frequent loss of heterozygosity (LOH) 10q (63% to 70%), but differ significantly with respect to the frequency of other genetic alterations: LOH 10p, *EGFR* amplification, *MDM2* amplification, and *PTEN* mutations are typical of primary glioblastomas,[3,4] whereas *TP53* mutations, LOH 19q, and LOH 22q are more frequent in secondary glioblastomas.[3,5]

Acta Neuropathol
DOI 10.1007/s00401-009-0550-z

ORIGINAL PAPER

Combined molecular analysis of *BRAF* and *IDH1* distinguishes pilocytic astrocytoma from diffuse astrocytoma

Andrey Korshunov · Jochen Meyer · David Capper · Arne Christians · Marc Remke · Hendrik Witt · Stefan Pfister · Andreas von Deimling · Christian Hartmann

Received: 29 April 2009 / Revised: 20 May 2009 / Accepted: 20 May 2009

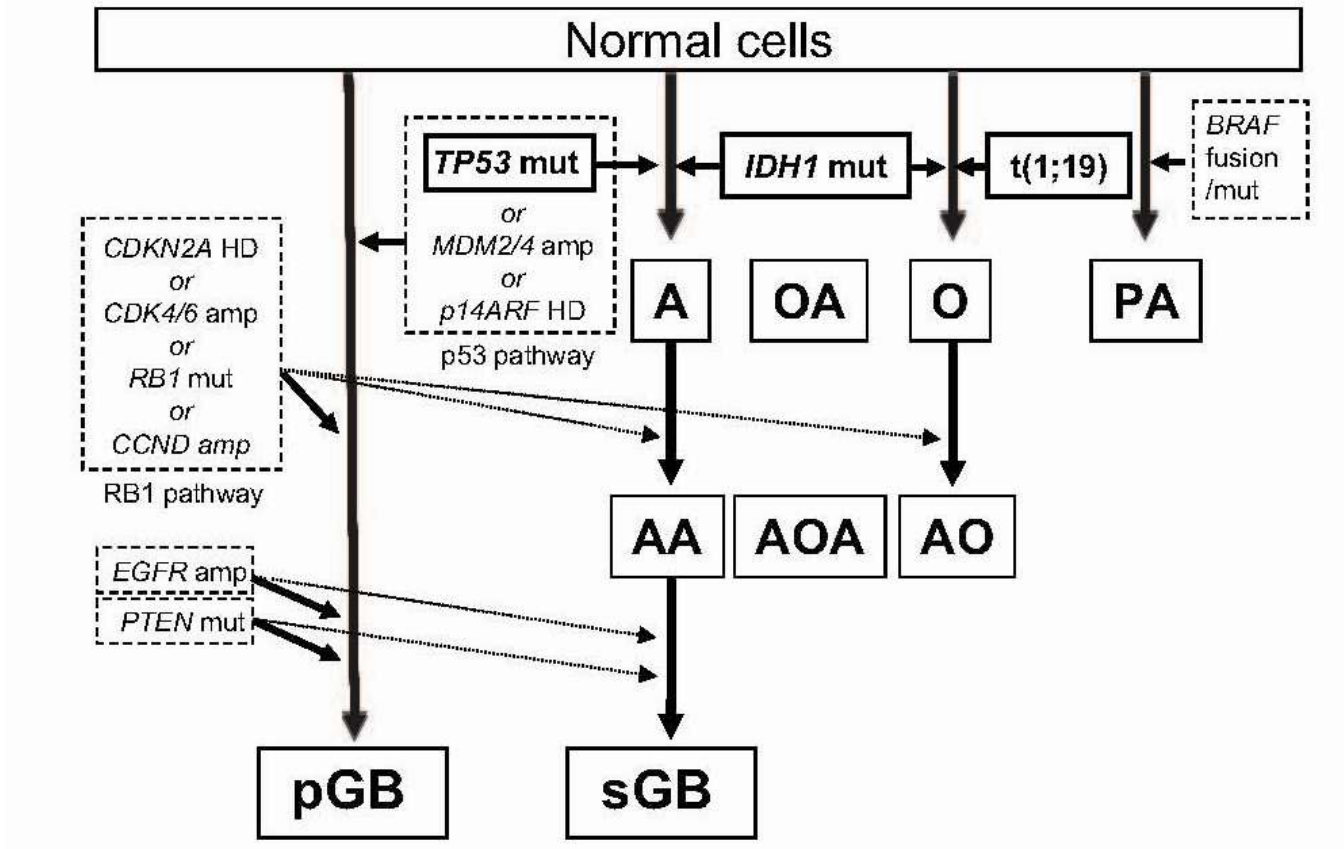
Abstract Separation of pilocytic astrocytoma from diffuse astrocytomas frequently poses problems mostly related to small sample size. Precise classification and grading are essential due to different therapeutic strategies prompted by diagnoses of pilocytic astrocytoma WHO grade I, diffuse astrocytomas WHO grade II or anaplastic astrocytoma WHO grade III. Recently, genomic aberrations with a high specificity for distinct glioma entities have been described. Pilocytic astrocytomas carry a duplication at chromosome band 7q34 containing a *BRAF–KIAA1549* gene fusion in the majority of cases. *IDH1* mutations are observed very frequently in adult astrocyto- *KIAA1549* fusion with a newly developed FISH assay and mutations in *IDH1* and *IDH2* by direct sequencing. Pilocytic astrocytomas contained the *BRAF* fusion in 49 cases (70%) but neither *IDH1* nor *IDH2* mutations. Astrocytomas WHO grade II exhibited *IDH1* mutations in 38 cases (76%) but neither *IDH2* mutations nor *BRAF* fusions. Thus, combined molecular analysis of *BRAF* and *IDH1* is a sensitive and highly specific approach to separate pilocytic astrocytoma from diffuse astrocytoma.

Keywords *BRAF* · *IDH1* · *IDH2* · Pilocytic astrocytoma · Diffuse astrocytoma

NEURO-ONCOLOGY
11(4):341-7, 2009

IDH1 mutations are present in the majority of common adult gliomas but rare in primary glioblastomas

Koichi Ichimura, Danita M. Pearson, Sylvia Kocialkowski, L. Magnus Bäcklund, Raymond Chan, David T.W. Jones, and V. Peter Collins



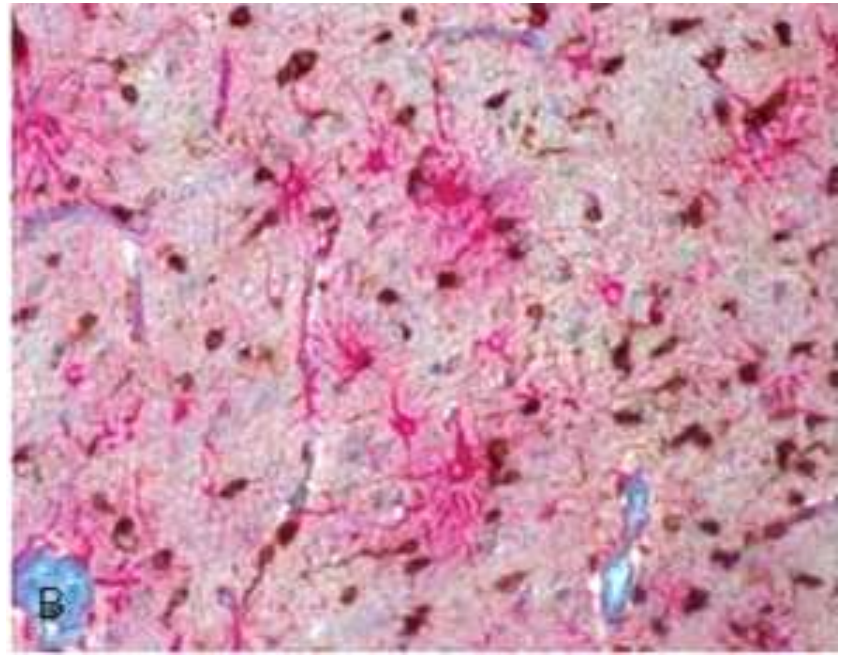
Brain Pathology ISSN 1015-6305
20: 245-54, 2009

RESEARCH ARTICLE

Characterization of R132H Mutation-specific IDH1 Antibody Binding in Brain Tumors

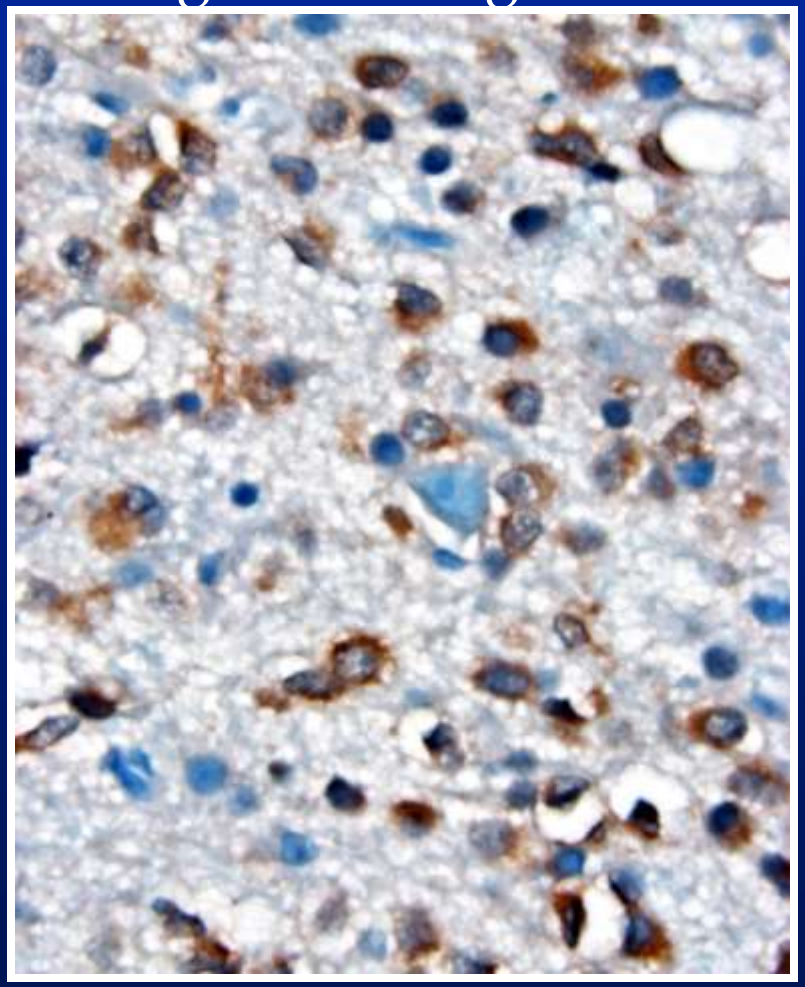
David Capper[1]; Susanne Weißert[1]; Jörg Balss[2]; Antje Habel[1]; Jochen Meyer[2]; Diana Jäger[1]; Ulrike Ackermann[3]; Claudia Tessmer[3]; Andrey Korshunov[2]; Hanswalter Zentgraf[3]; Christian Hartmann[1,2]; Andreas von Deimling[1,2]

[1] Department of Neuropathology, Institute of Pathology, Ruprecht-Karls-University Heidelberg, [2] Clinical Cooperation Unit Neuropathology G380, and [3] Monoclonal Antibody Unit, German Cancer Research Center, Heidelberg, Germany.

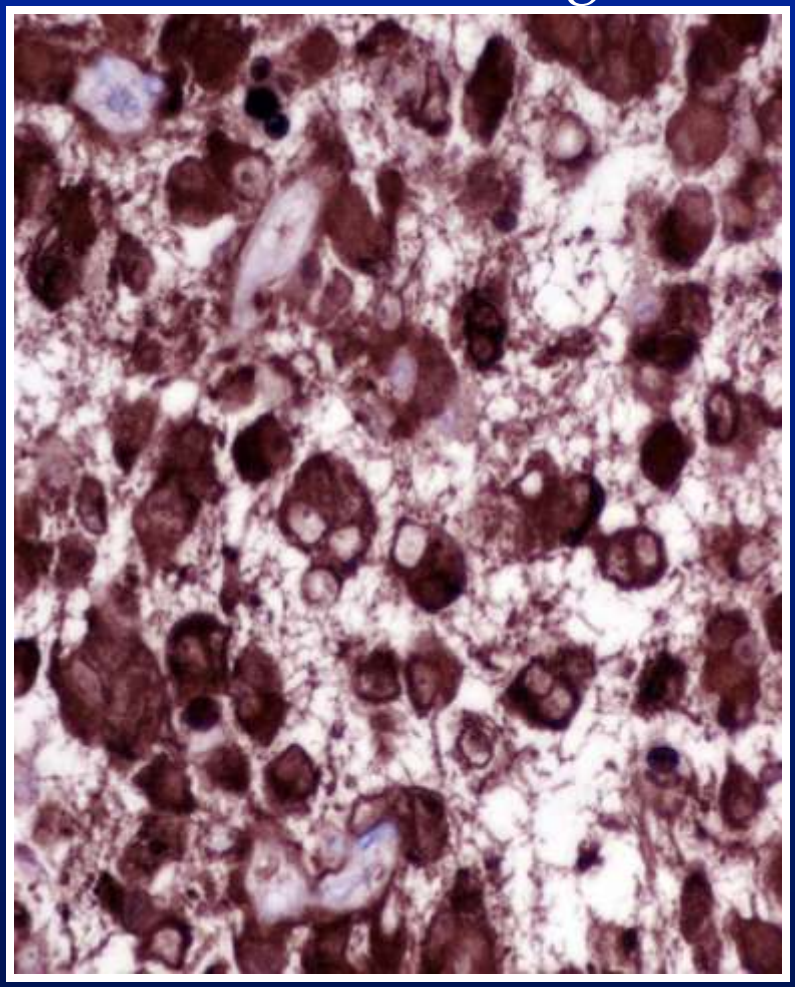


IDH1 R132H IHC

Oligo Invading Cortex



GGLF in an Oligo



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Oligodendroglioma

Oligodendroglioma

Music to Ave Maria by F. Schubert, Lyrics by Arie Perry, MD

O----ligodendroglio-oh-oh-ma, diffuse cerebral tumor of adults
Invading cortex, causing epilepsy; on imaging, often you are calcified
And although, you tend to progress over time, for long periods your fine
You're famous for your rounded nuclei,
Clear haloes look like honeycombs or fried eggs
With branching chicken wire capillaries, and perineuronal satellitosis

O----ligodendroglio-oh-oh-ma, genetically, you are quite unique
With 1p and 19q deletions, from translocation with loss of one derivative
Represents a genetically favorable set, when FISH criteria are met

Anaplastic cases grow more rapidly, assigned a W.H.O. grade III
With microvascular proliferation, or increased mitotic activity
O----ligodendroglio-oh-oh-ma