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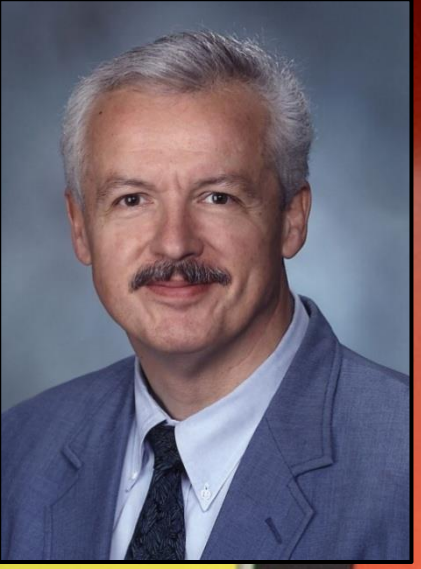
MENINGIOMA GRADING AND POTENTIAL BIOMARKERS

Arie Perry, M.D.

Director, Neuropathology



Dedicated to Dr. Bernd Walter Scheithauer

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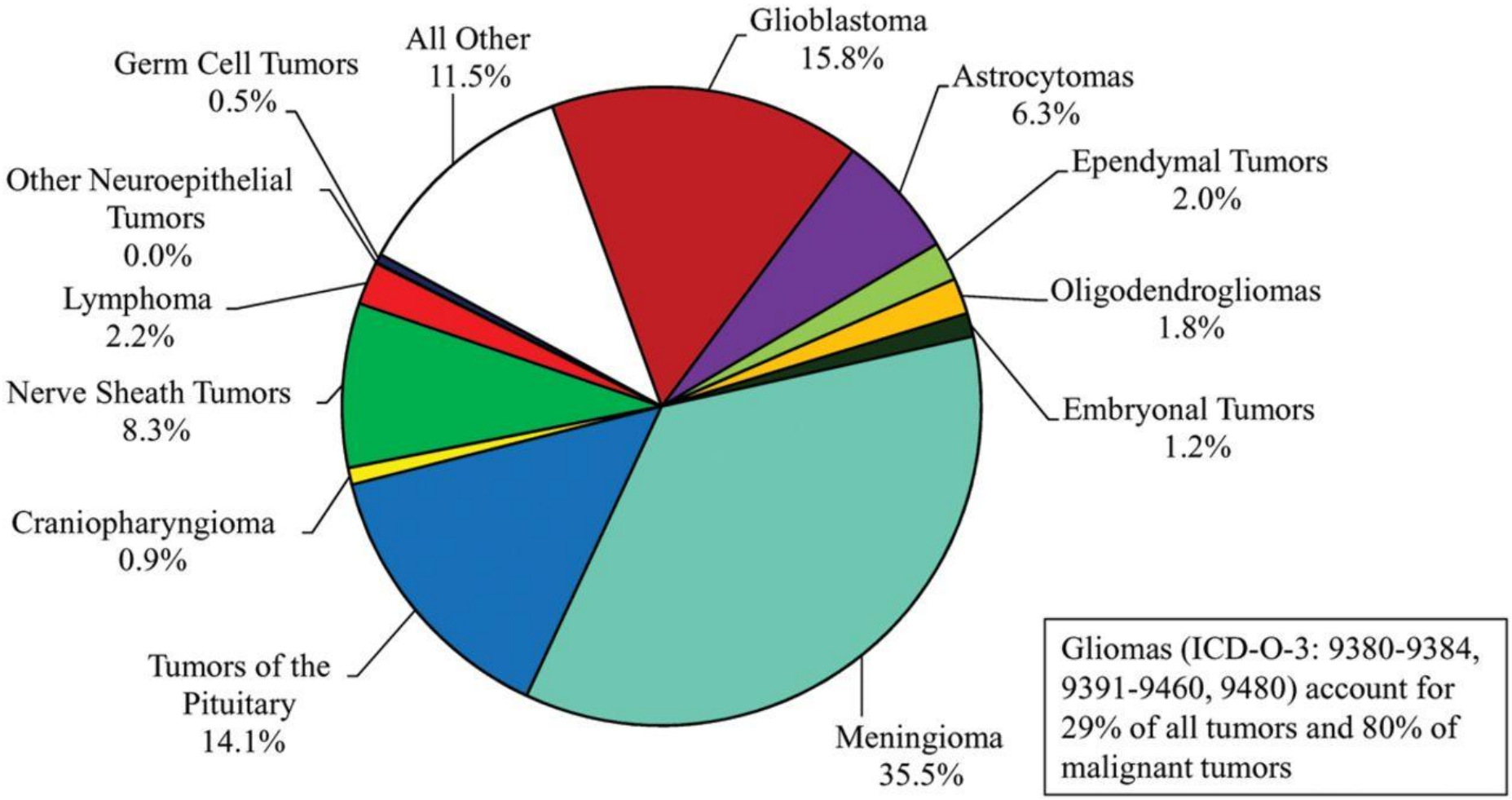

Dolecek T A et al. Neuro Oncol 2012;14:v1-v49

SCIENCE

CHANGE TEXT SIZE

AUTHOR

Daniel Stone

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Sheryl Crow's Meningioma, an Exceedingly Common Brain Tumor

Jun 6, 2012 12:23 PM EDT

The pop singer announced she has a meningioma, a type of benign brain tumor. Don't panic, reports Daniel Stone, but lots of us might have them, too.

Sheryl Crow performs onstage during the Stagecoach Country Music Festival in Indio, Calif., April 29, 2012. (Kevin Winter / Getty Images)

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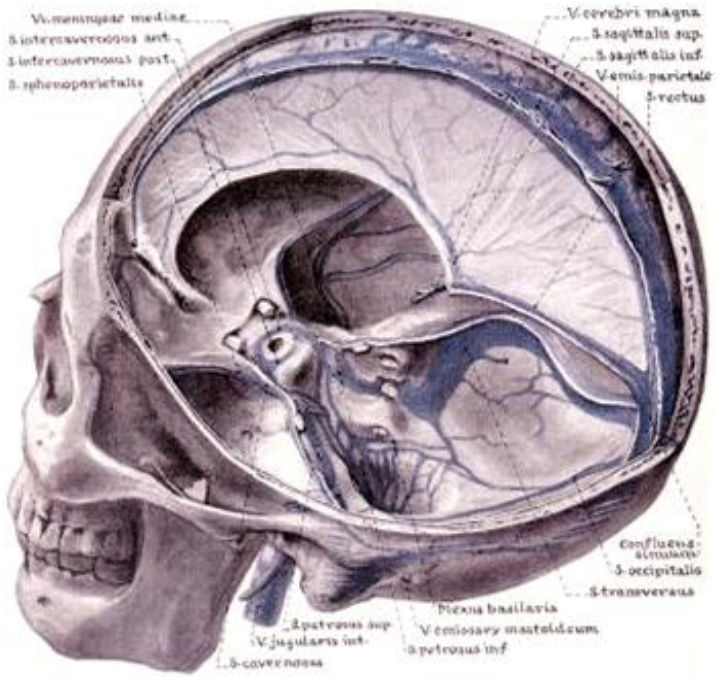

MENINGIOMAS

THEIR CLASSIFICATION, REGIONAL BEHAVIOUR, LIFE HISTORY, AND SURGICAL END RESULTS

By

HARVEY CUSHING, M.D.

Sometime Associate Professor of Surgery, Johns Hopkins University; Moseley Professor of Surgery, Harvard University, and Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston; Sterling Professor of Neurology, Yale University

With the Collaboration of

LOUISE EISENHARDT, M.D.

Assistant Professor of Pathology, Yale University School of Medicine. Formerly Associate in Surgery, Peter Bent Brigham Hospital, Boston

CHARLES C THOMAS

1938

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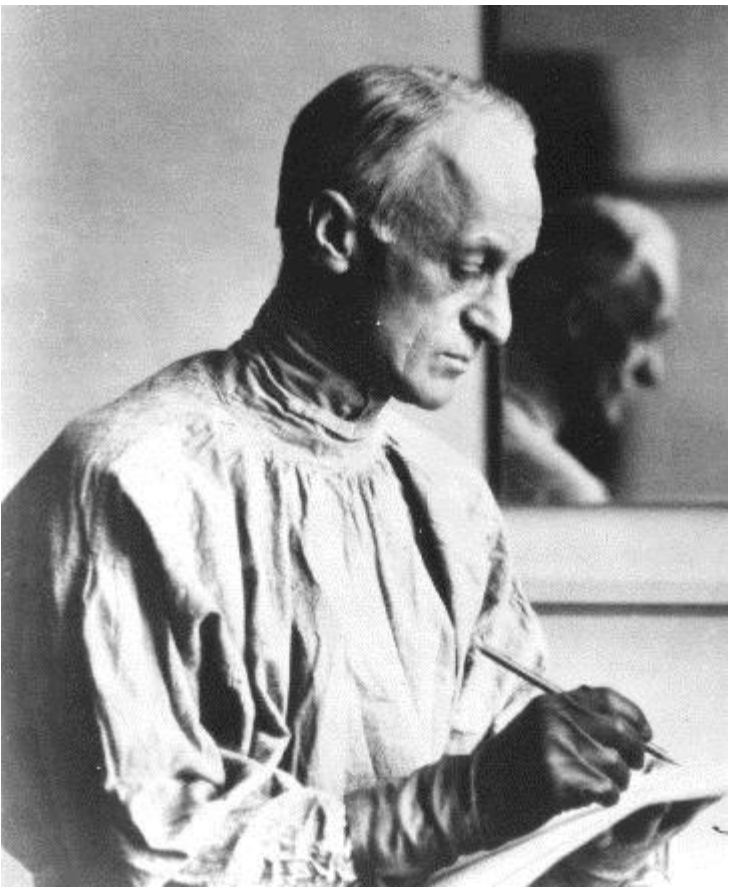

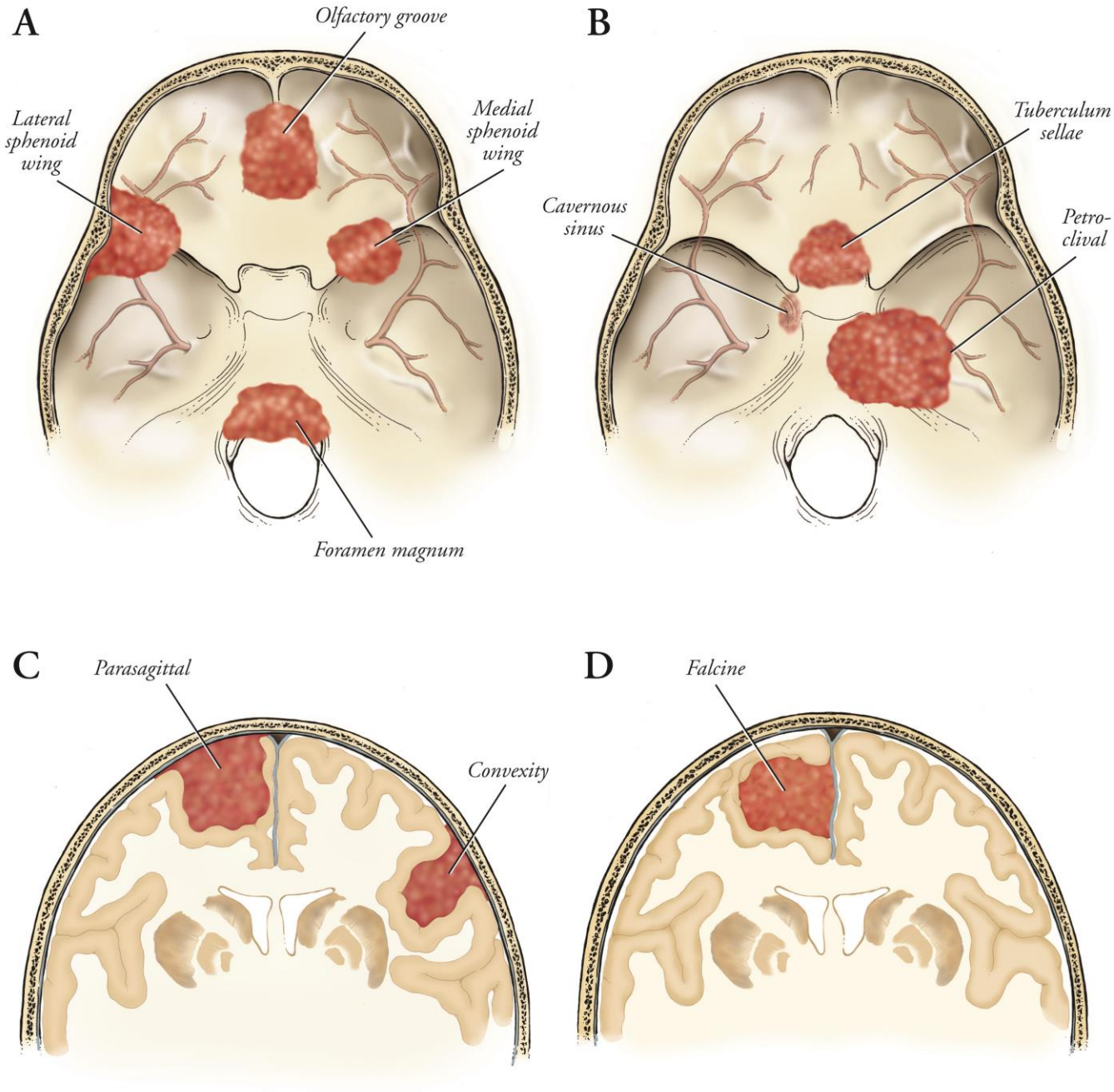
A
Olfactory groove
Lateral sphenoid wing
Medial sphenoid wing
Foramen magnum
B
Tuberculum sellae
Cavernous sinus
Petro-clival
C
Parasagittal
Convexity
D
Falcine

Louise Eisenhardt, M.D., 1891-1967, First Editor of J Neurosurg, 1944-1965

fers the term *exo*thelial to *endo*thelial and classifies the meningo-exotheliomas: (1) in relation to the cells (*syncitial* or *inoblásticos*); and (2) on the basis of their architecture, interposition of connective tissue, and abundance of vessels. More recently Globus (1935)[230] laying emphasis on the pial vascular elements in these tumors proposed the following divisions: (1) leptomeningioma; (2) pachymeningioma; (3) meningioma omniforme; (4) meningioma indifferentiale; and (5) meningioma piale.

These authors have been principally concerned with the histofunctional differentiation of the tumors' cellular components and little if at all with their gross appearance and behaviour, without which their life history in our opinion cannot be written. Fine architectural distinctions, while of academic interest, are unimportant unless they can be shown to have some bearing on clinical treatment and prognosis. While it is our purpose chiefly to dwell on these more practical features, it nevertheless is necessary for us as briefly as possible to describe and illustrate the type subdivisions of the tumors we have come to utilize. Unlike the classifications employed by others, we have chosen to arrange them in a descending scale from the most common in our experience to the least common architectural types.

One characteristic of these tumors we feel that we can emphasize: namely, that over the course of years they rarely if ever tend to alter in type. There have been only two cases, both from outside sources, in which a sarcomatous transition appears to have taken place. These are but exceptions that prove the rule. The tumor in Serial No. 4 (*cf.* Fig. 27) showed no appreciable change after 17 years. The same was true of the tumors in Serial Nos. 58 and 62 in the course of repeated operations over periods of 12 and 13 years.

The nine histological types into which we have come to divide the meningiomas in our series are presented in the following list in the order of their numerical frequency. The subdivisions under a given type represent variations in architectural structure that are pronounced enough to justify separate groupings for convenience of matching specimens, though with a few exceptions we regard them as fundamentally unimportant.

THE NINE MAJOR TUMOR TYPES AND FREQUENCY OF OCCURRENCE

Type I. Non-reticulin- or collagen-forming meningothelial tumors	**121**
Var. 1. Cells evenly distributed in sheets	32
Var. 2. Cells in alveolar arrangement	41
Var. 3. Spindle cells in interlacing bundles	22
Var. 4. Combination of variants 1, 2 and 3	26
Type II. Meningothelial tumors of whorl pattern with tendency to form reticulin or collagen	**78**
Var. 1. Variously distributed spindle, round and polyhedral cells	53
Var. 2. Combination of Type I, var. 1 or 2, with whorls	14
Var. 3. Uniform small whorls	6
Var. 4. Compact psammoma bodies	5

Type III. Reticulin- or collagen-forming fibroblastic tumors of benign type	**53**
Var. 1. Fibrils scanty	11
Var. 2. Fibrils abundant	36
Var. 3. Marked fibrosis	6
Type IV. Reticulin-forming angioblastic tumors	**23**
Var. 1. Incompletely differentiated, with mitoses	6
Var. 2. Transitional between meningothelial type and angioblastoma	11
Var. 3. Angioblastoma (capillary or cellular)	6
Type V. Non-reticulin- or collagen-forming epithelioid tumors	**18**
Var. 1. Cells in columnar arrangement	10
Var. 2. Roussy, Cornil and Oberling type	8
Type VI. Reticulin- or collagen-forming fibroblastic tumors of malignant type (sarcomatous meningiomas)	**6**
Var. 1. Spindle-cell type	5
Var. 2. Round-cell type	1
Type VII. Osteoblastic meningiomas	**6**
Type VIII. Chondroblastic meningiomas	**1**
Var. 1. Chondroma	1
Var. 2. Osteochondroma	0
Type IX. Lipoblastic meningiomas	**0**

TYPE I. These chiefly represent our original meningothelial tumors.[33] They comprise the largest group in the series (121 cases), and are composed of what we regard as non-fibroblastic cells; they at least in our opinion fail to produce the intra- and extracellular products of fibroblasts emphasized by Mallory and Penfield. Such reticulin or collagen as may be present is chiefly confined to the blood-vessels and stroma. Four architectural variants are easily distinguished; the prognosis for each of them is equally favourable.

Type I—Variant 1 (*cf.* Figs. 23 and 322)

Microscopical Description.—The usual low-power view shows a diffuse mass of cytoplasm in which are rather evenly distributed nuclei. There may be the slightest tendency here and there to a concentric arrangement or to grouping of the nuclei with palisading. Occasionally, among wide masses of these uniformly distributed cells, a rare small whorl or psammoma body may be found. The tissue is often finely vacuolated or oedematous.

The outlines of individual cells may be indistinct, but in many tumors they are sharply defined. The cells are roundish, elongated, polyhedral or fusiform, with a delicately granular cytoplasm. In preparations by the supravital technique such details may be well demonstrated (*cf.* Fig. 42). The angular polyhedral cells, though they usually have cleancut outlines, may show fine cytoplasmic prolongations giving them an appearance of glial cells for which, indeed, they have on occasion been mistaken (*cf.* Fig. 645). The nuclei are round, oval or elongated, with a well marked nuclear membrane and a prominent nucleolus. They usually contain a moderate amount of chromatin but may show only a few particles at the periphery or even be quite clear. These clear vesicular nuclei stand out conspicuously among nuclei with greater chromatin content or in contrast to the more deeply stained cytoplasm. In Serial Nos. 20 and 239 some extraor-

Masson Monographs in Diagnostic Pathology

MENINGIOMAS

Biology, Pathology, and Differential Diagnosis

John J. Kepes, M.D.

World Health Organization
International Histological Classification of Tumours

Histological Typing of Tumours of the Central Nervous System

P. Kleihues, P. C. Burger, and B. W. Scheithauer
In Collaboration with L. H. Sobin and Pathologists in 14 Countries

Second Edition

Springer-Verlag

UCSF University of California San Francisco

PRIOR WHO GRADING CRITERIA

- **1979 Scheme**
  - Anaplastic: “Any meningioma that displays **anaplastic features** yet has not developed into a frank sarcoma”
- **1993 Scheme**
  - Atypical (WHO II): “Meningiomas in which **several** of the following features are evident: **frequent** mitoses, increased cellularity, small cells with high N/C ratios, uninterrupted patternless or sheet-like growth and foci of spontaneous or geographic necrosis.
  - Anaplastic (WHO III): “A meningioma exhibiting histological features of **frank malignancy** **far in excess** of the abnormalities noted in atypical meningioma. These include **obviously** malignant cytology, a **high** mitotic index and **conspicuous** necrosis.

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INCREDIBLE LUCK IN BEING AT RIGHT PLACE AND TIME: MAYO 1994

BWS suggests project evaluating Mayo clinic meningiomas for prognostic features and development of new grading scheme.

The American Journal of Surgical Pathology 21(12): 1455–1465, 1997

Reprinted from THE AMERICAN JOURNAL OF SURGICAL PATHOLOGY
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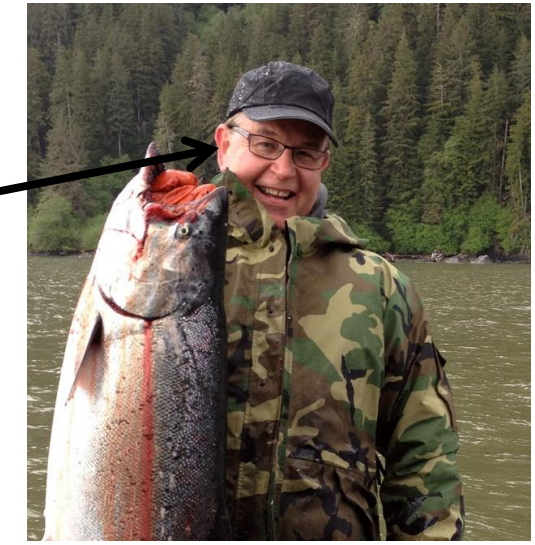
Meningioma Grading

An Analysis of Histologic Parameters



Arie Perry, M.D., Scott L. Stafford, M.D., Bernd W. Scheithauer, M.D.,
Vera J. Suman, Ph.D., and Christine M. Lohse, B.S.

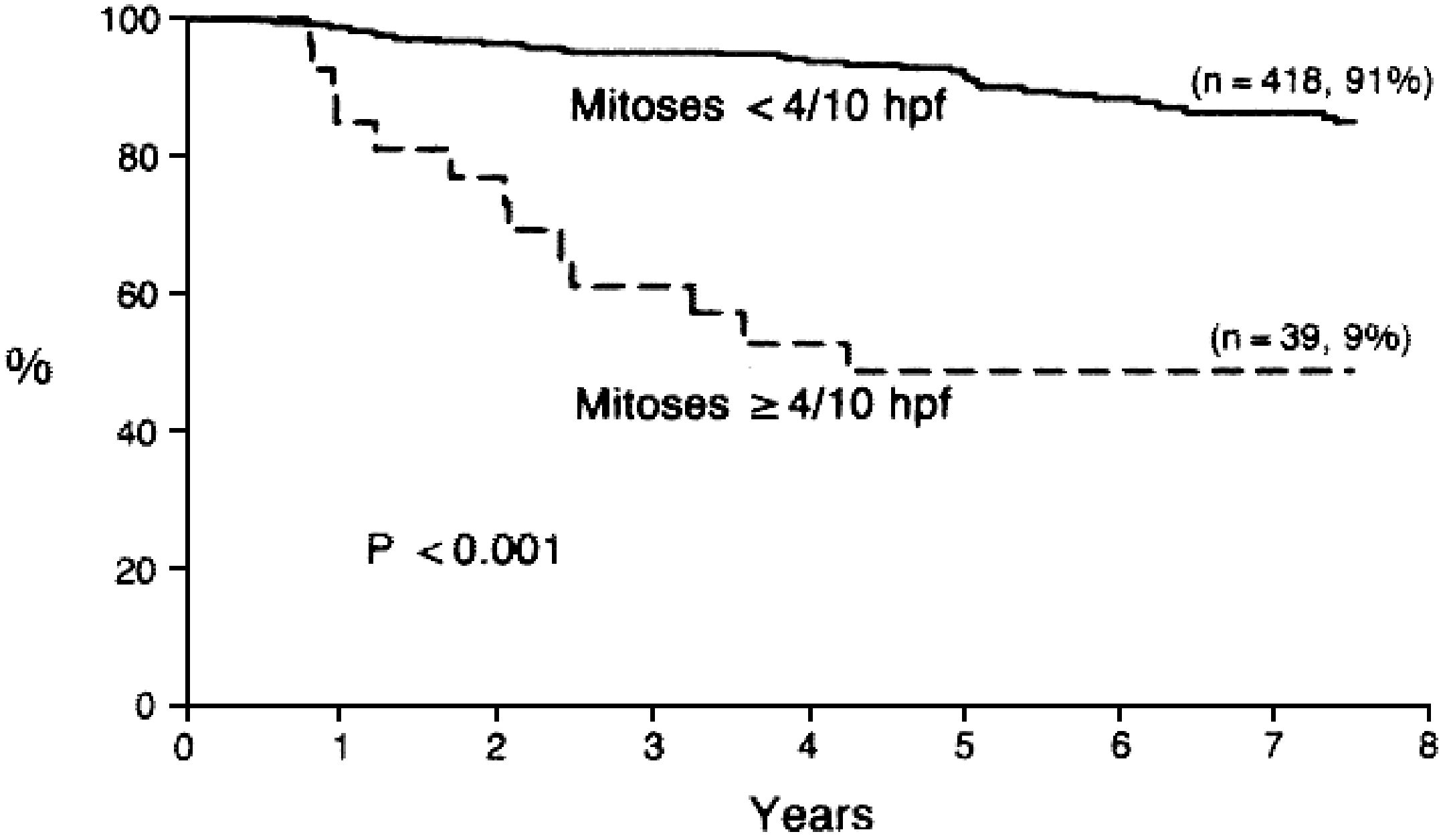
Histologic grading of meningiomas has prognostic and sometimes therapeutic implications, but diagnostic criteria for atypical meningioma are vague, and the significance of brain invasion in the determination of malignancy remains controversial. We reviewed our experience with 581 patients whose meningiomas were resected at Mayo Clinic during the years 1978 through 1988. All patients were followed until death or a median of 9.0 years. Ten histologic parameters were assessed and compared with recurrence-free survival. On univariate analysis, six variables were associated with recurrence, although most were statistically significant only in the subset of patients having undergone gross total tumor resection. On multivariate analyses, the most significant parameters were histologic brain invasion (when assessable) and maximal mitotic rate of at least four per 10 high-power fields (HPF). Also significant were combinations of at least three of the following four parameters: hypercellularity, architectural sheeting, macronucleoli, and small cell formation. Proposed grading criteria based on these

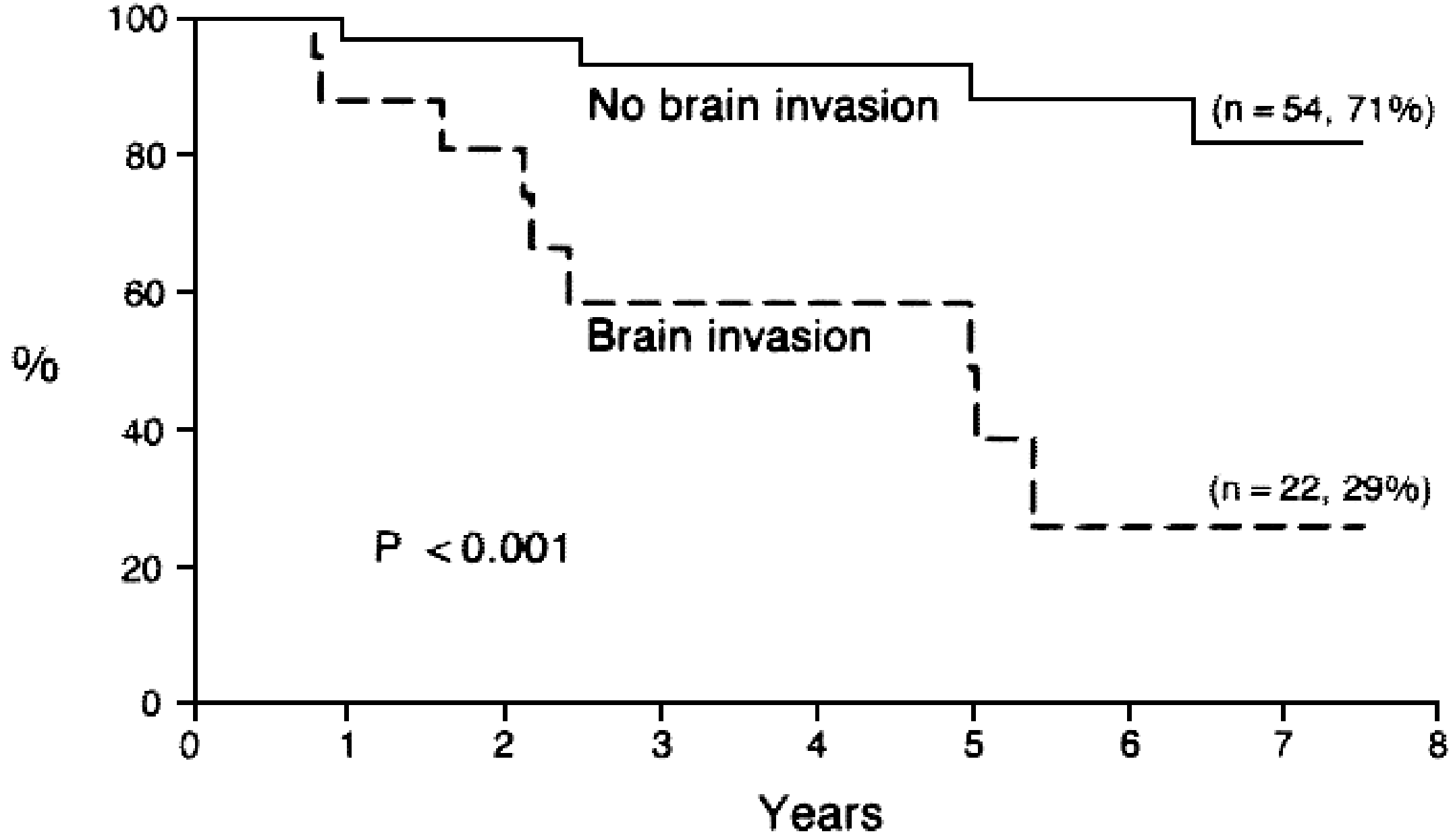
Although generally considered benign, meningiomas can cause significant morbidity and, in rare cases, death. A wide variety of clinical prognosticators have been reported (18,20,31,38,48,54). Anatomic factors, including adverse sites of disease (e.g., skull base), en-plaque growth, and invasion of bone, soft tissue, or dural sinuses, make gross total resection (GTR) less likely and are therefore closely linked to extent of surgical resection, a key predictor of outcome. Other known clinical prognosticators include patient age and sex. Most investigators agree that histologic grading provides additional prognostic data and, in some cases, guides further therapy (1,3,8,15,17,19,32–34,36,37,46,55,61). However, definitions of atypia and of anaplasia or malignancy in meningiomas have been subjective and inconsistent, thus leading to significant interobserver variabil-

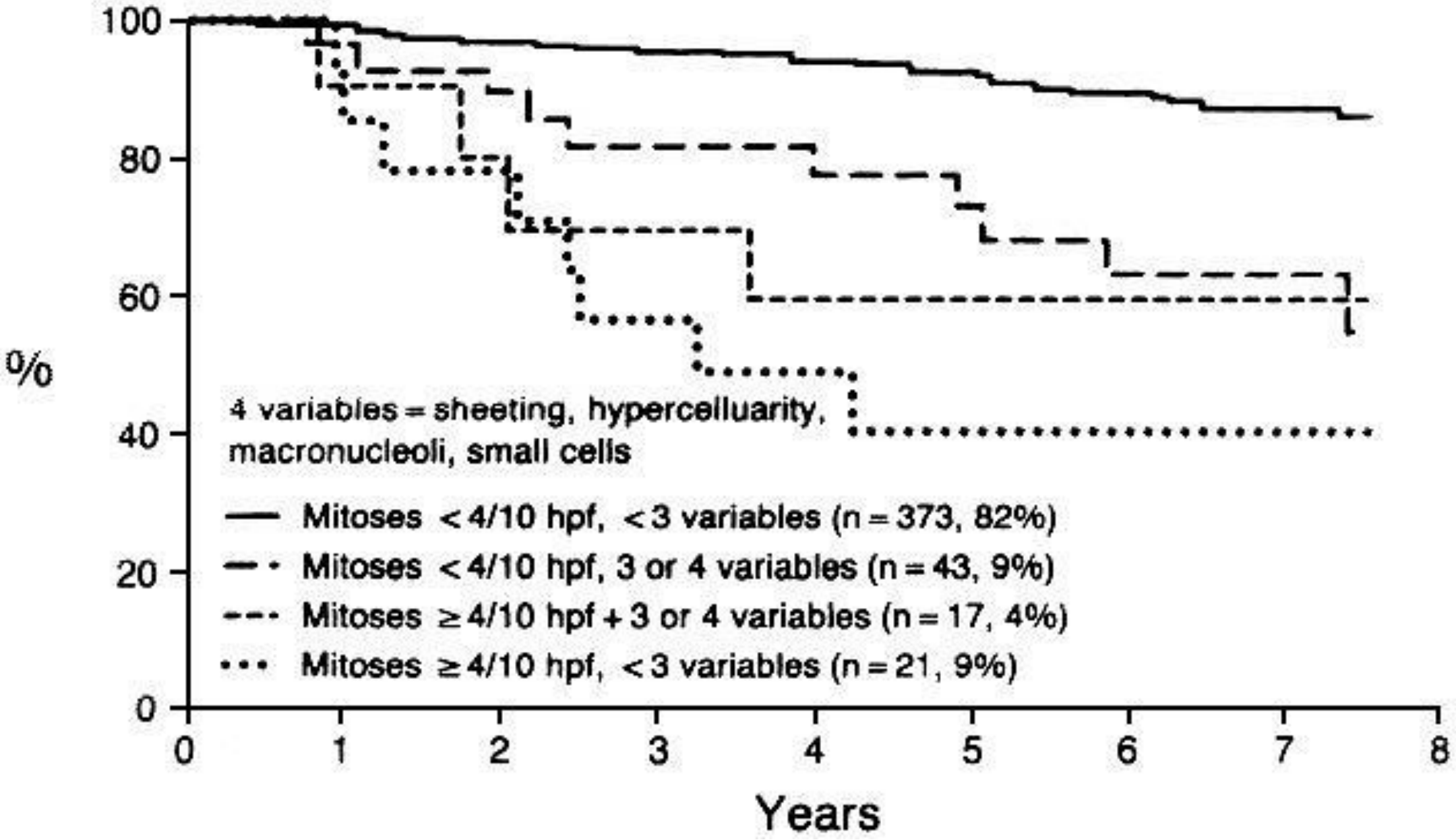
Parameter	STR (n = 114)		GTR (n = 455)	
	%	p	%	p
Brain invasion[a]	14	NA	28	<.001
Mitoses (≥4/10 HPF)	8	0.208	8	<.001
Sheeting	18	0.179	18	.018
Macronucleoli	21	0.120	28	.035
Necrosis	14	0.175	16	.051
Hypercellularity (>53 nuc./HPF diameter)	52	.019	54	0.195
Small cells	11	0.463	15	0.345
Pleomorphism	34	0.223	55	0.426
Nuclear atypia	40	0.406	58	0.450
Atypical mitoses	3	NA	3	0.640

NA, not assessable due to small number of cases

[a] Assessable in 14 STR and 75 GTR cases


100
80
60
40
20
0
%
0
1
2
3
4
5
6
7
8
Years
Mitoses < 4/10 hpf
(n = 418, 91%)
Mitoses ≥ 4/10 hpf
(n = 39, 9%)
P < 0.001


100
80
60
40
20
0
%
No brain invasion
(n = 54, 71%)
Brain invasion
(n = 22, 29%)
P < 0.001
0
1
2
3
4
5
6
7
8
Years


100
80
60
40
20
0
%
4 variables = sheeting, hypercelluarity, macronucleoli, small cells
Mitoses < 4/10 hpf, < 3 variables (n = 373, 82%)
Mitoses < 4/10 hpf, 3 or 4 variables (n = 43, 9%)
Mitoses ≥ 4/10 hpf + 3 or 4 variables (n = 17, 4%)
Mitoses ≥ 4/10 hpf, < 3 variables (n = 21, 9%)
0
1
2
3
4
5
6
7
8
Years

"Malignancy" in Meningiomas

A Clinicopathologic Study of 116 Patients, with Grading Implications

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Bernd W. Scheithauer, M.D.[2]
Scott L. Stafford, M.D.[3]
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BACKGROUND. Due to the rarity of malignancy in meningiomas, prior studies have been limited to small series. Controversies regarding the definition of malignant meningioma have complicated matters further. Although histologic anaplasia and extracranial metastasis are established criteria, the former is difficult to define and the latter represents a clinical finding. Traditionally, brain invasion has also been accepted, although this has recently been debated. In a prior series, the authors were unable to prove that 23 meningiomas that had invaded the brain were more aggressive than atypical meningiomas.

METHODS. The authors expanded their analysis to include 116 patients diagnosed with "malignant meningioma" due to brain invasion, frank anaplasia (20 mitoses per 10 high-power fields or histology resembling carcinoma, sarcoma, or melanoma), and/or extracranial metastasis. Patients were followed until death or for a median of 3.7 years.

RESULTS. Survival time was highly variable, ranging from 10 days to 24 years. In multivariate analysis, histologic anaplasia ($P = 0.0035$), subtotal resection ($P = 0.0038$), 20 mitoses per 10 high-power fields ($P = 0.0071$), and nuclear atypia ($P = 0.0068$) were associated with poor survival. Of the 89 cases of meningioma that had invaded the brain, 23% were otherwise benign, 61% were otherwise atypical, and 17% were frankly anaplastic. Those without anaplasia behaved similarly to atypical meningiomas from the authors' prior study. In contrast, anaplastic meningiomas were usually fatal, associated with a median survival of 1.5 years.

CONCLUSIONS. Based on these findings, the authors suggest that brain invasion constitutes an additional criterion for the diagnosis of atypical meningioma (World Health Organization [WHO] Grade II), whereas frank anaplasia indicates high grade (WHO Grade III–IV) malignancy. ***Cancer* 1999;85:2046–56.**

TABLE 2
Univariate Associations of Clinical Variables at First Malignant Diagnosis with Overall Survival

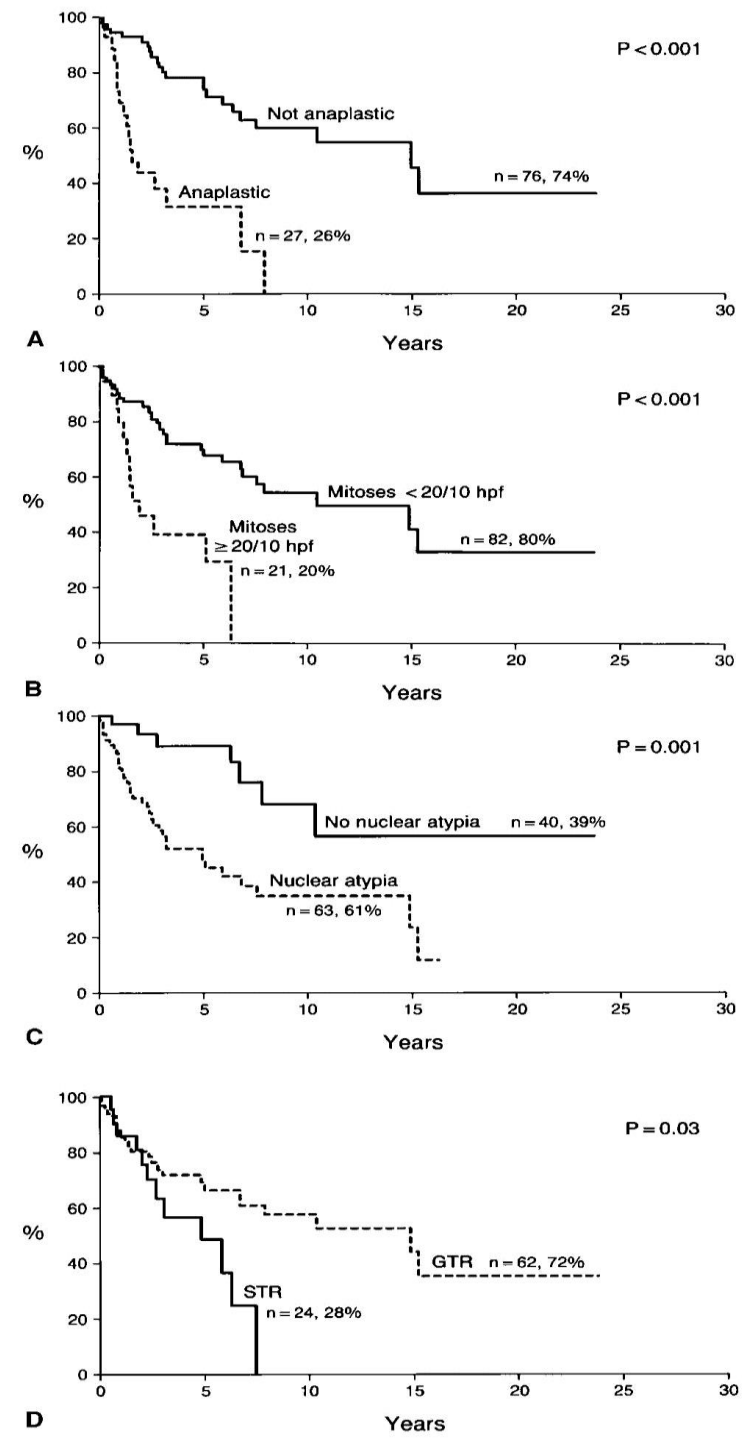
Variable	Frequency (%)	Risk ratio (confidence interval)	*P* value
Gross total resection	72	0.455 (0.217–0.953)	0.0367
Male gender	54	1.479 (0.788–2.776)	0.2234
Age (continuous variable)	—	1.012 (0.992–1.032)	0.2555
Age <40 yrs	14	0.815 (0.333–1.993)	0.6534
Prior nonmalignant diagnosis[a]	14	0.661 (0.288–1.517)	0.3291
Adjuvant radiation therapy within 6 mos of surgery	17	1.513 (0.659–3.472)	0.0568

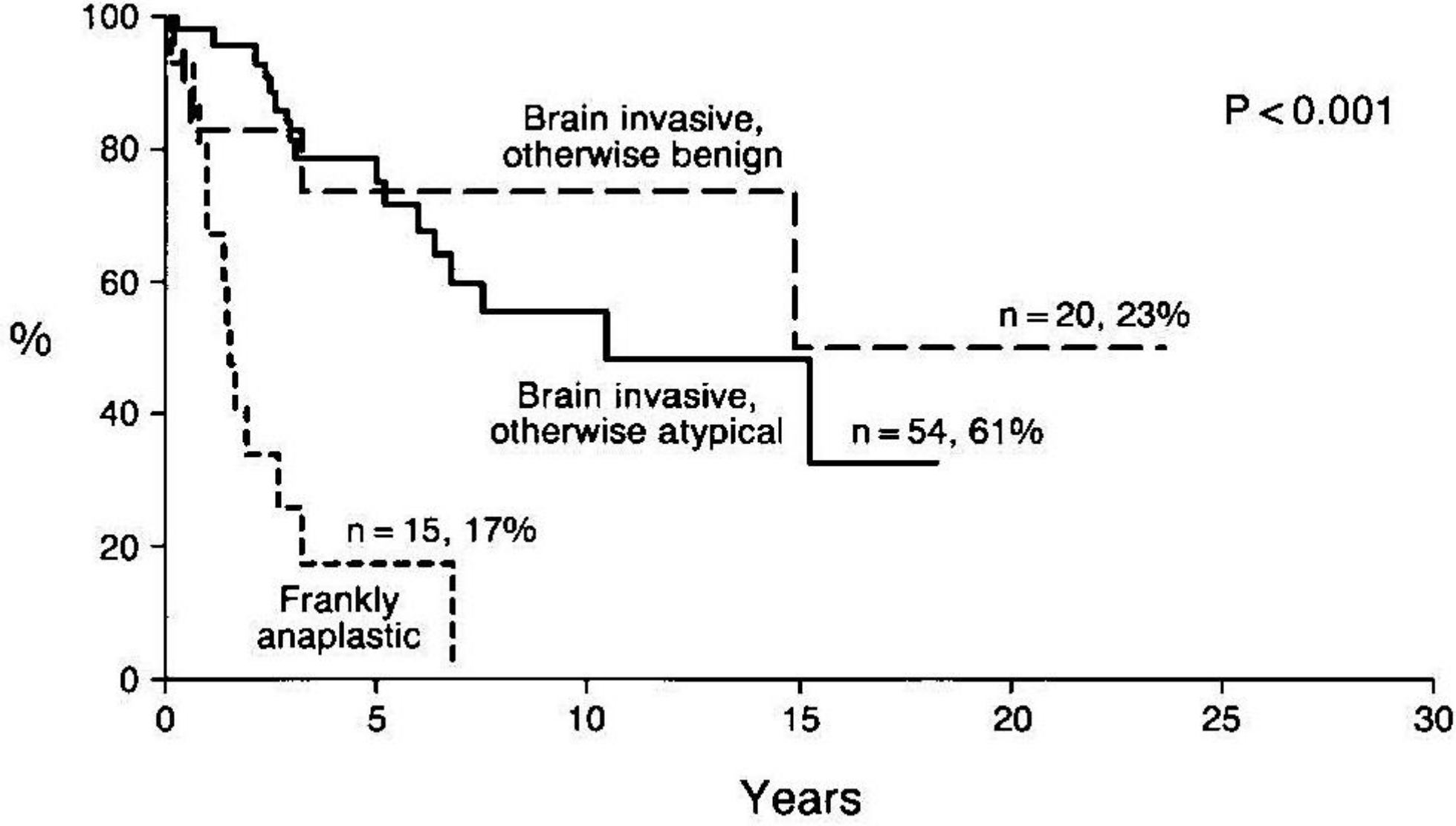
[a] Benign or atypical meningioma.

TABLE 3
Univariate Associations of Histologic Variables at First Malignant Diagnosis with Overall Survival

Variable	Frequency (%)	Risk ratio (confidence interval)	*P* value
Histologic anaplasia	26	4.698 (2.427–9.095)	<0.0001
≥4 mitoses per 10 high power fields	63	2.971 (1.433–6.159)	0.0034
≥20 mitoses per 10 high power fields	20	3.521 (1.737–7.137)	0.0005
Abnormal mitoses	18	2.600 (1.214–5.571)	0.0140
MIB-1 ≥4.2%	42	2.306 (0.894–5.946)	0.0840
MIB-1 ≥20.0%	10	3.704 (1.021–13.444)	0.0465
Sheeting	62	1.925 (0.971–3.816)	0.0608
Extensive sheeting	32	2.983 (1.535–5.798)	0.0013
Necrosis	66	0.939 (0.490–1.799)	0.8486
Extensive necrosis	19	2.842 (1.422–5.681)	0.0031
Necrosis with palisading	27	1.039 (0.519–2.079)	0.9145
Nuclear atypia	61	3.754 (1.660–8.488)	0.0015
Extensive nuclear atypia	18	2.941 (1.370–6.318)	0.0057
Cellular pleomorphism	57	2.975 (1.462–6.053)	0.0026
Extensive cellular pleomorphism	14	2.351 (1.462–6.053)	0.0572
Macronucleoli	52	1.448 (0.771–2.718)	0.2496
Extensive macronucleoli	11	2.438 (1.099–5.888)	0.0476
Small cells	41	0.838 (0.435–1.614)	0.5968
Extensive small cells	5	1.484 (0.456–4.830)	0.5124
Hypercellularity	70	0.849 (0.432–1.670)	0.6357

mine cause of death. Nevertheless, the subjective clinical impression for the vast majority of fatal cases was that patients died as a result of tumor progression. Estimated 5- and 10-year mortality rates were 38% and




100
80
60
40
20
0
%
0
5
10
15
20
25
30
Years
Brain invasive,
otherwise benign
P < 0.001
n = 20, 23%
Brain invasive,
otherwise atypical
n = 54, 61%
n = 15, 17%
Frankly
anaplastic

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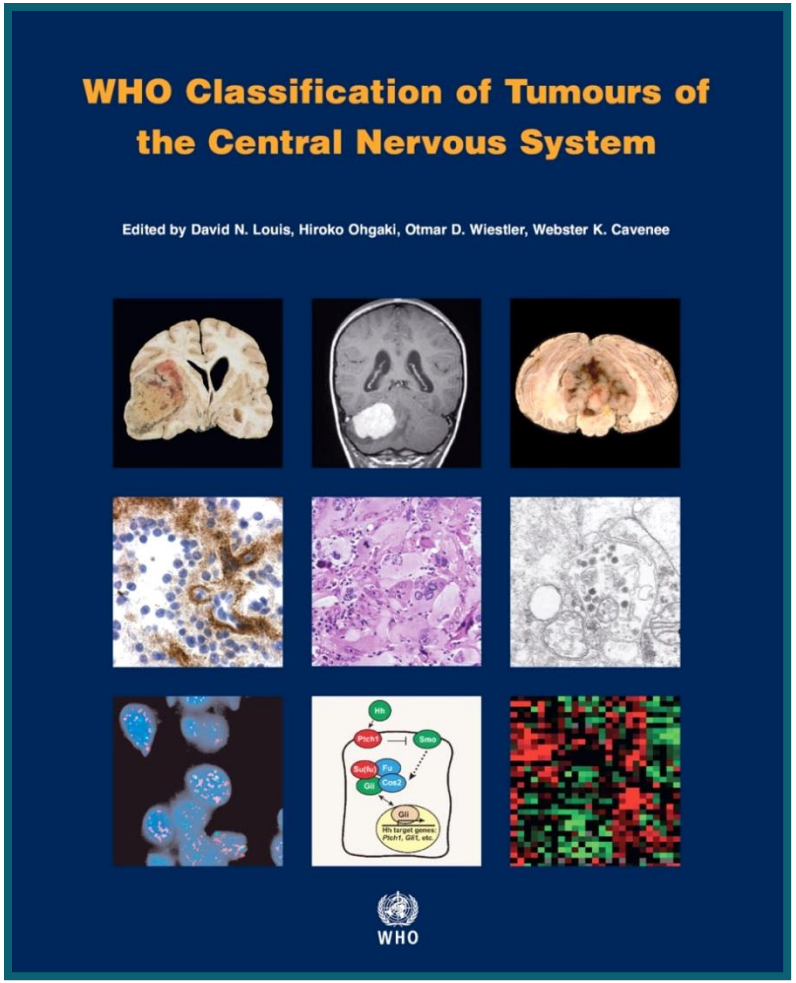
CLASSIFICATION/GRADING SCHEME: WHO 2007

- WHO I = Benign
- WHO II = Atypical
- WHO III = Anaplastic



Meningiomas

A. Perry
D.N. Louis
B.W. Scheithauer
H. Budka
A. von Deimling

Definition

Meningothelial (arachnoidal) cell neoplasms, typically attached to the inner surface of the dura mater.

ICD-O code

Meningioma 9530/0

Grading

Most meningiomas are benign and correspond to WHO grade I. Certain histological subtypes or meningiomas with specific combinations of morphologic parameters are associated with less favourable clinical outcomes and correspond to WHO grades II (atypical) and III (anaplastic or malignant).

Incidence

Meningiomas account for about 24-30% of primary intracranial tumours occurring in the USA {305,359}, with an annual incidence rate of up to 13 per 100,000 population in Italy {381}. Many small meningiomas are asymptomatic incidental neuroimaging findings. In Scandinavia, the incidence has increased between 1968 and 1997 from 2.6 to 4.5 per 100,000 in women, and from 1.4 to 1.9 in men {1119}. In one Italian study, the numbers have remained stable for decades {381}. At autopsy, meningiomas are found incidentally in 1.4% {1836}. Meningiomas are often multiple in patients with neurofibromatosis 2 (NF2) and in other, non-NF2 families with a hereditary predisposition to meningioma {1352}.

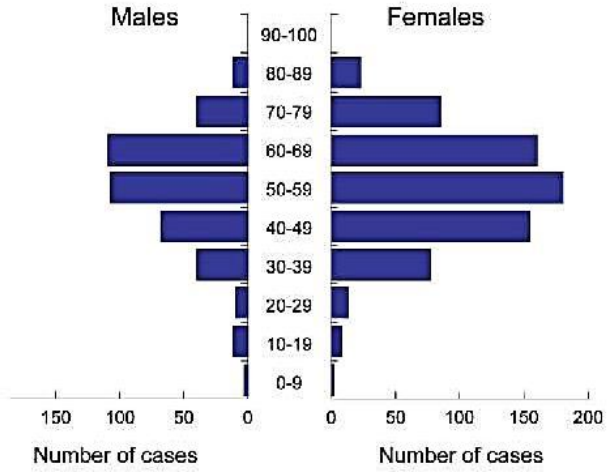


Fig. 10.01 Age and sex distribution of meningiomas, based on 1078 cases treated at the University Hospital Zurich.

Sporadic meningiomas are multiple in somewhat less than 10% of cases. Atypical meningiomas comprise between 4.7% and 7.2% of meningiomas, although using more current definitions, it has been reported in up to 20%; anaplastic (malignant) meningiomas account for between 1.0% and 2.8% {941, 1384, 1734, 1736, 2413}. An annual incidence of anaplastic (malignant) meningiomas of 0.17 per 100,000 persons has been reported {1911}.

Age and sex distribution

Meningiomas occur most commonly in middle-aged and elderly patients, with a peak during the sixth and seventh decades. Nonetheless, they also occur in children and the elderly. Childhood examples tend to include more aggressive forms of meningioma. Among middle-aged patients, there is a marked female bias, the female:male ratio being approximately 1.7:1 {381}; the ratio peaks at 3.5:1 in the patients 40-44 yeasr of age {1119}. Spinal meningiomas show a marked predominance in women, the frequency

Table 10.01 Meningiomas grouped by likelihood of recurrence and grade

		ICD-O
Meningiomas with low risk of recurrence and aggressive growth:		
Meningothelial meningioma	WHO grade I	9531/0
Fibrous (fibroblastic) meningioma	WHO grade I	9532/0
Transitional (mixed) meningioma	WHO grade I	9537/0
Psammomatous meningioma	WHO grade I	9533/0
Angiomatous meningioma	WHO grade I	9534/0
Microcystic meningioma	WHO grade I	9530/0
Secretory meningioma	WHO grade I	9530/0
Lymphoplasmacyte-rich meningioma	WHO grade I	9530/0
Metaplastic meningioma	WHO grade I	9530/0
Meningiomas with greater likelihood of recurrence and/or aggressive behavior:		
Chordoid meningioma	WHO grade II	9538/1
Clear cell meningioma (intracranial)	WHO grade II	9538/1
Atypical meningioma	WHO grade II	9539/1
Papillary meningioma	WHO grade III	9538/3
Rhabdoid meningioma	WHO grade III	9538/3
Anaplastic (malignant) meningioma	WHO grade III	9530/3
Meningiomas of any subtype or grade with high proliferation index and/or brain invasion		

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MENINGIOMA GRADING

- **Atypical (WHO II) (~20%)**
  - **High** mitotic index (≥4/10 HPF)
  - Presence of **multiple** (at least 3 of 5) variables: sheeting, macronucleoli, small cells, hypercellularity, necrosis
- **Anaplastic (Malignant) (WHO III) (~1-2%)**
  - **Excessive** mitotic index (≥20/10 HPF)
  - **Frank anaplasia** = sarcoma, carcinoma, or melanoma-like histology

Perry A et al., Am J Surg Pathol 21: 1455, 1997
Perry A et al., Cancer 85:2046, 1999

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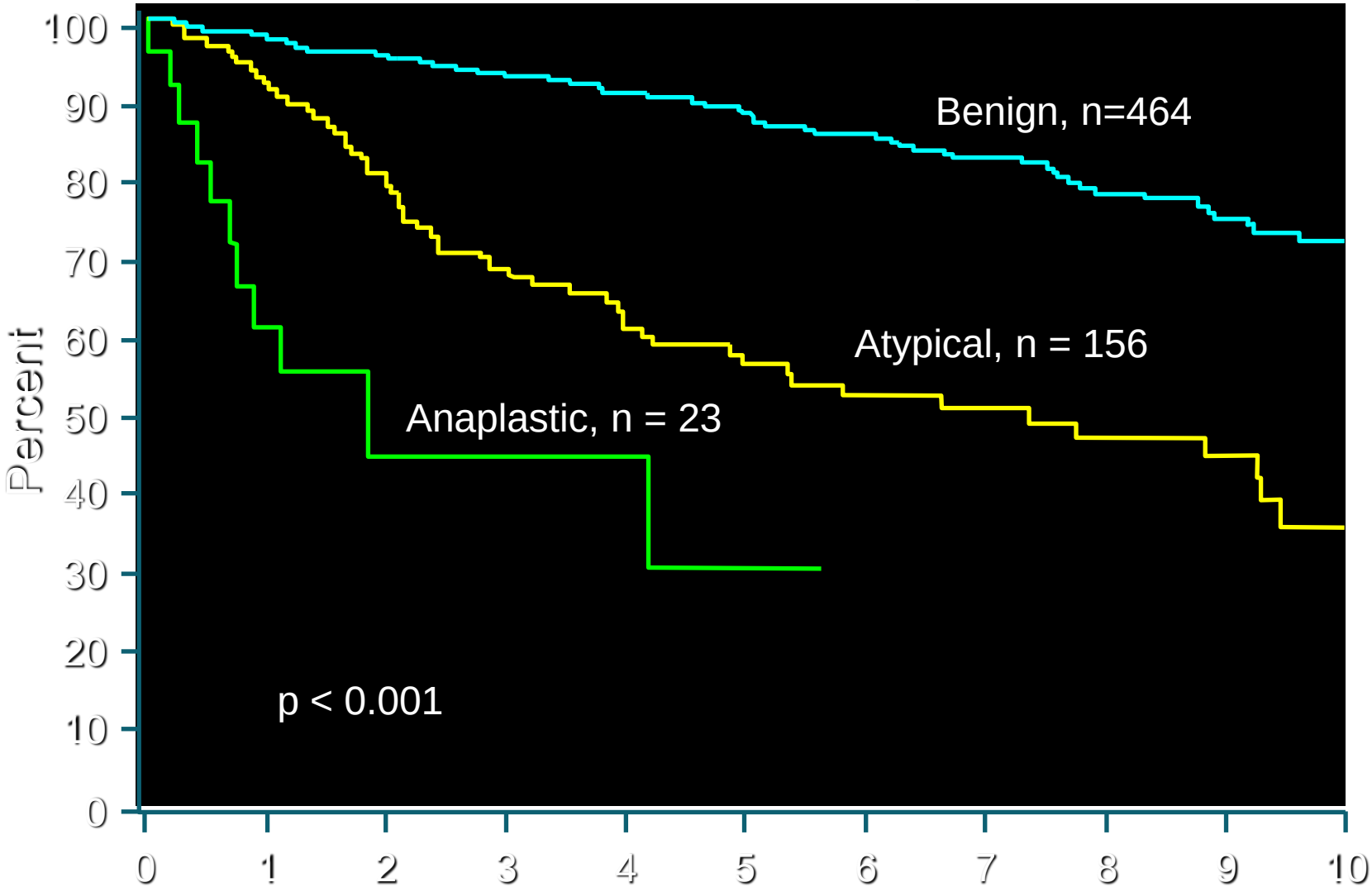
Recurrence-free Survival in 643 Patients with Primary Meningioma



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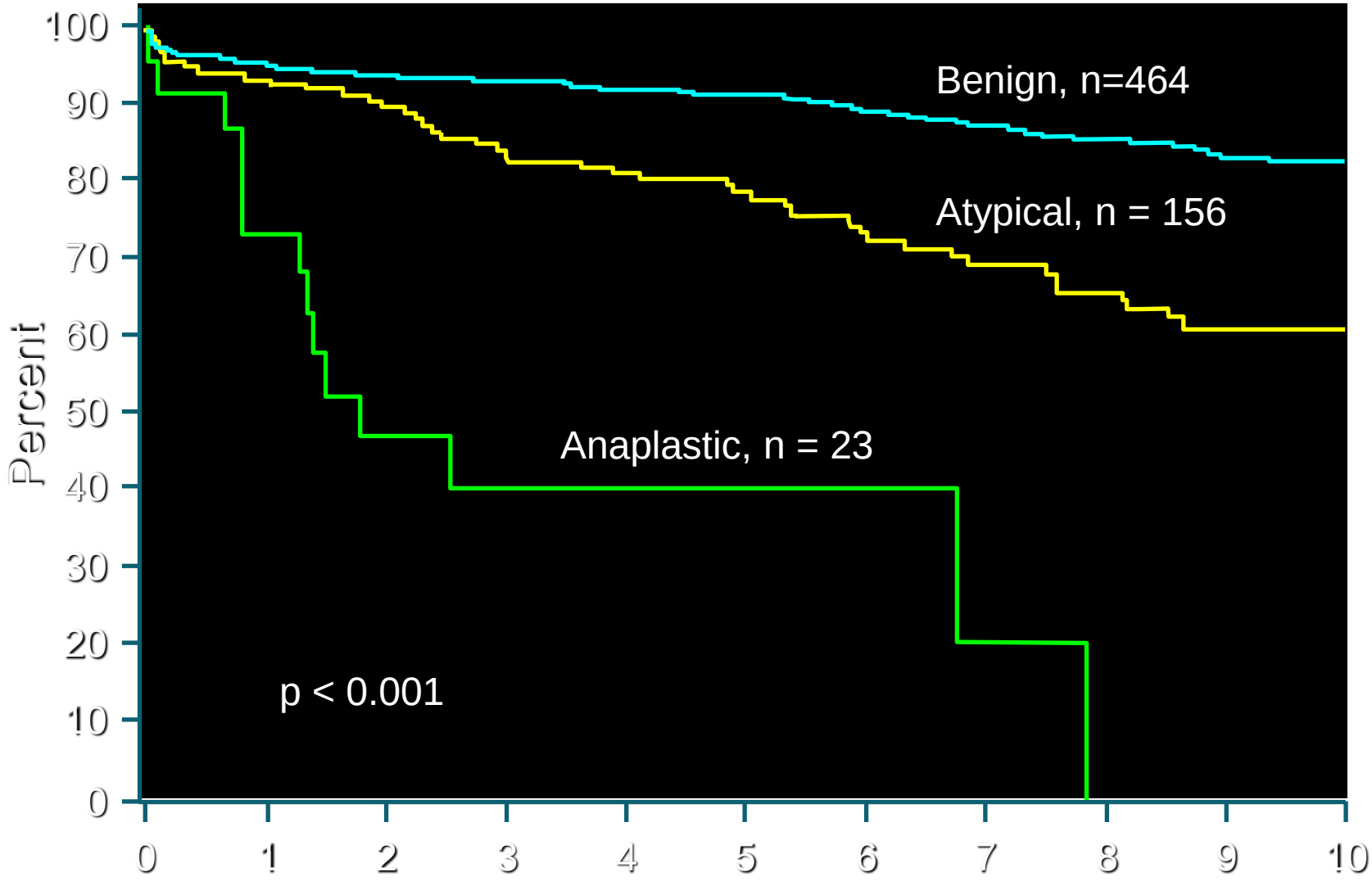
Overall Survival in 643 Patients with Primary Meningioma



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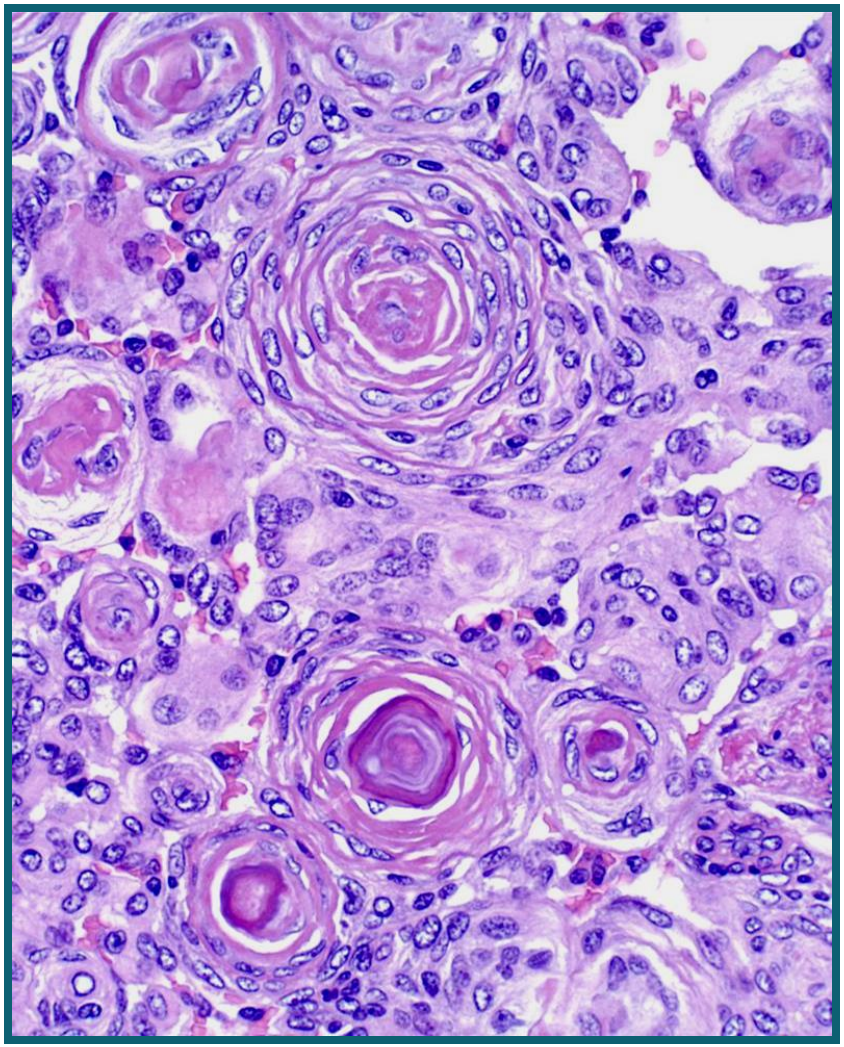
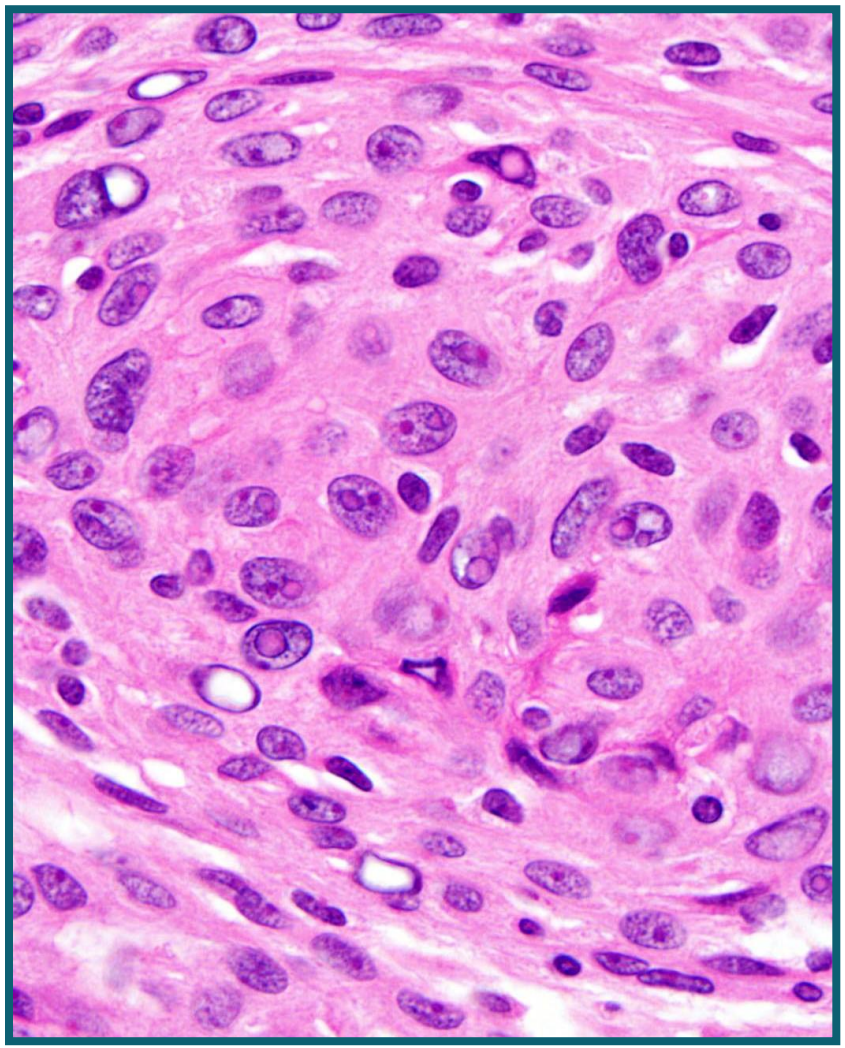
MENINGIOMA, WHO I (75-80%)





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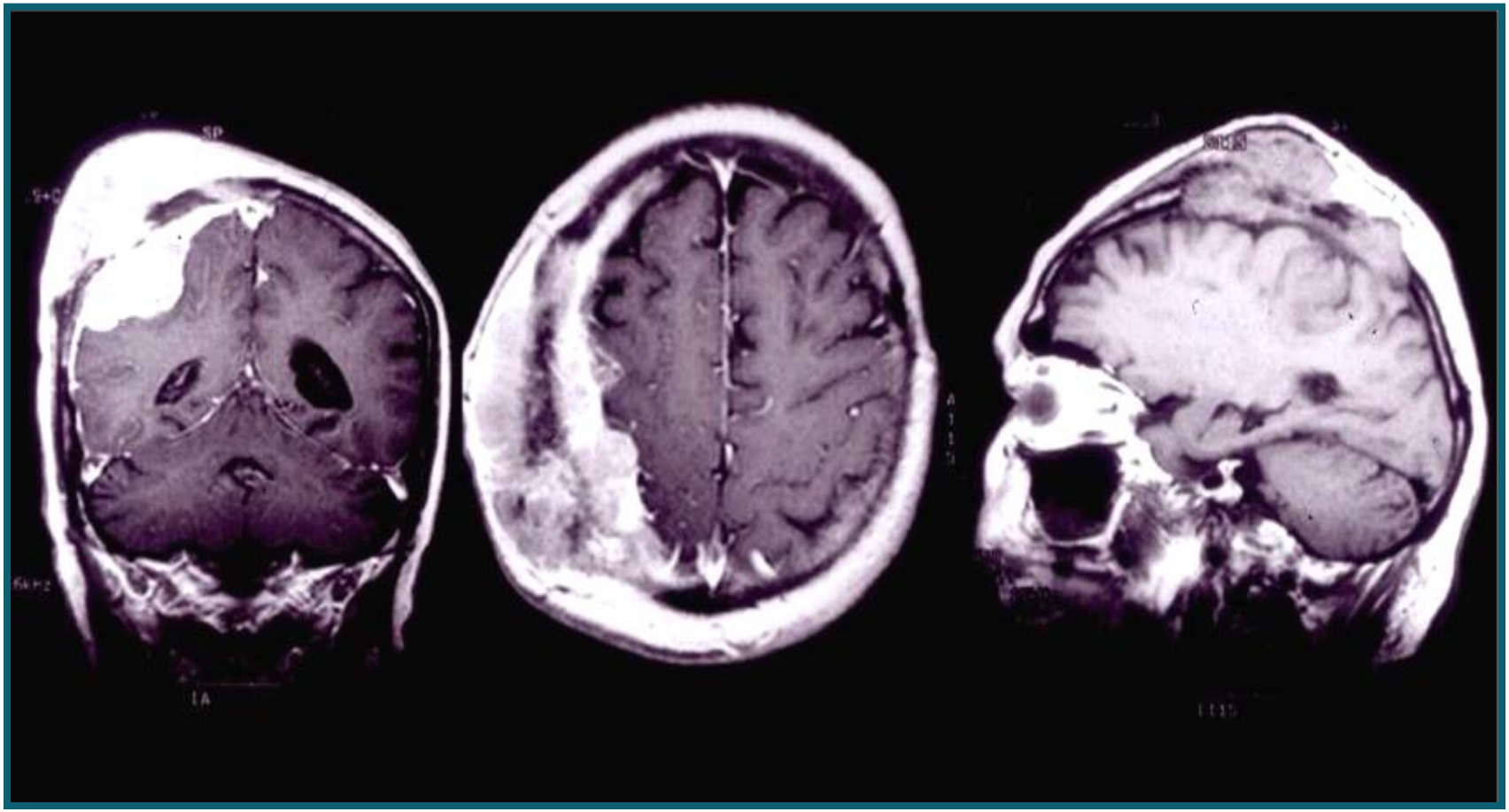
ATYPICAL MENINGIOMA, WHO II (20%)



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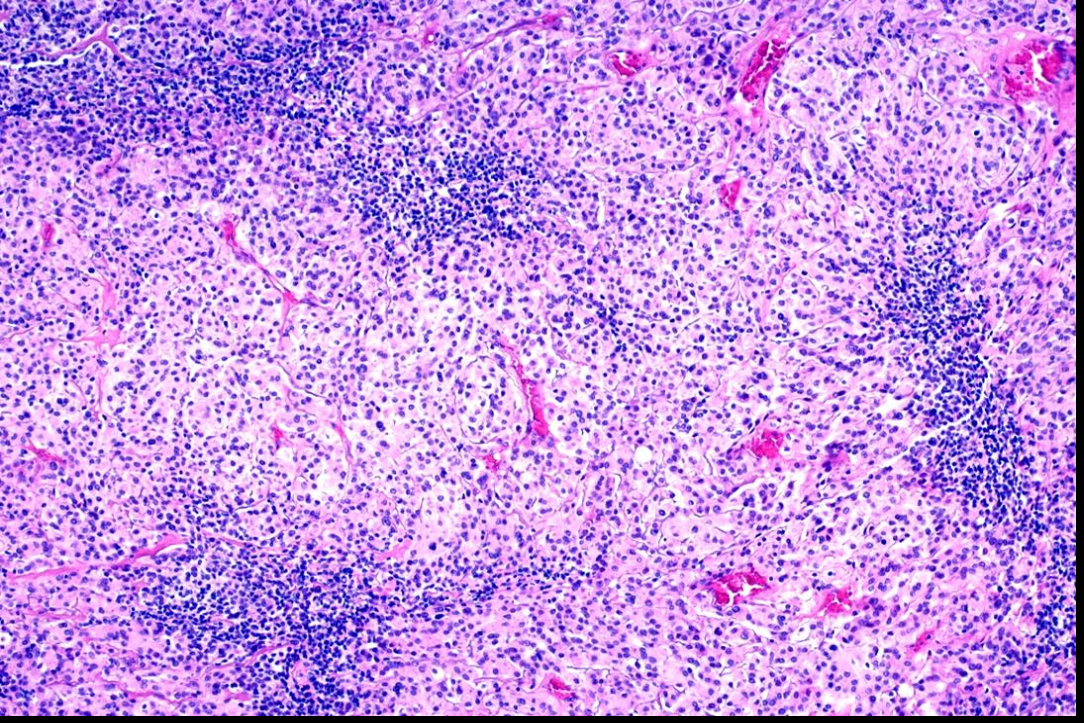
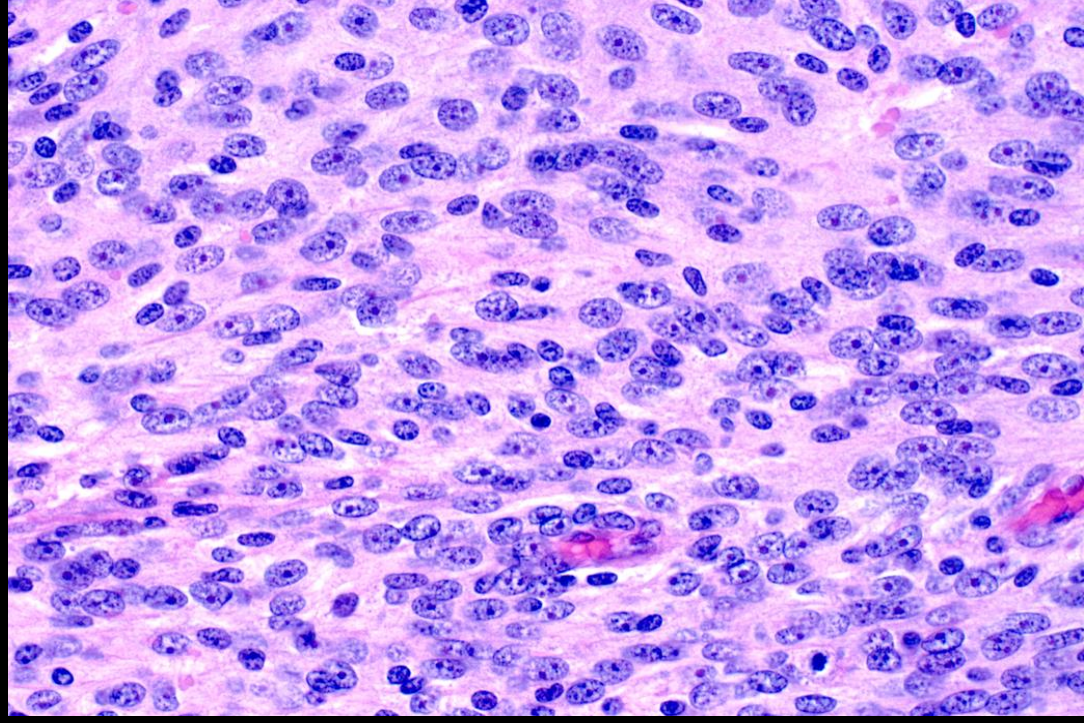
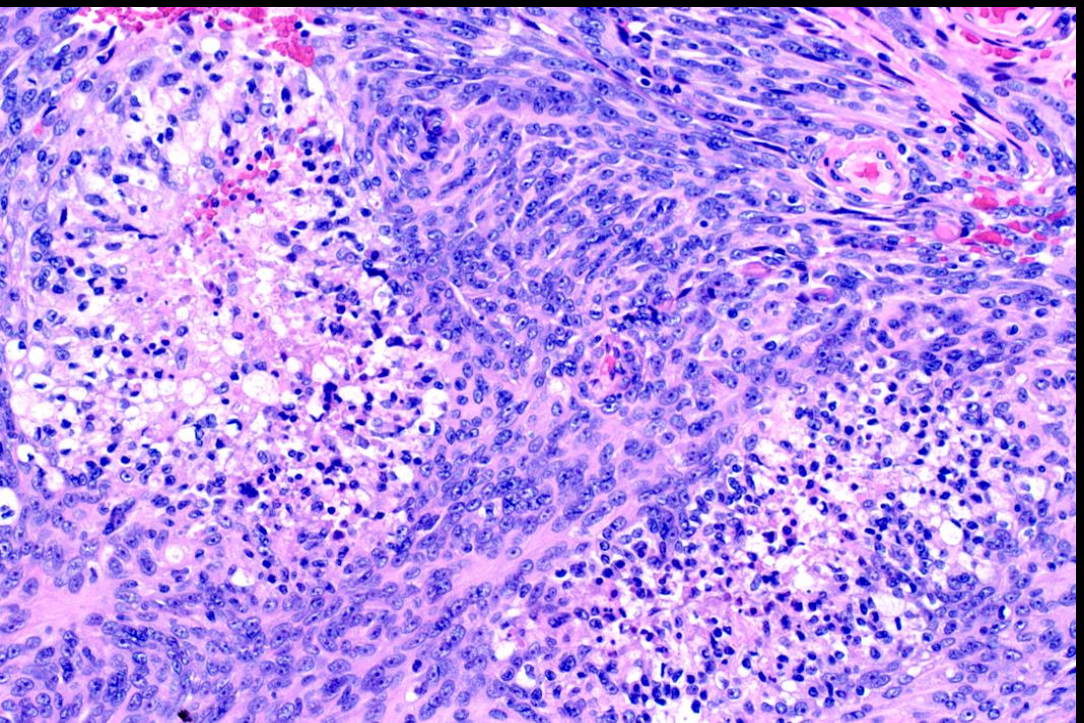
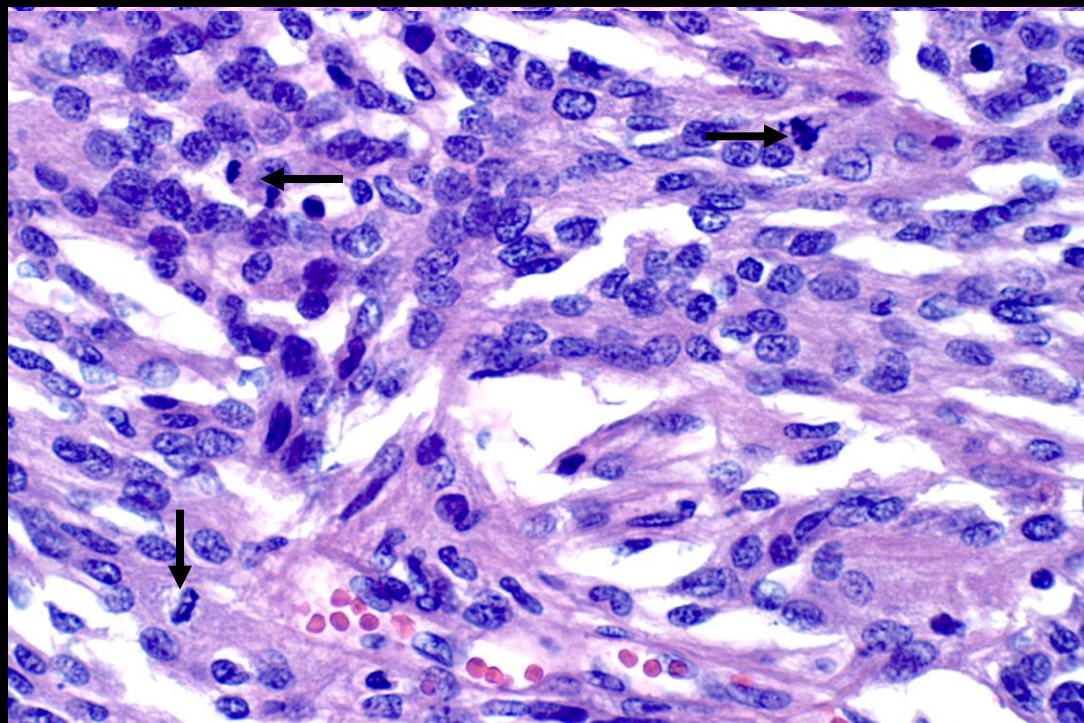

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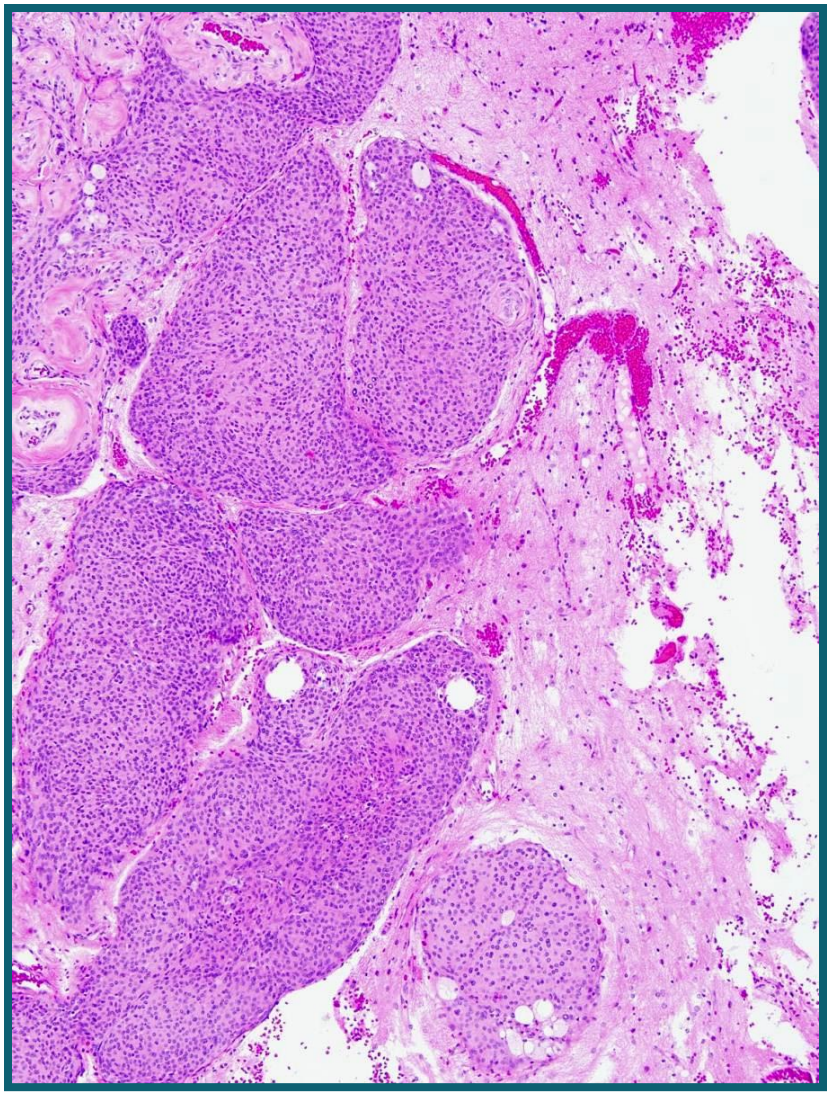
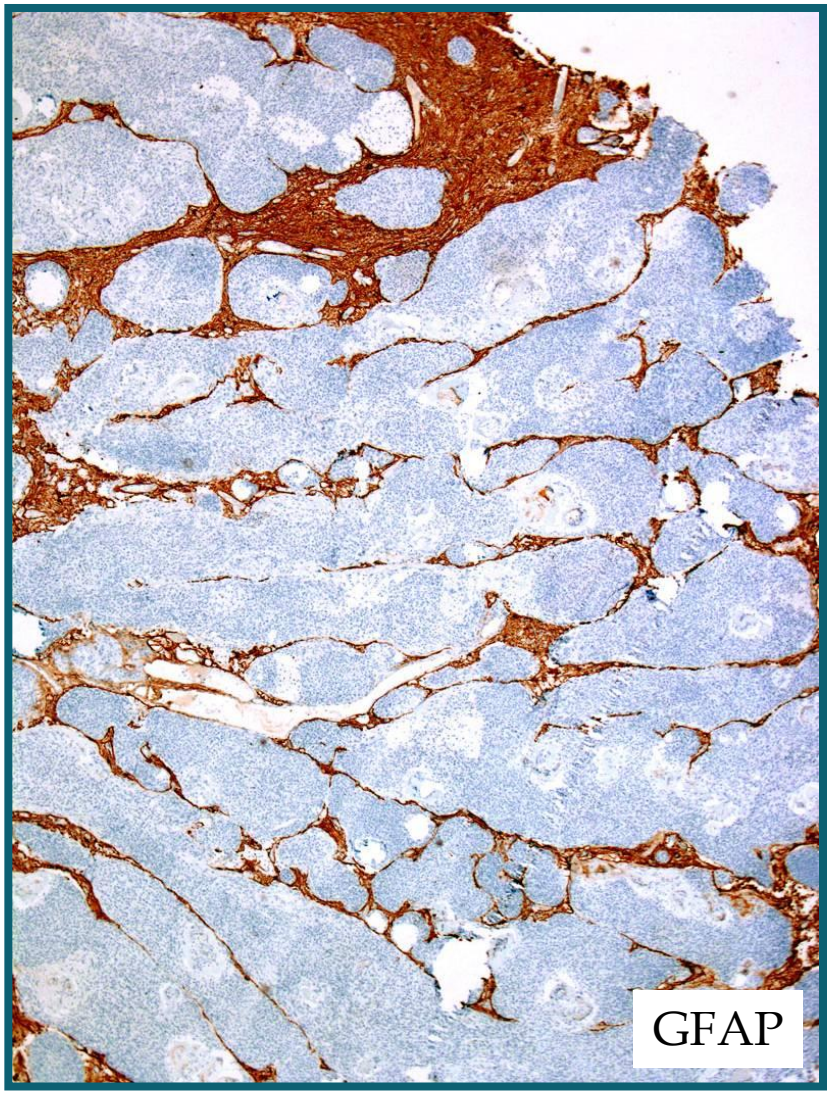
BRAIN INVASIVE MENINGIOMAS





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BRAIN INVASIVE MENINGIOMAS

The presence of brain invasion connotes a greater likelihood of recurrence. Brain-invasive, histologically benign and histologically atypical meningiomas both have recurrence and mortality rates similar to those of atypical meningiomas in general {1736}. As such, they should prognostically be considered WHO grade II. Whereas the genetic changes

WHO 2007

The American Journal of Surgical Pathology *19(5): 493–505, 1995*

Clear Cell Meningioma

A Clinicopathologic Study of a Potentially Aggressive Variant of Meningioma

S. Zorludemir, M.D., B.W. Scheithauer, M.D., T. Hirose, M.D., C. Van Houten, G. Miller, M.D., and F.B. Meyer, M.D.

Since clear cell meningioma has only recently been recognized as a morphologic entity, its pathobiology has not been studied. Fourteen examples occurring in seven females and six males, ages 9 to 82 years (mean 29 years), were examined; one was associated with type 2 neurofibromatosis. Of these cases, seven (50%) were spinal-intradural (six lumbar, one thoracic), three (21%) arose in the posterior fossa (cerebellopontine angle), three (21%) were supratentorial, and one (7%) was centered upon the foramen magnum. In one case (8%), two tumors were considered to be independent primaries. One tumor (8%) appeared to show no dural attachment. Thirteen tumors were subject to complete study. All were composed of sheets of clear, glycogen-rich, polygonal cells forming only a few vague whorls. Hyalinization, both stromal and mary, clear cell meningiomas are morphologically unique, show no sex predilection, affect primarily the lumbar region and cerebellopontine angle, and despite their benign appearance, may be inordinately aggressive, particularly intracranial examples. No close association was noted between recurrence or clinical outcome and such factors as mitotic activity, PCNA proliferation indices, percent S-phase determination, or DNA ploidy status. In contrast, MIB-1 proliferation indices were appreciably higher among recurring tumors.

Key Words: Clear cell meningioma—Proliferative markers—Flow cytometry—Electron microscopy.

Am J Surg Pathol 19(5): 493–505, 1995.

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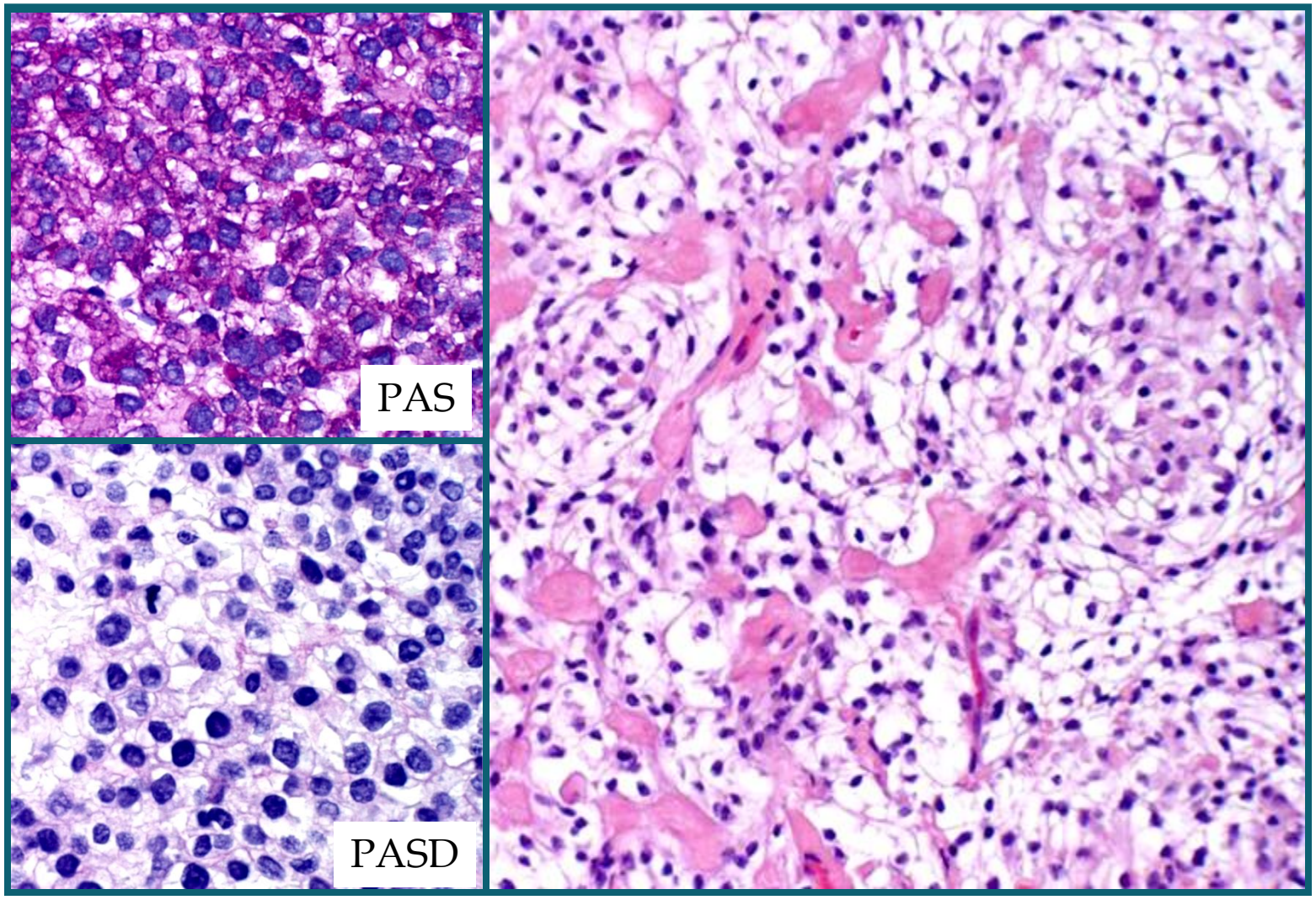
CLEAR CELL MENINGIOMA (WHO II)



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The American Journal of Surgical Pathology 24(7): 899–905, 2000

Chordoid Meningioma

A Clinicopathologic Study of 42 Cases

M. E. Couce, M.D., Ph.D., F. V. Aker, M.D., and B. W. Scheithauer, M.D.

The term chordoid meningiomas was first used by Kepes et al. in 1987 to describe a meningeal tumor in young patients associated with microcytic anemia and/or dysgammaglobulinemia. Such tumors were composed of spindle or epithelioid cells disposed in chordoma-like clusters and cords in a myxoid matrix and often featured a prominent lymphoplasmacellular infiltrate. Our study includes 42 chordoid meningiomas that represented 0.5% of all meningiomas operated at Mayo Clinic during the interval 1975 to 1997. The male to female ratio was 1:1 and the age range was 12 to 77 years (mean, 47.4 yrs). Only two (5.2%) occurred in children. The majority (88%) were large and supratentorial. No manifestation of systemic disease was noted. Chordoid elements comprised 10% to 100% of the tumors; 34 (81%) were more than 50% chordoid. Thirty-seven tumors (88%) were classified as typical and five as atypical. Lymphoplasmacytic infiltrates varied, being moderate in 10

(hypercellularity, "sheeting growth," prominent nucleoli, presence of small cells), or (3) the finding of brain invasion, were indicators of frequent recurrence. Recently, these same authors established simple morphologic criteria for the diagnosis of anaplastic meningioma.[48] The 1993 WHO Classification[58] of Tumours of the Central Nervous System describes 14 variants of meningioma, ranging from the common meningothelial and transitional forms to rare types such as clear cell,[59] papillary, and chordoid meningiomas.[28] Since its publication, an aggressive, rhabdoid variant has also been described.[25,47] This neoplastic spectrum underscores the capacity of arachnoid cells to exhibit divergent differentiation.

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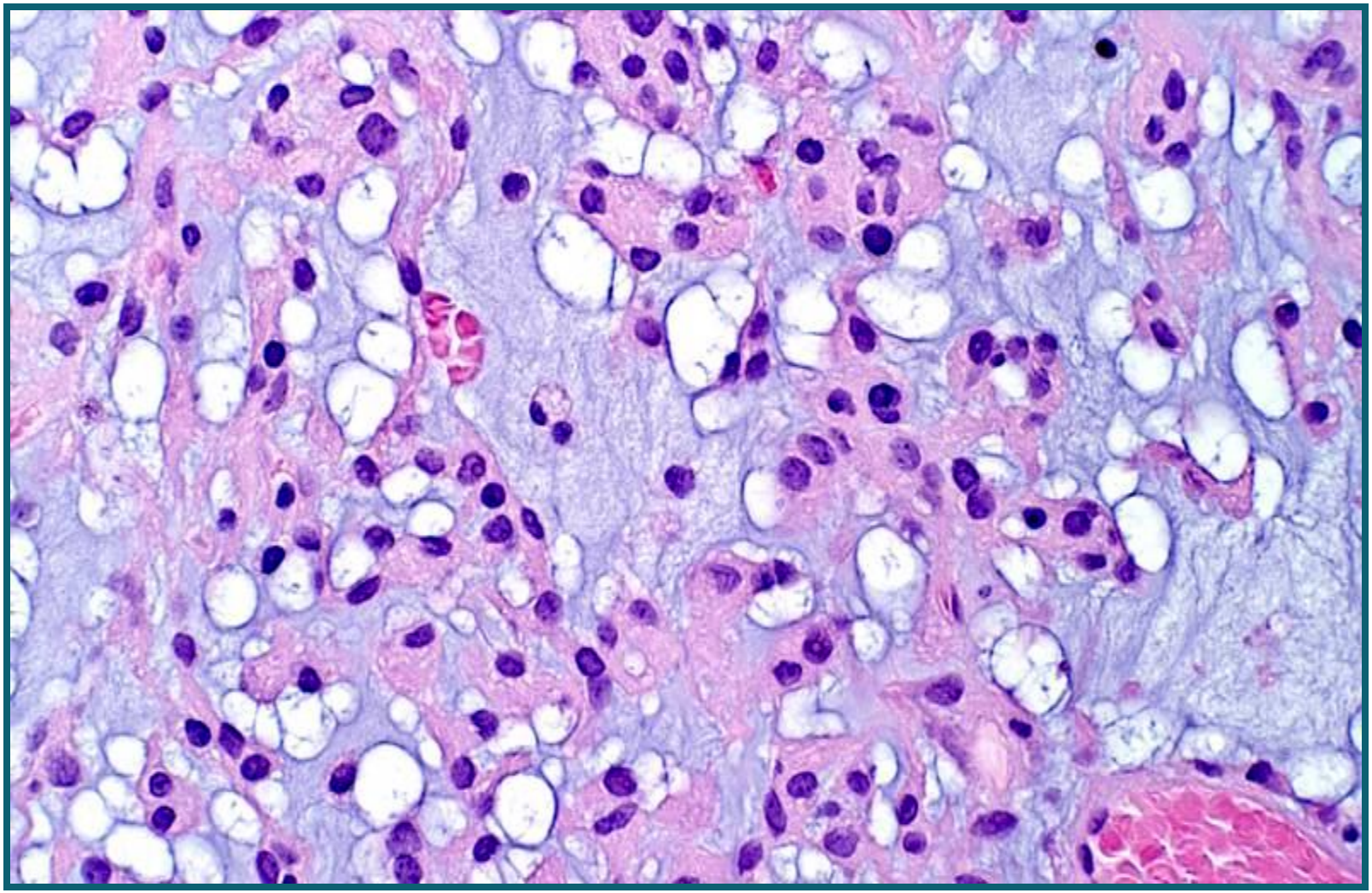
CHORDOID MENINGIOMA (WHO II)



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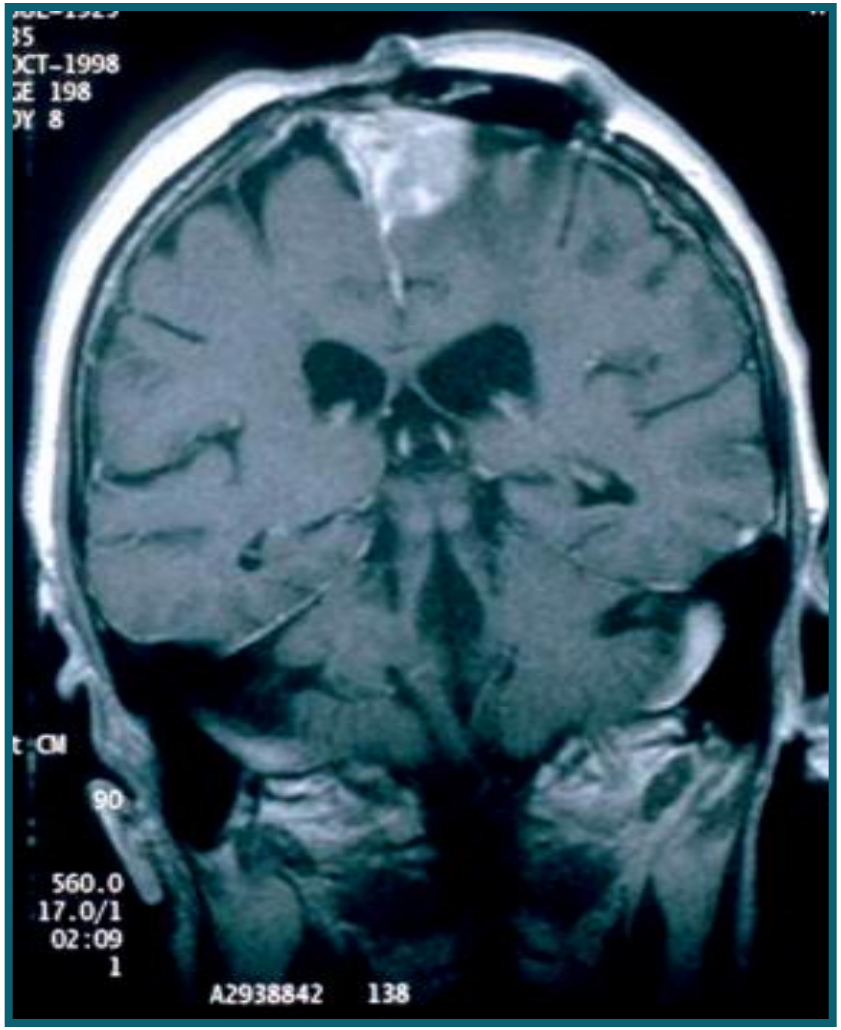
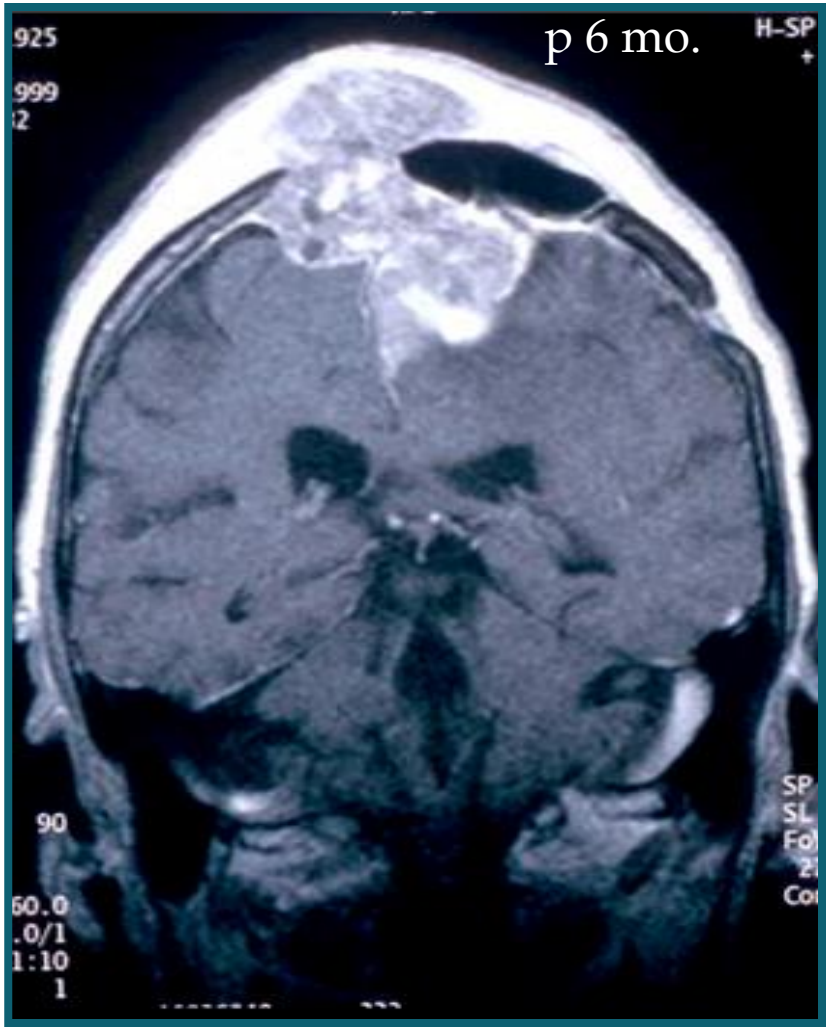
ANAPLASTIC (MALIGNANT) MENINGIOMA, WHO III (1-3%)





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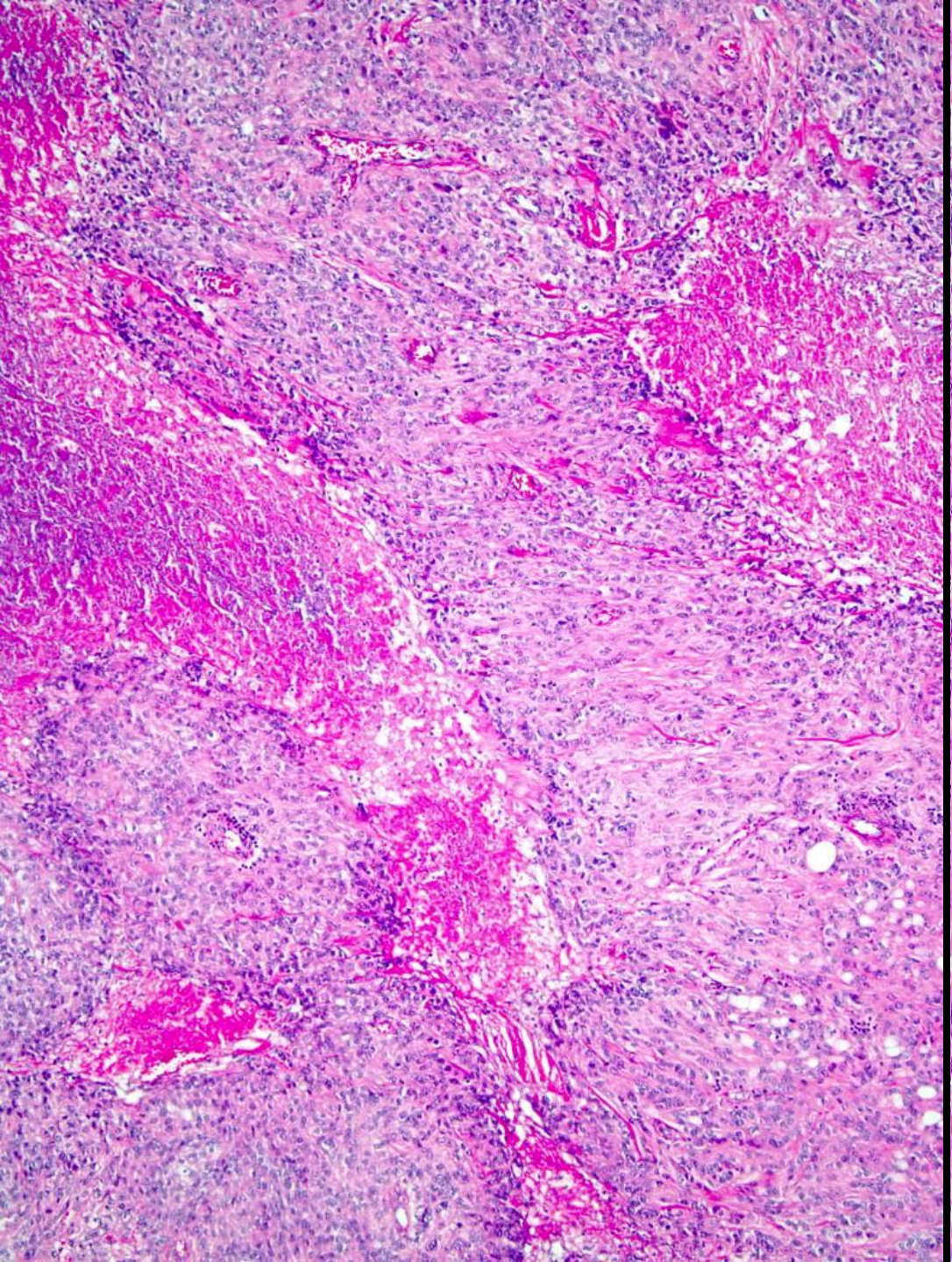
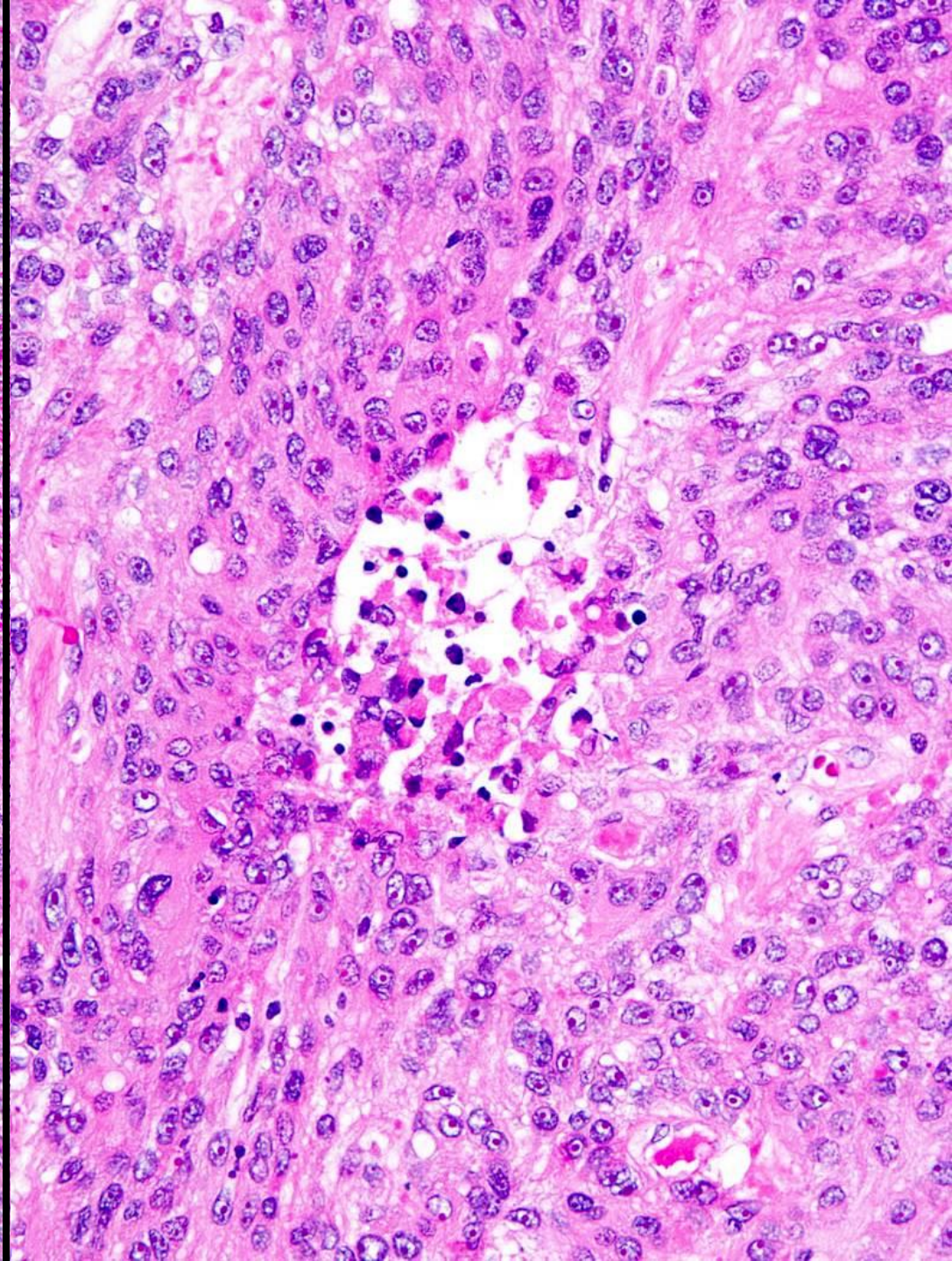

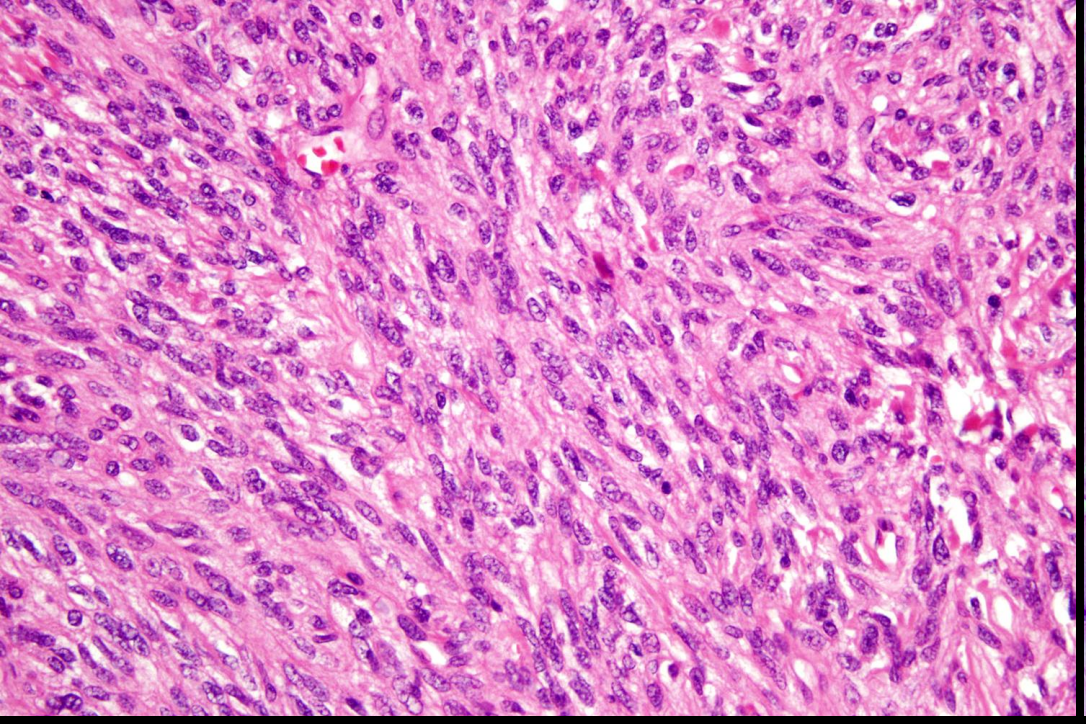
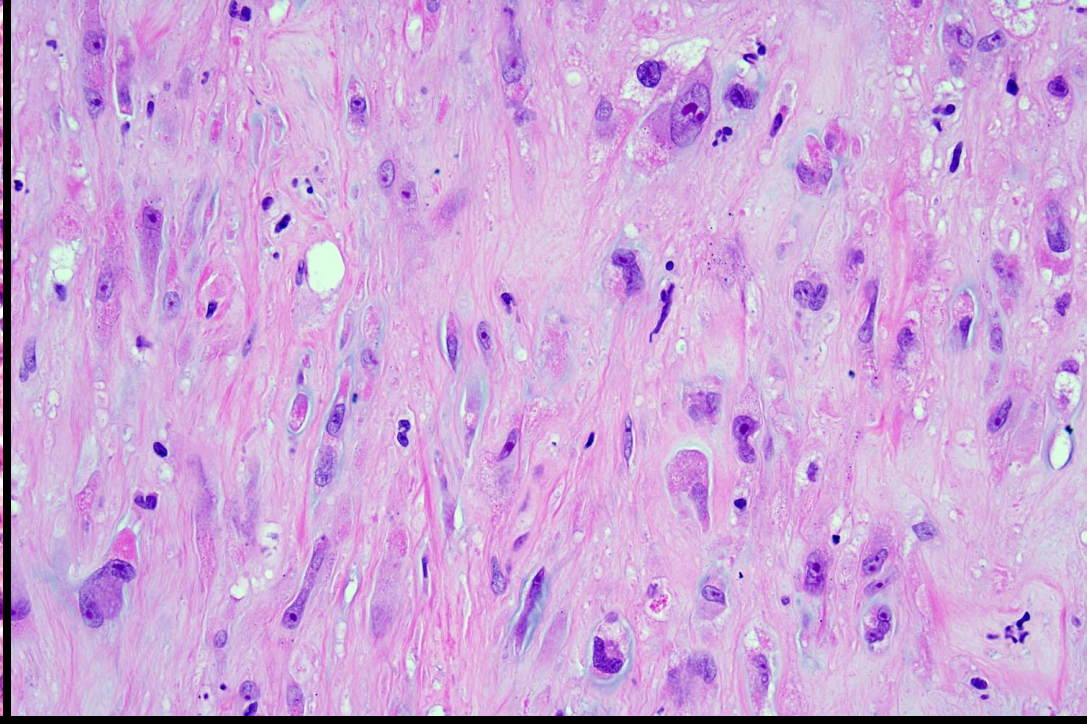
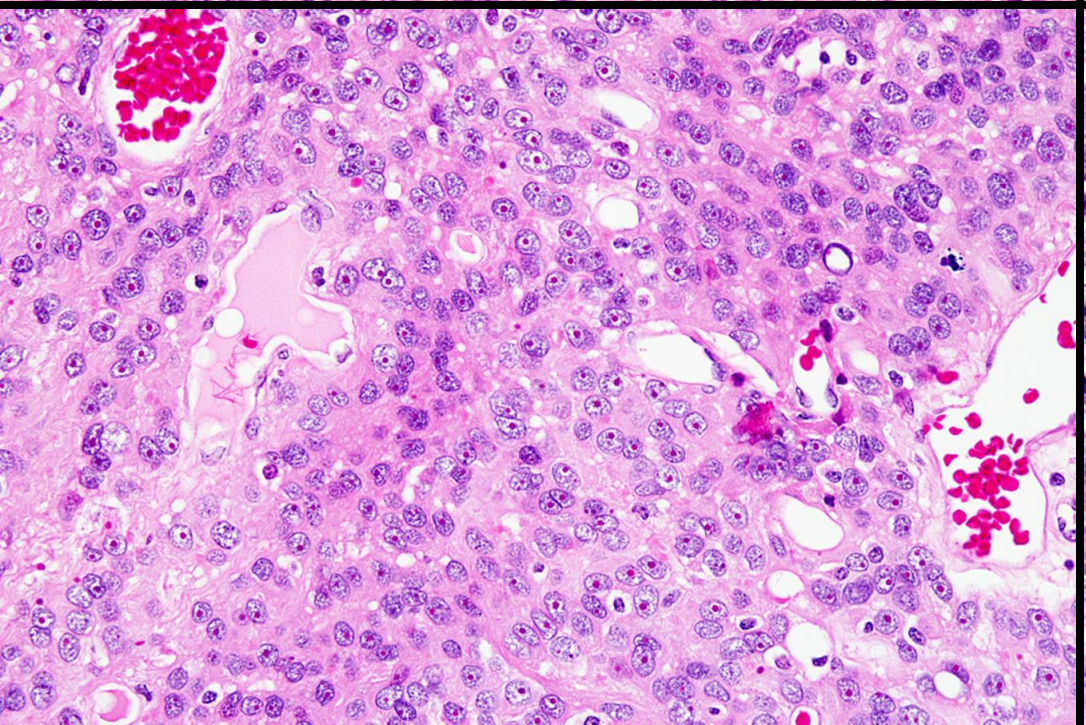
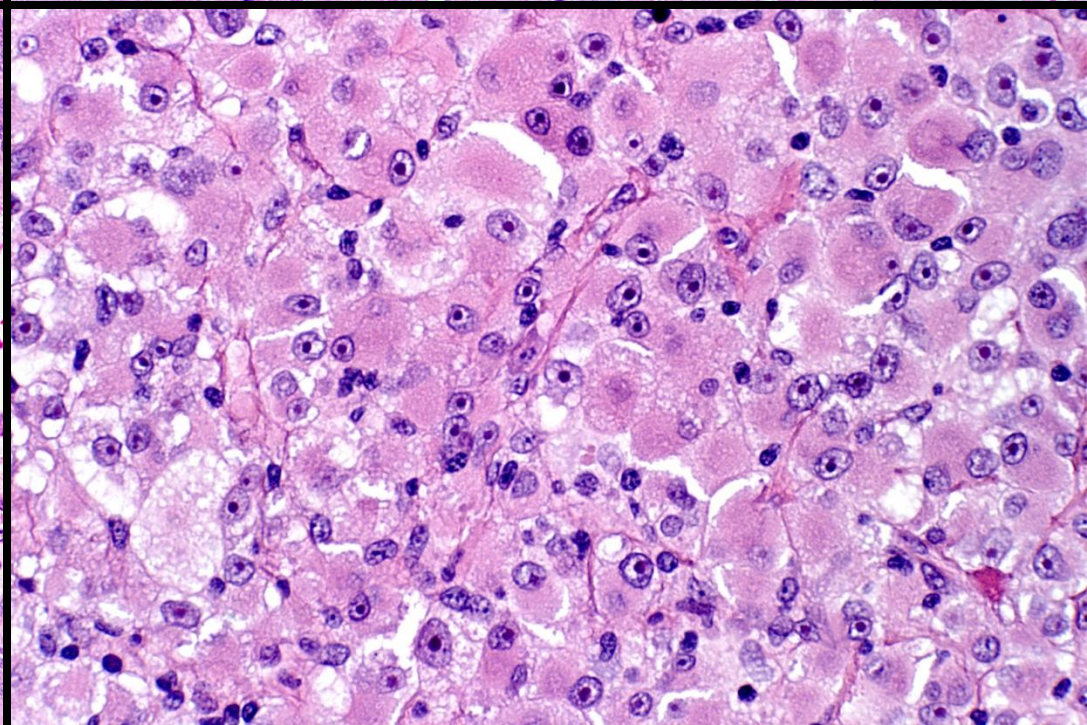

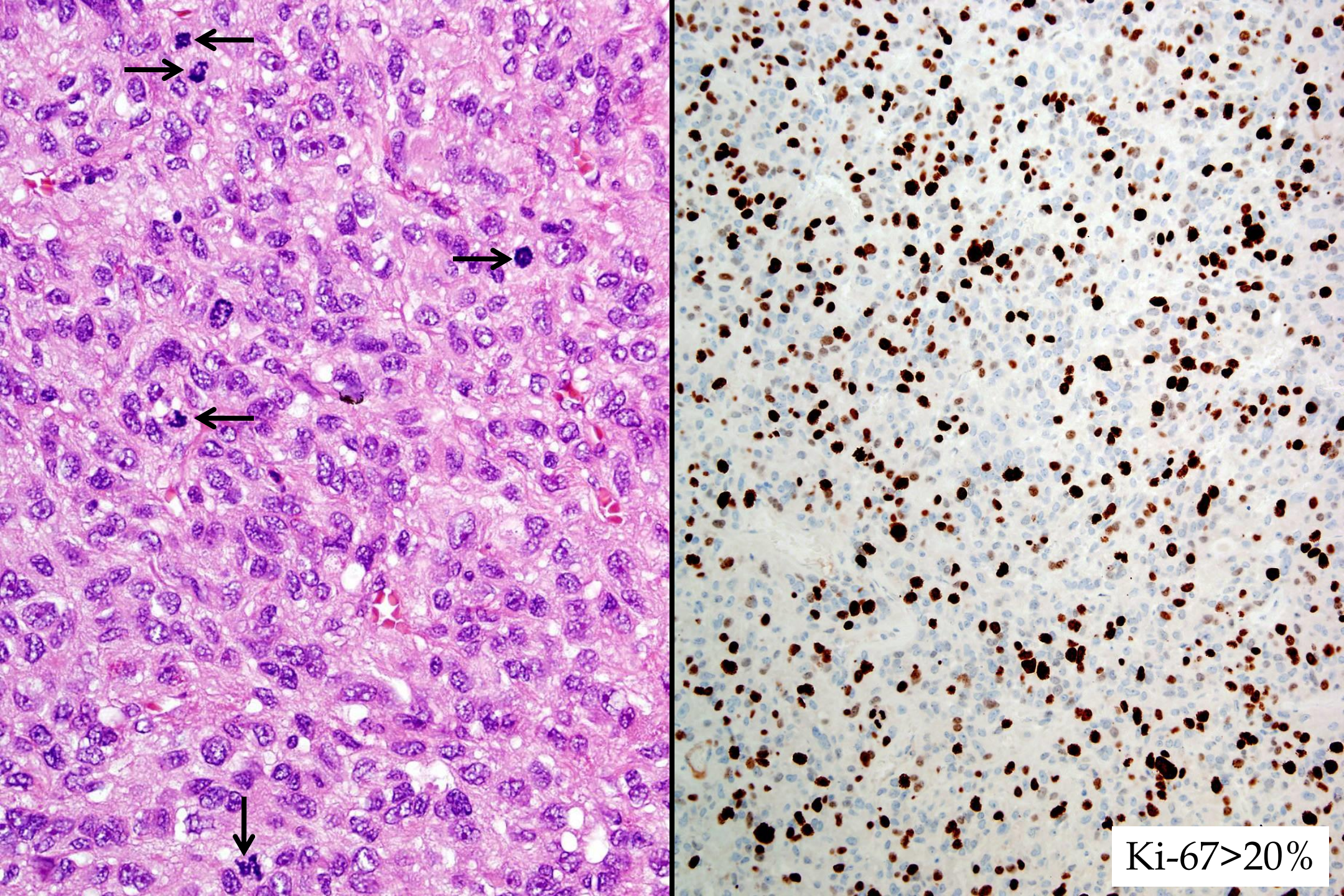
Ki-67>20%

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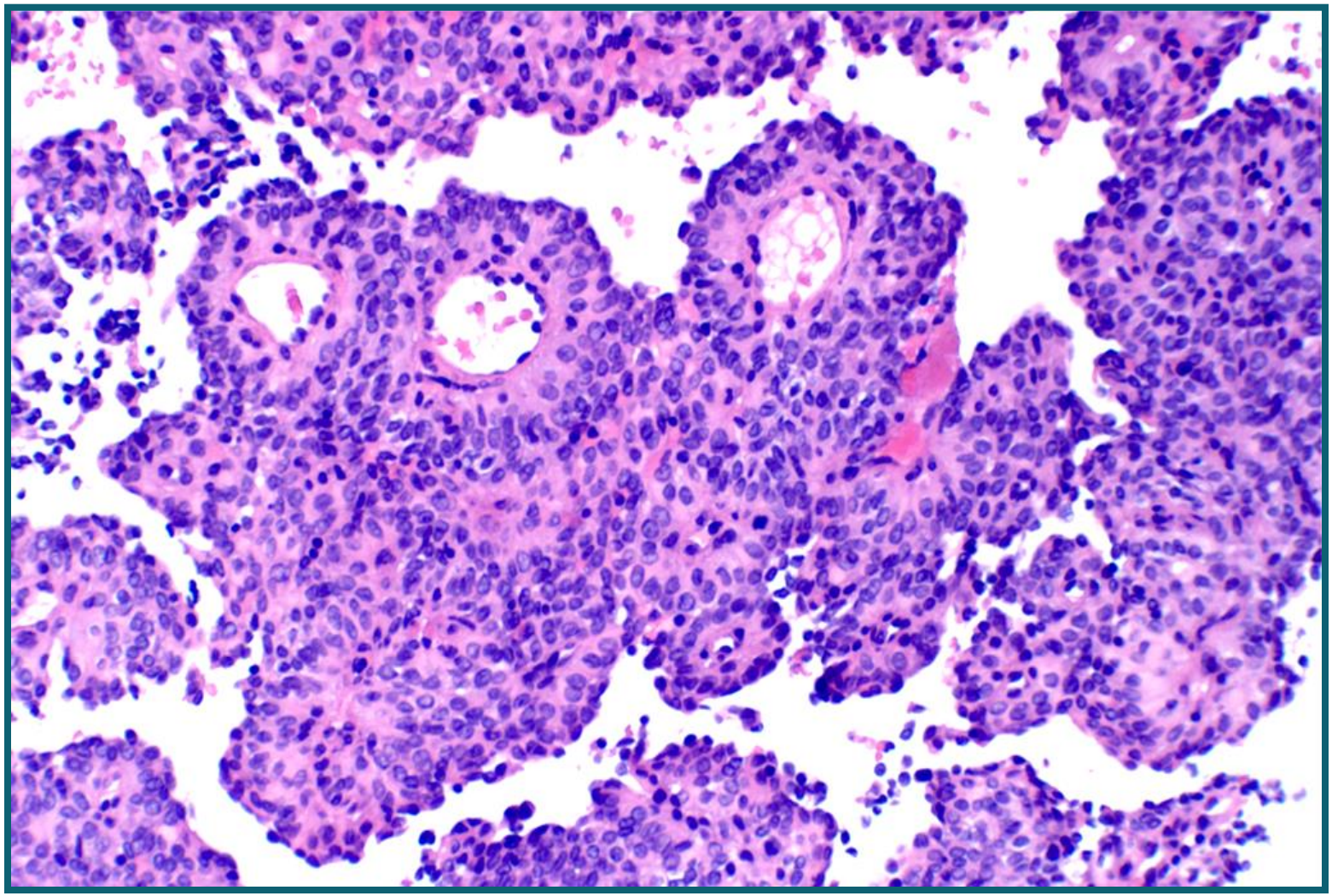
PAPILLARY MENINGIOMA (WHO III)



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The American Journal of Surgical Pathology 22(12): 1482–1490, 1998

Reprinted from THE AMERICAN JOURNAL OF SURGICAL PATHOLOGY
Vol. 22, No. 12 December 1998
Lippincott Williams & Wilkins Printed in U.S.A.

"Rhabdoid" Meningioma

An Aggressive Variant

Arie Perry, M.D., Bernd W. Scheithauer, M.D., Scott L. Stafford, M.D.,
Patrice C. Abell-Aleff, and Fredric B. Meyer, M.D.

It is has been suggested that rhabdoid morphology is associated with a poor prognosis, regardless of tumor histogenesis. We report a series of 15 meningiomas with rhabdoid features. Nine patients had undergone multiple resections. In six, the rhabdoid component was histologically apparent only in recurrences. Rhabdoid morphology was defined as sheets of loosely cohesive cells with eccentric nuclei and hyaline, paranuclear inclusions. Ultrastructurally, the latter consisted of whorls of intermediate filaments often entrapping lysosomes or other organelles. Meningothelial features included whorl formation and nuclear pseudoinclusions, immunohistochemical coexpression of vimentin and epithelial membrane antigen, and the ultrastructural finding of interdigitating cell membranes and intercellular junctions. At the histologic level, a conventional meningioma component was noted in most tumors; only four lesions were entirely rhabdoid. Histologic malignancy (brain invasion or anaplasia) was observed in nine cases, another two tumors being considered malignant on the basis of extracranial

The term malignant rhabdoid tumor (MRT) was first used to describe a distinctive pediatric renal neoplasm with cytologic features reminiscent of large rhabdomyoblasts, albeit ones lacking skeletal muscle differentiation.[1,14] Despite the occurrence of morphologically similar tumors at a variety of sites, including soft tissues and the CNS,[2,12,17,38] the demonstration of rhabdoid morphology in diverse, histogenetically unrelated tumors led to the concept that, outside the kidney, rhabdoid histology represents a phenotype rather than an entity.[4–9,13,15,19,21–23,25–28,34,36,39,40,46] Therefore, the term "rhabdoid" has evolved to denote a tumor resembling MRT of the kidney. The analogy appears to have come full circle, some rhabdomyosarcomas being described as having rhabdoid tumor-like features.[6,21] It is of particular

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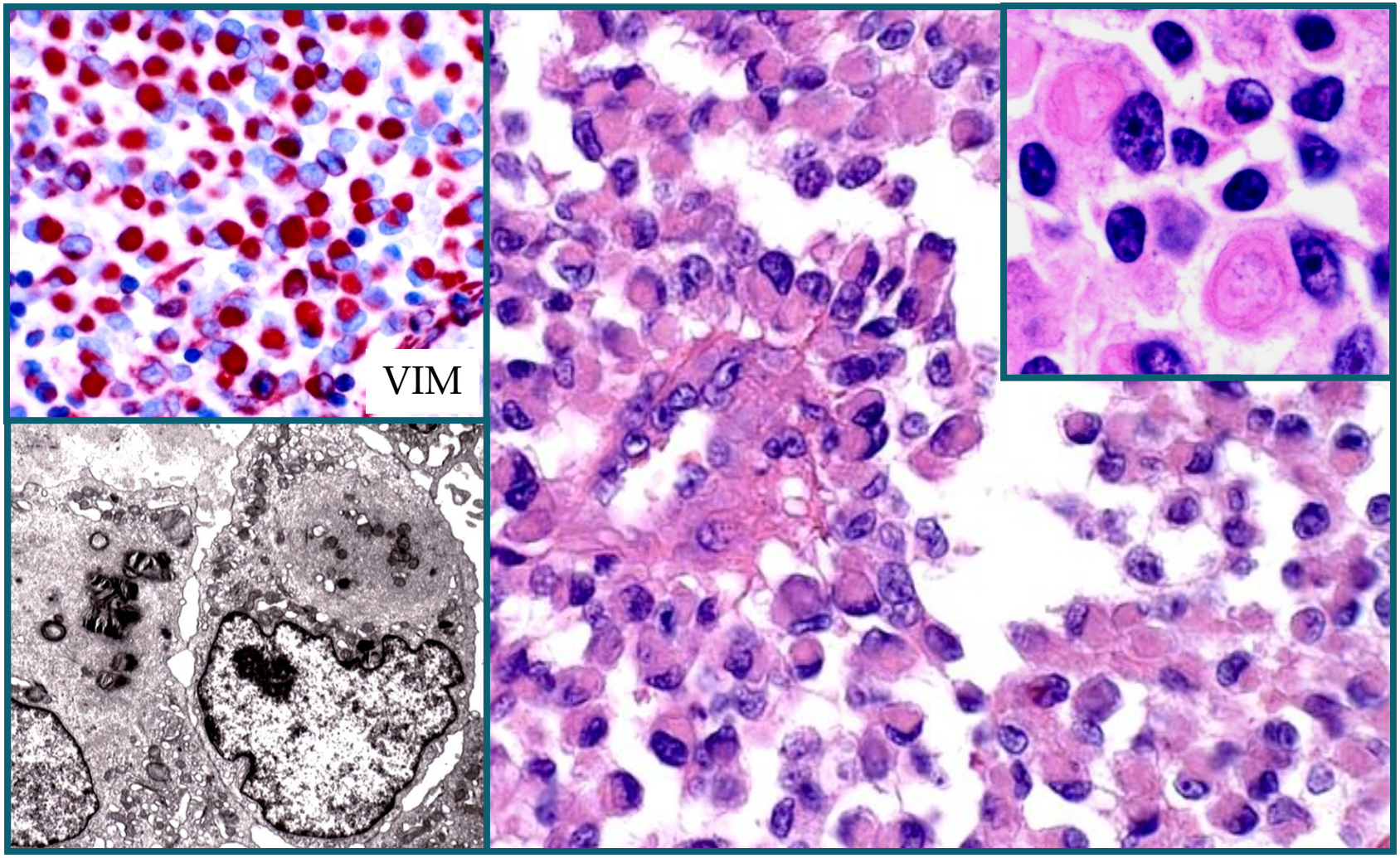
RHABDOID MENINGIOMA, WHO III



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Hitting a moving target: evolution of a treatment paradigm for atypical meningiomas amid changing diagnostic criteria

A case series

Blake E. Pearson M.D.,[1] James M. Markert, M.D., M.P.H.,[1] Winfield S. Fisher, M.D.,[1] Barton L. Guthrie, M.D.,[1] John B. Fiveash, M.D.,[2] Cheryl A. Palmer, M.D.,[3] and Kristen Riley, M.D.[1]

Divisions of [1]Neurosurgery and [3]Neuropathology, and [2]Department of Radiation Oncology, University of Alabama at Birmingham, Alabama

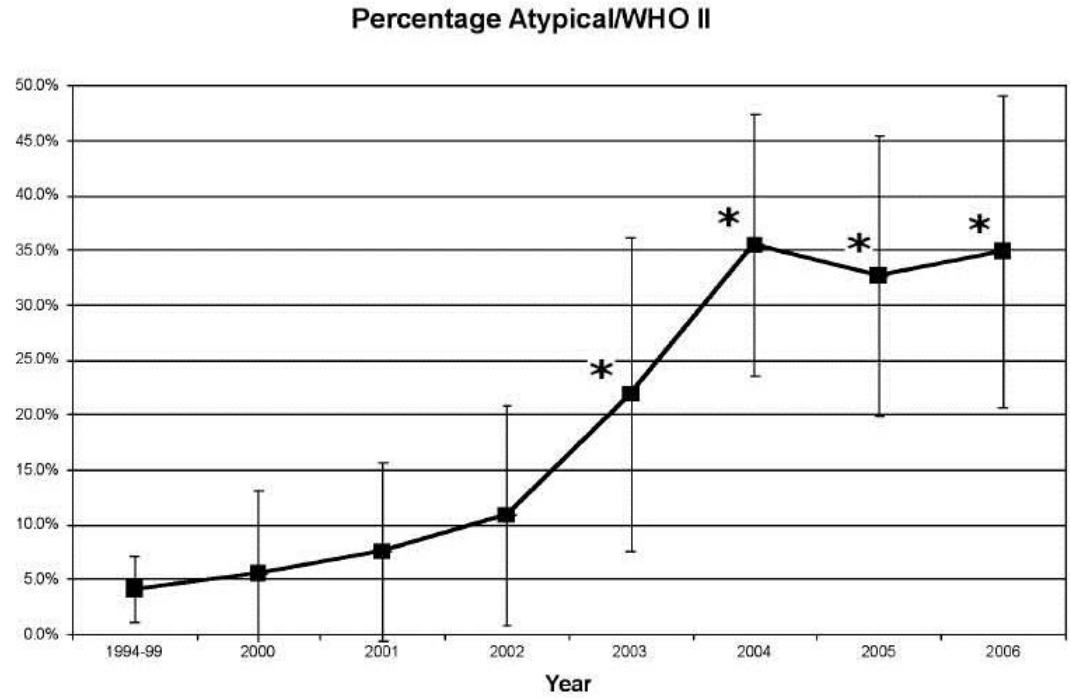


FIG. 2. Line graph showing the percentage of total meningiomas designated as atypical (WHO Grade II) per year. Data points are the total percentage in each calendar year (2006 does not include December). Bars represent the 95% CI. *$p < .001$ compared with the 1994–99 group.

1) Ho et al. Cancer 2002;1538-47

TABLE 3
Grading of the Current Study Materials Using the Model by Perry et al. and Model 1 from the Current Study

Study	No.	Recurrence (%) < 5 yrs	5–10 yrs	> 10 yrs	None[a]	P value
Perry et al.[12]						
Benign	58	4 (6.9)	3 (5.2)	9 (15.5)	42 (72.4)	< 0.001
Atypical	25	18 (72)	5 (20)	0	2 (8)	–
Current study (Model 1)						
Benign[b]	52	0	1 (1.9)	8 (15.4)	43 (82.7)	< 0.001
Atypical[c]	31	22 (71)	7 (22.6)	1 (3.2)	1 (3.2)	–

[a] Follow-up time > 10 years.
[b] Scores of 0 or 1.
[c] Scores of 2 or 3.

2) Korshunov et al. Int J Cancer 2003;728-34

TABLE

Prognostic factor	Total (p)	Benign (p)
Age, <40 years *vs.* >40 years	NS	0.04
Gender, male *vs.* female	0.02	0.005
Location, convexity *vs.* basal	NS	NS
Volume of resection, total *vs.* subtotal	NS	0.005
Tumor grade, benign *vs.* atypical *vs.* anaplastic	0.00001	
Ki-67 LI, <4.4% *vs.* >4.4%	0.0001	0.0001
topoII LI <3.2% *vs.* >3.2%	0.00001	0.00001
p14 positive *vs.* negative	NS	NS
p16 positive *vs.* negative	0.01	NS
p18 positive *vs.* negative	0.0001	0.0003
p21 positive *vs.* negative	0.001	0.003
p27 positive *vs.* negative	NS	NS
p73 positive *vs.* negative	NS	NS

3) Combs et al. IJROBP 2011; 81:1415-21

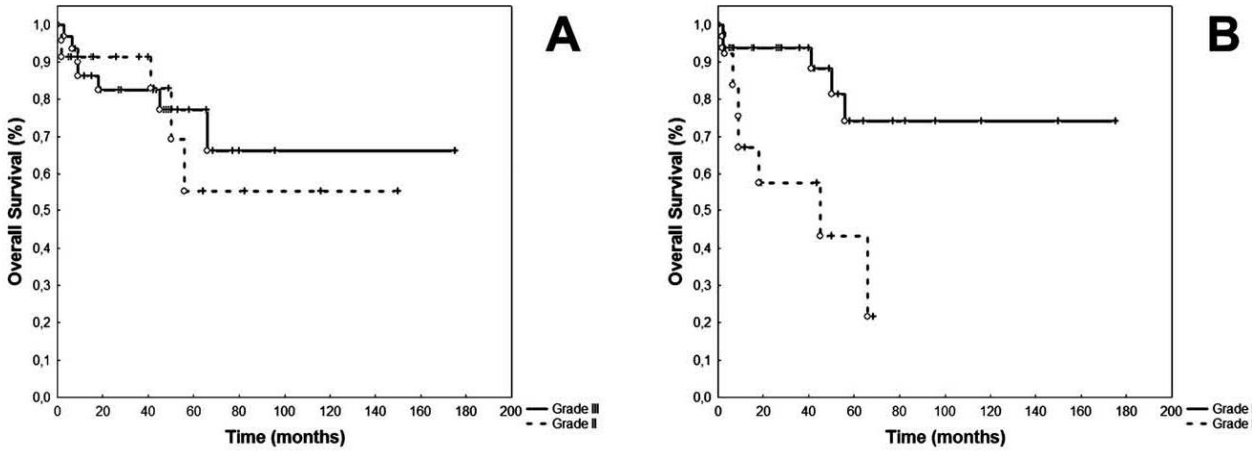
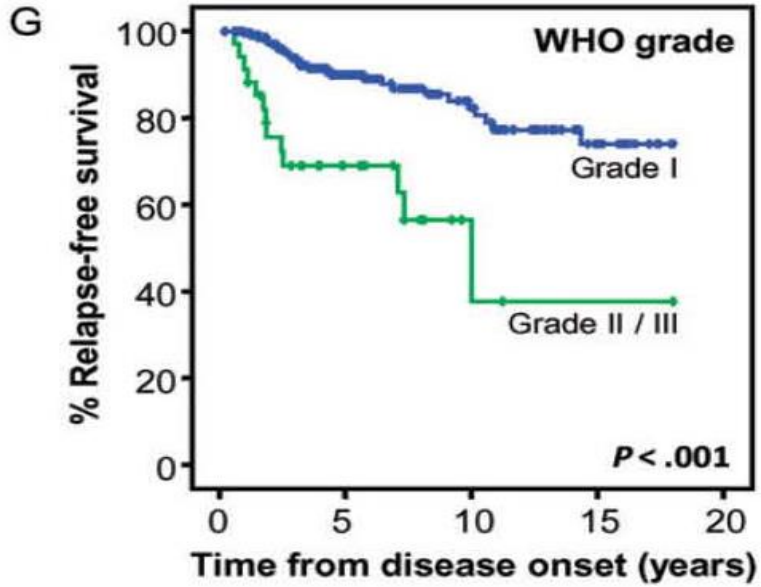


Fig. 1. Overall survival according to meningioma histologic grade in 62 patients reclassified according to World Health Organization 1993 and 2000/2007 classification systems. (A) Difference in overall survival was not statistically significant between World Health Organization Grade II and III as classified using 1993 system ($p = .96$). (B) After classification using 2000/2007 meningioma classification system, overall survival became significantly different ($p = .02$).

4) Domingues et al. Neuro-Oncology 2014 (in press)



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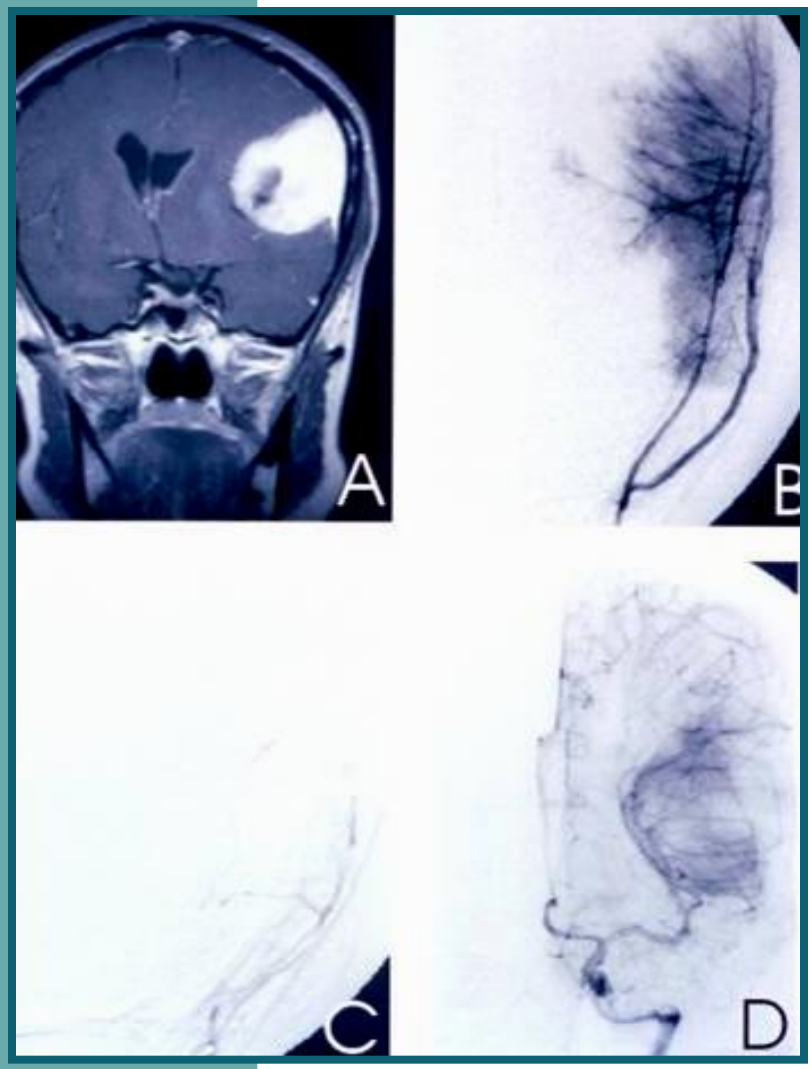
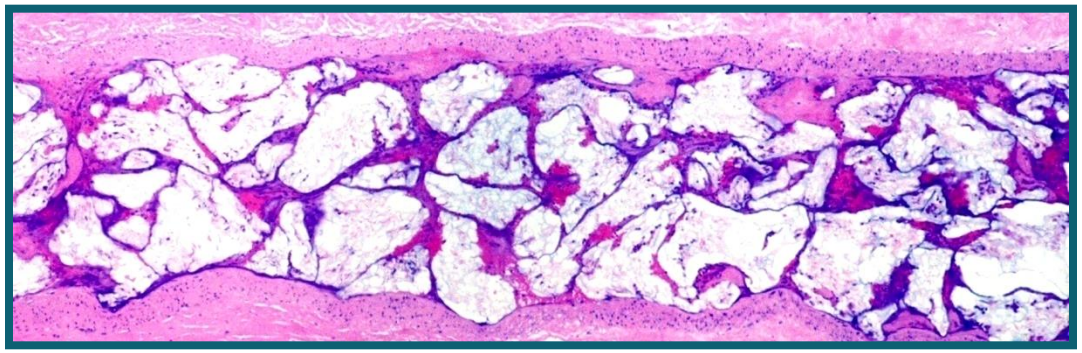
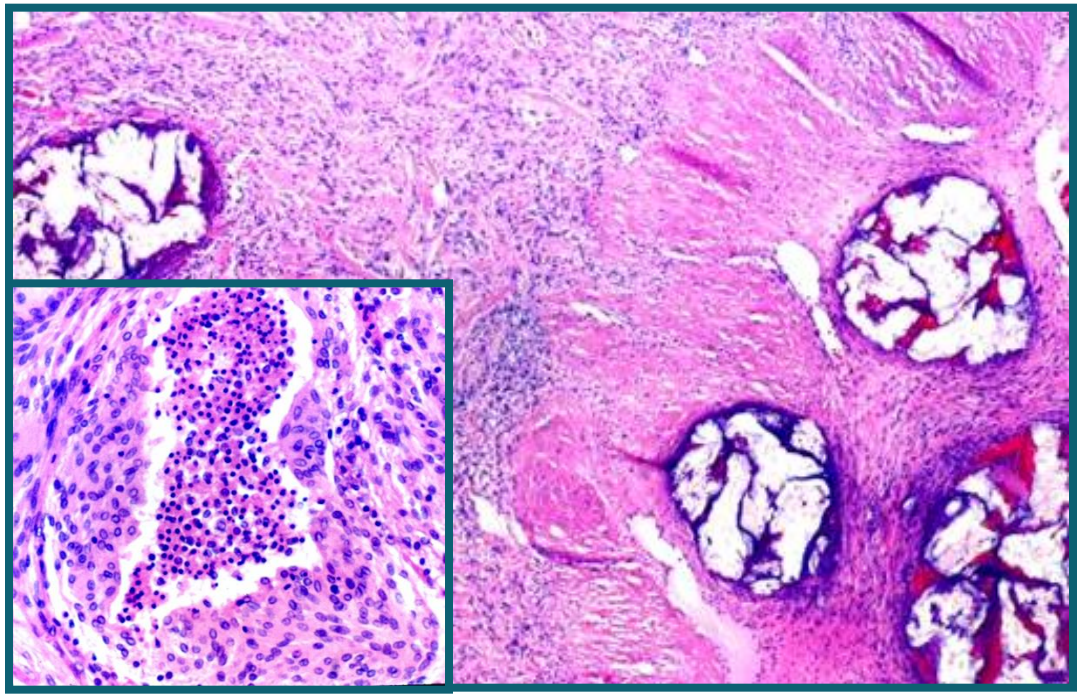
EMBOLIZED MENINGIOMAS







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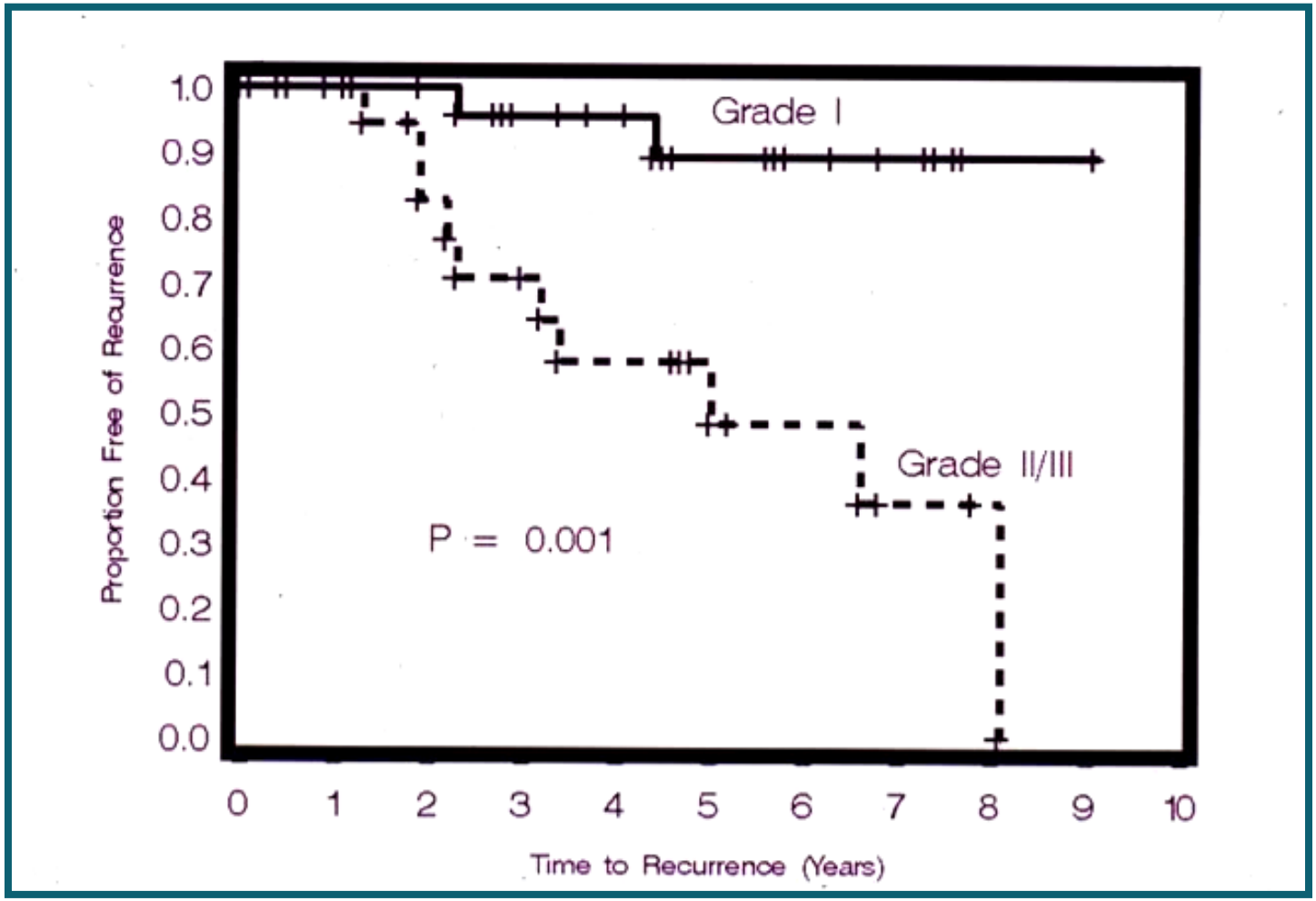
EMBOLIZED MENINGIOMAS



Perry A et al. Cancer 92:701, 2001

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Goldman Sachs:
How the culture of traders infected Wall Street

Iceland Volcano:
The cloud that closed a continent

TIME

THE 50TH ANNIVERSARY OF

THE PILL

So small. So powerful. And so misunderstood

BY NANCY GIBBS

JULY 22, 2002

WALL STREET: LOSING SAVINGS—AND TRUST

TIME

IS THIS OUR FIRST ANCESTOR?

Susan Pierres, 60, of Miami, has been on hormones for 10 years. She is angry and confused but not yet ready to stop taking them

THE TRUTH ABOUT HORMONES

Hormone-replacement therapy is riskier than advertised. What's a woman to do?

Meningiomas in Pregnancy: A Clinicopathologic Study of 17 Cases

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Bernd W. Scheithauer, MD‡†
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Bernhard R. Fischer, MD¶
Michael R. Chicoine, MD*
Werner Paulus, MD||
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BACKGROUND: Dramatic growth of meningiomas is occasionally encountered during pregnancy. While cell proliferation is often assumed, hemodynamic changes have also been touted as a cause.

OBJECTIVE: We identified 17 meningiomas resected during pregnancy or within 3 weeks post-partum and characterized them to determine the cause of occasional rapid growth in pregnancy.

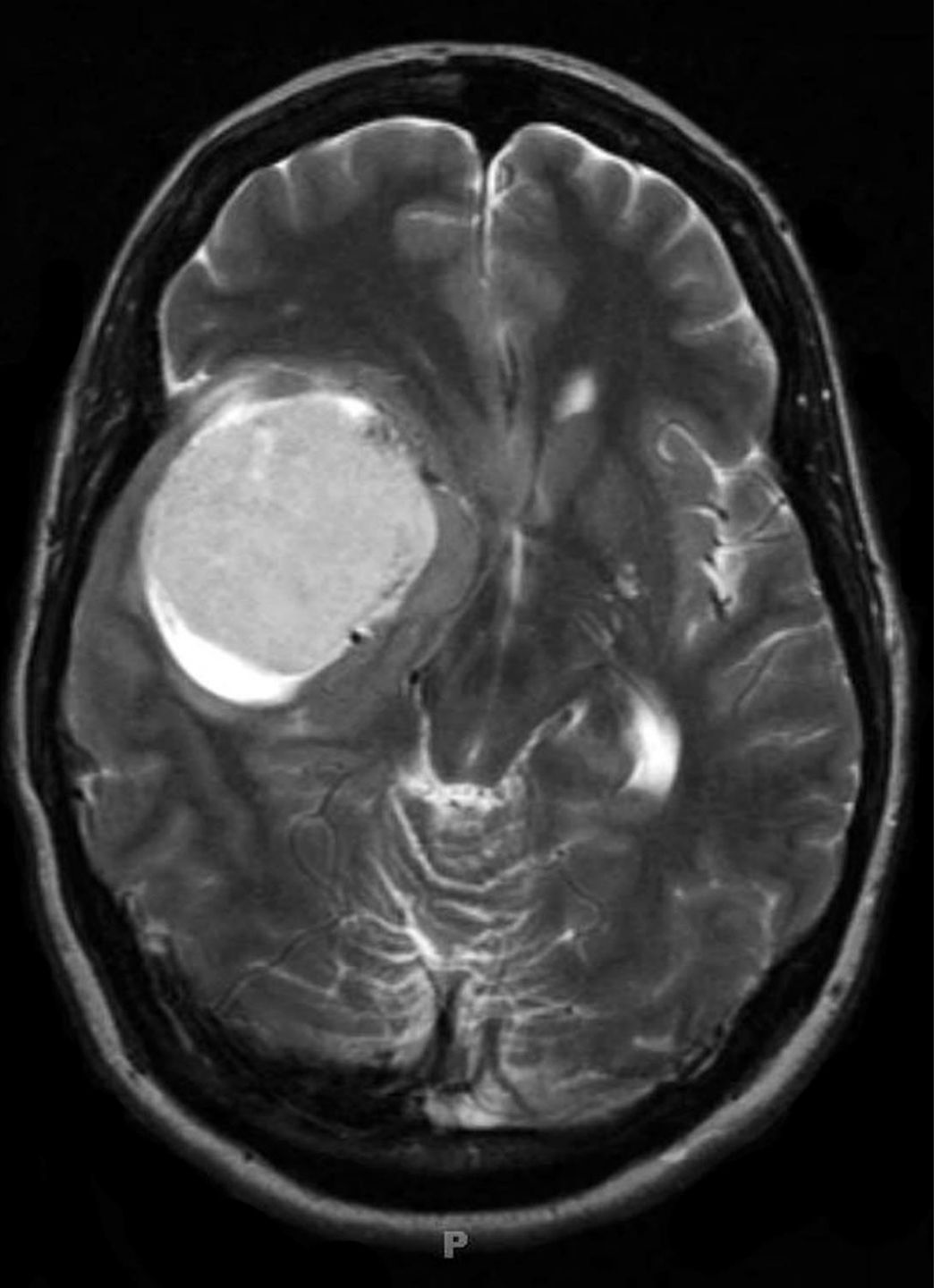
METHODS: Seventeen tumors were identified from searches at 4 university centers. All available clinical records, radiology images, and tissue specimens were reviewed, with immunohistochemical studies performed as needed.

RESULTS: Sixteen patients underwent tumor resection and 1 died of complications prior to surgery. Average patient age was 32 years. Nine experienced onset of symptoms in the third trimester or within 8 days post-partum. Principle physical findings included visual complaints (59%) and cranial nerve palsies (29%). Ten tumors (59%) were located in the skull base region. The Ki-67 labeling index was low (0.5-3.6%) in 11 of 13 benign (grade I) tumors and elevated (11-23.2%) in 3 of 4 atypical (grade II) meningiomas. Eight (50%) tumors featured hypervascularity with at least focal CD34-positive hemangioma-like microvasculature. Fourteen (82%) showed evidence of intra- and/or extracellular edema, 1 so extensive that its meningothelial nature was not apparent. Five tumors (29%) exhibited intratumoral hemorrhage and/or necrosis.

CONCLUSION: Our series suggests that pregnancy-associated meningiomas located in the skull base are likely to require surgical intervention for visual complaints and cranial nerve palsies. The rapid tumor growth is more often due to potentially reversible hemodynamic changes rather than hormone-induced cellular proliferation.

KEY WORDS: Meningioma, Pathology, Pregnancy

Neurosurgery 71:951–961, 2012 DOI: 10.1227/NEU.0b013e31826adf65 www.neurosurgery-online.com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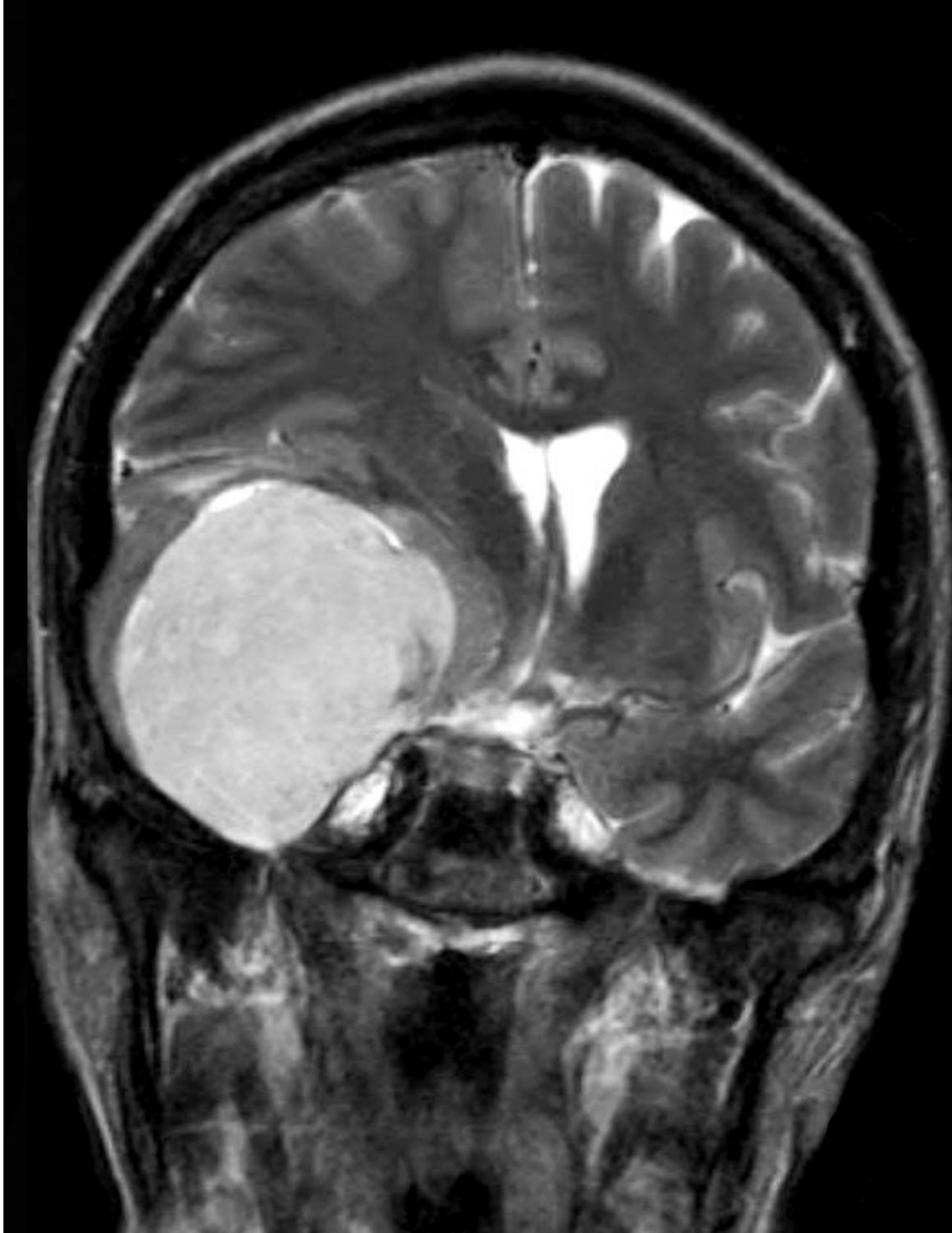
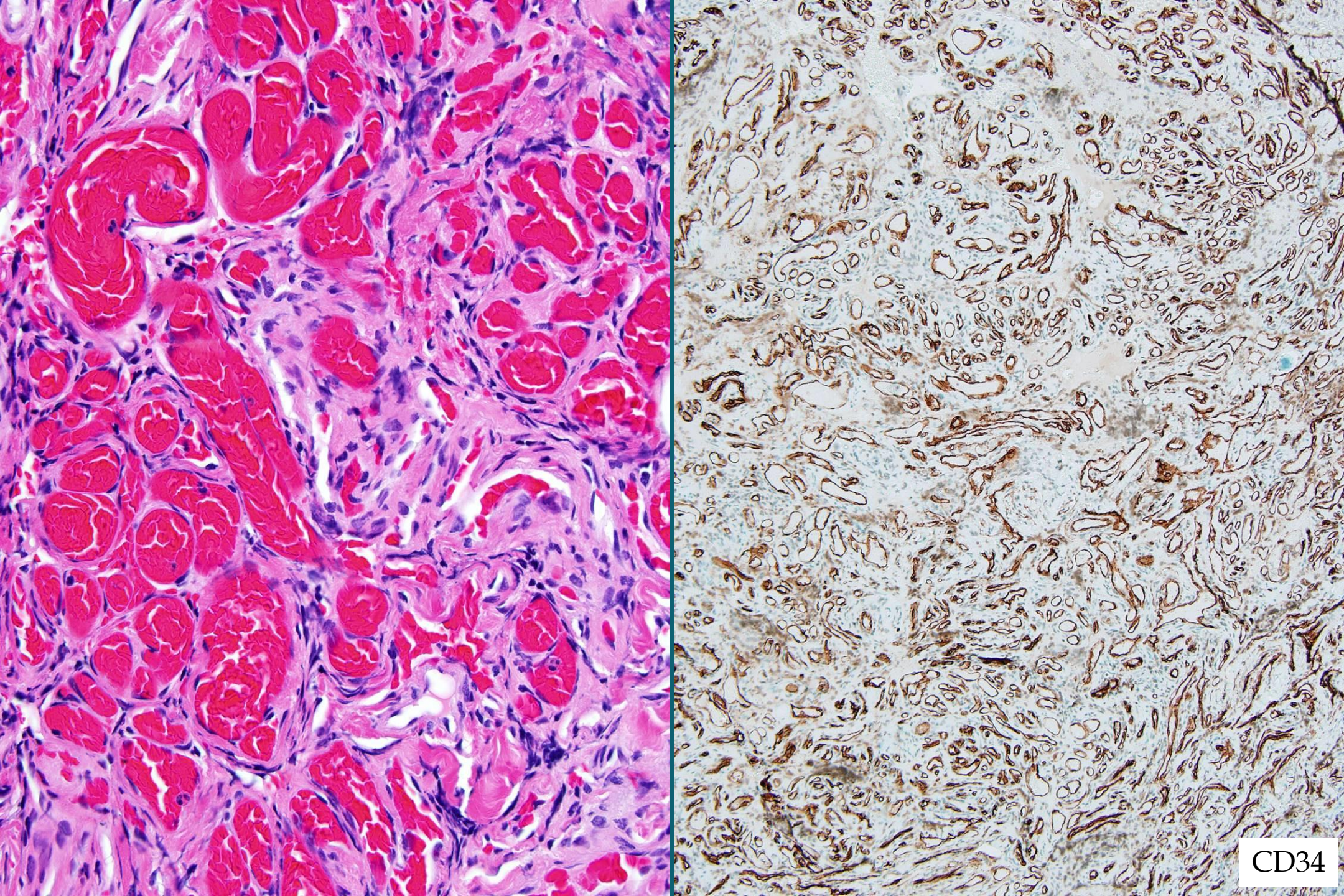
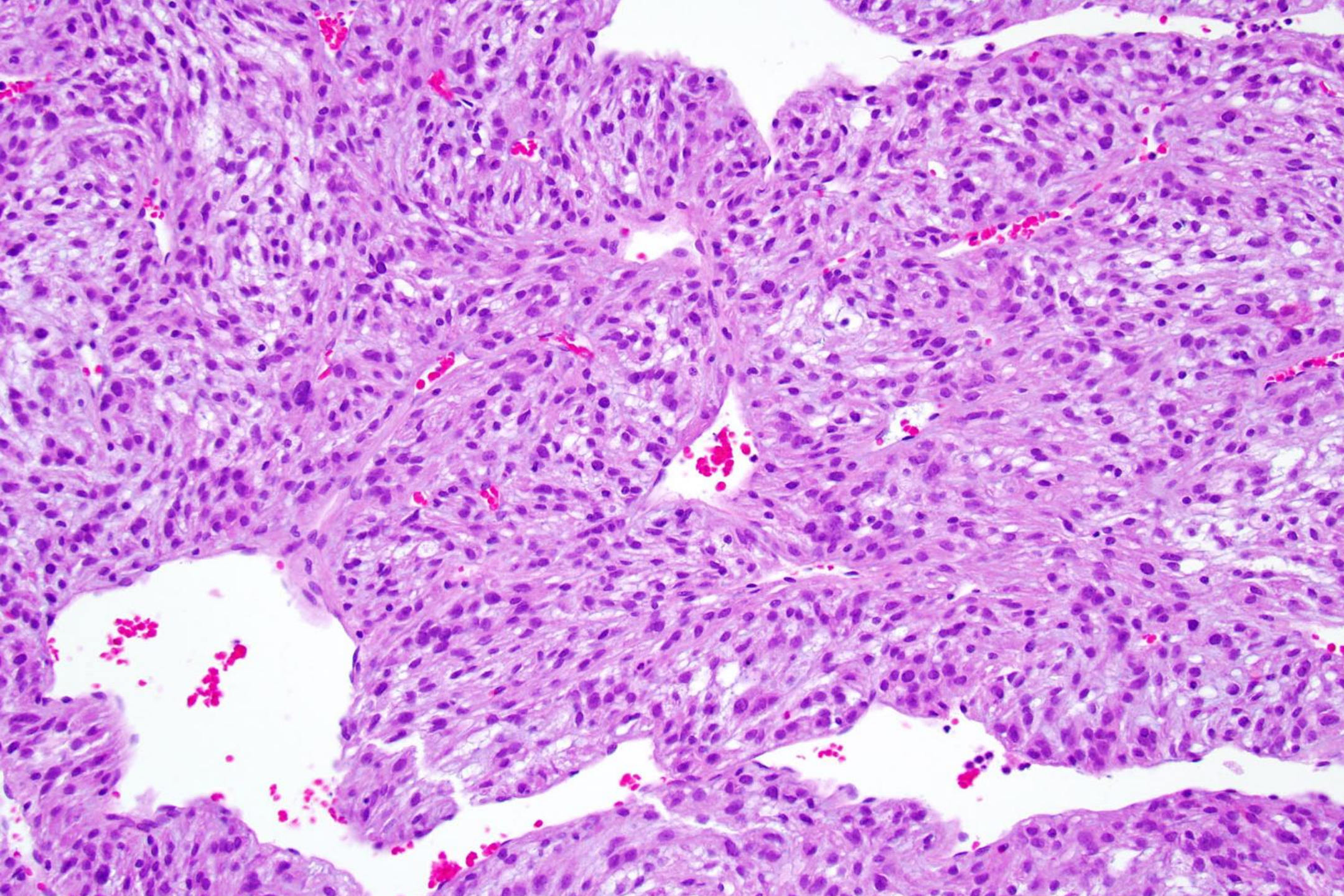
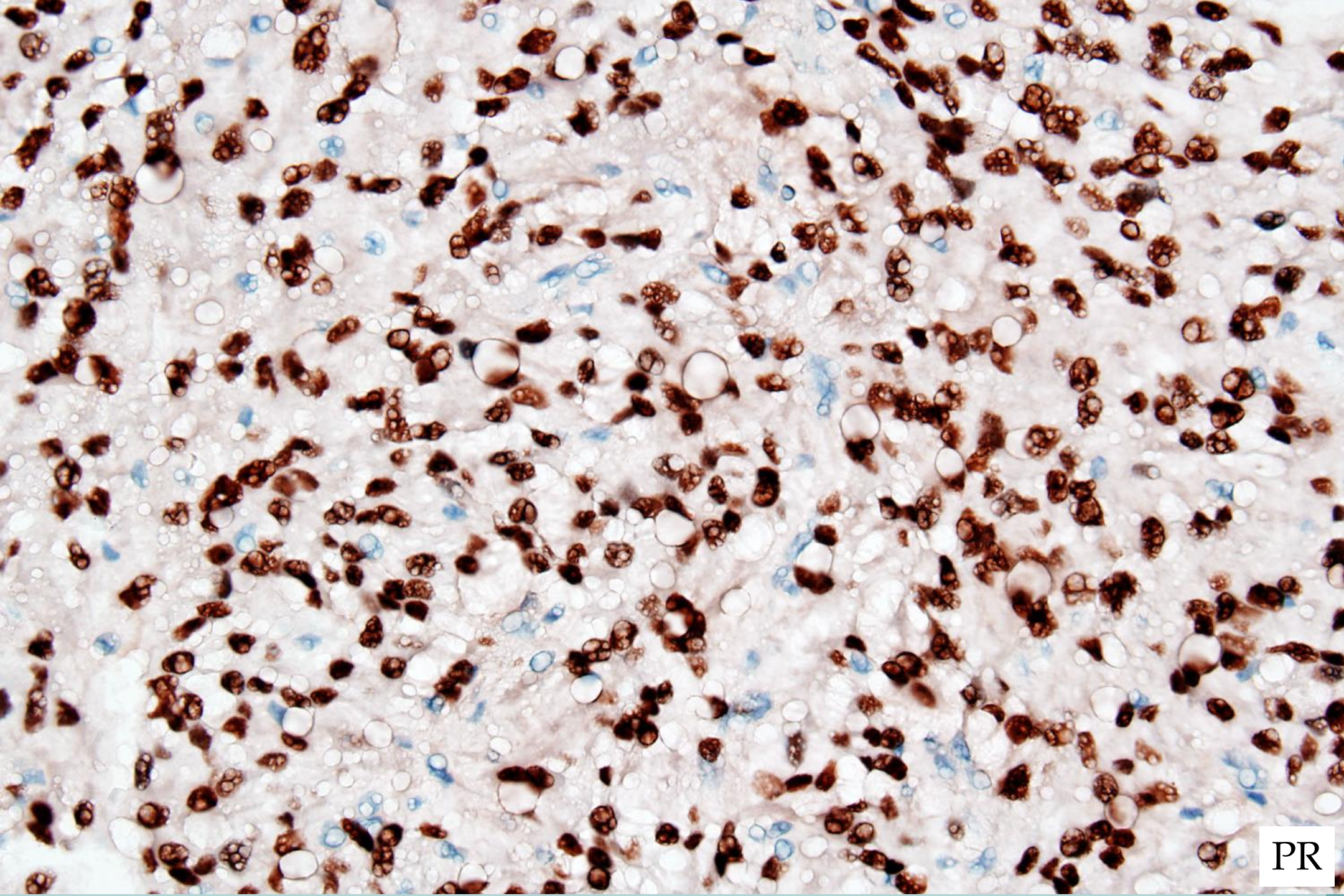



CD34




PR

UCSF University of California San Francisco

RTOG TRIAL 0539 (N=220)

	Central Review			
	Benign (n=93)	Atypical (n=96)	Anaplastic (n=29)	Kappa statistic (95% CI)
Site	(n=93)	(n=96)	(n=29)	0.69*
Benign, WHO I	85 (91.4%)	20 (20.8%)	1 (3.4%)	(0.60, 0.77)
Atypical, WHO II	8 (8.6%)	72 (75.0%)	8 (27.6%)	
Anaplastic, WHO III	0 (0.0%)	4 (4.2%)	20 (69.0%)	

*p-value < 0.0001

	Central Review		Kappa statistic
	No	Yes	(95% CI)
Site Review			
Benign, WHO I	(n=125)	(n=93)	0.73*
No	104 (47.7%)	8 (3.7%)	(0.64, 0.82)
Yes	21 (9.6%)	85 (39.0%)	
Atypical, WHO II	(n=122)	(n=96)	0.62*
No	106 (48.6%)	24 (11.0%)	(0.52, 0.73)
Yes	16 (7.3%)	72 (33.0%)	
Anaplastic, WHO III	(n=189)	(n=29)	0.72*
No	185 (84.9%)	9 (4.1%)	(0.58, 0.86)
Yes	4 (1.8%)	20 (9.2%)	

	Concordance Rate	Discordance Rate
>=4 mitoses/10 HPF	79.1%	20.9%
>=20 mitoses/10 HPF	95.3%	4.7%
Brain invasion	92.4%	7.6%
Sheeting	74.4%	25.6%
Small cells	79.1%	20.9%
Macronucleoli	76.7%	23.3%
Hypercellularity	73.3%	26.7%
Spontaneous Necrosis	85.5%	14.5%
Anaplasia	93.6%	6.4%

	Central Review		Kappa statistic
	No	Yes	(95% CI)
Site Review			
>=4 mitoses/10 HPF	(n=133)	(n=85)	0.48*
No	127 (95.5%)	44 (51.8%)	(0.36, 0.59)
Yes	6 (4.5%)	41 (48.2%)	
>=20 mitoses/10 HPF	(n=200)	(n=18)	0.70*
No	200 (100.0%)	8 (44.4%)	(0.50, 0.89)
Yes	0 (0.0%)	10 (55.6%)	
Brain Invasion	(n=172)	(n=46)	0.71*
No	168 (97.7%)	15 (32.6%)	(0.59, 0.83)
Yes	4 (2.3%)	31 (67.4%)	
Sheeting	(n=127)	(n=91)	0.44*
No	115 (90.6%)	44 (48.4%)	(0.33, 0.56)
Yes	12 (9.4%)	47 (51.6%)	
Small Cells	(n=155)	(n=63)	0.42*
No	147 (94.8%)	37 (58.7%)	(0.28, 0.55)
Yes	8 (5.2%)	26 (41.3%)	
Macronucleoli	(n=125)	(n=93)	0.51*
No	117 (93.6%)	42 (45.2%)	(0.40, 0.62)
Yes	8 (6.4%)	51 (54.8%)	
Hypercellularity	(n=108)	(n=110)	0.44*
No	102 (94.4%)	55 (50.0%)	(0.34, 0.55)
Yes	6 (5.6%)	55 (50.0%)	
Spontaneous Necrosis	(n=137)	(n=81)	0.68*
No	130 (94.9%)	24 (29.6%)	(0.55, 0.78)
Yes	7 (5.1%)	57 (70.4%)	
Anaplasia	(n=199)	(n=19)	0.55*
No	196 (98.5%)	10 (52.6%)	(0.33, 0.77)
Yes	3 (1.5%)	9 (47.4%)	

*p-value < 0.0001

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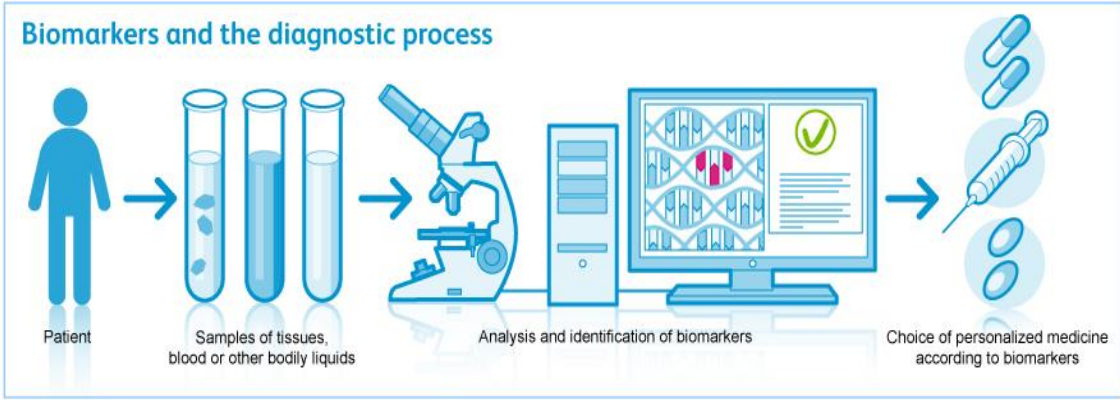
ANCILLARY BIOMARKERS

- **Types**
  - Diagnostic
  - Prognostic
  - Predictive
  - (Elucidate Biology)



- **Practicality and regulatory issues**
  - Cost and ease of implementation
  - IHC vs. FISH vs. PCR vs. genomics
  - Reimbursement and regulatory guidelines

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WHO 2007 GENETIC MODEL

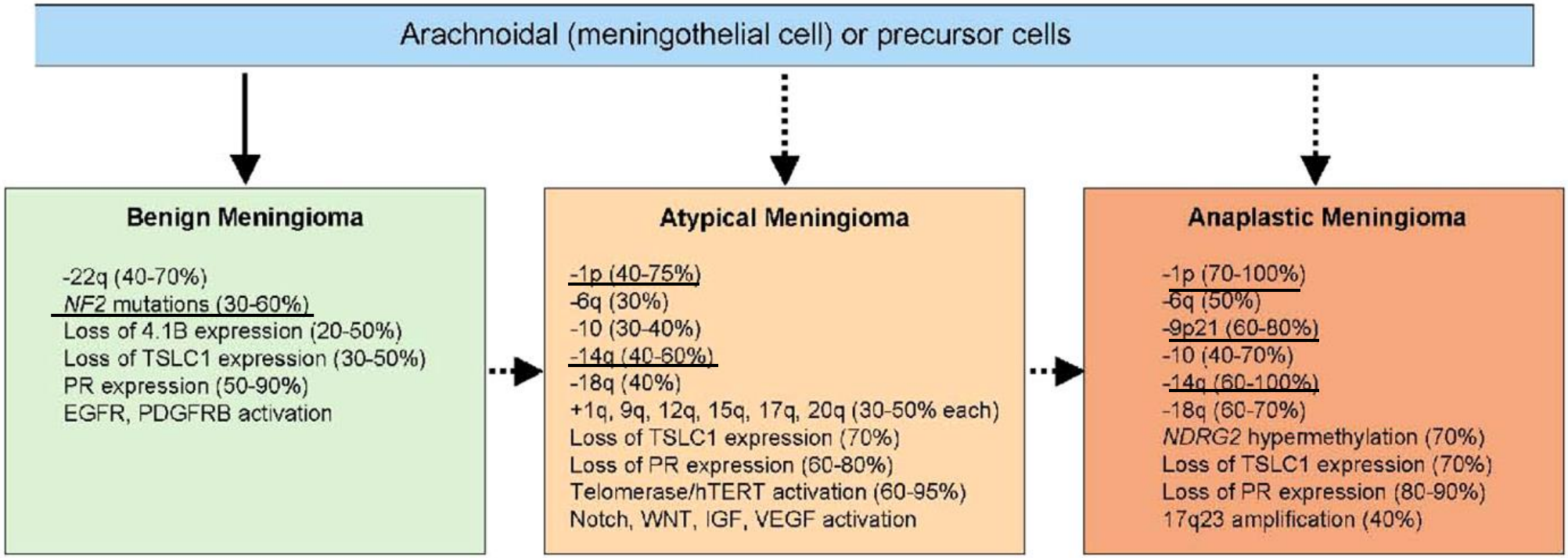
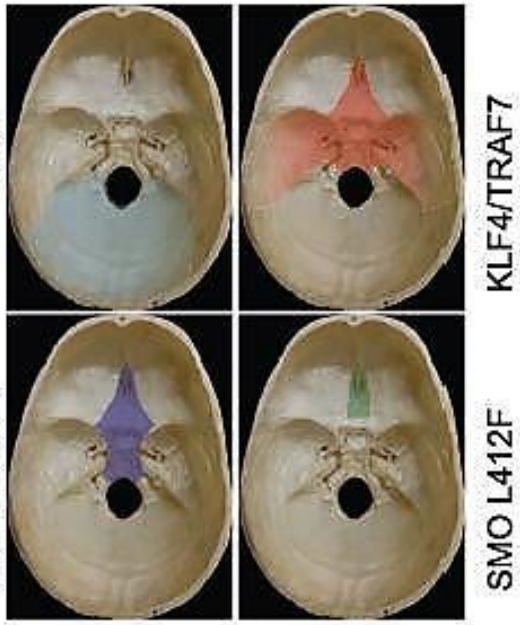


Fig. 10.14 Genetic model of meningioma tumorigenesis and malignant progression.

Genomic Analysis of Non-*NF2* Meningiomas Reveals Mutations in *TRAF7*, *KLF4*, *AKT1*, and *SMO*

Victoria E. Clark,[1] E. Zeynep Erson-Omay,[1] Akdes Serin,[1] Jun Yin,[2] Justin Cotney,[2] Koray Özduman,[3] Timuçin Avşar,[4] Jie Li,[5] Phillip B. Murray,[1] Octavian Henegariu,[1] Saliha Yilmaz,[1] Jennifer Moliterno Günel,[6] Geneive Carrión-Grant,[1] Baran Yılmaz,[7] Conor Grady,[1] Bahattin Tanrıkulu,[7] Mehmet Bakırcıoğlu,[1] Hande Kaymakçalan,[8] Ahmet Okay Caglayan,[1] Leman Sencar,[1] Emre Ceyhun,[1] A. Fatih Atik,[7] Yaşar Bayri,[7] Hanwen Bai,[1] Luis E. Kolb,[1] Ryan M. Hebert,[1] S. Bulent Omay,[1] Ketu Mishra-Gorur,[1] Murim Choi,[2] John D. Overton,[9] Eric C. Holland,[10] Shrikant Mane,[2,9] Matthew W. State,[11] Kaya Bilgüvar,[1] Joachim M. Baehring,[12] Philip H. Gutin,[6] Joseph M. Piepmeier,[13] Alexander Vortmeyer,[5] Cameron W. Brennan,[14] M. Necmettin Pamir,[3] Türker Kılıç,[15] Richard P. Lifton,[2,16] James P. Noonan,[2,17] Katsuhito Yasuno,[1] Murat Günel[1,18]*

We report genomic analysis of 300 meningiomas, the m
discovery of mutations in *TRAF7*, a proapoptotic E3 ubi
meningiomas. Mutations in *TRAF7* commonly occurred
transcription factor known for its role in inducing pluri
activate the PI3K pathway. *SMO* mutations, which activat
non-*NF2* mutant meningiomas. These non-*NF2* mening
benign, with chromosomal stability, and originating fro
with mutant *NF2* and/or chromosome 22 loss were more
and localizing to the cerebral and cerebellar hemispher
meningioma subtypes, suggesting avenues for targeted



Meningiomas, arising from the meninges of the central nervous system, are the most common primary brain tumors,

Tumor	Grade	Chr22 loss	NF2	TRAF7	AKT1	KLF4	SMO
MN-95	1	Yes					
MN-290	1	Yes					
MN-1041	1	Yes					
MN-1047	1	Yes					
MN-1137	1	Yes					
MN-47	1	Yes	p.Q453X				
MN-52	1	Yes	p.F256fs				
MN-71	1	Yes	p.T59fs				
MN-81	1	Yes	p.Q65fs				
MN-169	1	Yes	p.E460X				
MN-288	1	Yes	p.K17_M29del				
MN-291	1	Yes	p.I210fs				
MN-293	1	Yes	p.Q459X				
MN-294	1	Yes	c.363+1G>C				
MN-297	1	Yes	p.K99fs				
MN-301	1	Yes	p.W41fs				
MN-306	1	Yes	p.K44X				
MN-1091	1	Yes	p.L14fs				
MN-1133	1	Yes	p.Y207fs				
MN-26	1			p.C388Y	p.E17K		
MN-105	1			p.R641C	p.E17K		
MN-292	1			p.Q637H	p.E17K		
MN-191	1			p.K615E		p.K409Q	
MN-201	1			p.L580del		p.K409Q	
MN-249	1			p.R641C		p.K409Q	
MN-1025	1			p.G536S		p.K409Q	
MN-1066	1			p.N520S		p.K409Q	
MN-303	1			p.S561N			
MN-206	1			p.G390E			
MN-304	1			p.R653Q			
MN-305	1			p.G536S			
MN-1053	1			p.E353insFRRDAS			
MN-1045	1						p.L412F
MN-1132	1						p.W535L
MN-164	2	Yes					
MN-22	2	Yes	c.115-1G>A				
MN-54	2	Yes	p.Q319X				
MN-96	2	Yes	p.L14fs				
MN-97	2	Yes	p.M426fs				
MN-171	2	Yes	p.L208P				
MN-295	2	Yes	p.E103fs				
MN-298	2	Yes	p.V24fs				
MN-1054	2	Yes	p.R262X				
MN-16	2	Yes		p.T145M	p.E17K		
MN-1144	2	Yes		p.F337S			

Acta Neuropathol (2013) 125:351–358
DOI 10.1007/s00401-013-1093-x

ORIGINAL PAPER

Secretory meningiomas are defined by combined *KLF4* K409Q and *TRAF7* mutations

David E. Reuss · Rosario M. Piro · David T. W. Jones · Matthias Simon · Ralf Ketter · Marcel Kool · Albert Becker · Felix Sahm · Stefan Pusch · Jochen Meyer · Christian Hagenlocher · Leonille Schweizer · David Capper · Phillipp Kickingereder · Jana Mucha · Christian Koelsche · Natalie Jäger · Thomas Santarius · Patrick S. Tarpey · Philip J. Stephens · P. Andrew Futreal · Ruth Wellenreuther · Jürgen Kraus · Doris Lenartz · Christel Herold-Mende · Christian Hartmann · Christian Mawrin · Nathalia Giese · Roland Eils · V. Peter Collins · Rainer König · Otmar D. Wiestler · Stefan M. Pfister · Andreas von Deimling

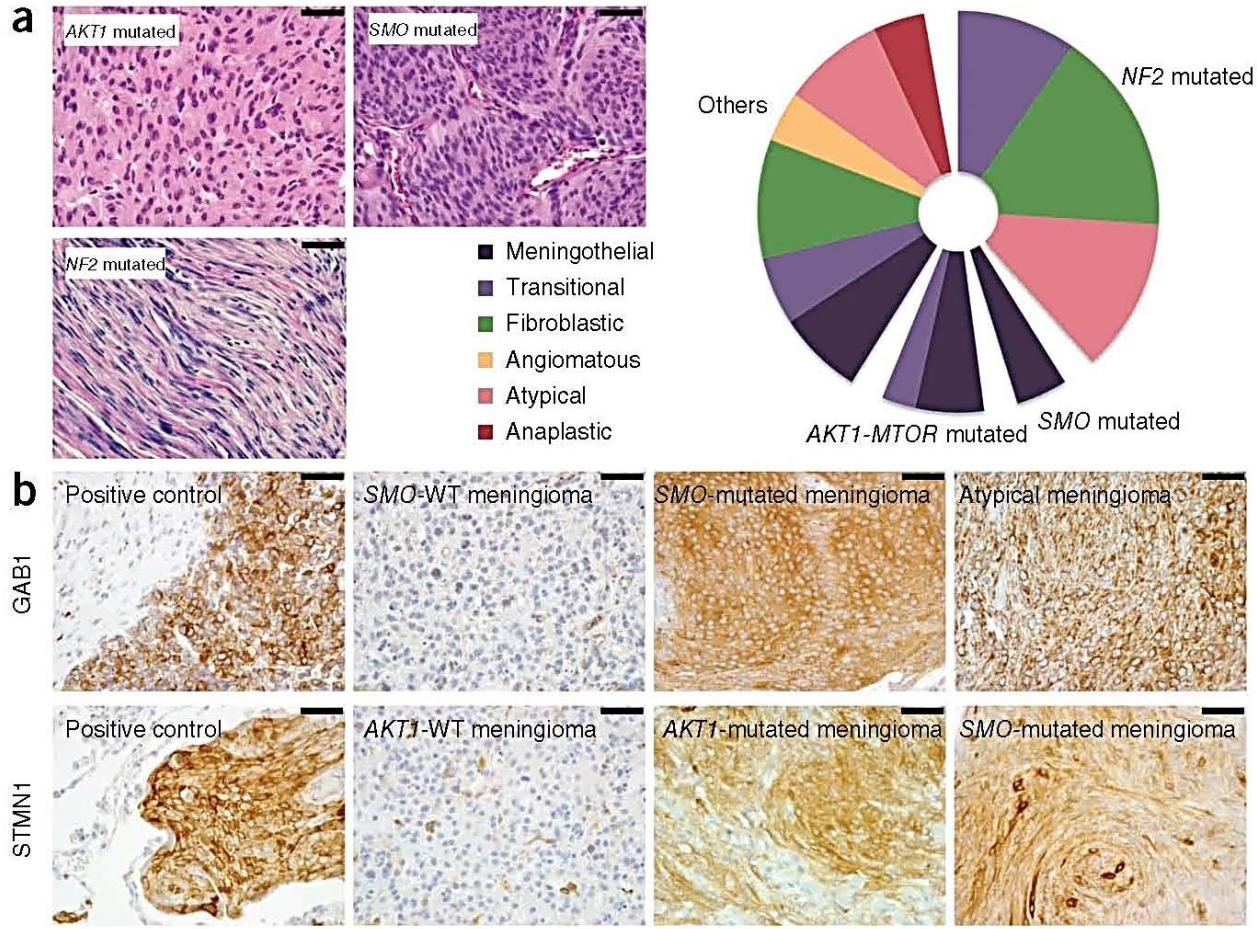
Received: 28 January 2013 / Revised: 28 January 2013 / Accepted: 28 January 2013 / Published online: 12 February 2013

Abstract Meningiomas are among the most frequent intracranial tumors. The secretory variant of meningioma is characterized by glandular differentiation, formation of intracellular lumina and pseudopsammoma bodies, expression of a distinct pattern of cytokeratins and clinically by pronounced perifocal brain edema. Here we describe whole-exome sequencing analysis of DNA from 16 secretory meningiomas and corresponding constitutional tissues. All secretory meningiomas invariably harbored a mutation in both *KLF4* and *TRAF7*. Validation in an independent cohort of 14 secretory meningiomas by Sanger sequencing or derived cleaved amplified polymorphic sequence (dCAPS) assay detected the same pattern, with *KLF4* mutations observed in a total of 30/30 and *TRAF7* mutations in 29/30 of these tumors. All *KLF4* mutations were identical, affected codon 409 and resulted in a lysine to glutamine exchange (K409Q). *KLF4* mutations were not found in 89 non-secretory meningiomas, 267 other intracranial tumors including gliomas, glioneuronal tumors, pituitary adenomas and metastases, 59 peripheral nerve sheath tumors and 52 pancreatic tumors. *TRAF7* mutations were restricted to the WD40 domains. While *KLF4*

Genomic sequencing of meningiomas identifies oncogenic *SMO* and *AKT1* mutations

Nat Genet 45(3): 285, 2013

Priscilla K Brastianos[1–4,11], Peleg M Horowitz[3–6,11], Sandro Santagata[3,7], Robert T Jones[1,8], Aaron McKenna[4], Gad Getz[4], Keith L Ligon[3,7], Emanuele Palescandolo[8], Paul Van Hummelen[1,8], Matthew D Ducar[1,8], Alina Raza[1,8], Ashwini Sunkavalli[1,8], Laura E MacConaill[1,8], Anat O Stemmer-Rachamimov[3,9], David N Louis[3,9,10], William C Hahn[1,3,4,8], Ian F Dunn[3,4,6] & Rameen Beroukhim[1,3–5,8]



Loss-of-function mutations in *SMARCE1* cause an inherited disorder of multiple spinal meningiomas

Miriam J Smith[1], James O'Sullivan[1], Sanjeev S Bhaskar[1], Kristen D Hadfield[1], Gemma Poke[2], John Caird[3], Saba Sharif[4], Diana Eccles[5], David Fitzpatrick[6], Daniel Rawluk[3], Daniel du Plessis[7,8], William G Newman[1,9] & D Gareth Evans[1,9]

Nat Genet 45(3): 295, 2013

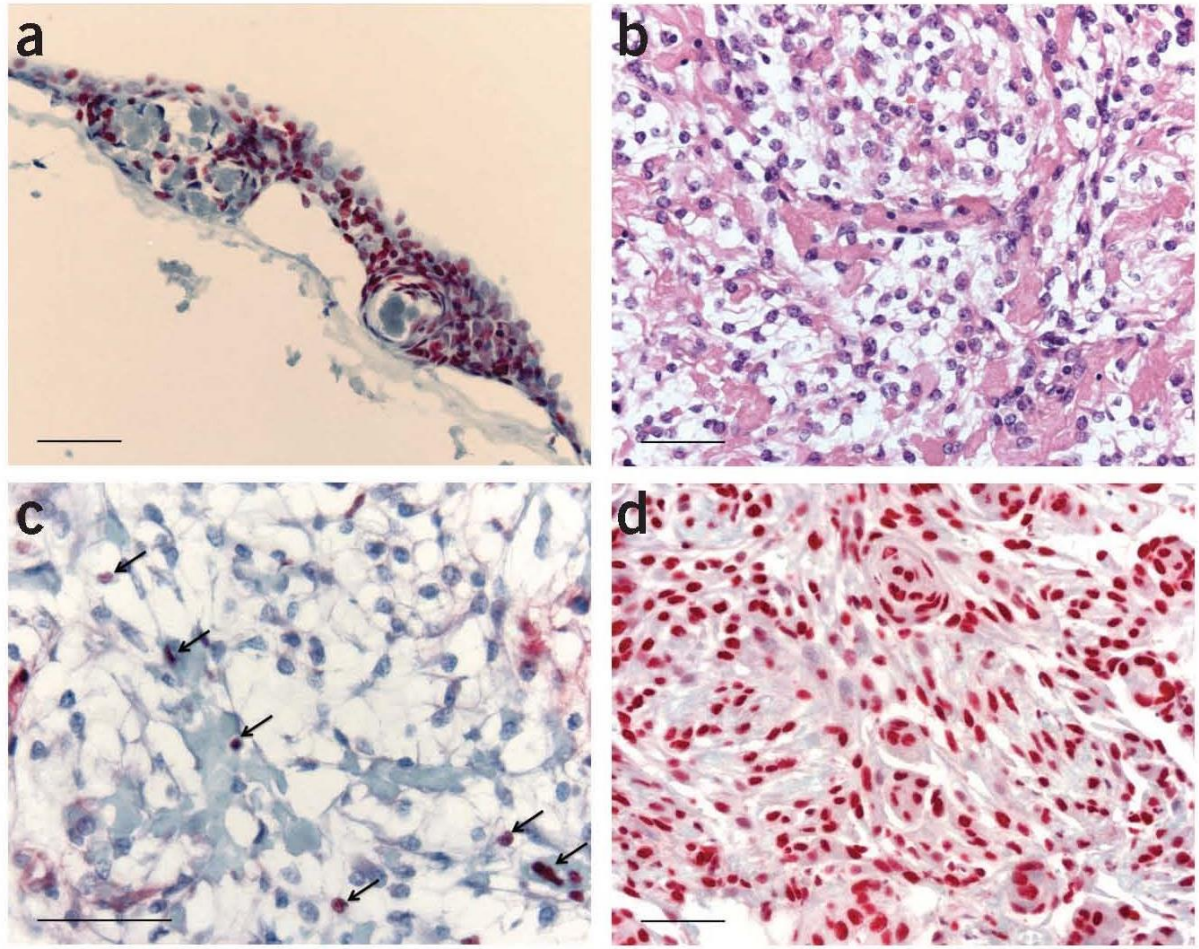
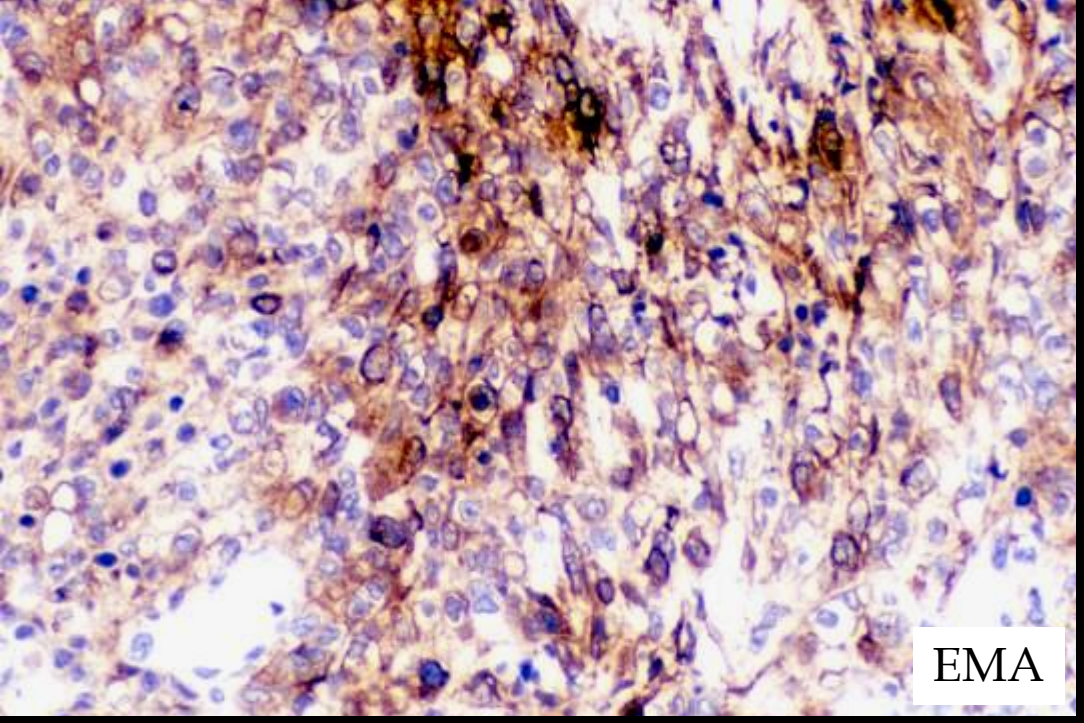
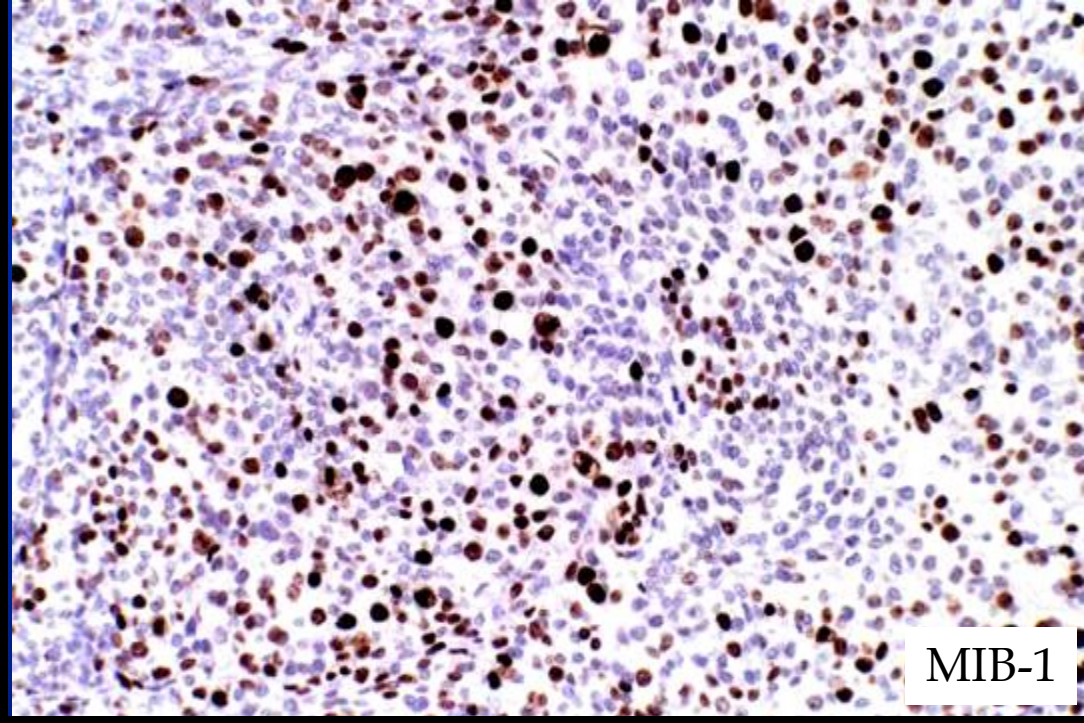
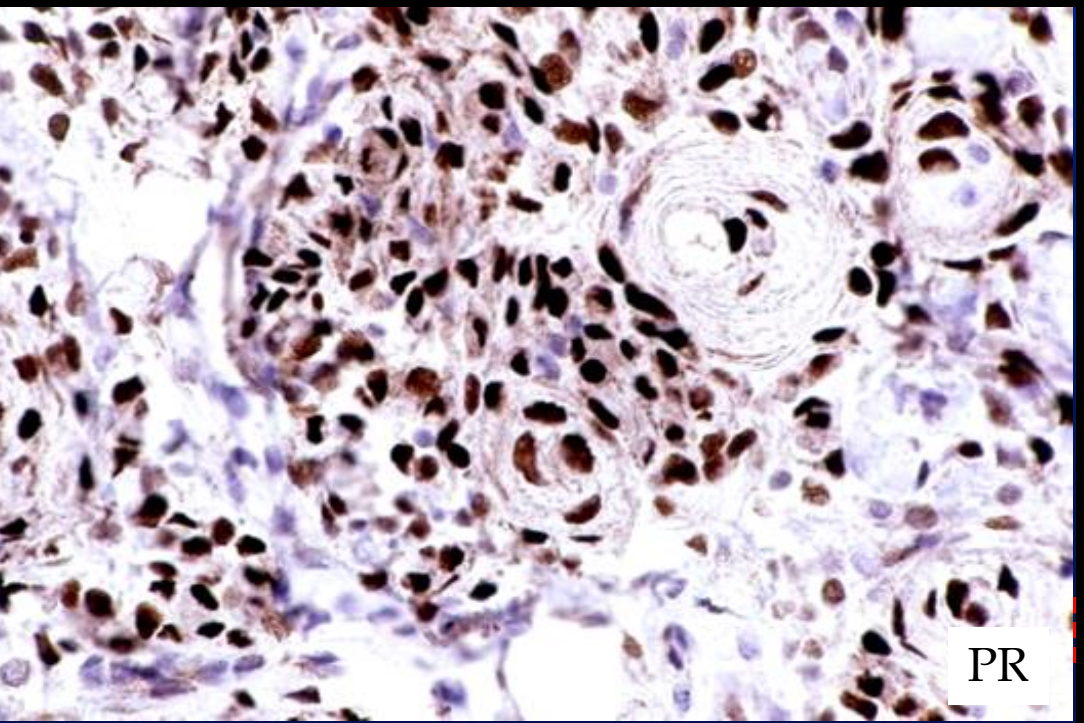
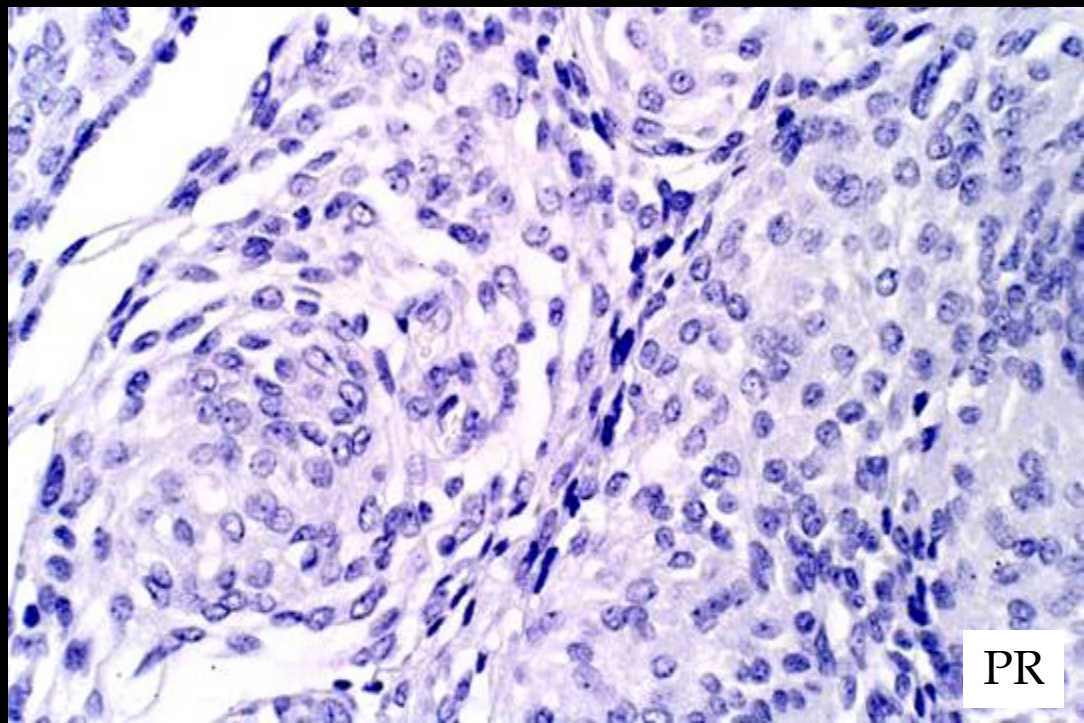


Figure 2 SMARCE1 immunohistochemistry. (**a**) Normal leptomeningeal


EMA


MIB-1


PR


PR

[1801] Reliability of Somatostatin Receptor 2a as a Marker of Meningioma: An Immunohistochemical Study

Joshua R Menke, Allen M Gown, Sean Thomas, Arie Perry, Tarik Tihan. UCSF, San Francisco, CA; PhenoPath, Seattle, WA

Background: Meningioma is the most common extraaxial primary CNS tumor. While most meningiomas are easily diagnosed on routine stains, immunohistochemistry may become necessary for diagnosis in some tumors. However, a robust immunohistochemical marker has been elusive. Currently the most reliable meningioma markers are epithelial membrane antigen (EMA) and progesterone receptor (PR). Recent studies suggest somatostatin receptor 2a (SSTR2a) may also be a good meningioma marker.

Design: We identified cases of meningioma with an unequivocal diagnosis and WHO grade at our institution between 2002 and 2012. Small biopsy material and decalcified or frozen tissues were excluded. Slides were reviewed for diagnosis and selection of the appropriate block for microarray generation. Two 2 mm cores were taken from each block to generate microarrays along with control tissue from normal meninges, normal brain, lung adenocarcinoma and placenta. Immunohistochemical stains for SSTR2a, EMA and PR were performed following optimization of pretreatment and primary antibody dilutions. Each tissue core was assigned a score (0 to 3+) indicating signal intensity. The Mann Whitney Wilcoxon test was used determine whether each marker showed significantly different score distributions between normal meninges and meningiomas.

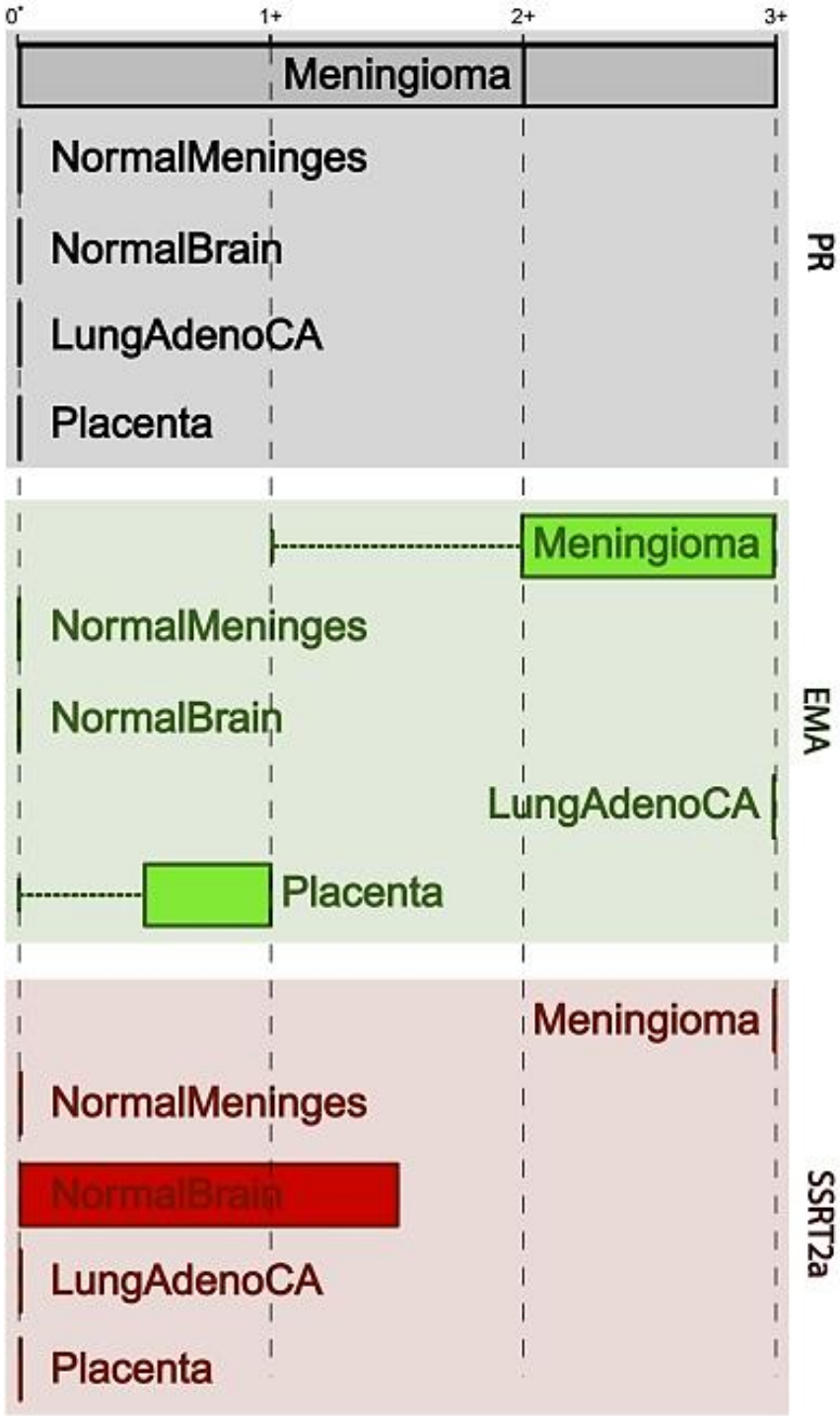
Results: 176 cases were included in the study. SSTR2a was positive in all 176 cases, EMA was positive in 168 cases and PR was positive in 171 cases. The differences in staining among normal meninges, meningioma and lung adenocarcinoma were analyzed. SSRT2a was most striking in its ability to stain positively for meningiomas as opposed to controls ($p < 6.3$ e-7), followed by EMA ($p < 4.8$ e-6) and PR ($p < 0.01$). The interquartile ranges of different factors' scores (Figure 1) showed that SSTR2a is the most reliable marker for meningiomas and that normal meninges were essentially negative for this marker.

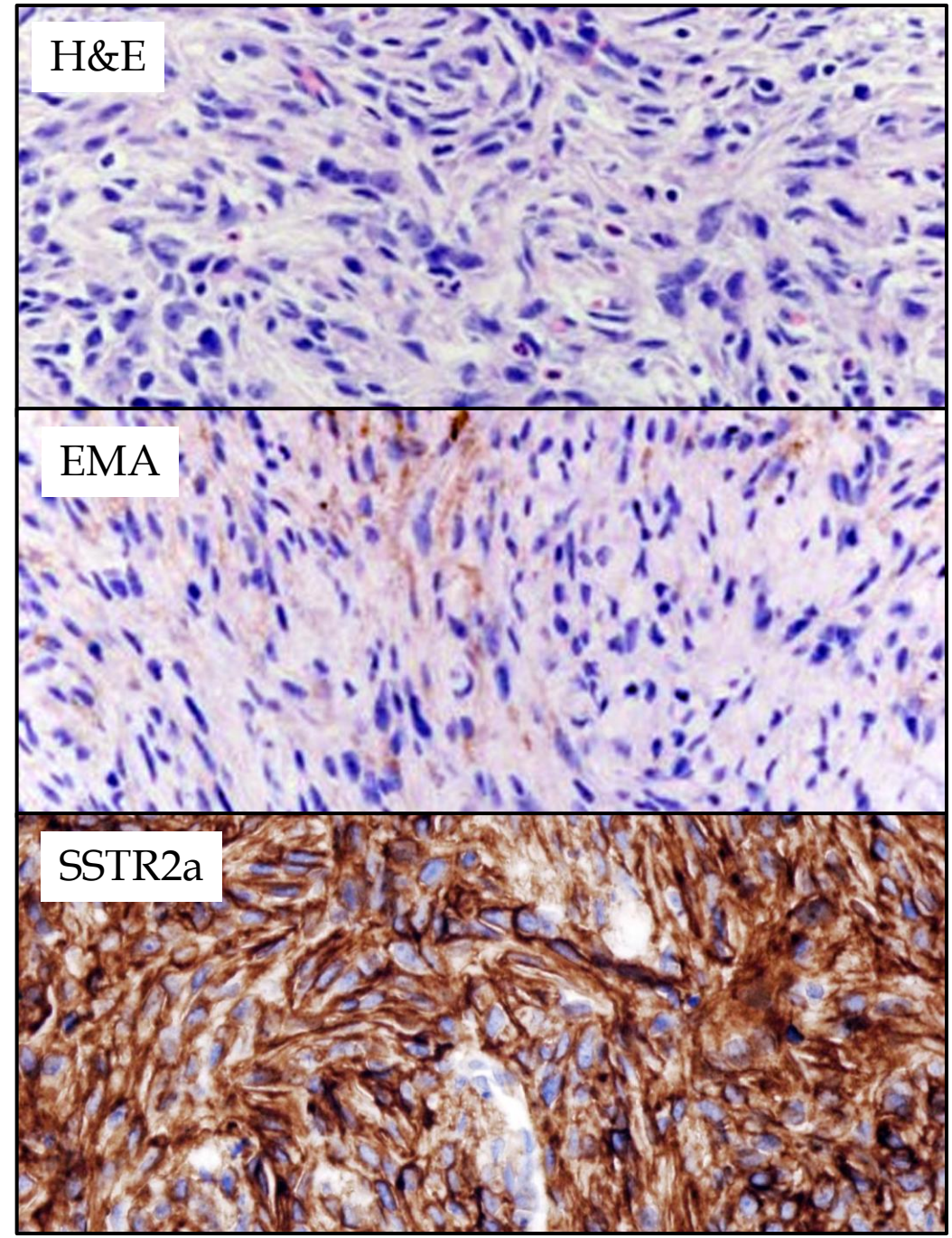
SSTR2a was positive in 5 cases, in which both EMA and PR failed to stain tumor.

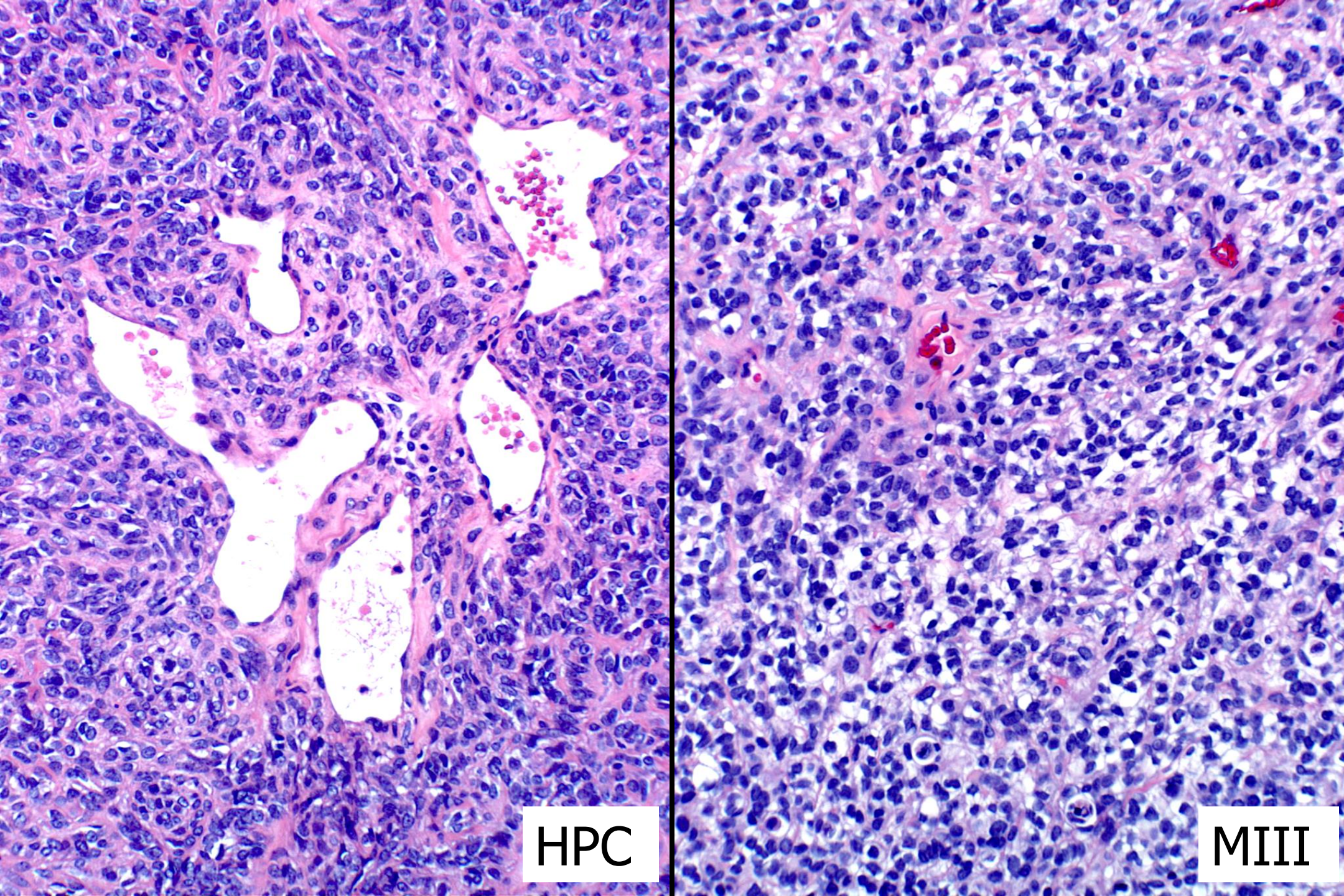
Conclusions: SSTR2a appeared to be a robust marker for meningiomas and even stained some meningiomas that classical markers did not. Studies are underway to determine SSTR2a staining in schwannomas, solitary fibrous tumors and other mesenchymal neoplasms to further characterize the specificity of this marker.

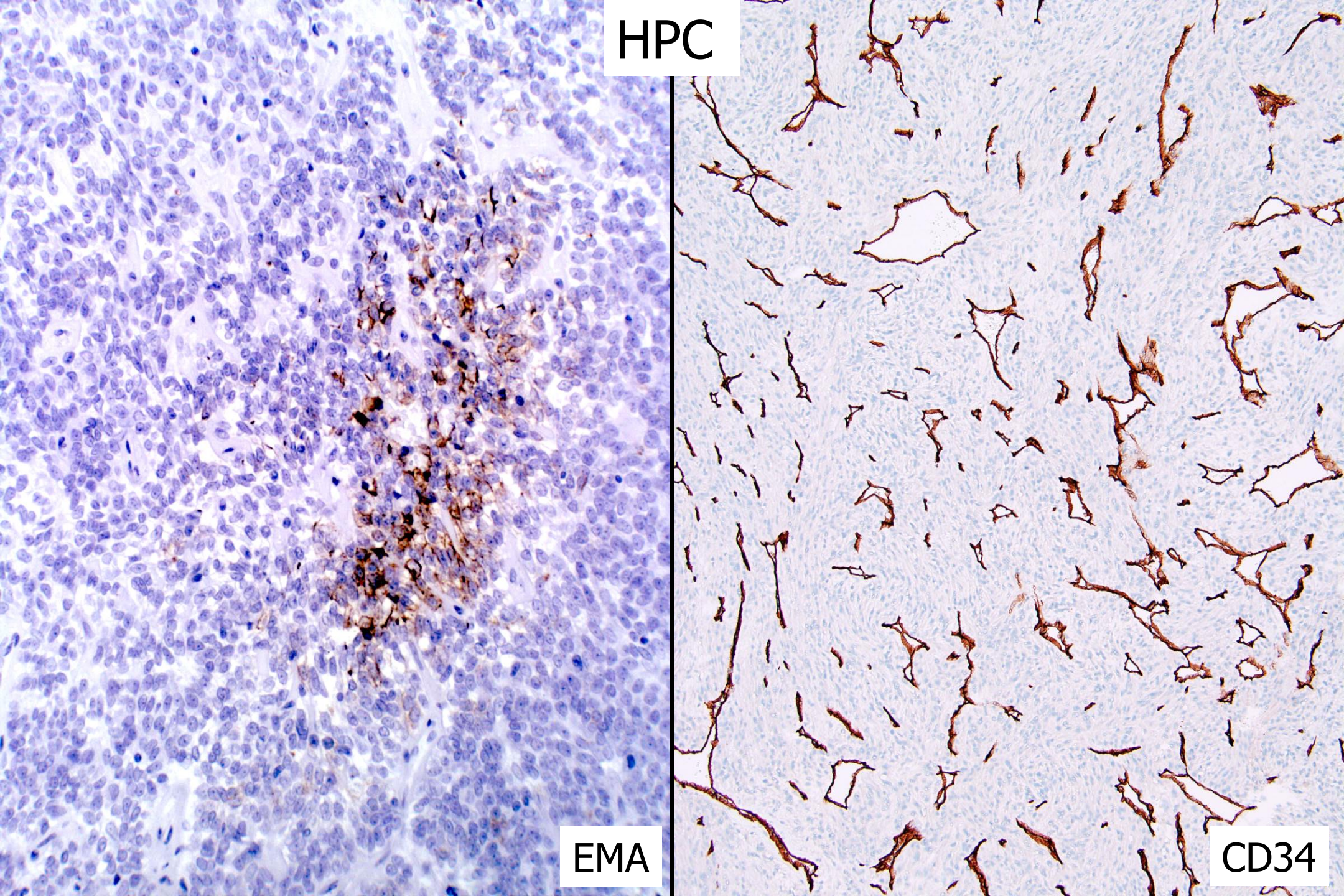
Category: Neuropathology

USCAP Meeting 2014:
Mod Pathol 27;Supp 2, 439A, 2014


0+
1+
2+
3+
Meningioma
NormalMeninges
NormalBrain
LungAdenoCA
Placenta
PR
Meningioma
NormalMeninges
NormalBrain
LungAdenoCA
Placenta
EMA
Meningioma
NormalMeninges
NormalBrain
LungAdenoCA
Placenta
SSRT2a

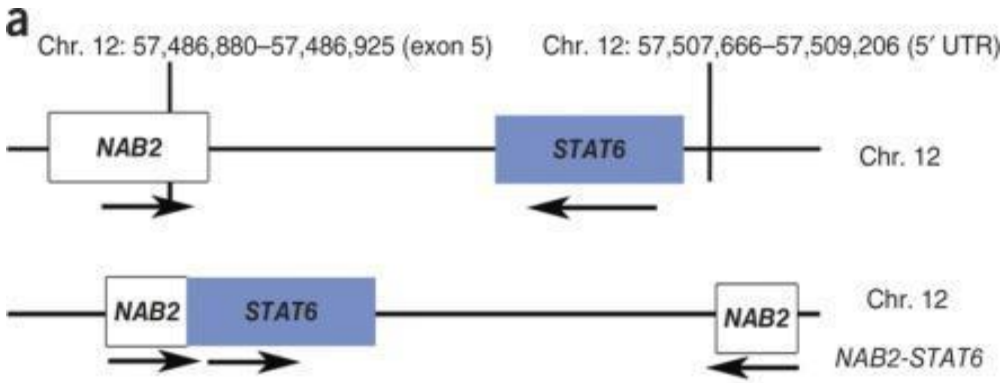

H&E
EMA
SSTR2a

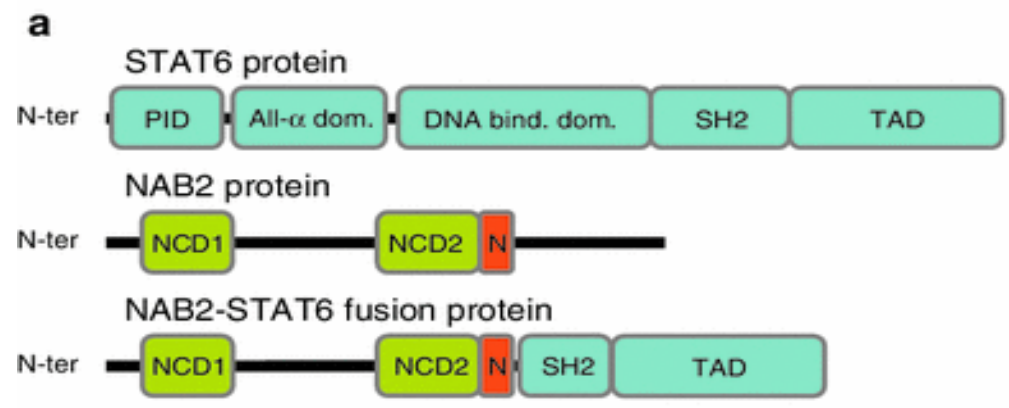

HPC
MIII

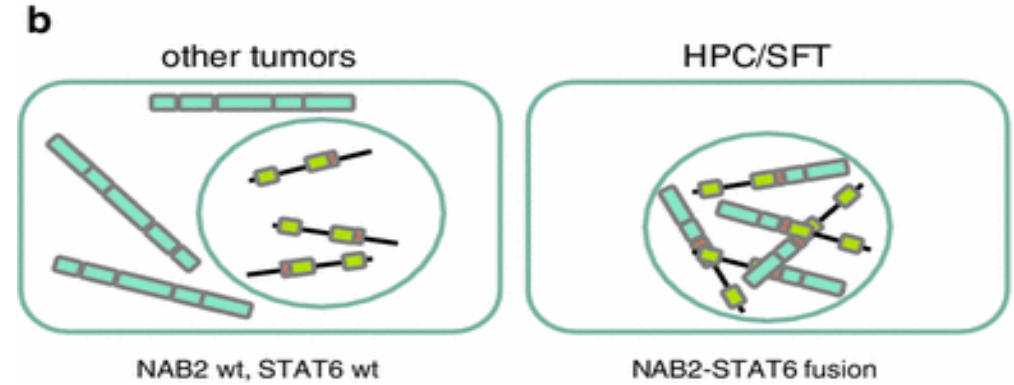

HPC
EMA
CD34

Genetics

- Translocations and inversions of Chr 12q13
- *NAB2-STAT6* fusion





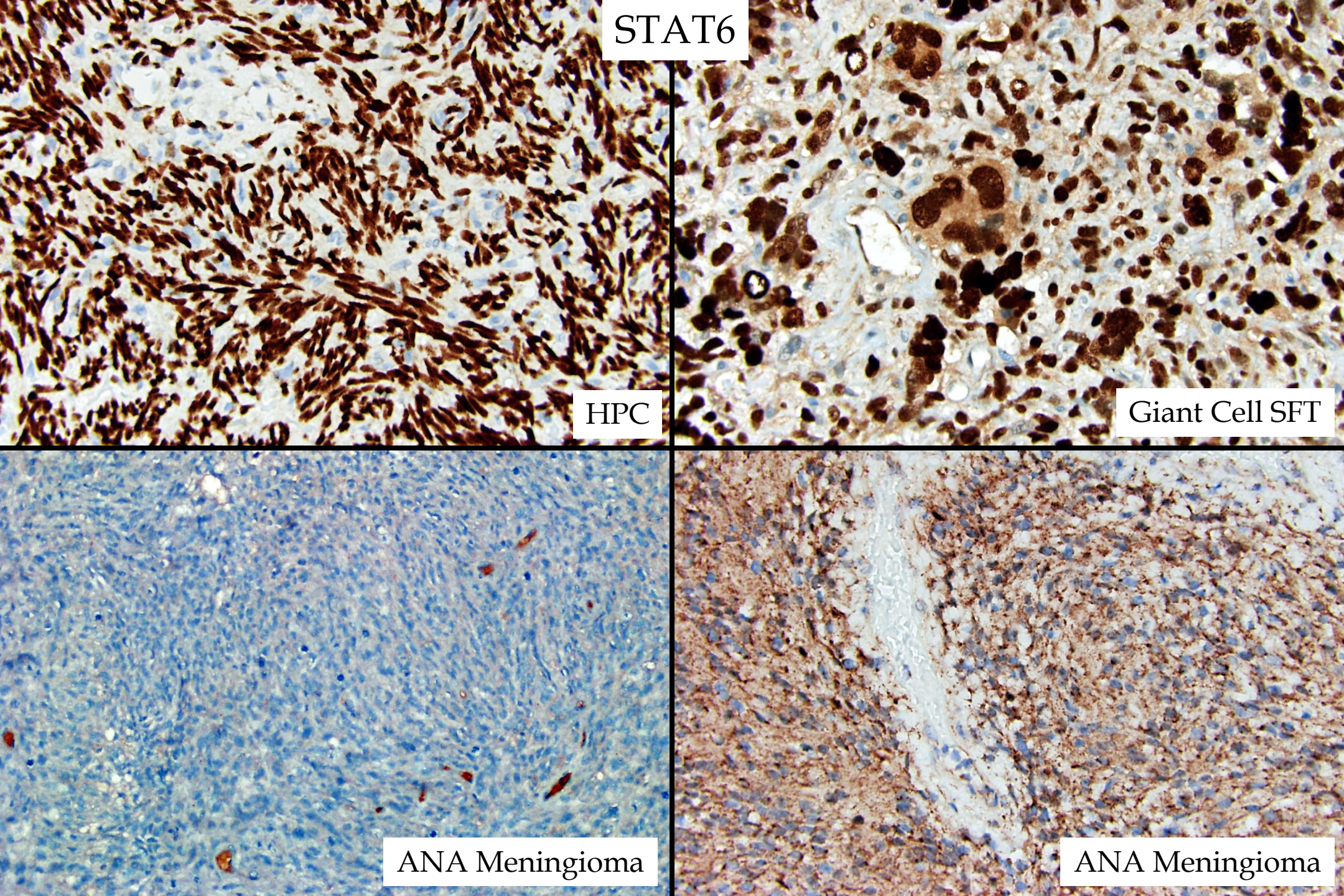


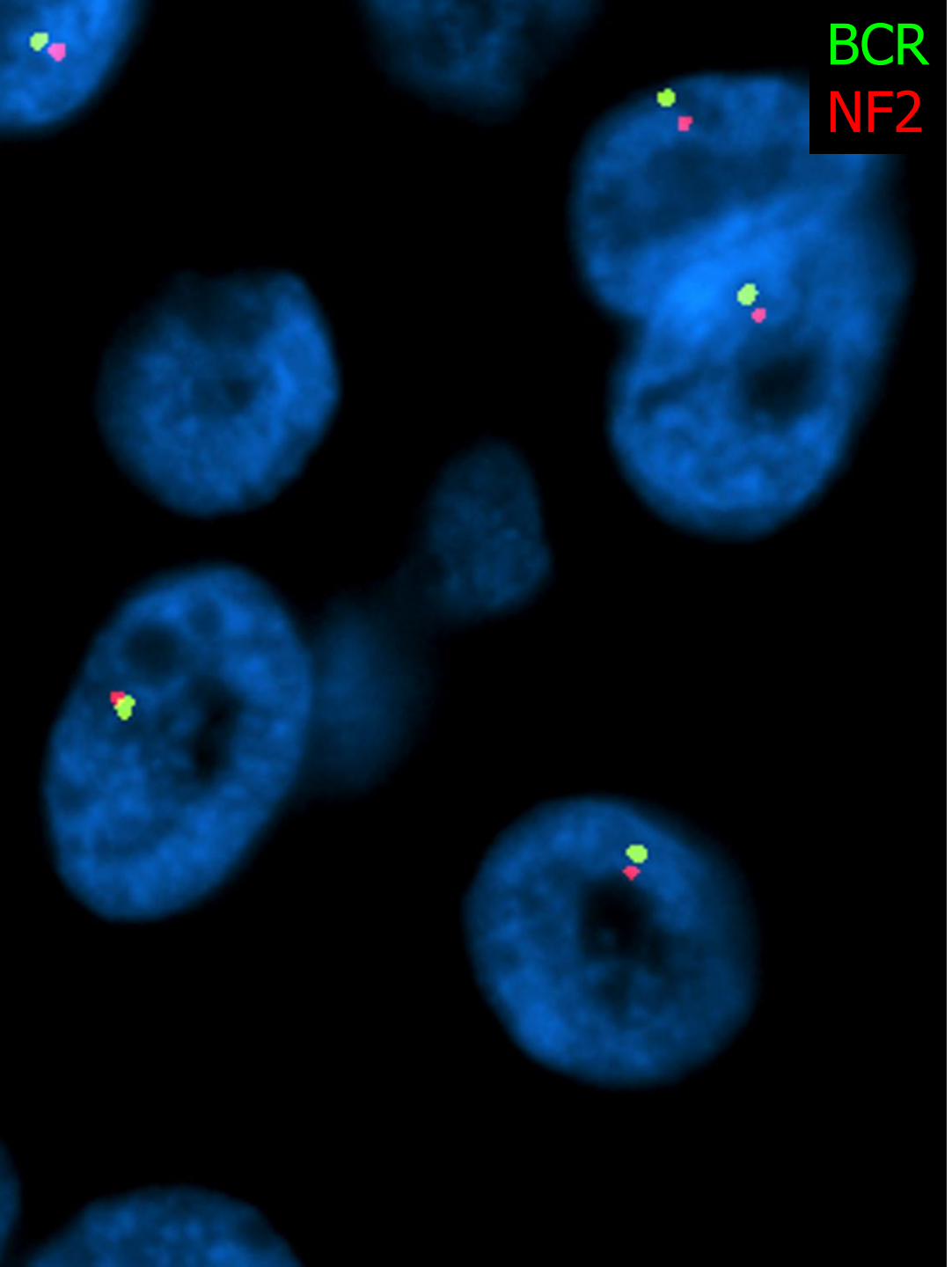
Nat Genet. 2013;45(2):131-2.

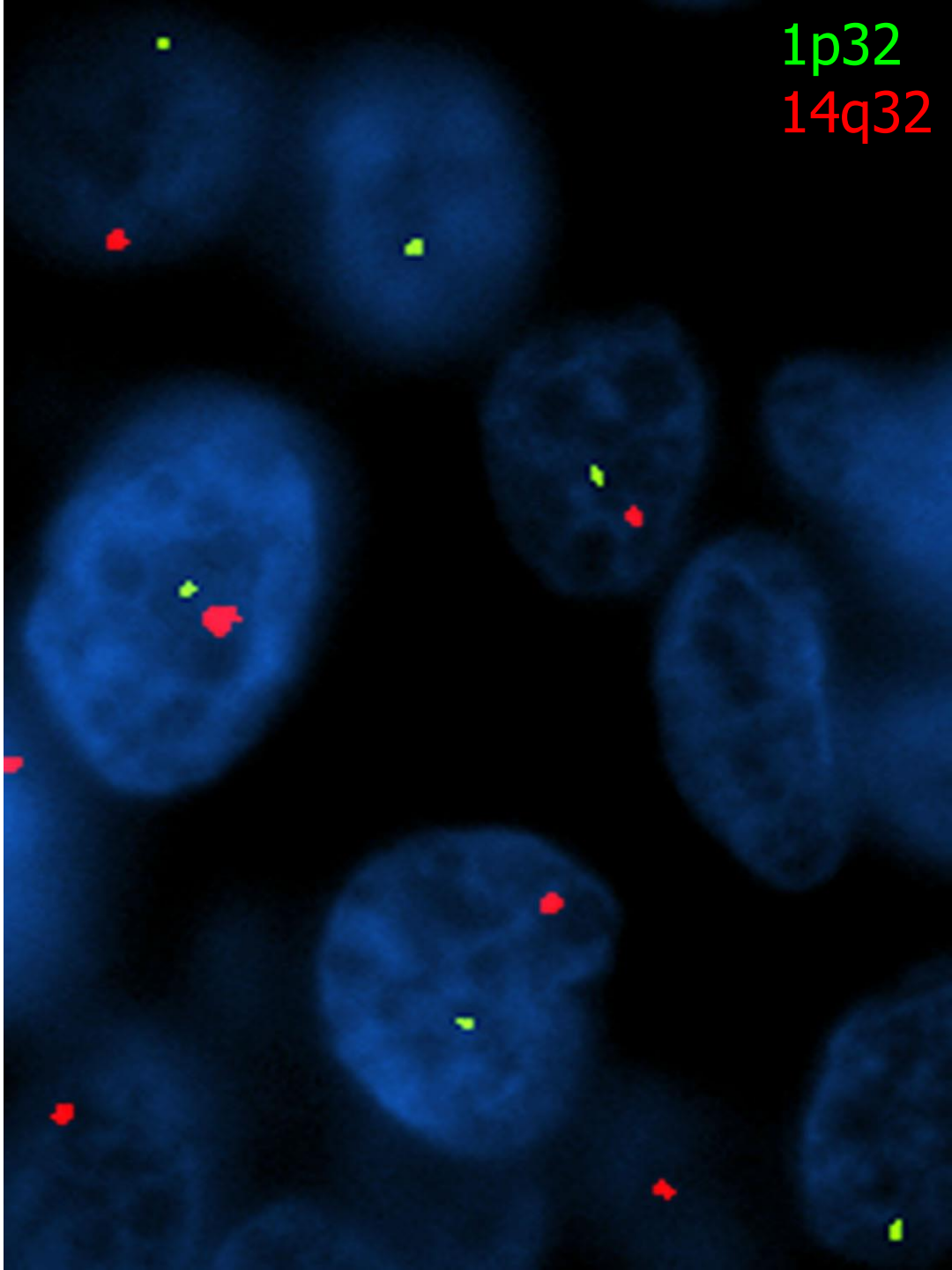
Acta Neuropathol. 2013;125(5):651-8.

Diagnosis	*N*	NAB2 IHC	STAT6 IHC	
		Nucleus	Nucleus	Cytoplasm
Hemangiopericytoma	37	35/37	35/37	0/37
Solitary fibrous tumor	25	25/25	25/25	0/25
Fibroblastic meningioma WHO grade I	16	15/16	0/16	16/16
Transitional meningioma WHO grade I	15	12/15	0/15	15/15
Atypical meningioma WHO grade II	18	18/18	0/18	18/18
Chordoid meningioma WHO grade II	16	16/16	0/16	16/16
Anaplastic meningioma WHO grade III	18	18/18	0/18	18/18
Rhabdoid meningioma WHO grade III	4	4/4	0/4	3/4
Glioblastoma WHO grade IV	10	10/10	0/10	8/10
Gliosarcoma WHO grade IV	9	9/9	0/9	9/9
Meningeal sarcoma	4	4/4	1/4	3/4
Mesenchymal tumor not classifiable	3	3/3	3/3	0/3
Hemangioblastoma	12	12/12	0/12	10/12
Cellular schwannoma	9	9/9	0/9	9/9
Capillary hemangioma	4	3/4	0/4	3/4
Myopericytoma	1	1/1	0/1	1/1

Acta Neuropathol. 2013;125(5):651-8.


STAT6
HPC
Giant Cell SFT
ANA Meningioma
ANA Meningioma


BCR
NF2


1p32
14q32

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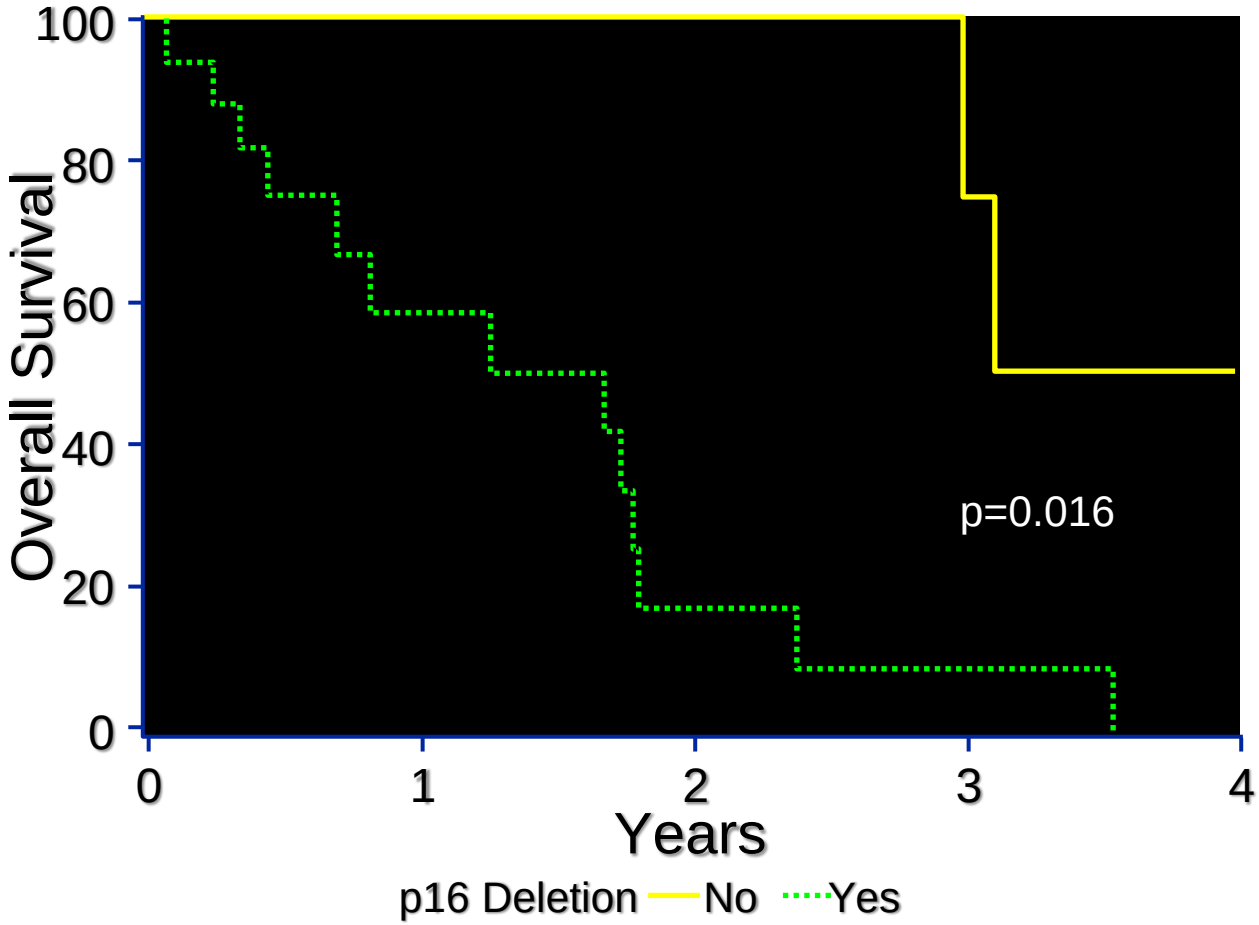
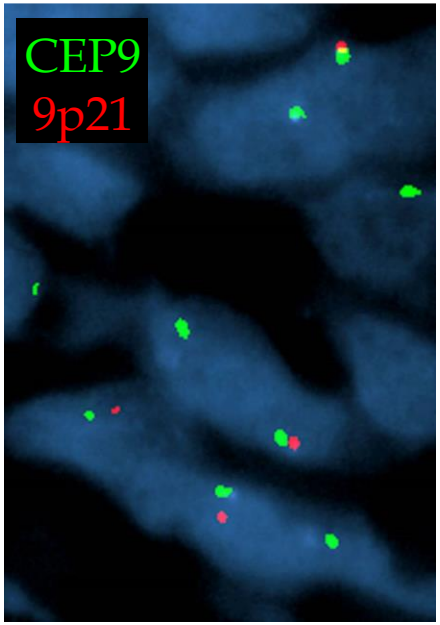
ANAPLASTIC MENINGIOMAS (N=23)

Perry A et al., Brain Pathol 12:183-190, 2002





Integrative Genomic Analysis Identifies *NDRG2* as a Candidate Tumor Suppressor Gene Frequently Inactivated in Clinically Aggressive Meningioma

Eriks A. Lusis,[1] Mark A. Watson,[2] Michael R. Chicoine,[3] Meghan Lyman,[4] Peter Roerig,[5] Guido Reifenberger,[5] David H. Gutmann,[4] and Arie Perry[1]

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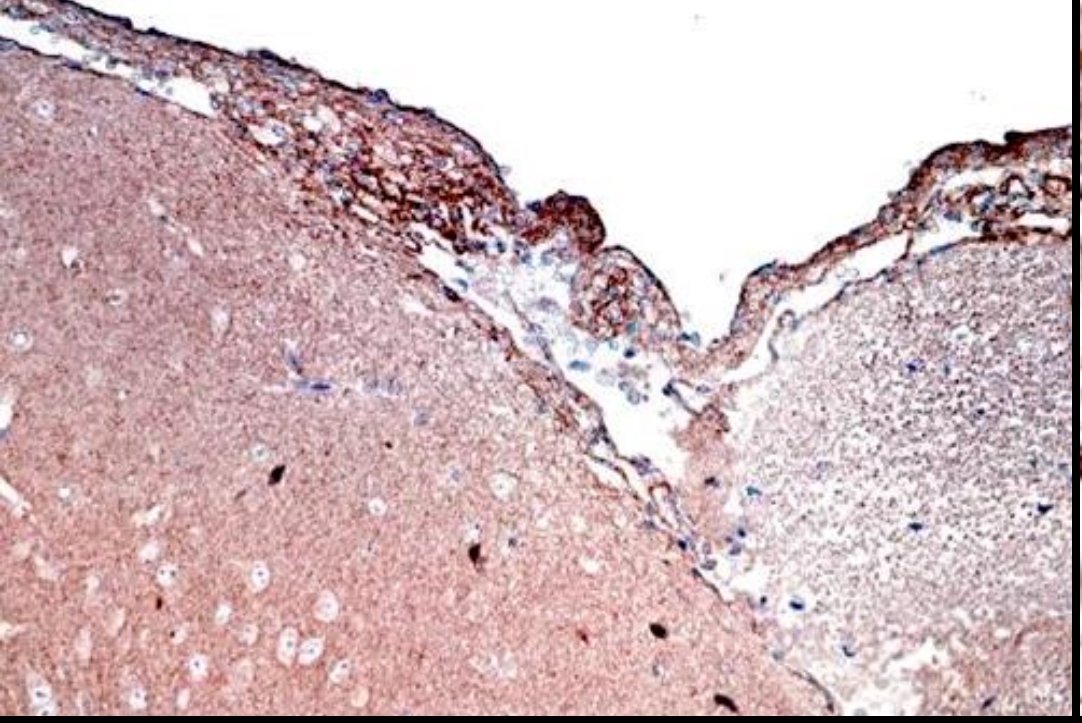
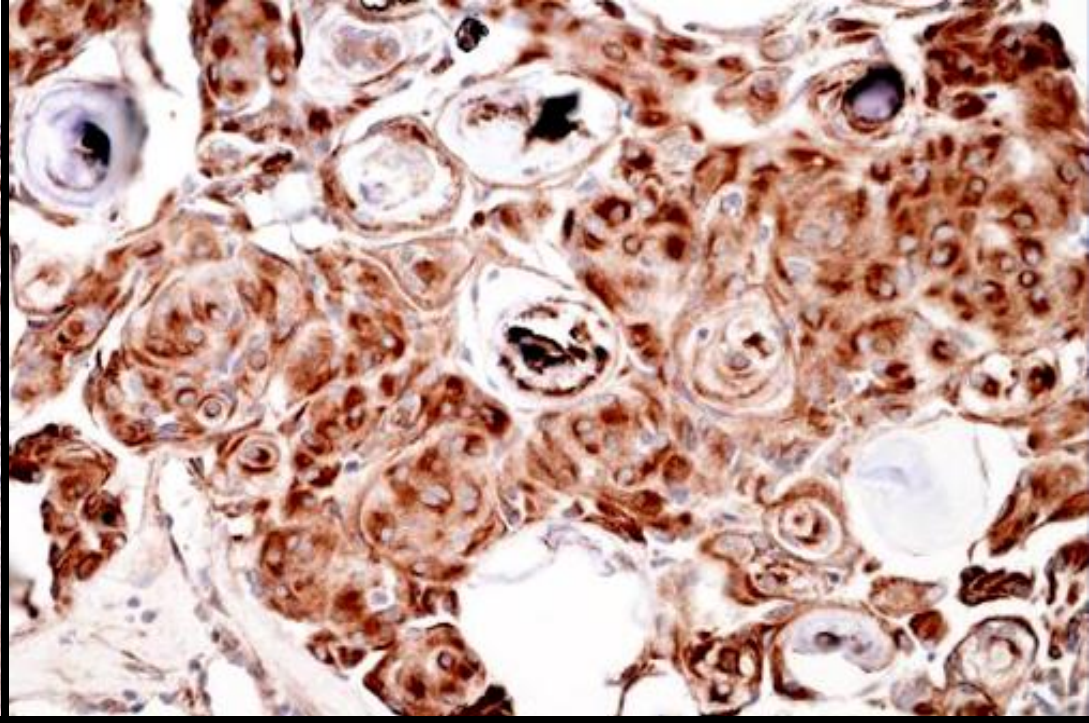
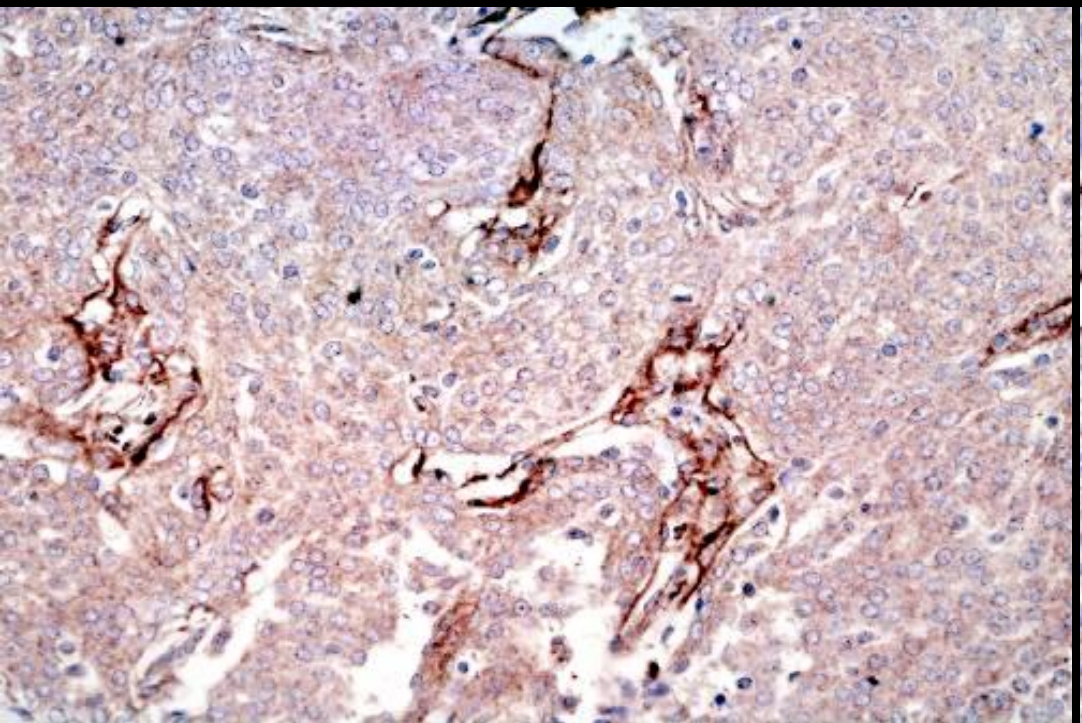
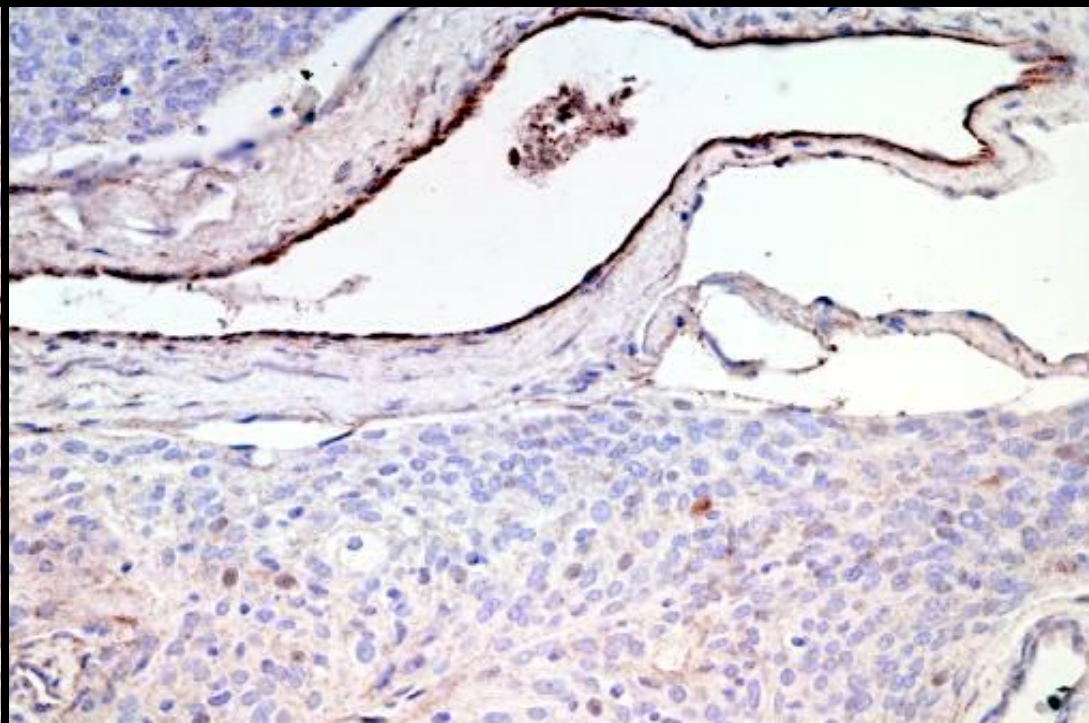
Abstract

Although meningiomas are common central nervous system tumors, little is known about the genetic events responsible for malignant progression. In this study, we employed gene expression profiling to identify transcripts whose expression was lost in anaplastic (WHO grade III) versus benign (WHO grade I) meningioma. Approximately 40% of genes down-regulated in anaplastic meningioma were localized to chromosomes 1p and 14q. One specific gene located at 14q11.2, *NDRG2*, was consistently down-regulated in grade III meningioma, a finding which we validated at both the transcript and protein levels in independent sets of clinically and pathologically diverse meningiomas. Loss of NDRG2 expression was also seen in a subset of lower-grade meningiomas, including atypical meningiomas (WHO grade II) with clinically aggressive behavior. Furthermore, we found that the loss of NDRG2 expression was significantly associated with hypermethylation of the *NDRG2* promoter. Collectively, these data identify *NDRG2* as the first specific candidate tumor suppressor gene on chromosome 14q that is inactivated during meningioma progression. In addition, these findings highlight the utility of combining genomic, epigenetic, and expression data to identify clinically significant tumor biomarkers, and suggest that NDRG2 expression will be a useful and functionally relevant biomarker to predict aggressive behavior in patients with meningioma. (Cancer Res 2005; 65(16): 7121-6)

and TSLC1 are also common (2, 4–6). However, there are few known genetic changes associated with the malignant progression of meningioma. Although losses of chromosomal arms 14q and 1p are common in anaplastic tumors (WHO grade III) and are generally associated with poor prognosis (7, 8), the relevant tumor suppressor genes that map to these loci have not been identified. Loss of heterozygosity studies have had limited success in identifying minimal regions of deletion, in part, due to the fact that the entire chromosome or chromosomal arm is lost in most examples. In the current study, we used a strategy combining expression profiling with known cytogenetic alterations, leading to the identification of *NDRG2* as a potential meningioma-associated tumor suppressor gene on 14q11.2. We subsequently validated its role in meningioma tumor progression using multiple methods for measuring RNA and protein expression within independent cohorts of clinically well-characterized meningiomas. Lastly, hypermethylation of the CpG island within the *NDRG2* promoter region was shown to be the likely mechanism of inactivation in the majority of meningiomas with loss of NDRG2 expression.

Materials and Methods

Tissue specimens. Tissue specimens were collected by the Siteman Cancer Center Tissue Procurement Facility and the Department of Neuropathology, Heinrich-Heine-University, under approved protocols from the Institutions' Review Boards. Snap-frozen tissue specimens from

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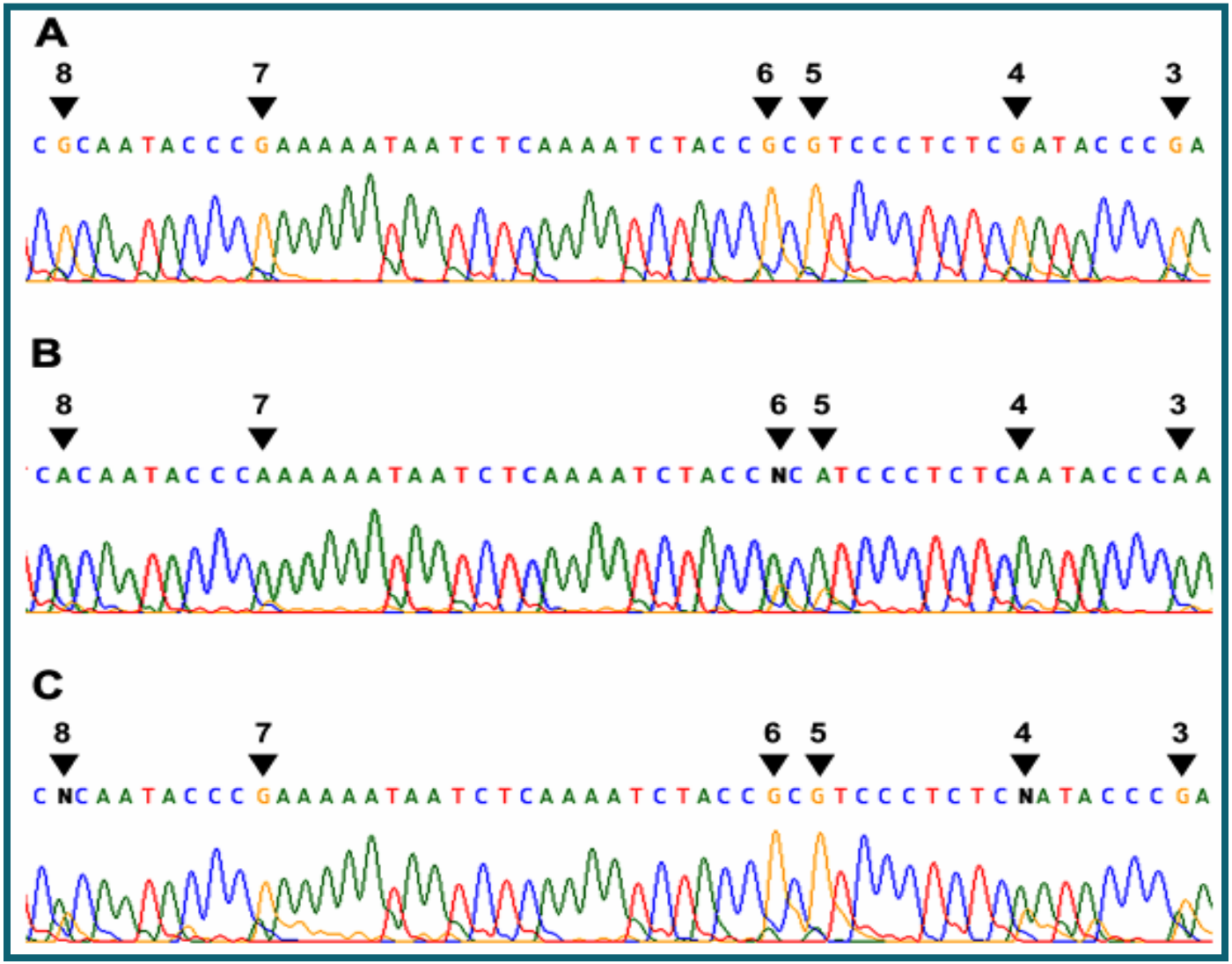
NDRG2 METHYLATION



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CURRENT PATHOLOGY INFORMATION

- **Confirm diagnosis of meningioma**
  - IHC for EMA, PR, SSTR2a, STAT6; FISH for 22q loss
- **Suggest NF2 in appropriate setting**
- **Identify high recurrence risk (WHO grade II)**
  - IHC for MIB-1, PR, GFAP (brain inv), NDRG2?
  - FISH for losses of 1p, 14q, others
  - Need for adjuvant radiotherapy vs. careful FU?
  - Frequency of neuroimaging?
- **Identify high mortality risk (WHO grade III)**
  - IHC and FISH for 9p21 deletions
- **Need for improved molecular schemes**

Neuro-Oncology 2014; **0**, 1–13, doi:10.1093/neuonc/not325

Proposal for a new risk stratification classification for meningioma based on patient age, WHO tumor grade, size, localization, and karyotype

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Center for Neurosciences and Cell Biology, and Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal (P.H.D., C.d.O., M.C.L.); Center for Cancer Research (CIC-IBMCC; CSIC/USAL) and Department of Medicine, University of Salamanca, Salamanca, Spain (P.H.D., A.O., M.D.T.); Neurosurgery Service, University Hospital of Salamanca, Salamanca, Spain (P.S., A.O., J.M.G., L.R.); Research Unity and IECSCYL, University Hospital of Salamanca IBSAL, Salamanca, Spain (M.D.T.)*

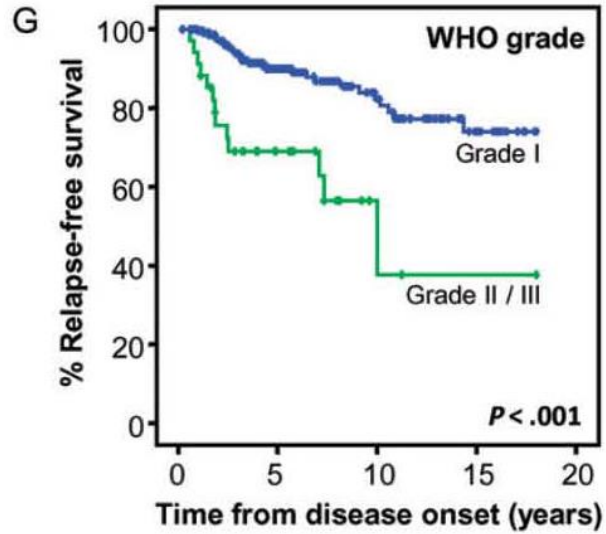
Corresponding Author: Maria Dolores Tabernero Redondo, MD, PhD, Unidad de Investigación, Hospital Universitario de Salamanca, Paseo de San Vicente 58, 37007 Salamanca, Spain (taberner@usal.es).

†These authors are co-first authors.

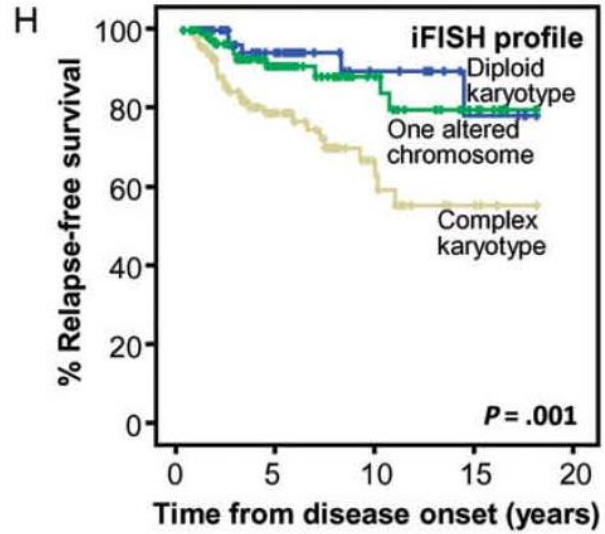
Background. Tumor recurrence remains the major clinical complication of meningiomas, the majority of recurrences occurring among WHO grade I/benign tumors. In the present study, we propose a new scoring system for the prognostic stratification of meningioma patients based on analysis of a large series of meningiomas followed for a median of >5 years.

Methods. Tumor cytogenetics were systematically investigated by interphase fluorescence in situ hybridization in 302 meningioma samples, and the proposed classification was further validated in an independent series of cases ($n = 132$) analyzed by high-density (500K) single-nucleotide polymorphism (SNP) arrays.

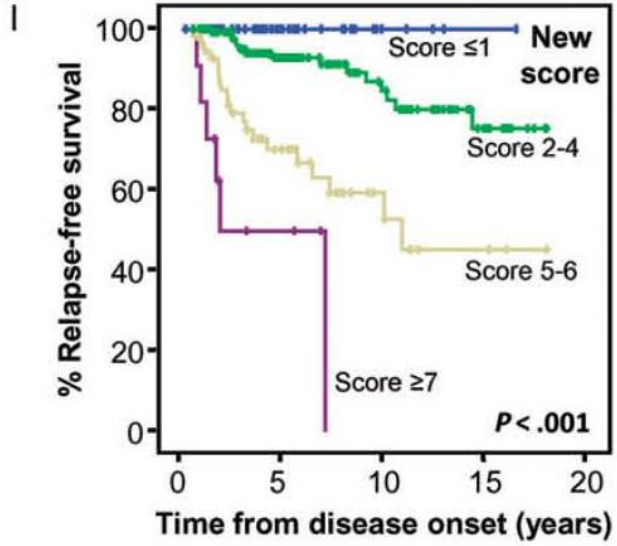
Results. Overall, we found an adverse impact on patient relapse-free survival (RFS) for males, presence of brain edema, younger patients (<55 years), tumor size >50 mm, tumor localization at intraventricular and anterior cranial base areas, WHO grade II/III meningiomas, and complex karyotypes; the latter 5 variables showed an independent predictive value in multivariate analysis. Based on these parameters, a prognostic score was established for each individual case, and patients were stratified into 4 risk categories with significantly different ($P < .001$) outcomes. These included a good prognosis group, consisting of approximately 20% of cases, that showed a RFS of 100% ± 0% at 10 years and a very poor-prognosis group with a RFS rate of 0% ± 0% at 10 years. The prognostic impact of the scoring system proposed here was also retained when WHO grade I cases were considered separately ($P < .001$).



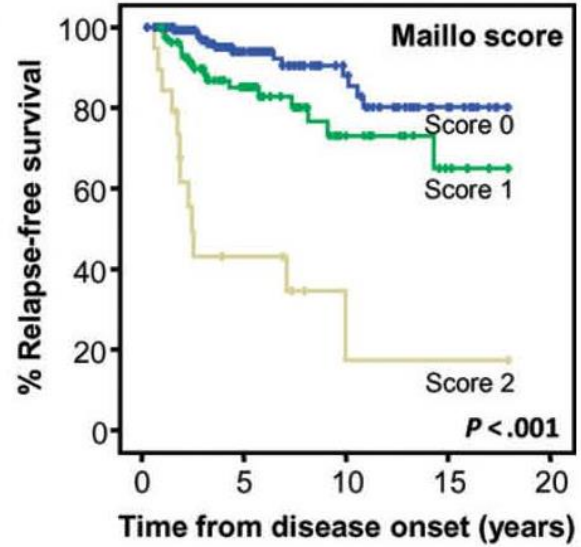
Grade I	227	111	51	21
Grade II / III	34	14	3	1



Diploid karyotype	70	33	15	7
One altered chromosome	94	45	22	10
Complex karyotype	97	46	17	5



Score ≤1	50	50	50	50
Score 2-4	144	75	37	14
Score 5-6	56	25	9	3
Score ≥7	11	3	0	0



Score 0	159	73	35	15
Score 1	83	45	17	6
Score 2	19	6	2	1

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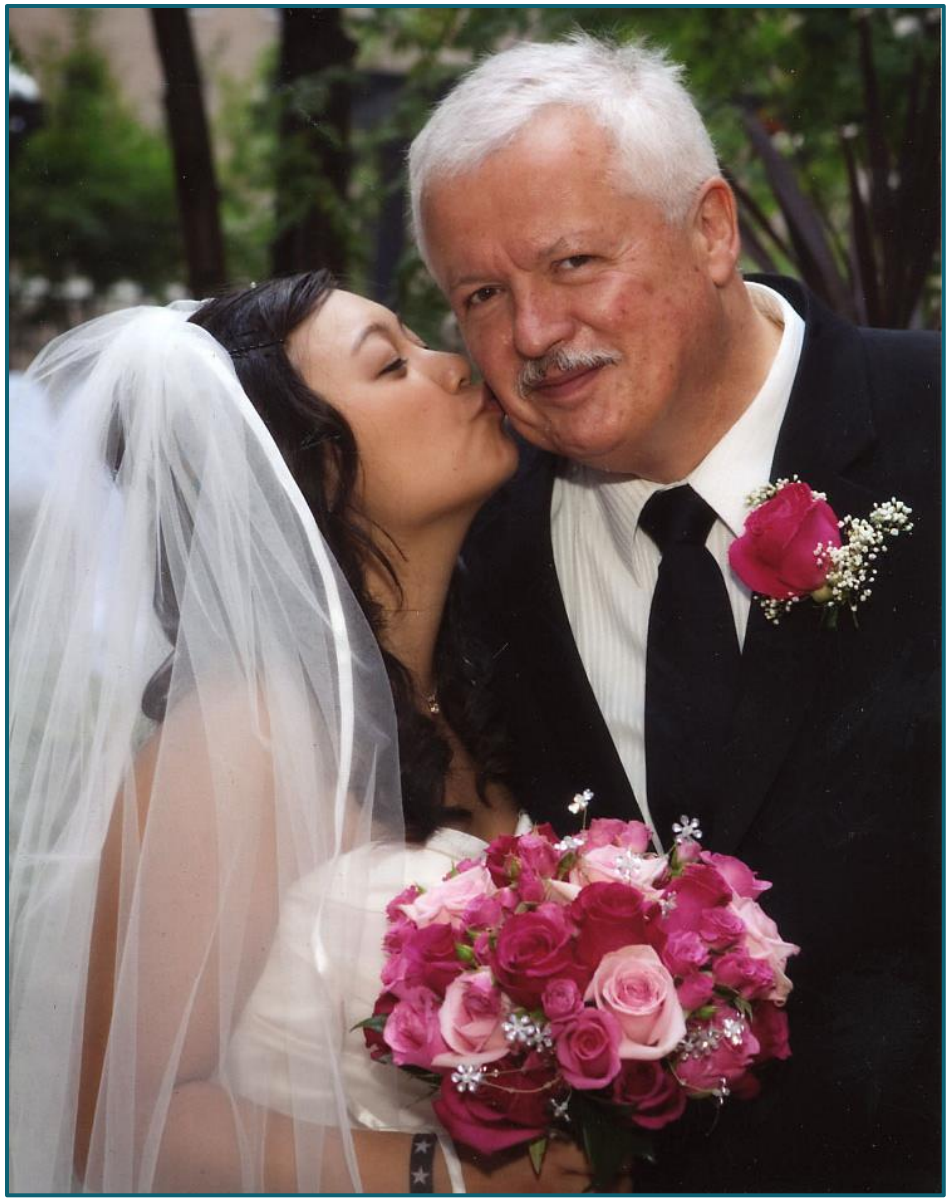
BWS (1946-2011)

Rest in peace Bernd. You are sorely missed, but live on in the hearts of those you've trained and mentored.



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