THE 2020 WORLD HEALTH ORGANIZATION CLASSIFICATION OF SOFT TISSUE TUMORS: AN UPDATE

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WHO Classification of Tumours 5th Edition: Soft Tissue and Bone Tumours
2nd Editorial Board meeting: 6-8 May 2019, IARC, Lyon FRANCE

Outline

- New tumor types
- New concepts/revised nomenclature
- New genetics and novel diagnostic markers

WHO 2020: NEW TUMOR TYPES

Adipocytic tumors
Atypical spindle cell/pleomorphic lipomatous tumor
Myxoid pleomorphic liposarcoma
Fibroblastic/myofibroblastic tumors
EWSR1-SMAD3-positive fibroblastic tumor (emerging)
Angiofibroma of soft tissue
Superficial CD34-positive fibroblastic tumor
Vascular tumors
Epithelioid hemangioendothelioma with *YAP1-TFE3*

Smooth muscle tumors
Inflammatory leiomyosarcoma
Tumors of uncertain differentiation
NTRK-rearranged spindle cell neoplasm (emerging)
Undifferentiated small round cell sarcomas of bone and soft tissue
CIC-rearranged sarcoma
Sarcomas with *BCOR* genetic alterations
Round cell sarcomas with *EWSR1*-non-ETS fusions

WHO 2020: NEW TUMOR TYPES

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- Atypical spindle cell/pleomorphic lipomatous tumor
- Myxoid pleomorphic liposarcoma

Fibroblastic/myofibroblastic tumors

- EWSR1-SMAD3-positive fibroblastic tumor (emerging)
- Angiofibroma of soft tissue
- Superficial CD34-positive fibroblastic tumor

Vascular tumors

- Epithelioid hemangioendothelioma with *YAP1-TFE3*

Smooth muscle tumors

- Inflammatory leiomyosarcoma

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Undifferentiated small round cell sarcomas of bone and soft tissue

- *CIC*-rearranged sarcoma
- Sarcomas with *BCOR* genetic alterations
- Round cell sarcomas with EWSR1-non-ETS fusions

"Spindle Cell Liposarcoma"

The American Journal of Surgical Pathology *18(9): 913–921, 1994*

Spindle Cell Liposarcoma, A Hitherto Unrecognized Variant of Liposarcoma

Analysis of Six Cases

Angelo P. Dei Tos, M.D., Thomas Mentzel, M.D.,
Paul L. Newman, M.R.C.Path.,
and Christopher D.M. Fletcher, M.D., M.R.C.Path.

MODERN PATHOLOGY (2010) 23, 729–736

Well-differentiated spindle cell liposarcoma ('atypical spindle cell lipomatous tumor') does not belong to the spectrum of atypical lipomatous tumor but has a close relationship to spindle cell lipoma: clinicopathologic, immunohistochemical, and molecular analysis of six cases

Thomas Mentzel[1], Gabriele Palmedo[1] and Cornelius Kuhnen[2]

Am J Surg Pathol • Volume 37, Number 9, September 2013

Fibrosarcoma-like Lipomatous Neoplasm

A Reappraisal of So-called Spindle Cell Liposarcoma Defining a Unique Lipomatous Tumor Unrelated to Other Liposarcomas

Andrea T. Deyrup, MD, PhD, Frederic Chibon, PhD,† Louis Guillou, MD,‡ Pauline Lagarde, MD,† Jean-Michel Coindre, MD,†§ and Sharon W. Weiss, MD‖*

Am J Surg Pathol • Volume 41, Number 2, February 2017

Atypical Spindle Cell Lipomatous Tumor

Clinicopathologic Characterization of 232 Cases Demonstrating a Morphologic Spectrum

Adrian Mariño-Enriquez, MD, PhD, Alessandra F. Nascimento, MD,* Azra H. Ligon, PhD,* Cherwei Liang, MD,† and Christopher D.M. Fletcher, MD, FRCPath**

M:F ratio: 3:2

Median age: 54 yr

Anatomic locations	
Lower limb	36%
Upper limb	27%
Head/neck/face	10%
Retroperitoneum	<1%

Depth	
Subcutaneous	56%
Deep/subfascial	44%

Local recurrence: 13%

Am J Surg Pathol • Volume 41, Number 2, February 2017

Atypical Spindle Cell Lipomatous Tumor

Clinicopathologic Characterization of 232 Cases Demonstrating a Morphologic Spectrum

Adrian Mariño-Enriquez, MD, PhD, Alessandra F. Nascimento, MD,* Azra H. Ligon, PhD,* Cherwei Liang, MD,† and Christopher D.M. Fletcher, MD, FRCPath**

Marker	Positive
CD34	64%
S100	40%
Desmin	22%
RB1 (loss)	57%

Marker	Positive
MDM2	6%
CDK4	5%
Both	0%

Am J Surg Pathol • Volume 41, Number 11, November 2017

"Atypical" Pleomorphic Lipomatous Tumor

A Clinicopathologic, Immunohistochemical and Molecular Study of 21 Cases, Emphasizing its Relationship to Atypical Spindle Cell Lipomatous Tumor and Suggesting a Morphologic Spectrum (Atypical Spindle Cell/Pleomorphic Lipomatous Tumor)

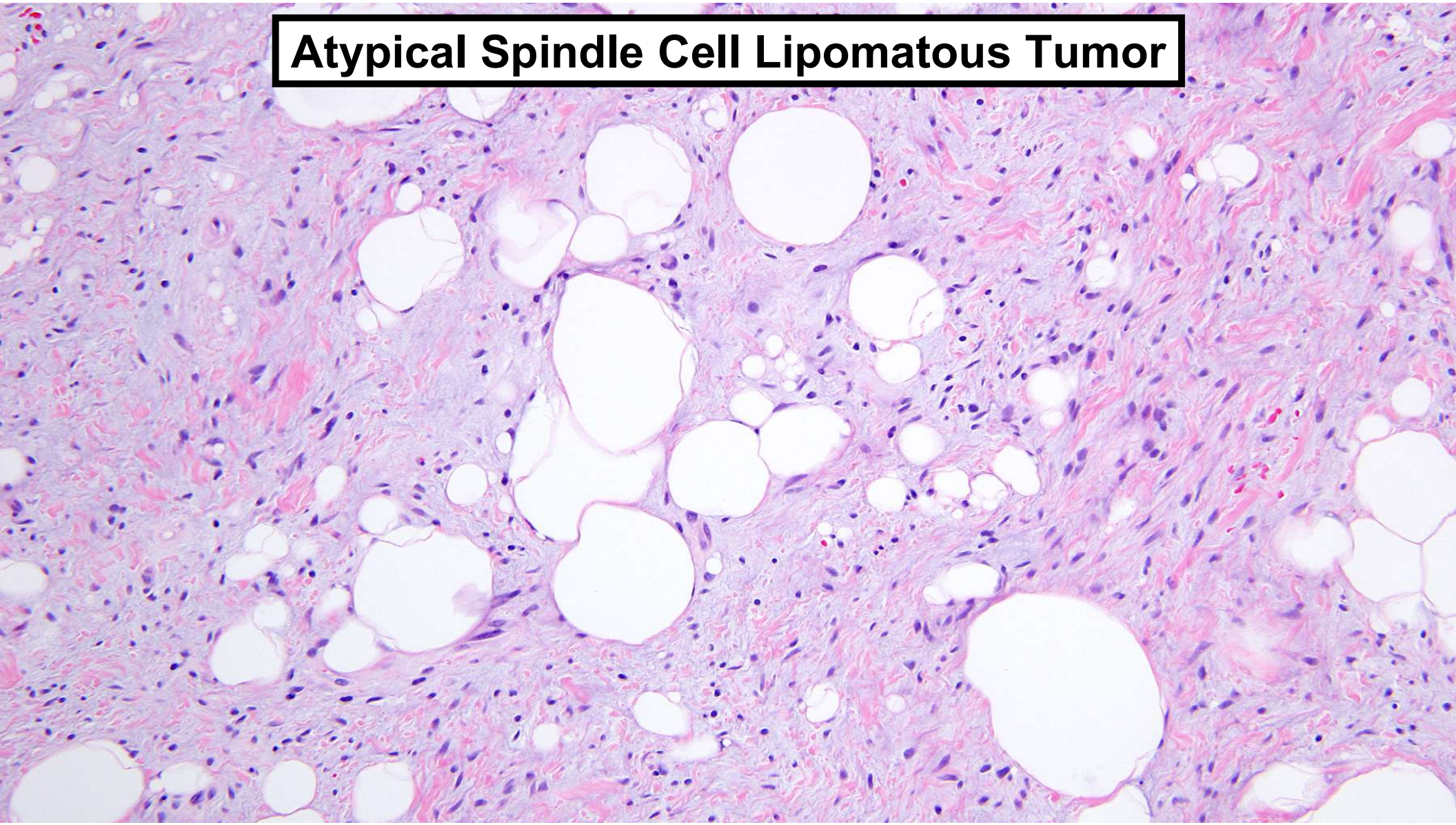
David Creytens, MD, PhD,† Thomas Mentzel, MD, PhD,‡ Liesbeth Ferdinande, MD, PhD,*† Evelyne Lecoutere, MD,* Joost van Gorp, MD, PhD,§ Lilit Atanesyan, PhD,‖ Karel de Groot, MSc,‖ Suvi Savola, PhD,‖ Nadine Van Roy, PhD,†¶ Jo Van Dorpe, MD, PhD,*† and Uta Flucke, MD, PhD#*

Am J Surg Pathol • Volume 45, Number 9, September 2021

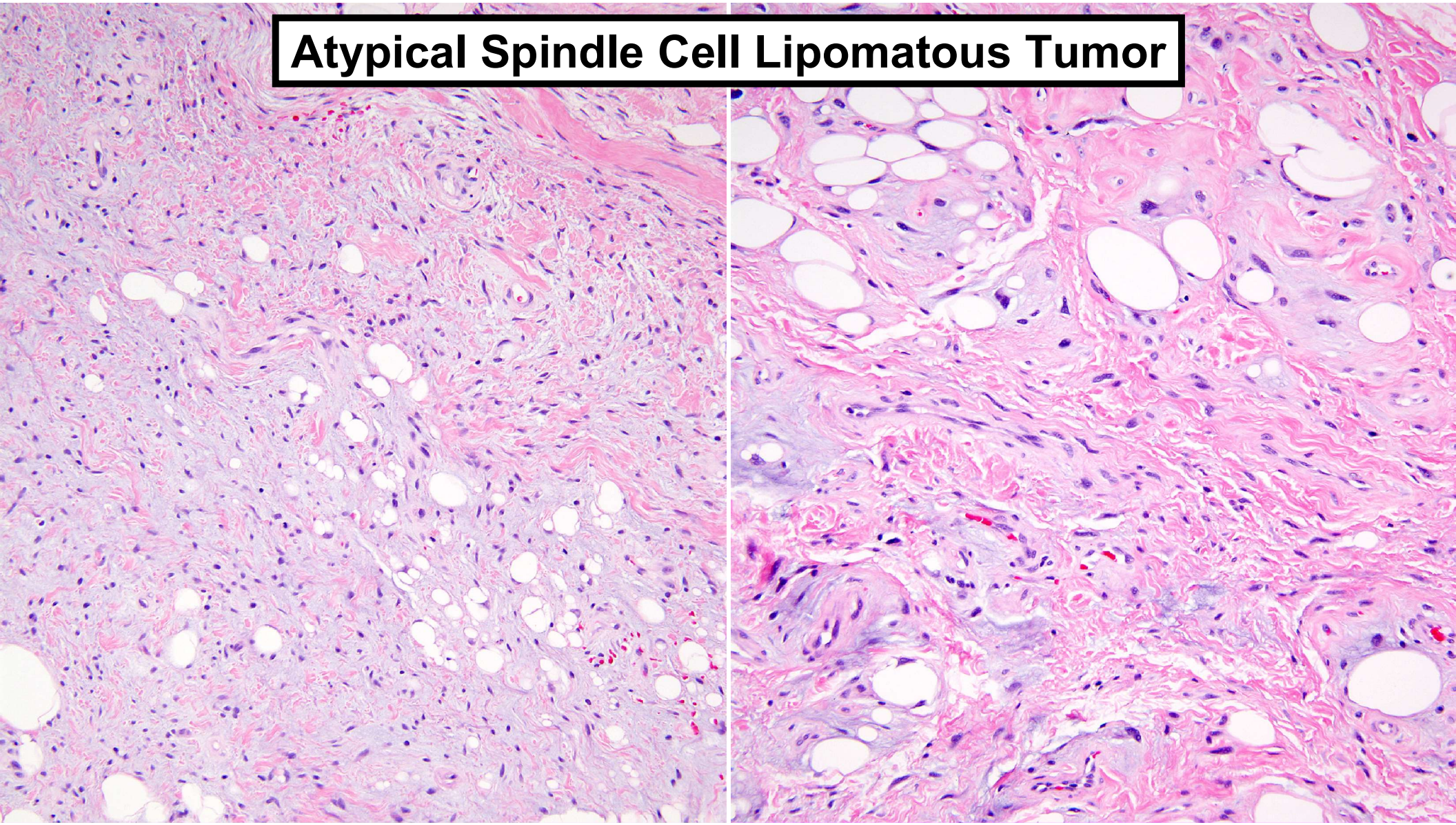
Atypical Pleomorphic Lipomatous Tumor

Expanding Our Current Understanding in a Clinicopathologic Analysis of 64 Cases

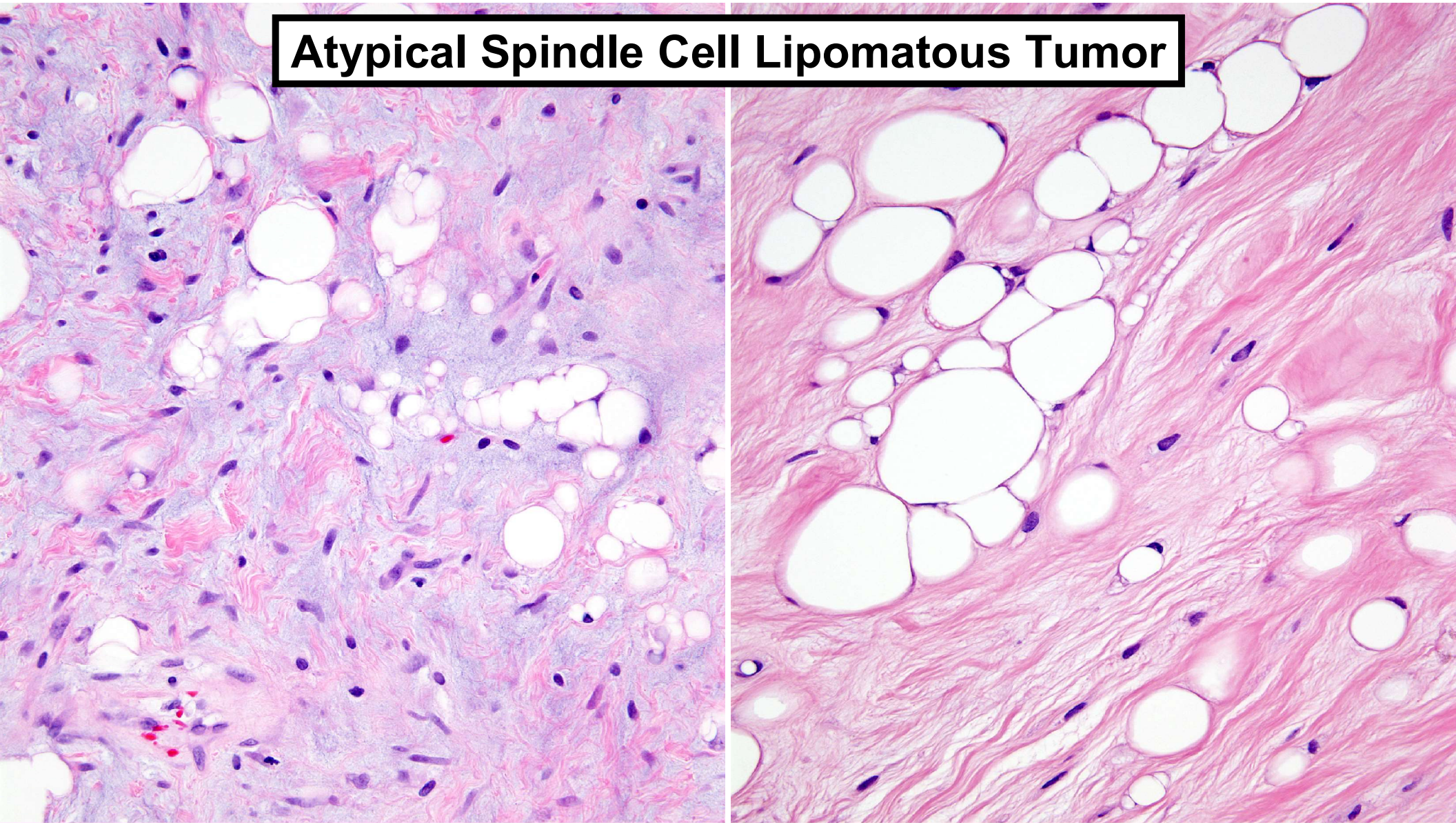
William J. Anderson, MBChB, Christopher D.M. Fletcher, MD, FRCPath, and Vickie Y. Jo, MD


Atypical Spindle Cell Lipomatous Tumor

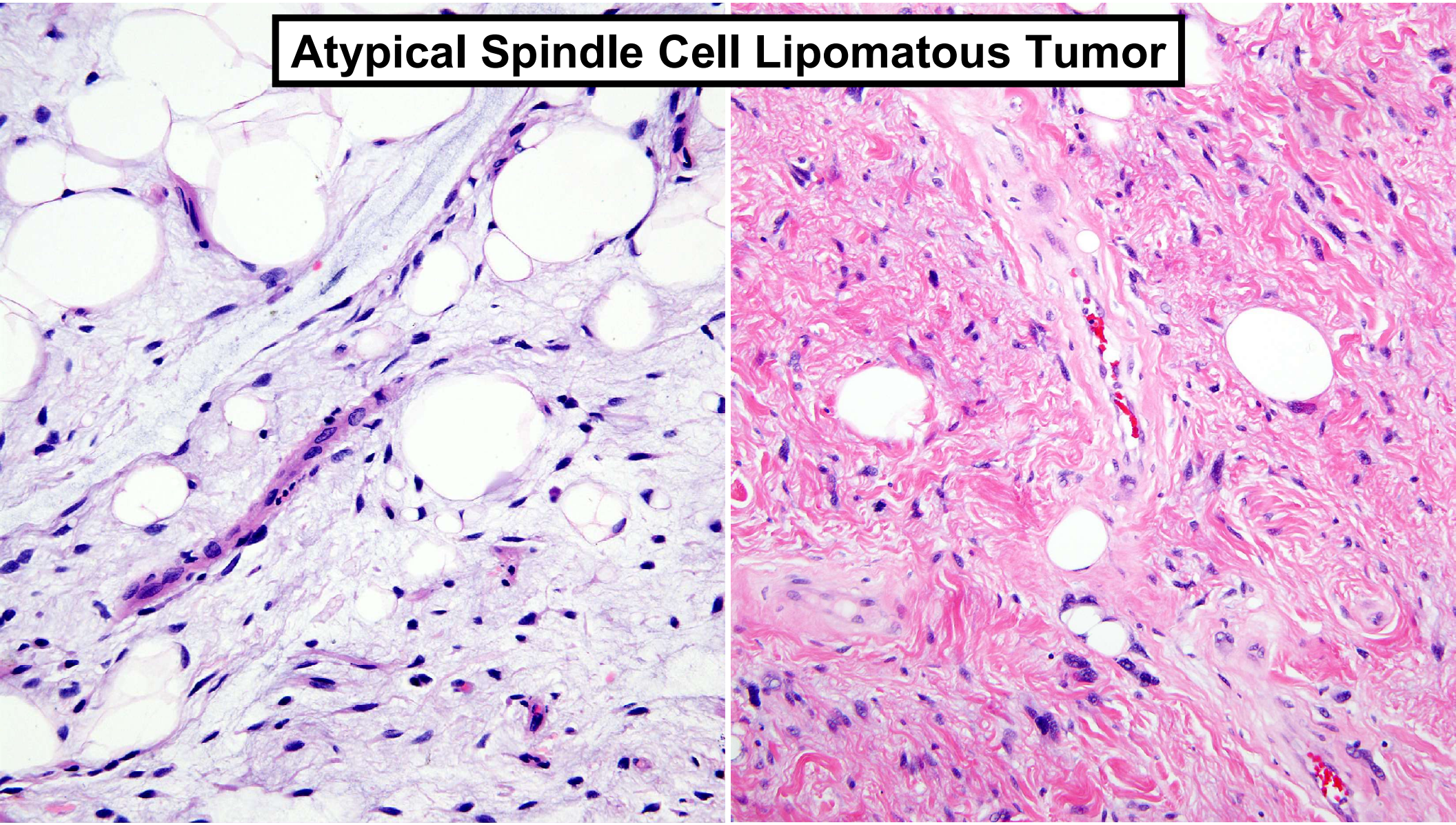
Atypical Spindle Cell Lipomatous Tumor



Atypical Spindle Cell Lipomatous Tumor



Atypical Spindle Cell Lipomatous Tumor



Liposarcomas in Young Patients

A Study of 82 Cases Occurring in Patients Younger Than 22 Years of Age

Rita Alaggio, MD, Cheryl M. Coffin, MD,† Sharon W. Weiss, MD,‡ Julia A. Bridge, MD,§ Josephine Issakov, MD,‖ Andre M. Oliveira, MD,¶ and Andrew L. Folpe, MD¶*

Am J Surg Pathol • Volume 33, Number 5, May 2009

Liposarcomas of the Mediastinum and Thorax

A Clinicopathologic and Molecular Cytogenetic Study of 24 Cases, Emphasizing Unusual and Diverse Histologic Features

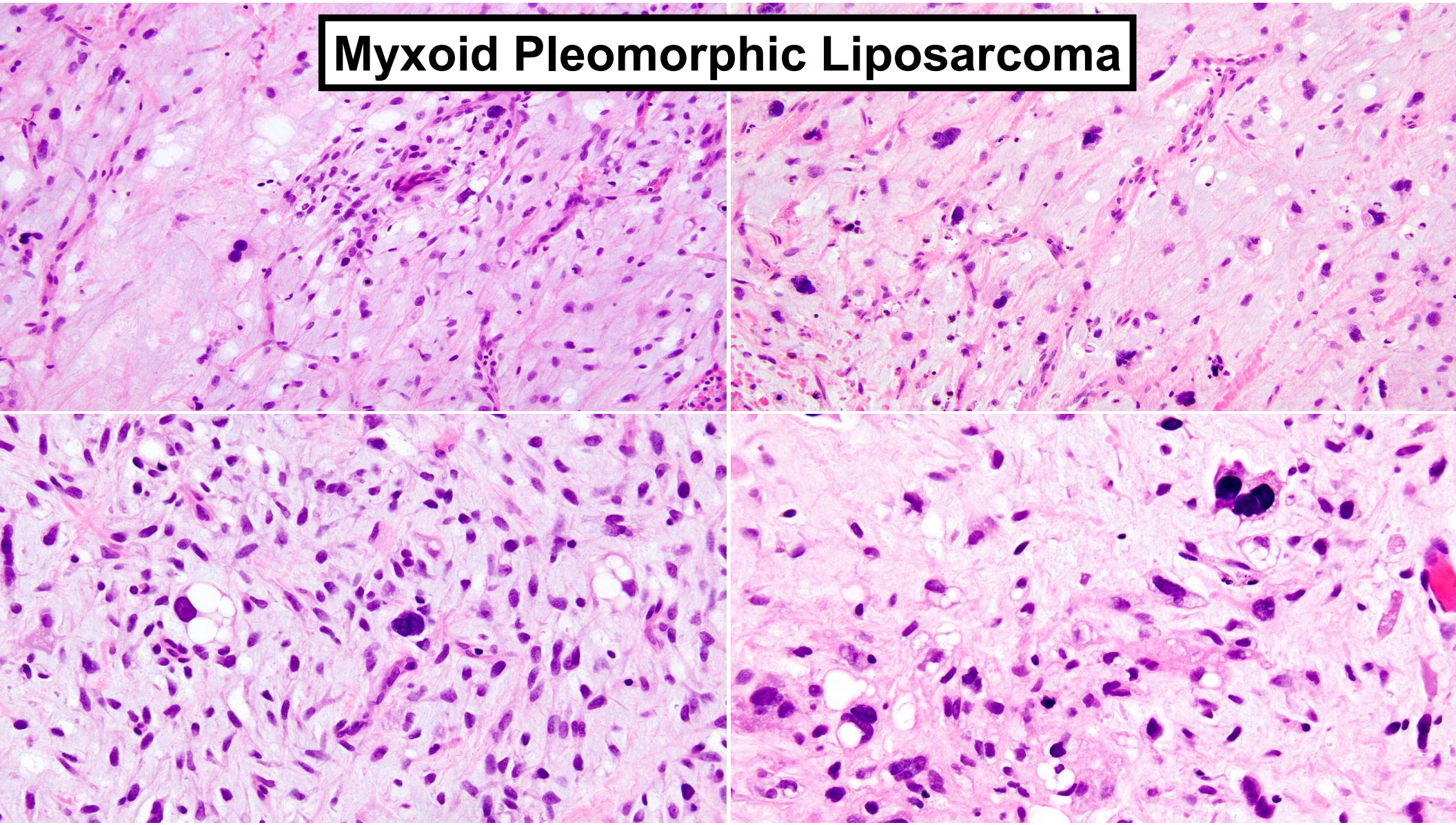
Jennifer M. Boland, MD, Thomas V. Colby, MD,† and Andrew L. Folpe, MD**

Am J Surg Pathol • Volume 36, Number 9, September 2012

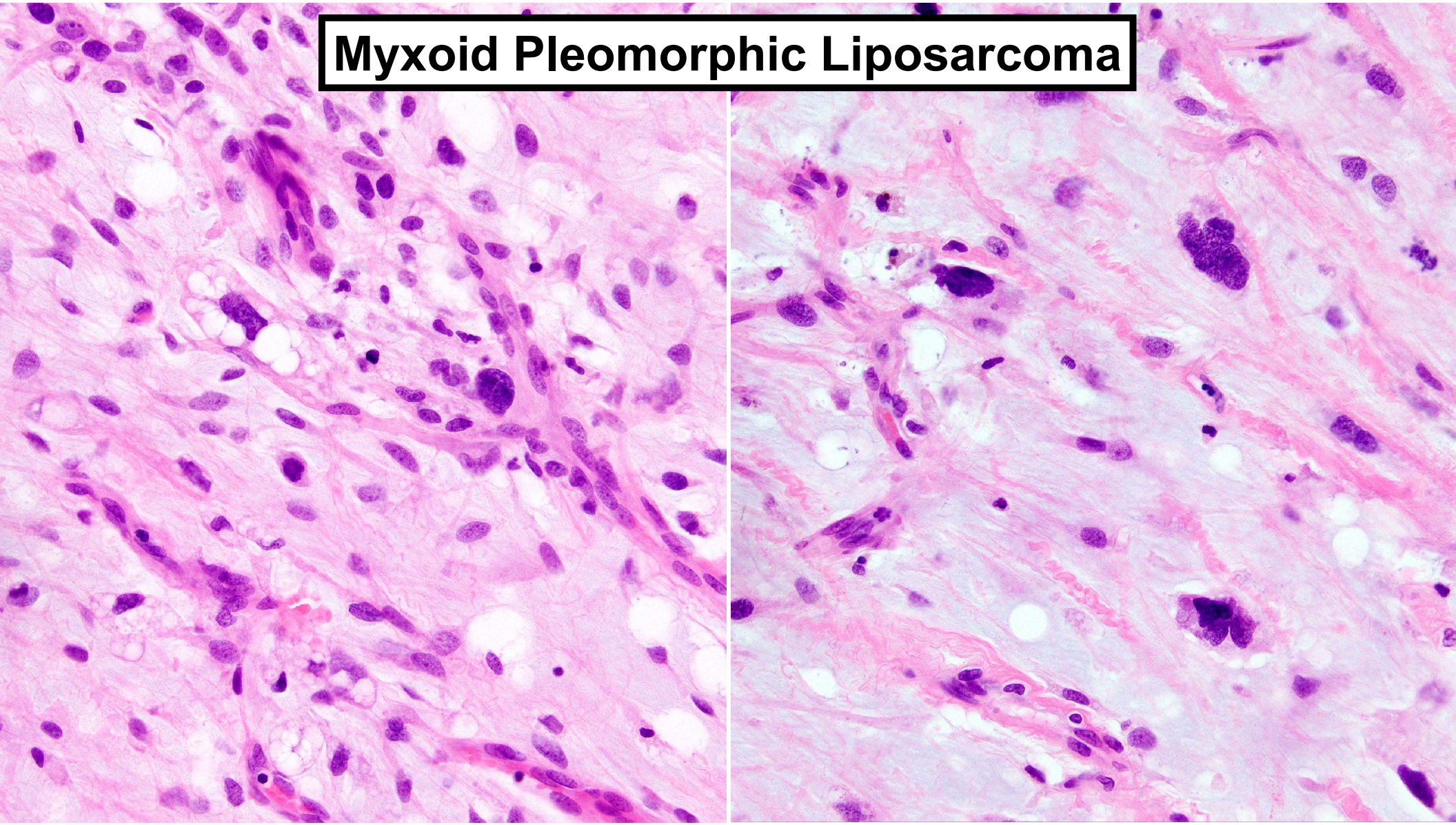
Myxoid pleomorphic liposarcoma

- **Predilection for the mediastinum of children and young adults**
- **Histology: admixture of hypocellular zones with myxoid stroma, bland nuclei, and delicate branching vessels and areas with atypia and pleomorphism**
- **Lack *DDIT3* rearrangements and *MDM2* amplification**
- **Some cases associated with Li-Fraumeni syndrome (germline *TP53* mutation)**
- **Clinically aggressive with high rate of local recurrence and distant metastasis**

Myxoid Pleomorphic Liposarcoma



Myxoid Pleomorphic Liposarcoma



Am J Surg Pathol • Volume 36, Number 4, April 2012

Angiofibroma of Soft Tissue: Clinicopathologic Characterization of a Distinctive Benign Fibrovascular Neoplasm in a Series of 37 Cases

Adrián Mariño-Enríquez, MD and Christopher D. M. Fletcher, MD, FRCPath

M:F ratio: 2:1

Median age: 49 yr

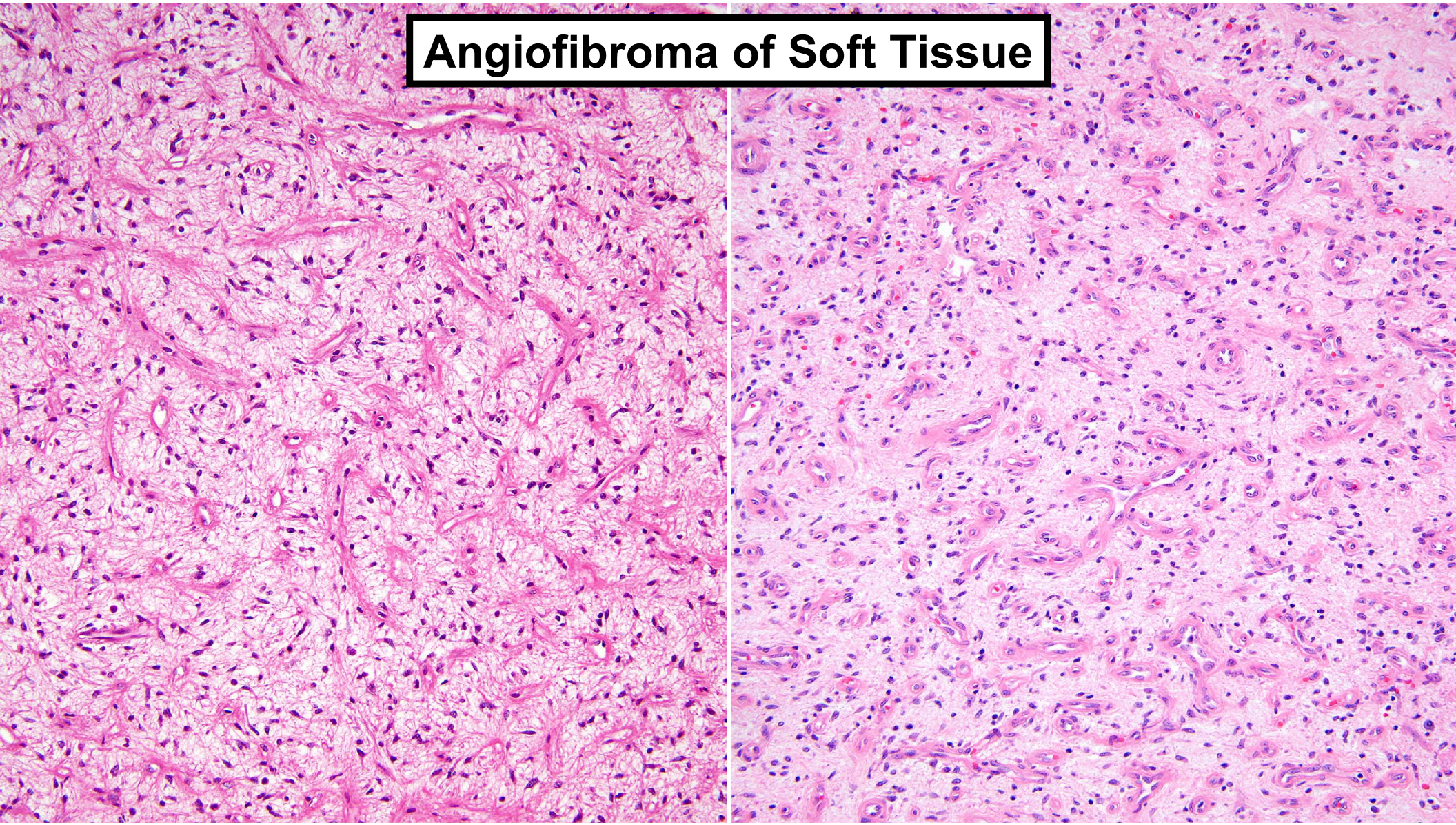
Anatomic locations	
Lower limb	62%
Upper limb	27%

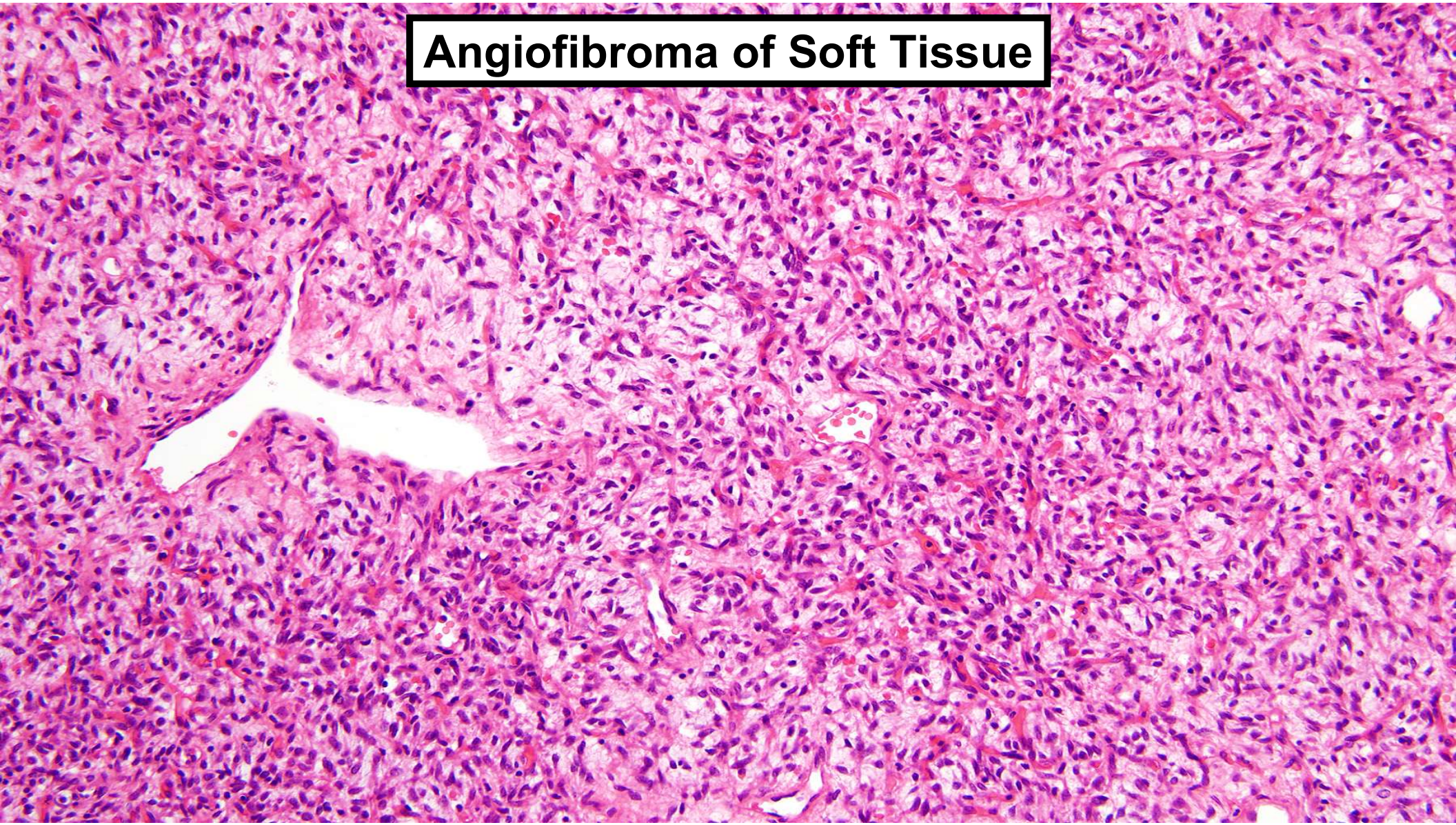
Depth	
Subcutaneous	56%
Deep/subfascial	44%

Marker	Positive
EMA	44%
CD34	15%
SMA	15%
Desmin	10%

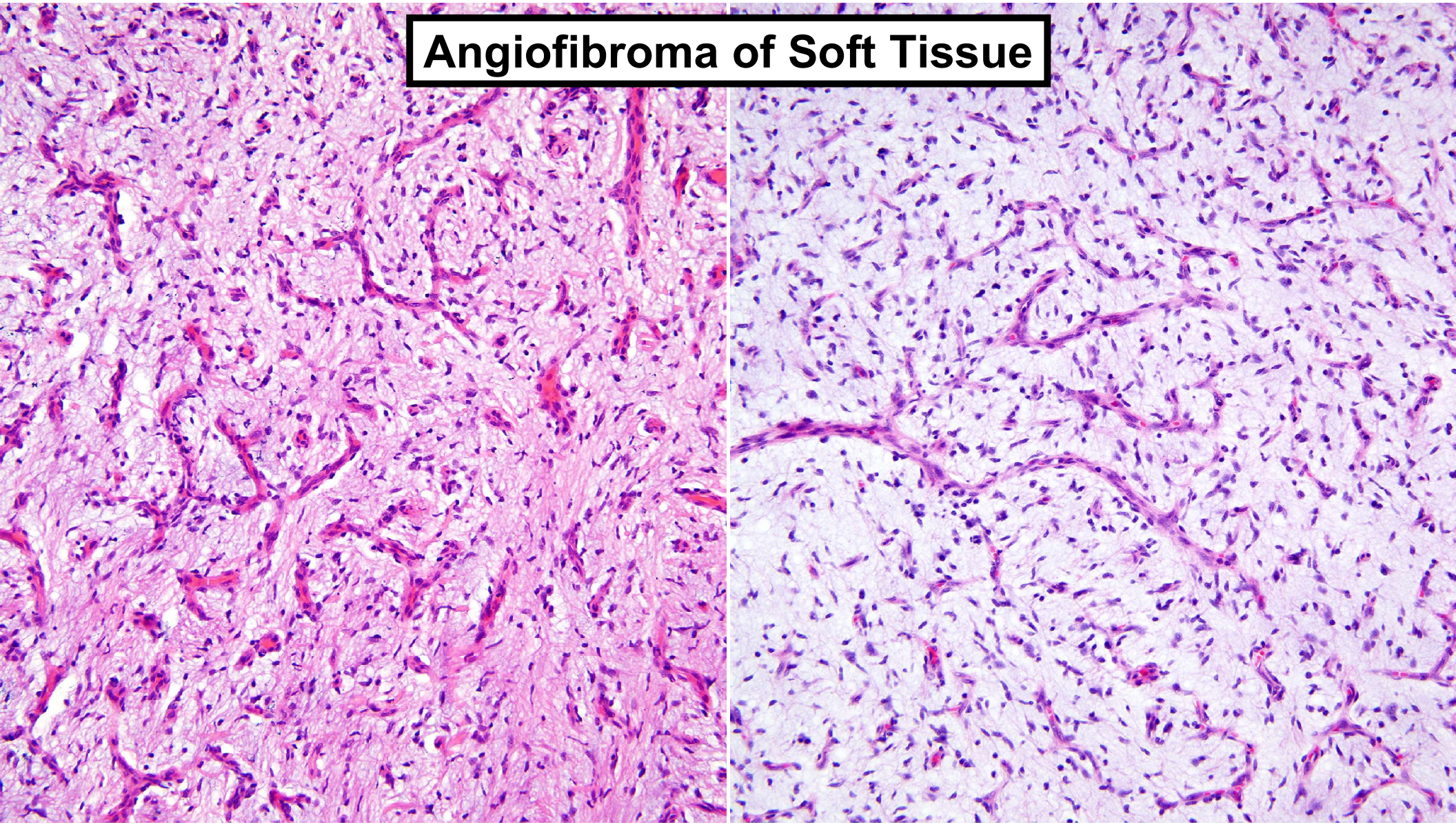
Low rate local recurrence

Angiofibroma of Soft Tissue

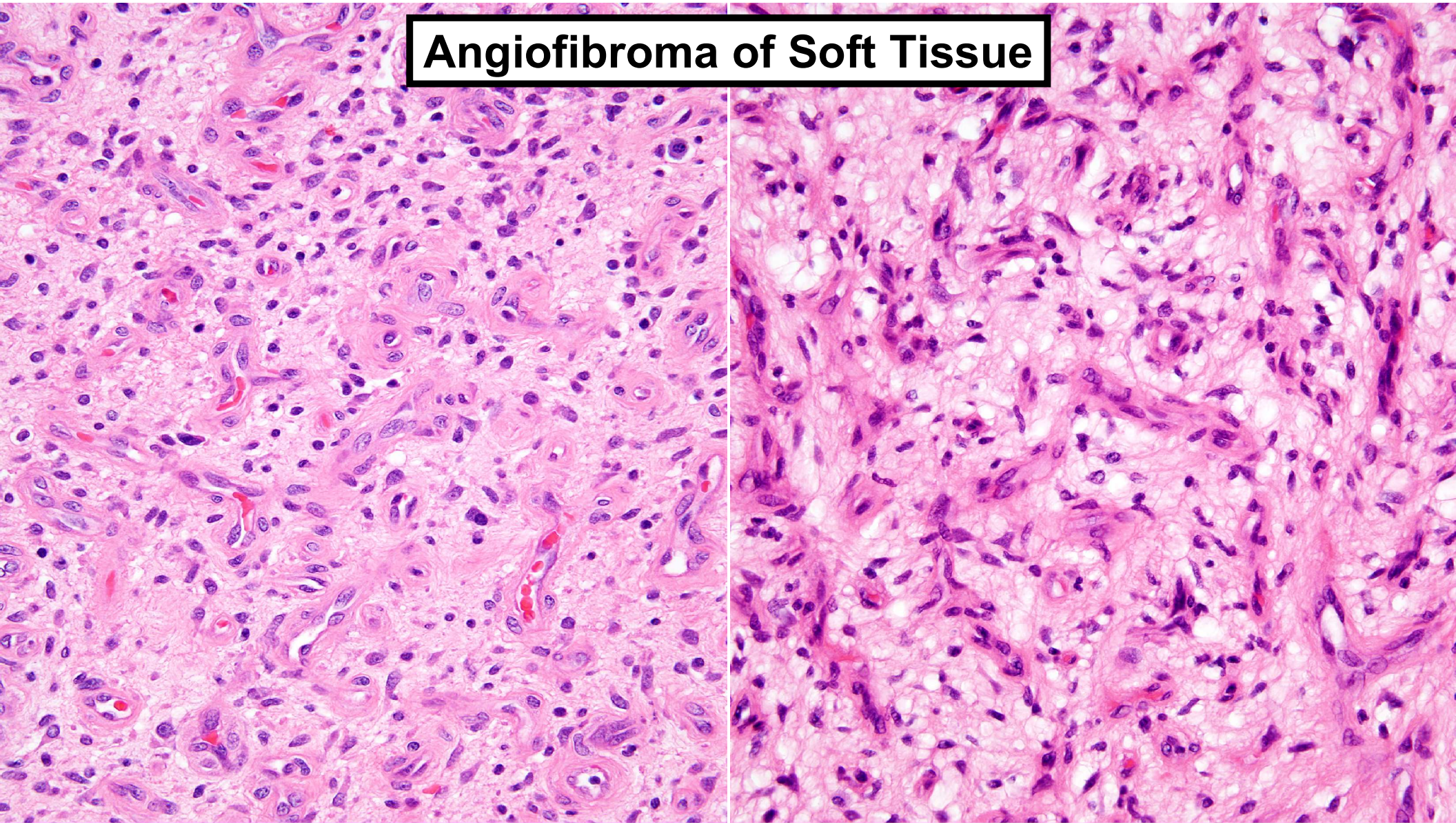



Angiofibroma of Soft Tissue

Angiofibroma of Soft Tissue



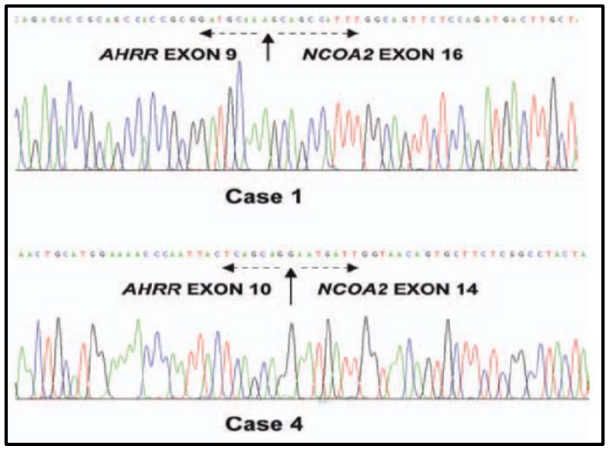
Angiofibroma of Soft Tissue

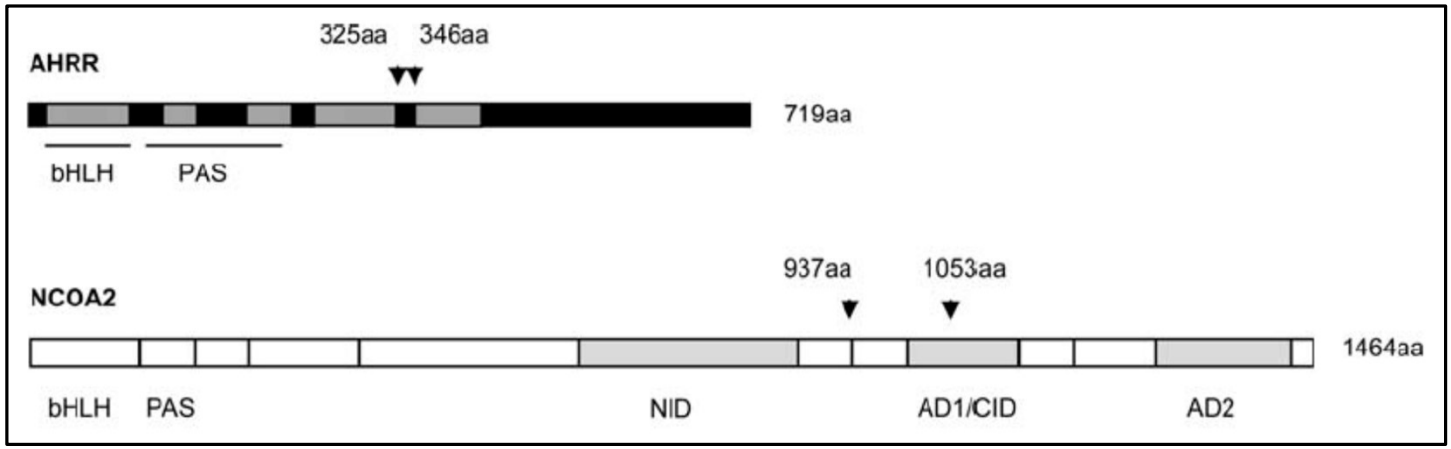


GENES, CHROMOSOMES & CANCER 51:510–520 (2012)

Fusion of the *AHRR* and *NCOA2* Genes Through a Recurrent Translocation t(5;8)(p15;q13) in Soft Tissue Angiofibroma Results in Upregulation of Aryl Hydrocarbon Receptor Target Genes

Yuesheng Jin,[1] Emely Möller,[1] Karolin H. Nord,[1] Nils Mandahl,[1] Fredrik Vult Von Steyern,[2] Henryk A. Domanski,[3] Adrian Mariño-Enríquez,[4] Linda Magnusson,[1] Jenny Nilsson,[1] Raf Sciot,[5] Christopher D. M. Fletcher,[4] Maria Debiec-Rychter,[6] and Fredrik Mertens[1]*

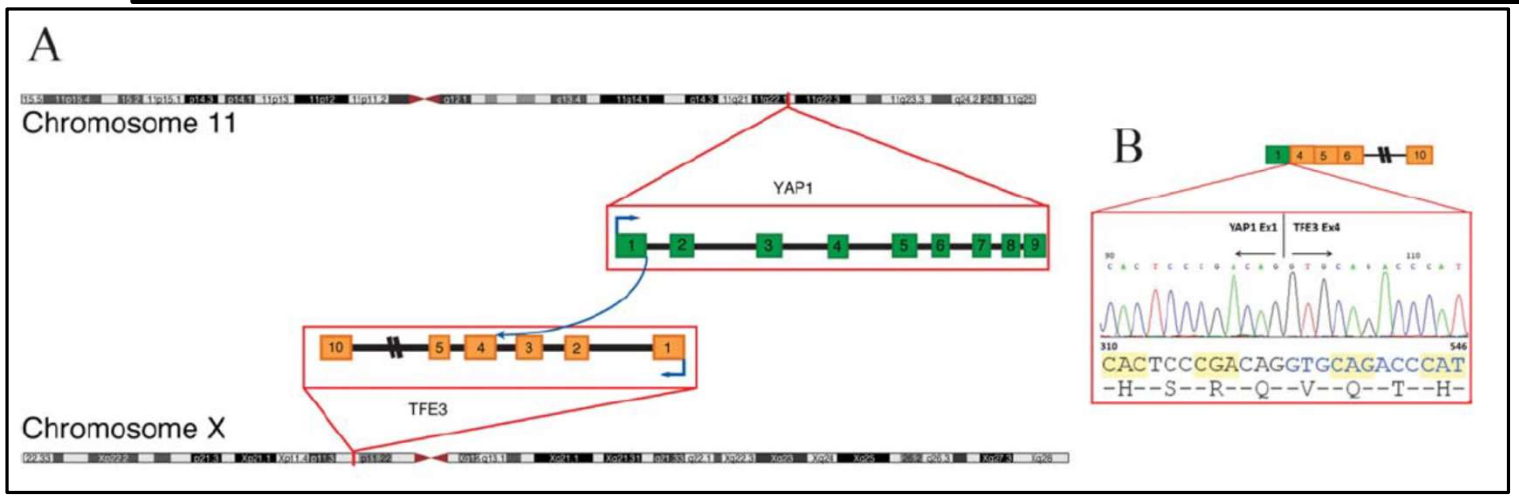


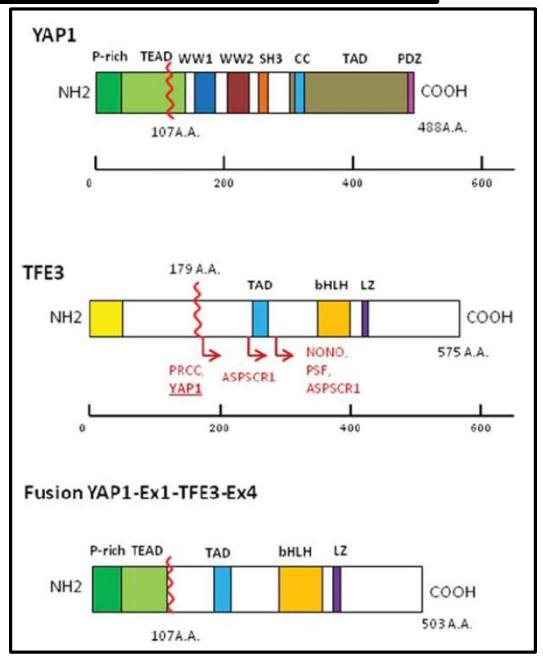


GENES, CHROMOSOMES & CANCER 52:775–784 (2013)

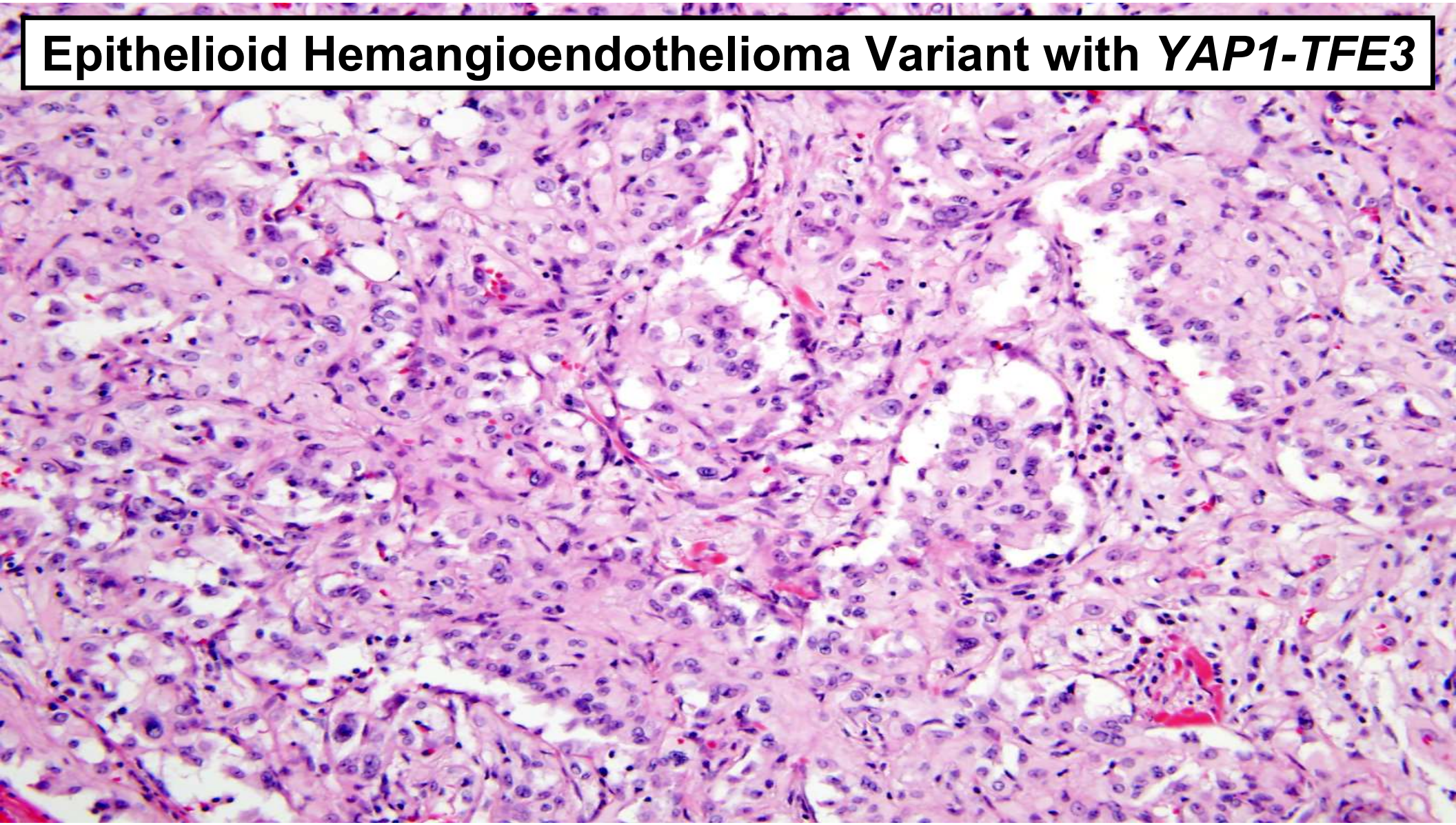
Novel *YAP1-TFE3* Fusion Defines a Distinct Subset of Epithelioid Hemangioendothelioma

Cristina R. Antonescu,[1*] Francois Le Loarer,[1] Juan-Miguel Mosquera,[2] Andrea Sboner,[2,3] Lei Zhang,[1] Chun-Liang Chen,[1] Hsiao-Wei Chen,[1] Nursat Pathan,[4] Thomas Krausz,[5] Brendan C. Dickson,[6] Ilan Weinreb,[7] Mark A. Rubin,[2] Meera Hameed,[1] and Christopher D. M. Fletcher[8*]

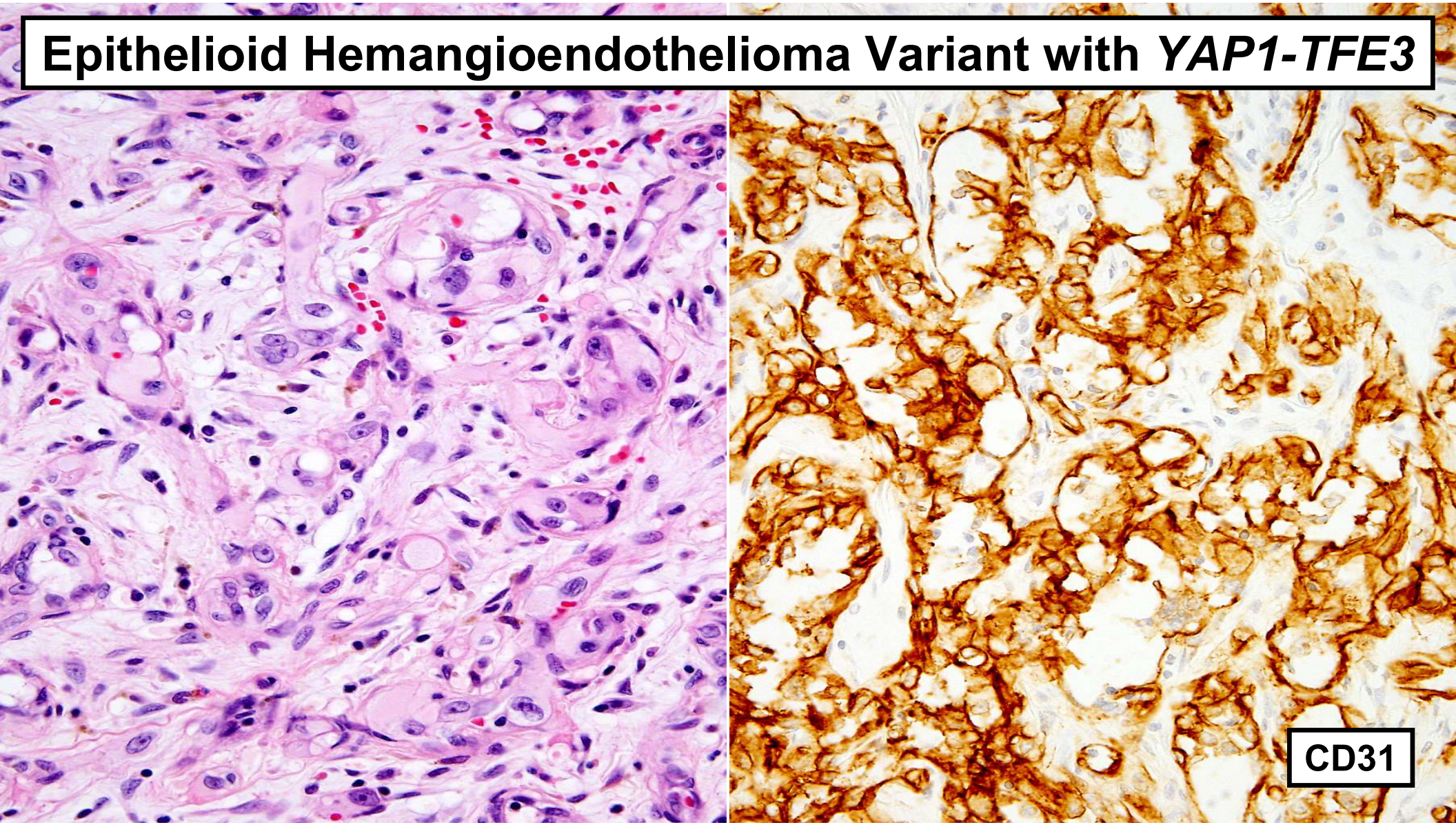




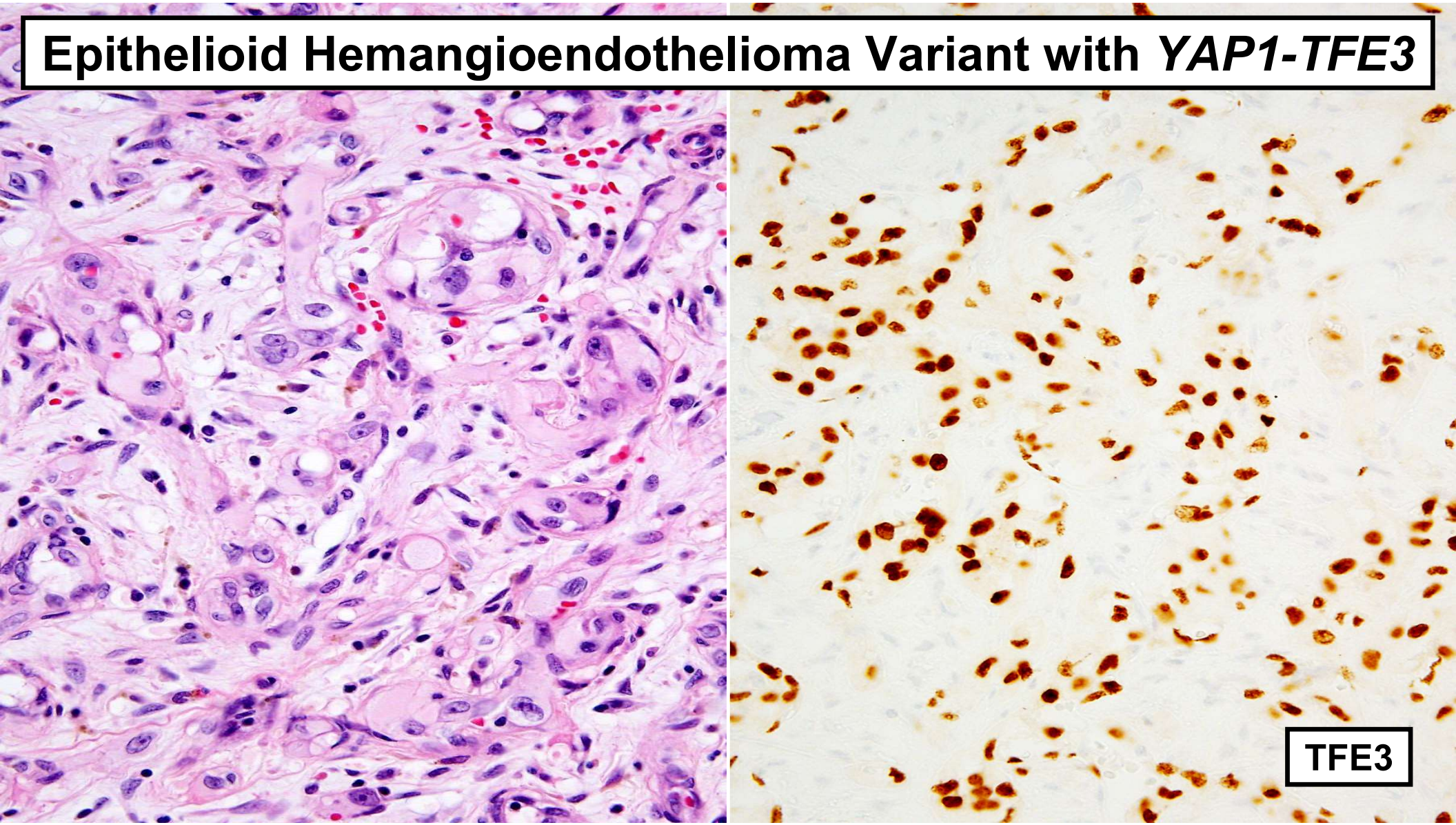
Epithelioid Hemangioendothelioma Variant with *YAP1-TFE3*



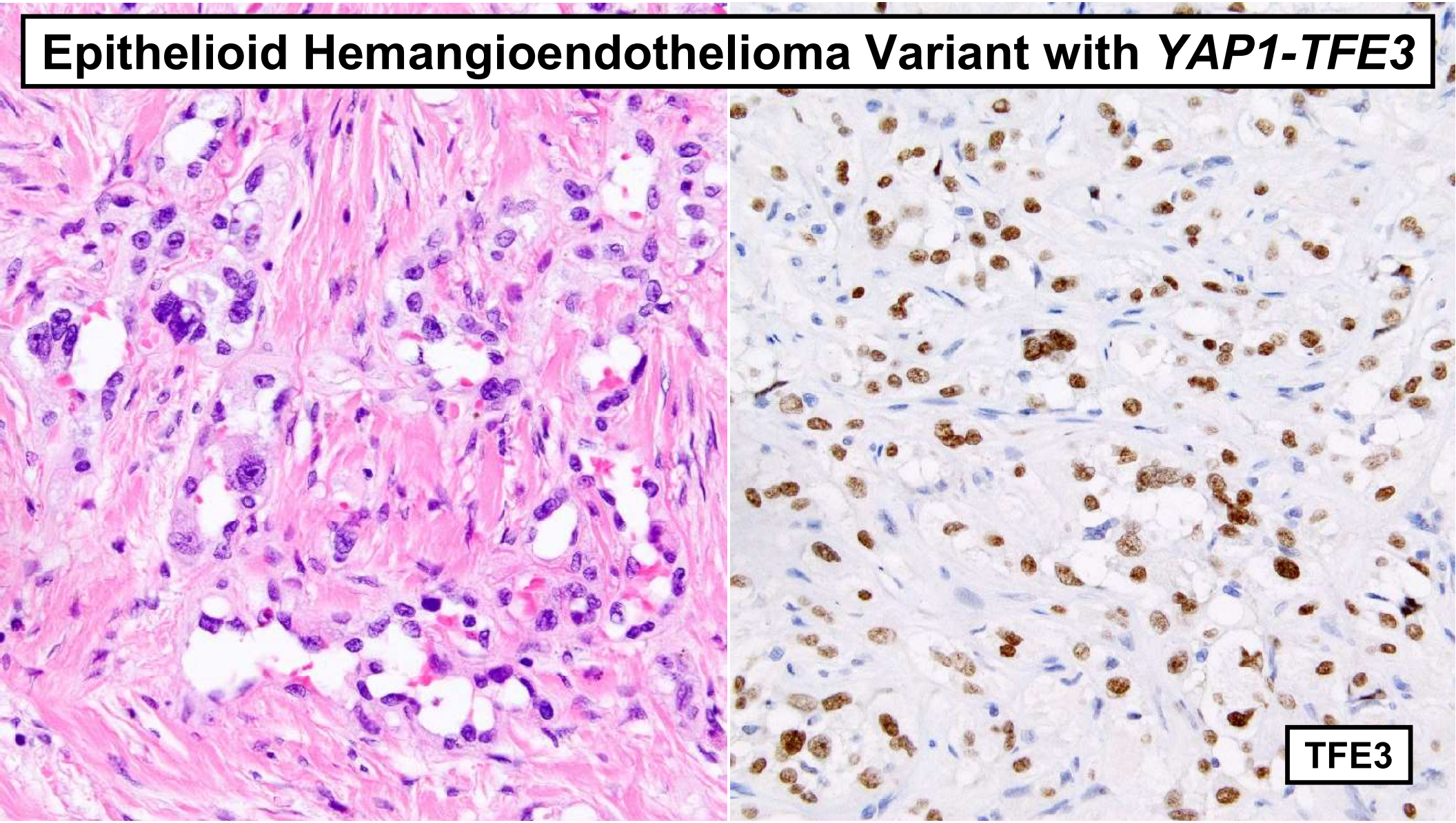
Epithelioid Hemangioendothelioma Variant with *YAP1-TFE3*



Epithelioid Hemangioendothelioma Variant with *YAP1-TFE3*



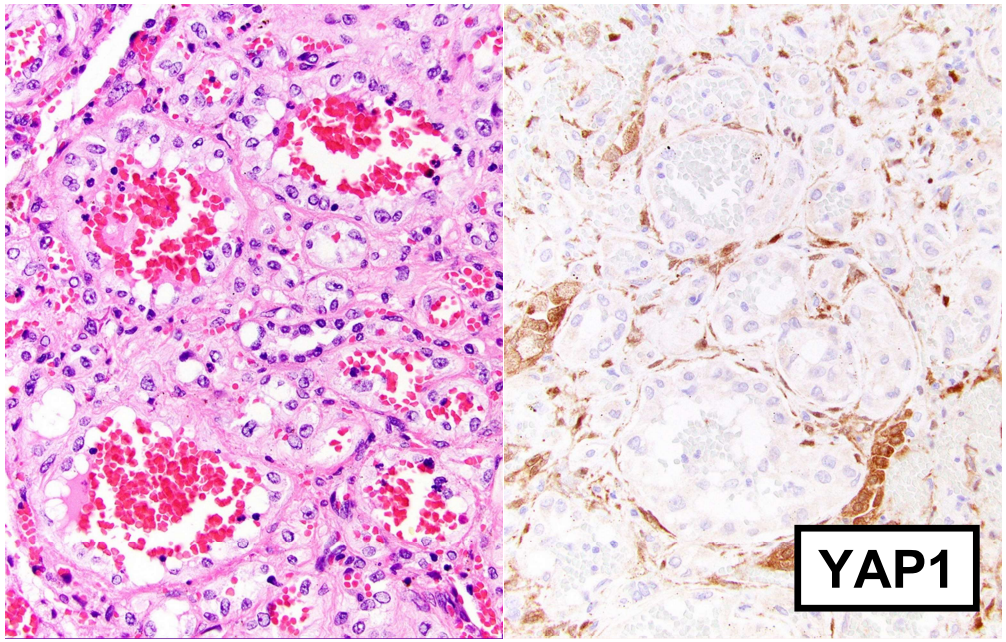
Epithelioid Hemangioendothelioma Variant with *YAP1-TFE3*

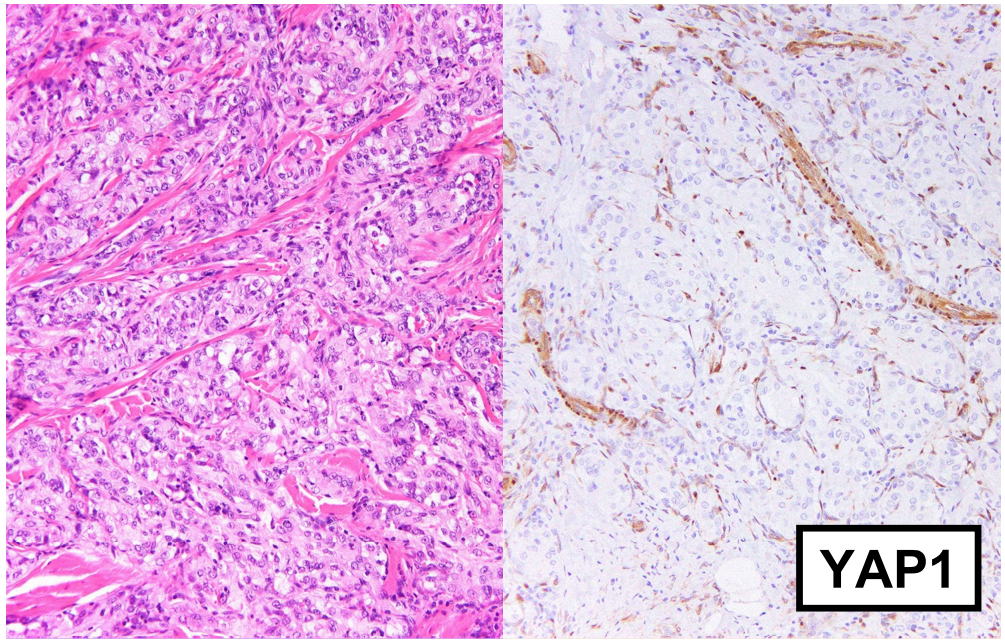


Loss of expression of YAP1 C-terminus as an ancillary marker for epithelioid hemangioendothelioma variant with *YAP1-TFE3* fusion and other YAP1-related vascular neoplasms

William J. Anderson[1], Christopher D. M. Fletcher[1] and Jason L. Hornick[1] ✉

Modern Pathology (2021) 34:2036 – 2042





WHO 2020: NEW CONCEPTS

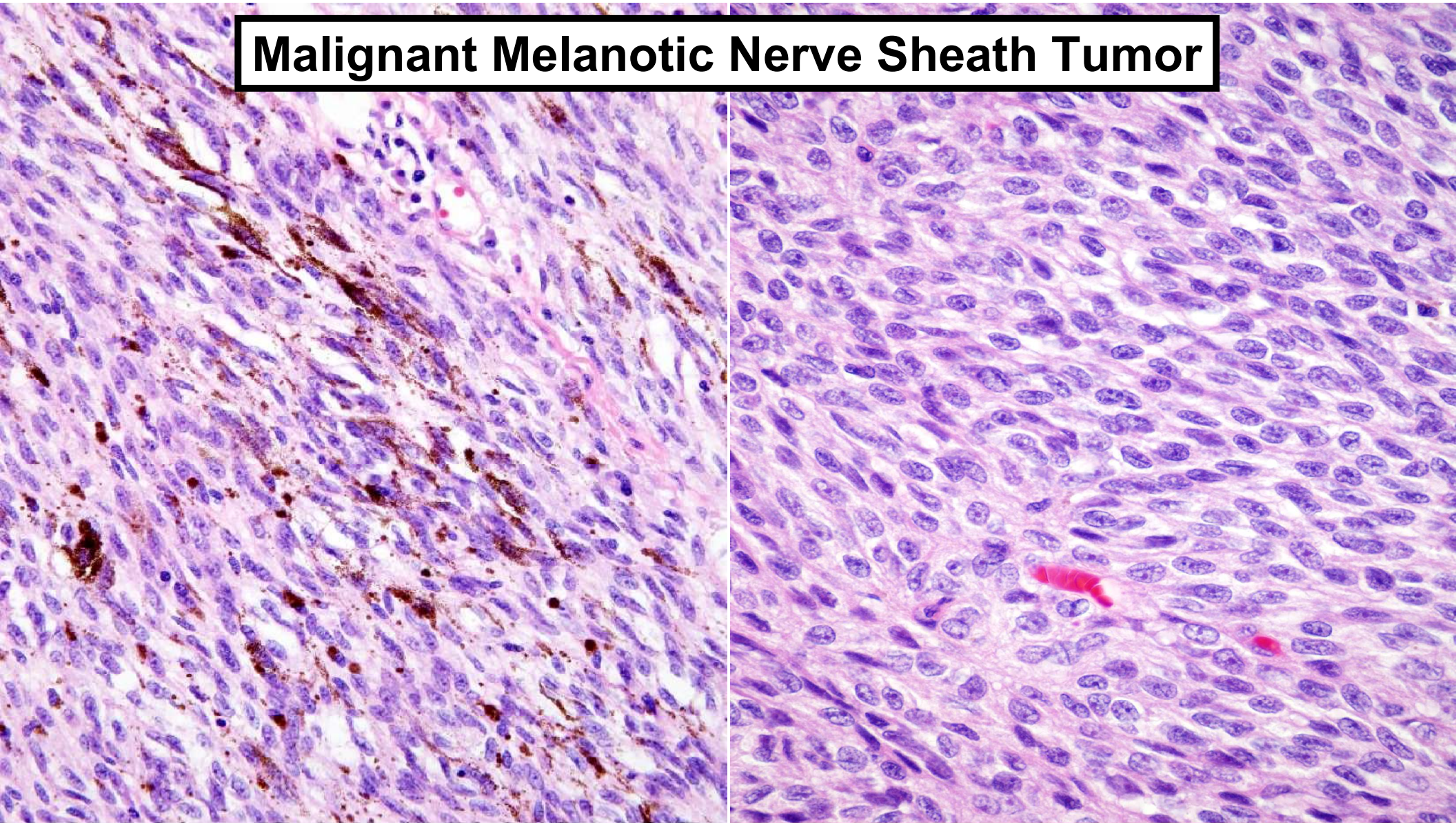
Tumor types	What's new?
Malignant melanotic nerve sheath tumor	New nomenclature
Solitary fibrous tumor	Risk stratification

Malignant Melanotic Nerve Sheath Tumor

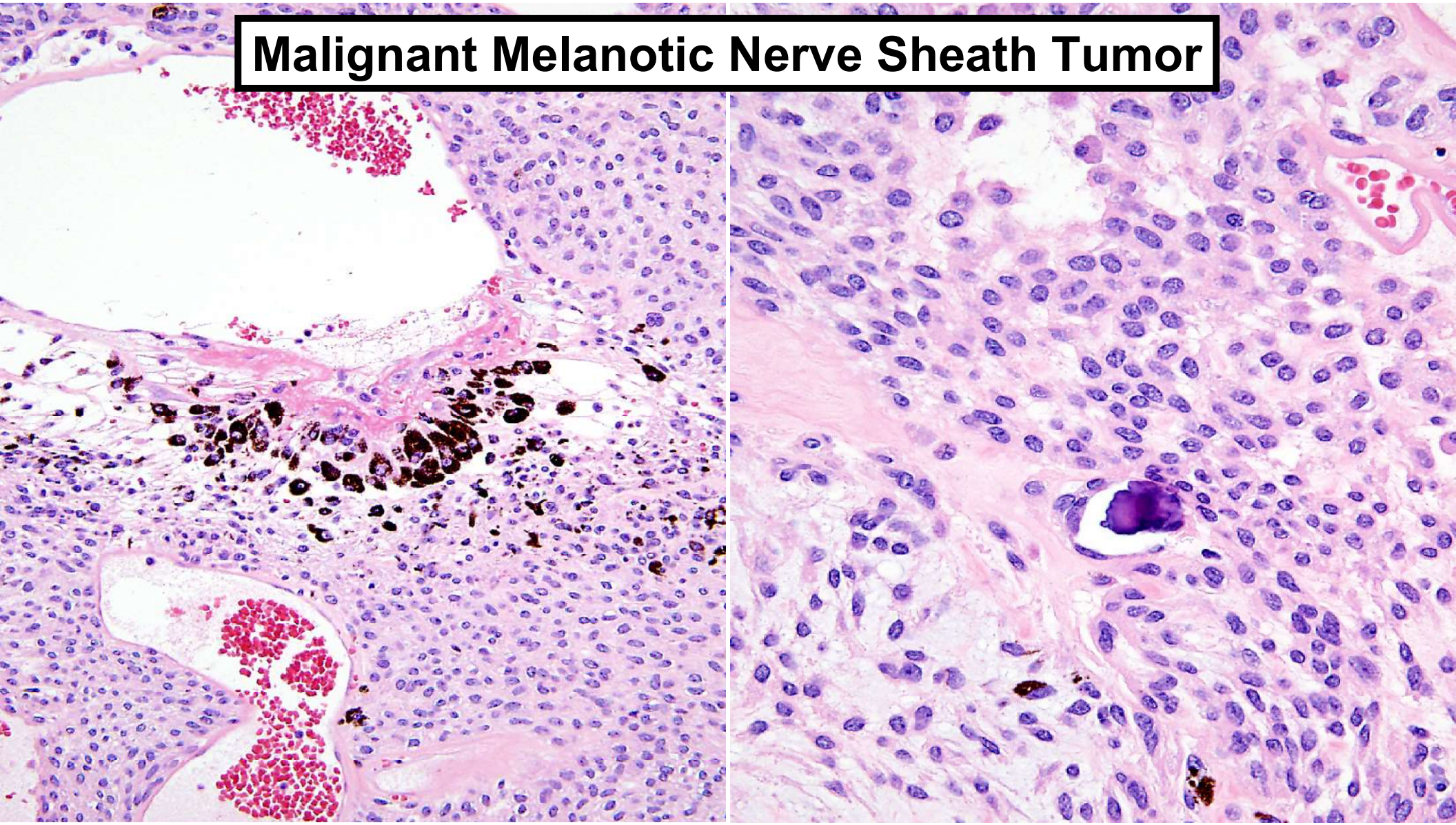
- Previously known as melanotic schwannoma
- Rare peripheral nerve sheath tumor composed of Schwann cells with melanocytic differentiation
- Usually associated with spinal or autonomic nerves
- Variable association with Carney complex
- Locally aggressive with significant metastatic potential
- Behavior difficult to predict


Malignant Melanotic Nerve Sheath Tumor

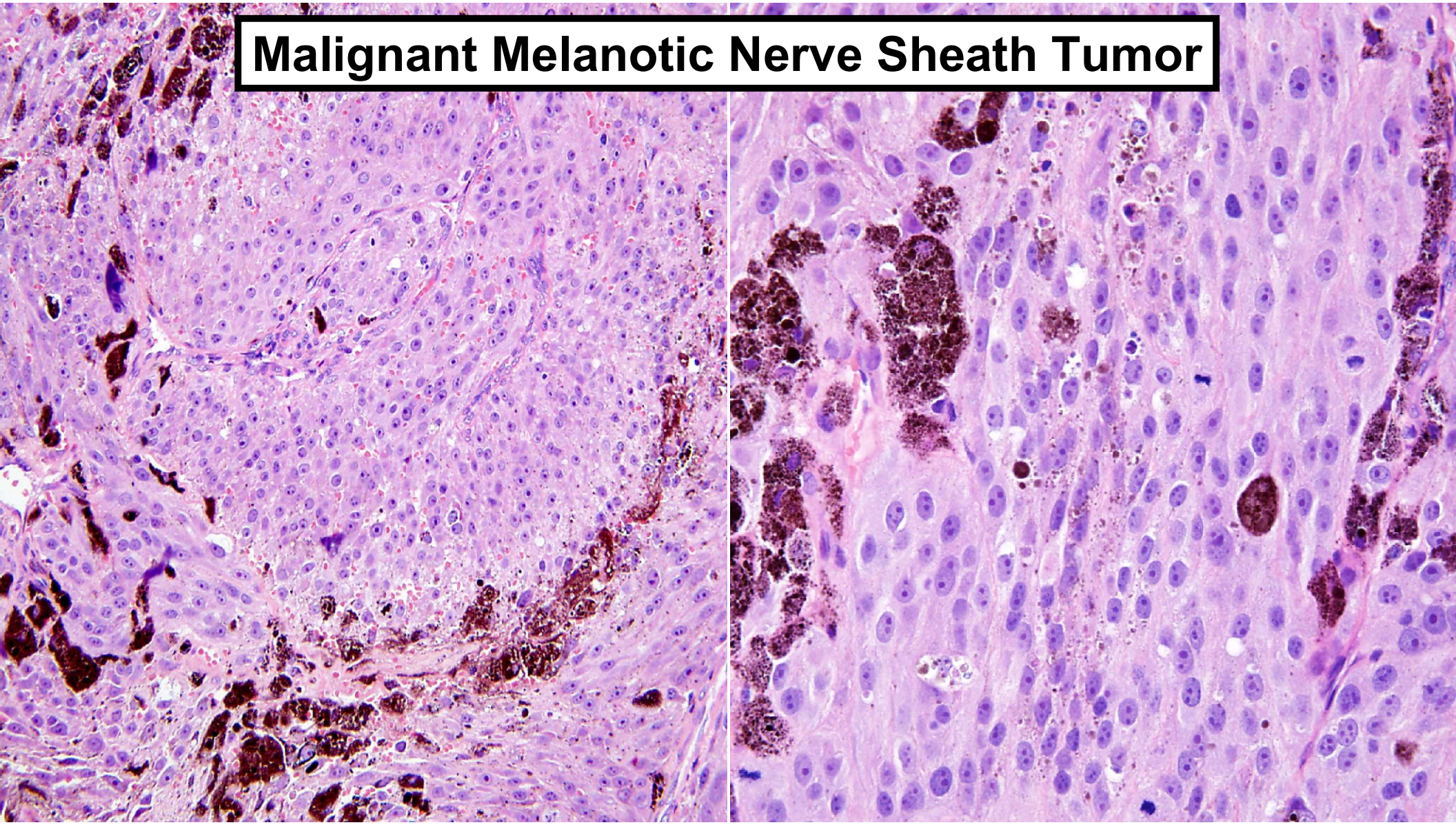
Malignant Melanotic Nerve Sheath Tumor

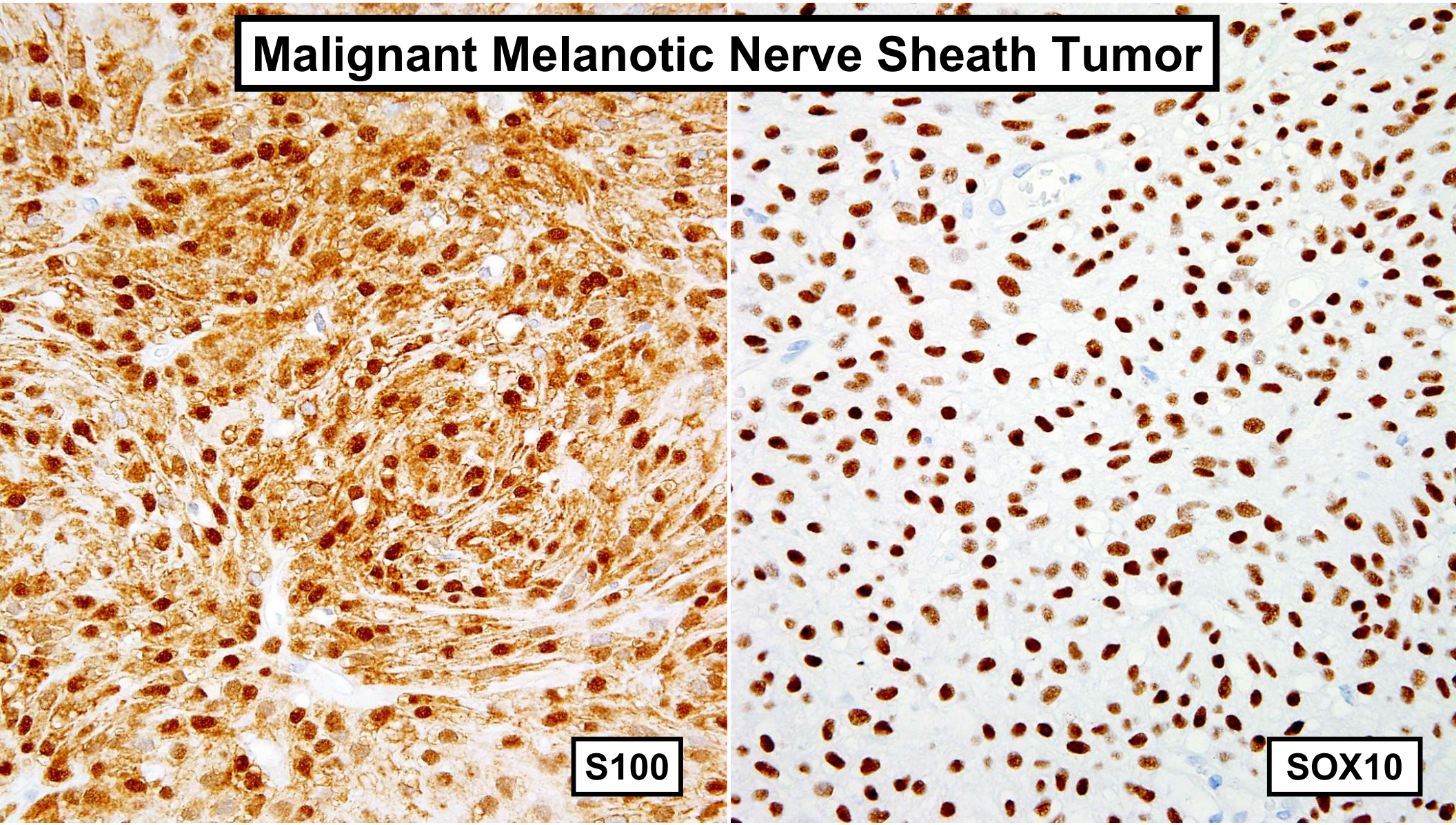


Malignant Melanotic Nerve Sheath Tumor



Malignant Melanotic Nerve Sheath Tumor

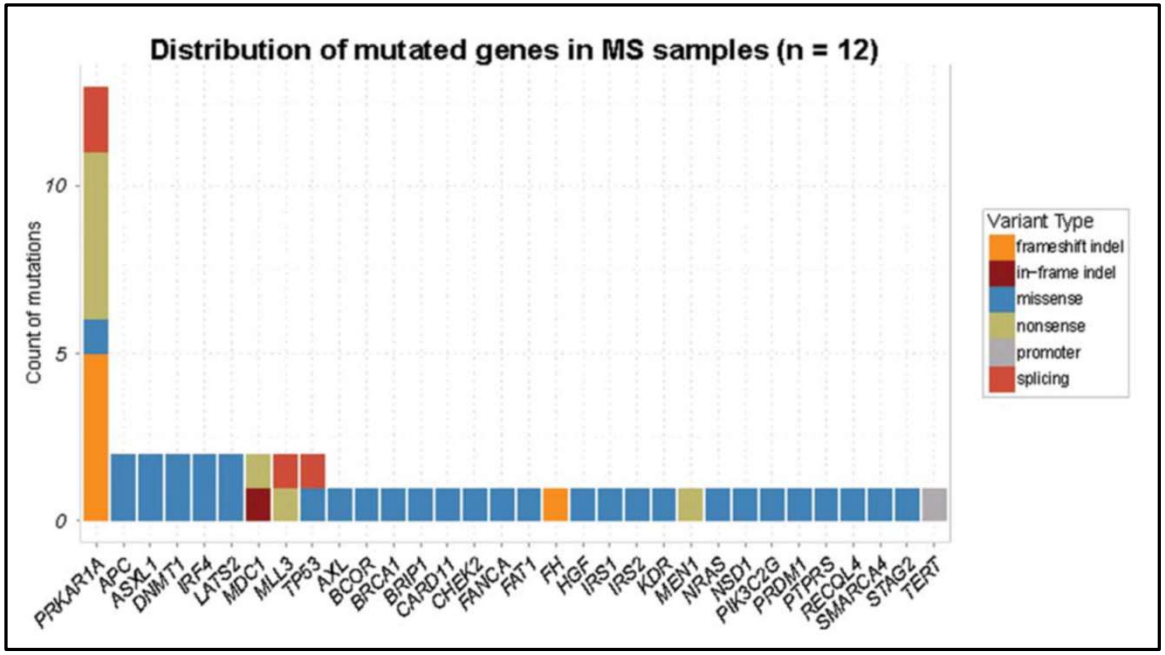


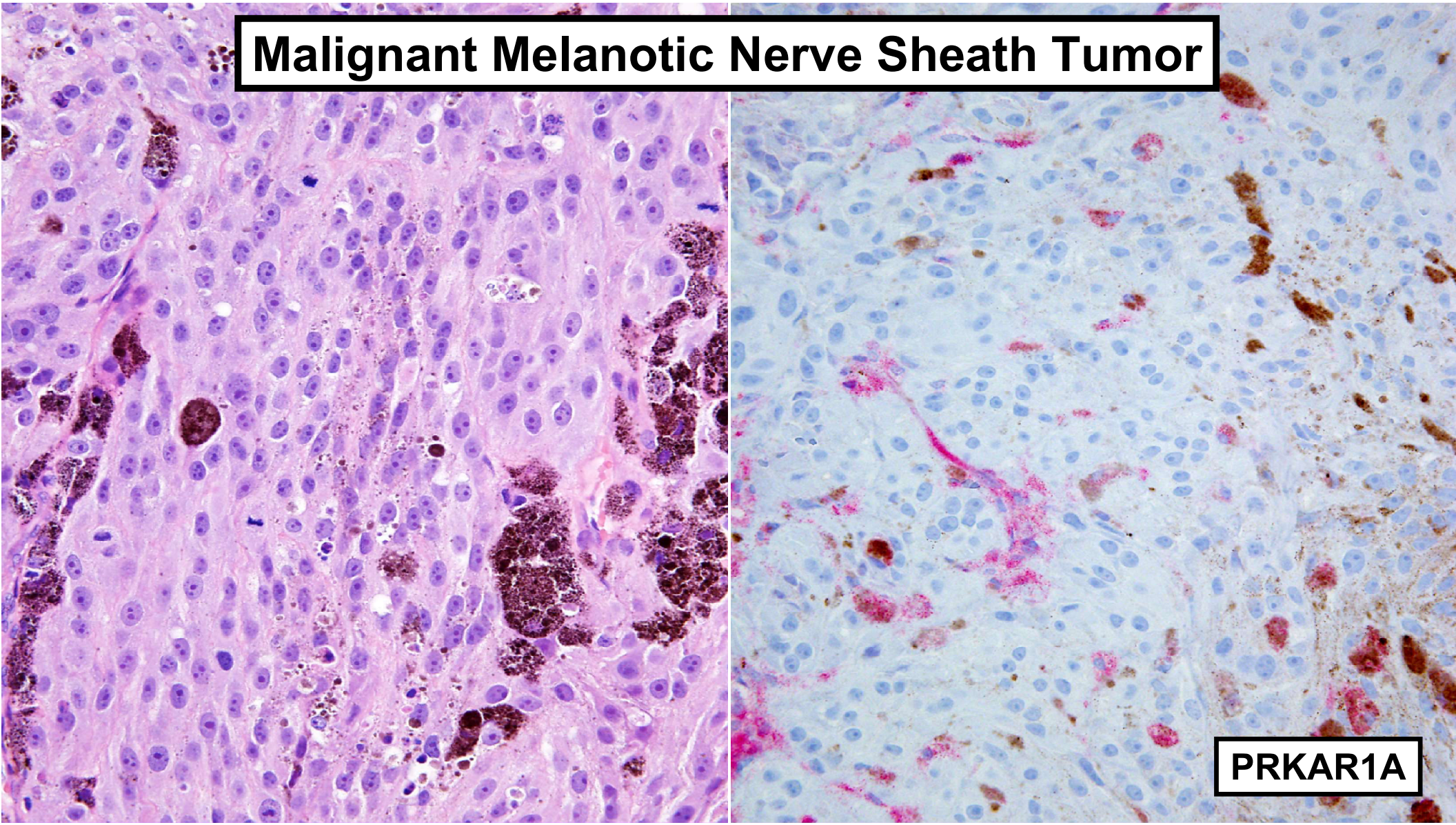

Malignant Melanotic Nerve Sheath Tumor
S100
SOX10

GENES, CHROMOSOMES & CANCER 54:463–471 (2015)

Consistent Copy Number Changes and Recurrent *PRKAR1A* Mutations Distinguish Melanotic Schwannomas from Melanomas: SNP-Array and Next Generation Sequencing Analysis

Lu Wang,[1] Ahmet Zehir,[1] Justyna Sadowska,[1] Nengyi Zhou,[1] Marc Rosenblum,[1] Klaus Busam,[1] Narasimhan Agaram,[1] William Travis,[1] Maria Arcila,[1] Snjezana Dogan,[1] Michael F. Berger,[1,2] Donavan T. Cheng,[1] Marc Ladanyi,[1,2] Khedoudja Nafa,[1] and Meera Hameed[1]*




Malignant Melanotic Nerve Sheath Tumor
PRKAR1A

Am J Surg Pathol • Volume 38, Number 1, January 2014

Malignant Melanotic Schwannian Tumor

A Clinicopathologic, Immunohistochemical, and Gene Expression Profiling Study of 40 Cases, With a Proposal for the Reclassification of "Melanotic Schwannoma"

Jorge Torres-Mora, MD, Sarah Dry, MD,† Xinmin Li, PhD,† Scott Binder, MD,† Mitual Amin, MD,‡ and Andrew L. Folpe, MD**

Local recurrence: 35%
Metastasis: 44%

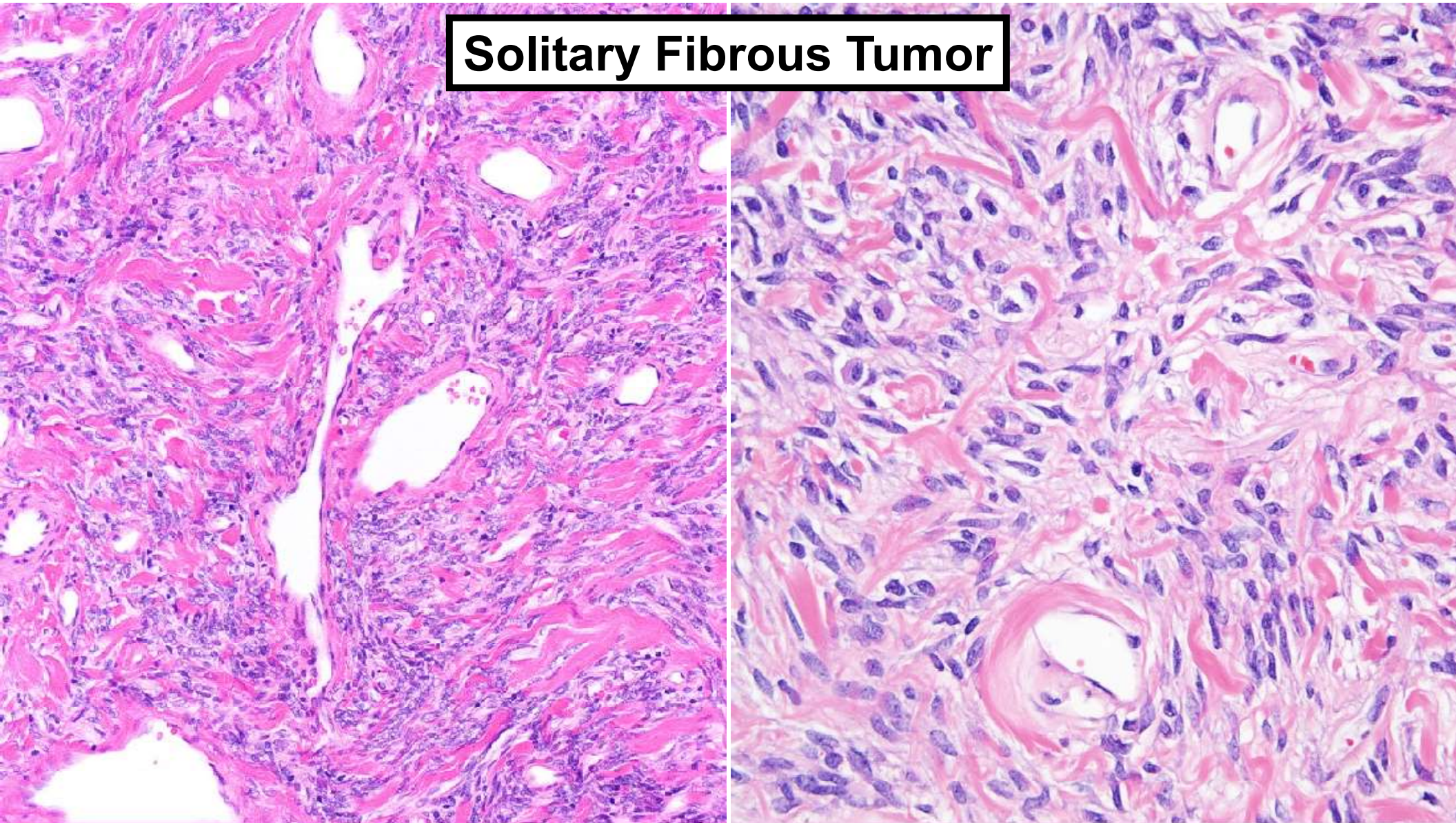
TABLE 2. Correlation of Pathologic Features With Metastases

Pathologic Feature	Metastases	*P* (Fisher Exact Test)
Mitotic activity >1/10 HPF		
Present	5/5	0.008
Absent	6/20	
Necrosis		
Present	3/7	1 (NS)
Absent	8/18	
Macronucleoli		
Present	5/11	1 (NS)
Absent	6/14	
Small cell change		
Present	2/3	0.56 (NS)
Absent	9/22	
Nuclear pleomorphism		
Present	4/8	1 (NS)
Absent	7/17	
Psammoma bodies		
Present	4/10	1 (NS)
Absent	7/15	

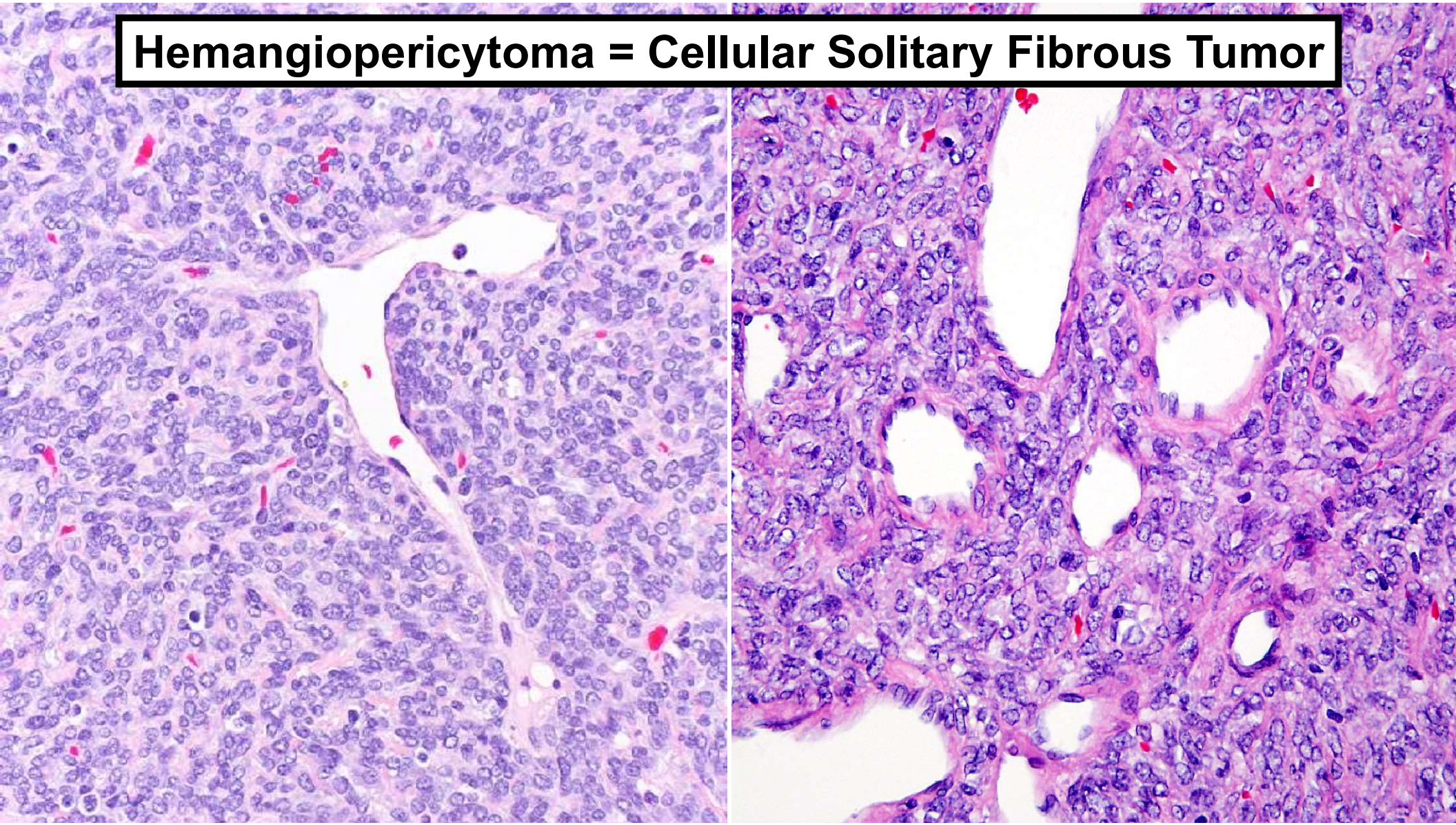
Solitary Fibrous Tumor

- Anatomically ubiquitous fibroblastic neoplasm (pleura, retroperitoneum, abdomen, head & neck)
- "Patternless" architecture, varying cellularity, prominent stromal collagen, dilated branching ("staghorn") vessels
- "Hemangiopericytoma" synonymous with SFT (uniform hypercellularity)
- CD34 positive in 95% of cases, but not specific
- Notoriously difficult to predict clinical behavior
- Mitotic rate ≥4 per 10 HPF = malignant?

Solitary Fibrous Tumor



Hemangiopericytoma = Cellular Solitary Fibrous Tumor



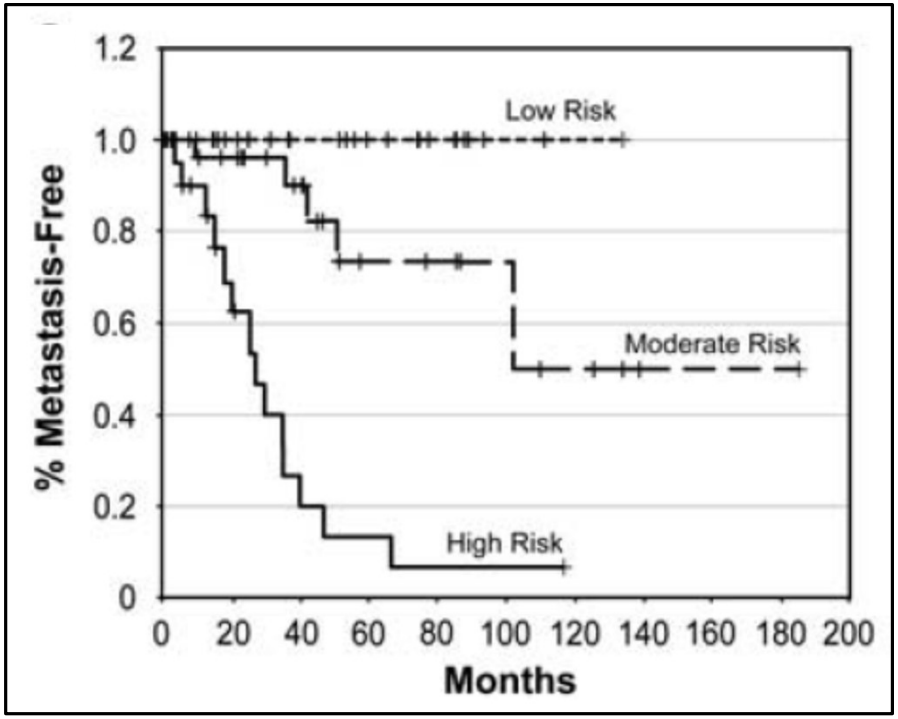
MODERN PATHOLOGY (2012) 25, 1298–1306

Solitary fibrous tumor: a clinicopathological study of 110 cases and proposed risk assessment model

Elizabeth G Demicco[1], Min S Park[2], Dejka M Araujo[2], Patricia S Fox[3], Roland L Bassett[3], Raphael E Pollock[4], Alexander J Lazar[1,5] and Wei-Lien Wang[1]

Table 5 Risk stratification model

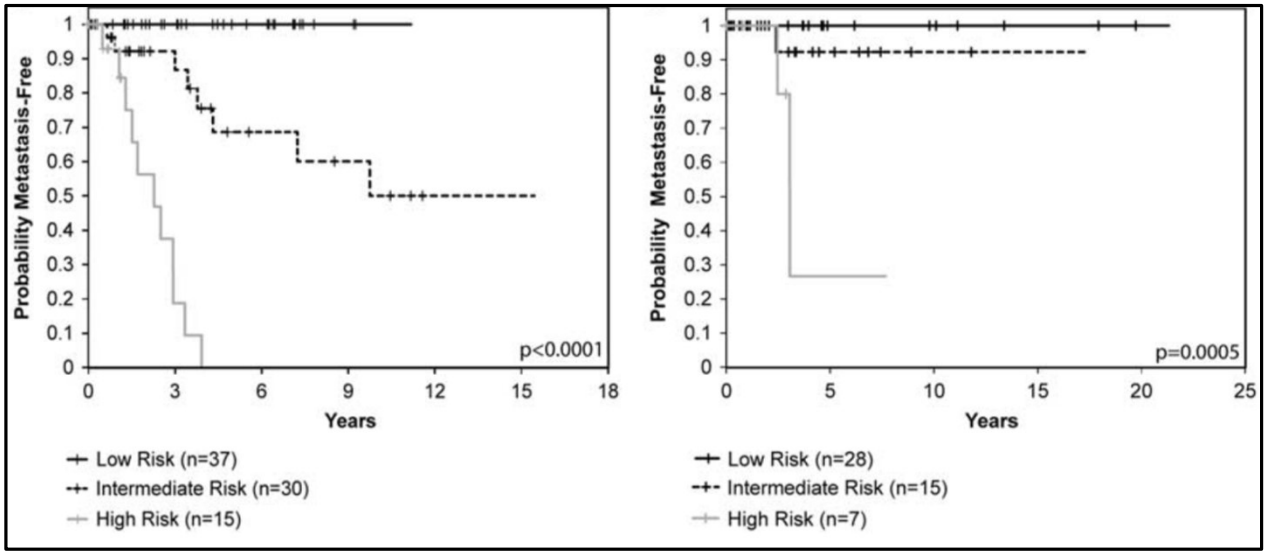
Risk factor	*Score*
Age	
<55	0
⩾55	1
Tumor size (cm)	
<5	0
5 to <10	1
10 to <15	2
⩾15	3
Mitotic figures (/10 high-power fields)	
0	0
1–3	1
⩾4	2
Risk	*Total score*
Low	0–2
Moderate	3–4
High	5–6



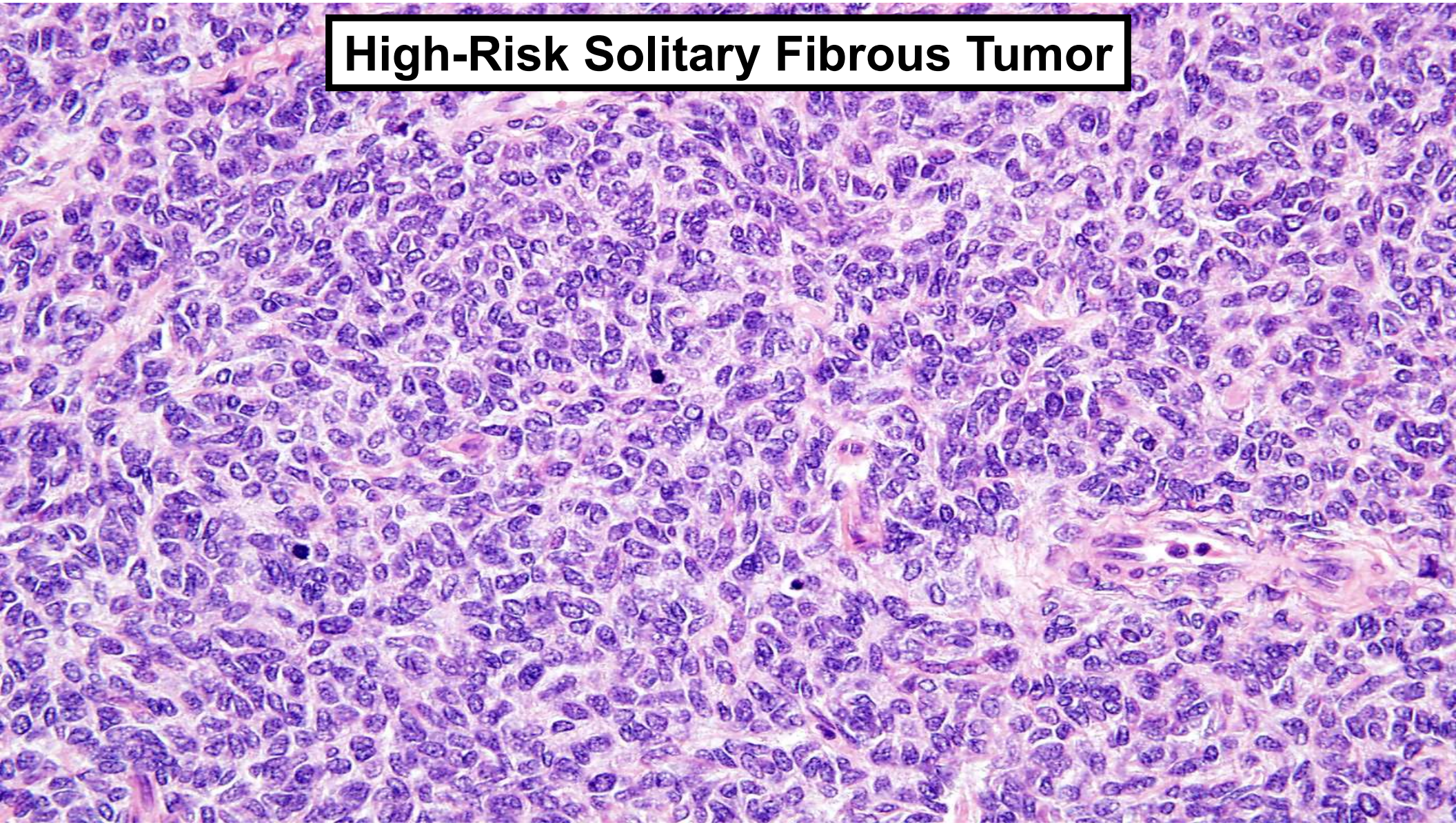
MODERN PATHOLOGY (2017) 30, 1433–1442

Risk assessment in solitary fibrous tumors: validation and refinement of a risk stratification model

Elizabeth G Demicco[1], Michael J Wagner[2], Robert G Maki[3,4], Vishal Gupta[5], Ilya Iofin[6], Alexander J Lazar[7] and Wei-Lien Wang[7]



Risk factor	*Score*
Age	
< 55	0
≥ 55	1
Tumor size (cm)	
< 5	0
5 to < 10	1
10 to < 15	2
≥ 15	3
Mitotic count (/10 high-power fields)	
0	0
1–3	1
≥ 4	2
Tumor necrosis	
< 10%	0
≥ 10%	1
Risk class	*Total score*
Low	0–3
Intermediate	4–5
High	6–7


High-Risk Solitary Fibrous Tumor

WHO 2020: NEW GENETICS

Fibroblastic/myofibroblastic tumors

Tumor type	New genetic alterations
Fibrous hamartoma of infancy	*EGFR* mutations
Calcifying aponeurotic fibroma	*FN1::EGF*
Lipofibromatosis	*FN1::EGF*, other RTK or EGFR ligand fusions
Dermatofibrosarcoma protuberans	*COL6A3::PDGFD*, *EMILIN2::PDGFD*
Solitary fibrous tumor	*NAB2::STAT6*
Myxoinflammatory fibroblastic sarcoma	*BRAF* fusions
Infantile fibrosarcoma	*EML4::NTRK3*, *NTRK1*, *NTRK2*, *BRAF*, *MET* fusions

Pericytic (perivascular) tumors

Tumor type	New genetic alterations
Glomus tumor	*MIR143::NOTCH1/2/3*
Myopericytoma/myofibroma	*PDGFRB* mutations, *SRF::RELA* (cellular myofibroma)

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Vascular tumors

Tumor type	New genetic alterations
Epithelioid hemangioma	*FOS* and *FOSB* fusions
Pseudomyogenic hemangioendothelioma	*SERPINE1::FOSB*, *ACTB::FOSB*

Skeletal muscle tumors

Tumor type	New genetic alterations
Spindle cell/sclerosing rhabdomyosarcoma	*MYOD1* mutations (adolescents/adults)
	SRF::NCOA2, *TEAD1::NCOA2*, *VGLL2::NCOA2*, *VGLL2::CITED2* (congenital/infantile)
	EWSR1::TFCP2, *FUS::TFCP2* (intraosseous; spindle cell and epithelioid)

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Vascular tumors

Tumor type	New genetic alterations
Epithelioid hemangioma	*FOS* and *FOSB* fusions
Pseudomyogenic hemangioendothelioma	*SERPINE1::FOSB*, *ACTB::FOSB*

Skeletal muscle tumors

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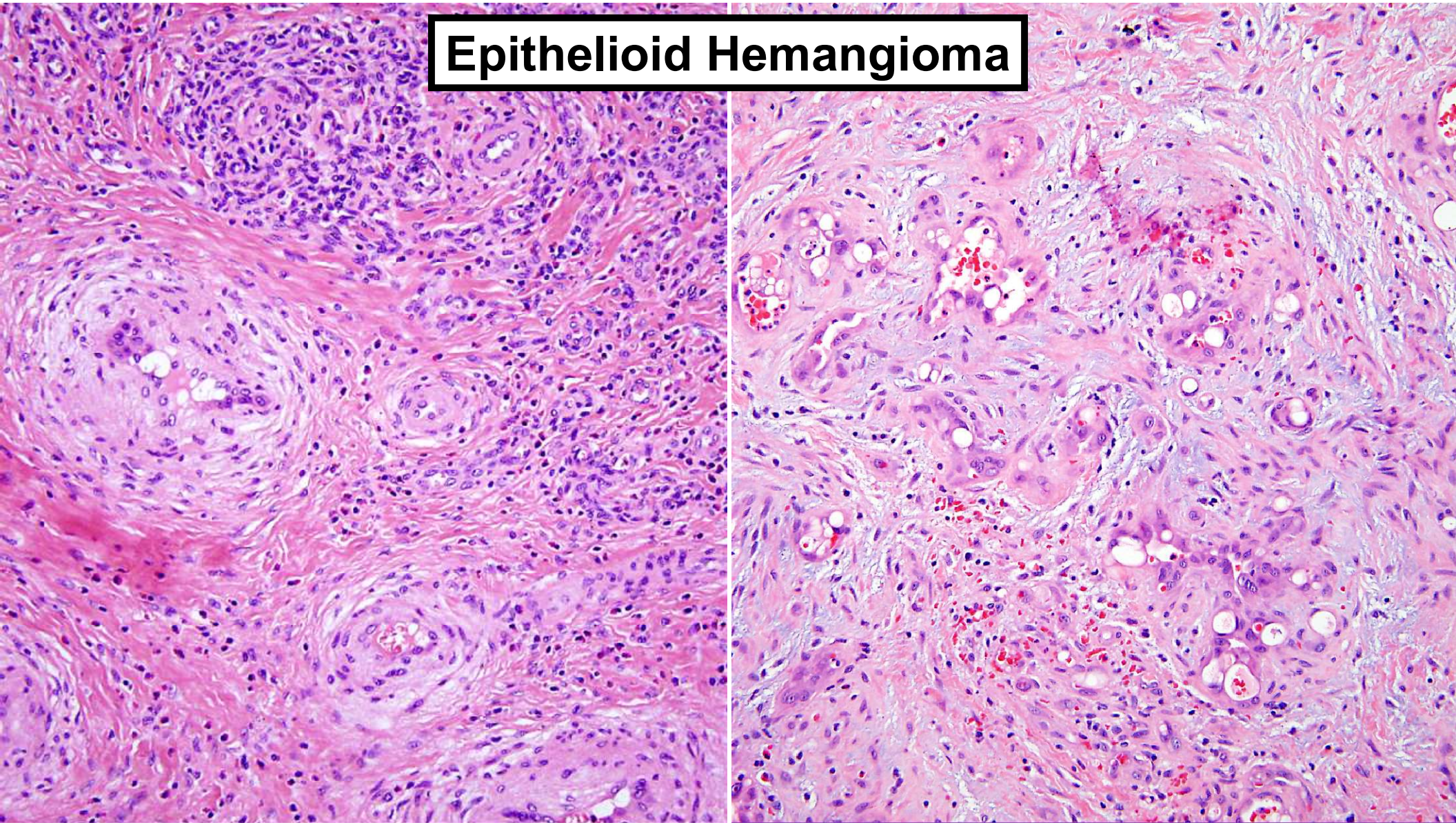
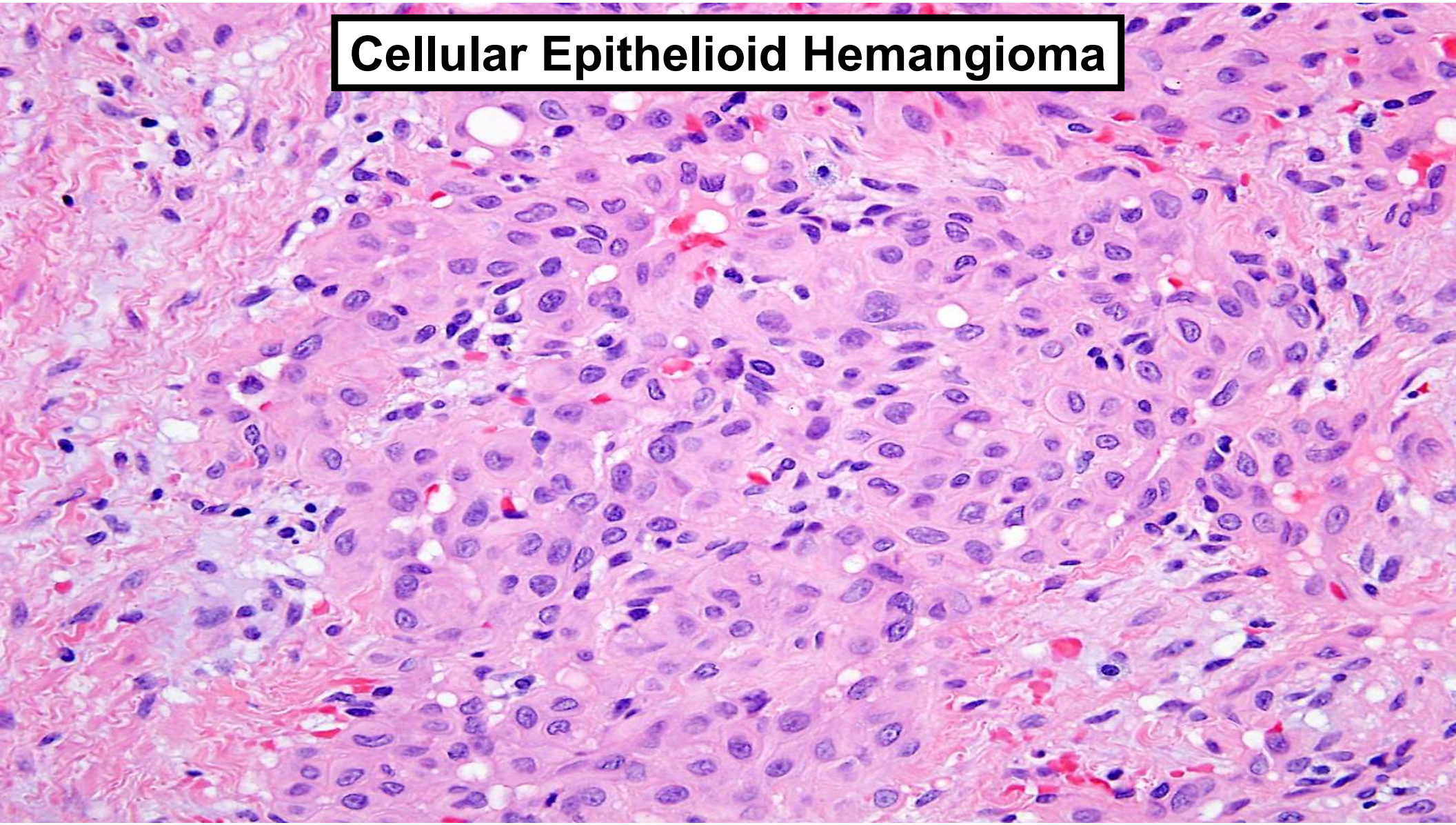
Epithelioid Hemangioma

- Subset also known as angiolymphoid hyperplasia with eosinophilia (head and neck)
- Head and neck (especially peri-auricular), bone, penis
- Small subcutaneous nodule +/- tender or pruritic
- 20% multiple lesions
- Up to 1/3 recur locally
- Cellular examples with poor canalization may be misdiagnosed as malignant (but minimal nuclear atypia)

Epithelioid Hemangioma




Cellular Epithelioid Hemangioma

GENES, CHROMOSOMES & CANCER 53:951–959 (2014)

ZFP36-FOSB Fusion Defines a Subset of Epithelioid Hemangioma with Atypical Features

Cristina R Antonescu,[1*] Hsiao-Wei Chen,[1] Lei Zhang,[1] Yun-Shao Sung,[1] David Panicek,[2] Narasimhan P Agaram,[1] Brendan C Dickson,[3] Thomas Krausz,[4] and Christopher D Fletcher[5*]

Frequent *FOS* Gene Rearrangements in Epithelioid Hemangioma

A Molecular Study of 58 Cases With Morphologic Reappraisal

Shih-Chiang Huang, MD,† Lei Zhang, MD,† Yun-Shao Sung, MSc,† Chun-Liang Chen, MSc,† Thomas Krausz, MD,‡ Brendan C. Dickson, MD,§ Yu-Chien Kao, MD,‖ Narasimhan P. Agaram, MBBS,† Christopher D.M. Fletcher, MD, FRCPath,¶ and Cristina R. Antonescu, MD†*

Am J Surg Pathol • Volume 39, Number 10, October 2015

GENES, CHROMOSOMES & CANCER 54:565–574 (2015)

Fusion Events Lead to Truncation of *FOS* in Epithelioid Hemangioma of Bone

David G. P. van IJzendoorn,[1] Danielle de Jong,[2] Cleofe Romagosa,[3] Piero Picci,[4] Maria Serena Benassi,[4] Marco Gambarotti,[4] Soeren Daugaard,[5] Michiel van de Sande,[6] Karoly Szuhai,[2] and Judith V. M. G. Bovée[1*]

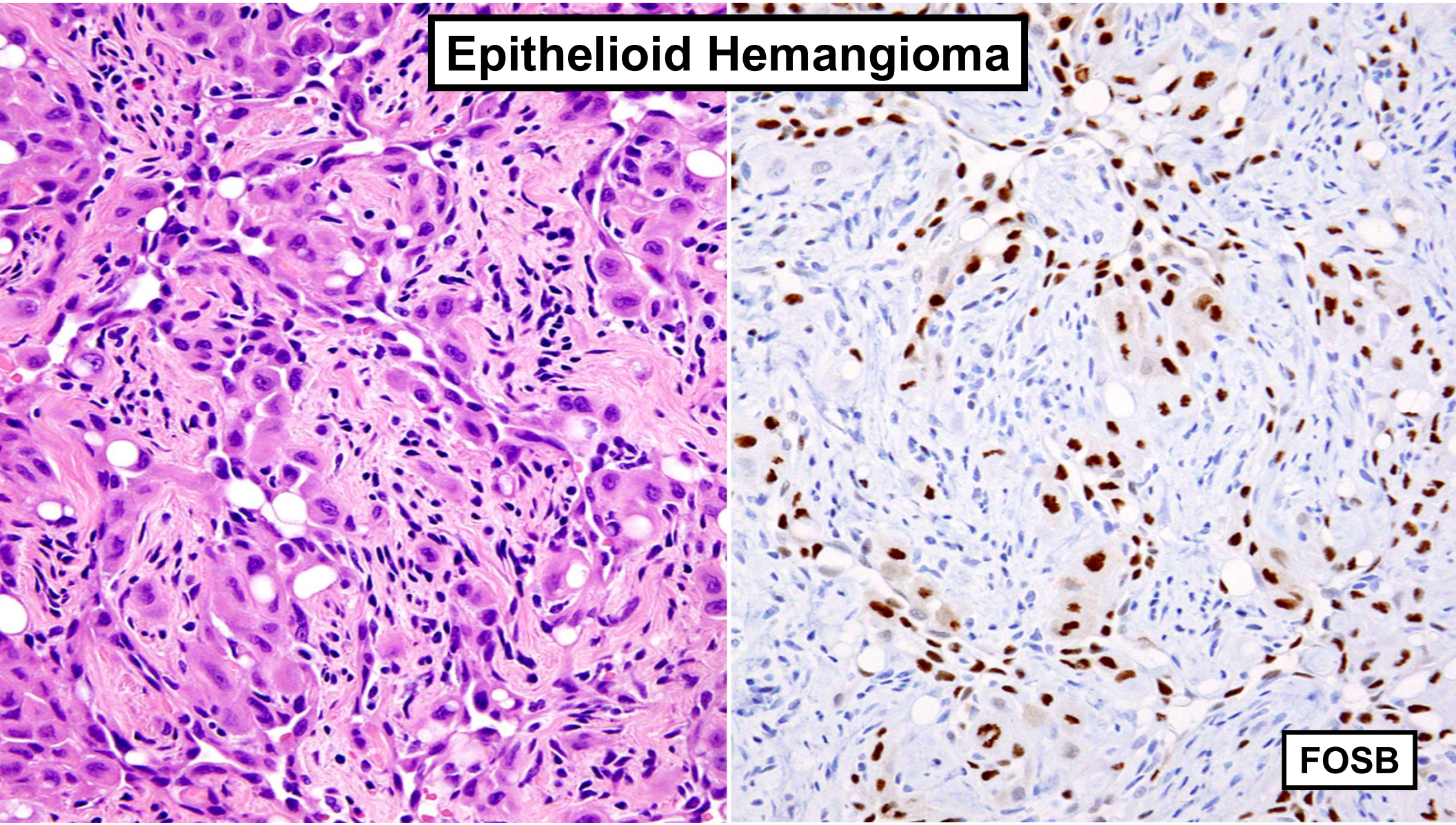
FOSB is a Useful Diagnostic Marker for Pseudomyogenic Hemangioendothelioma

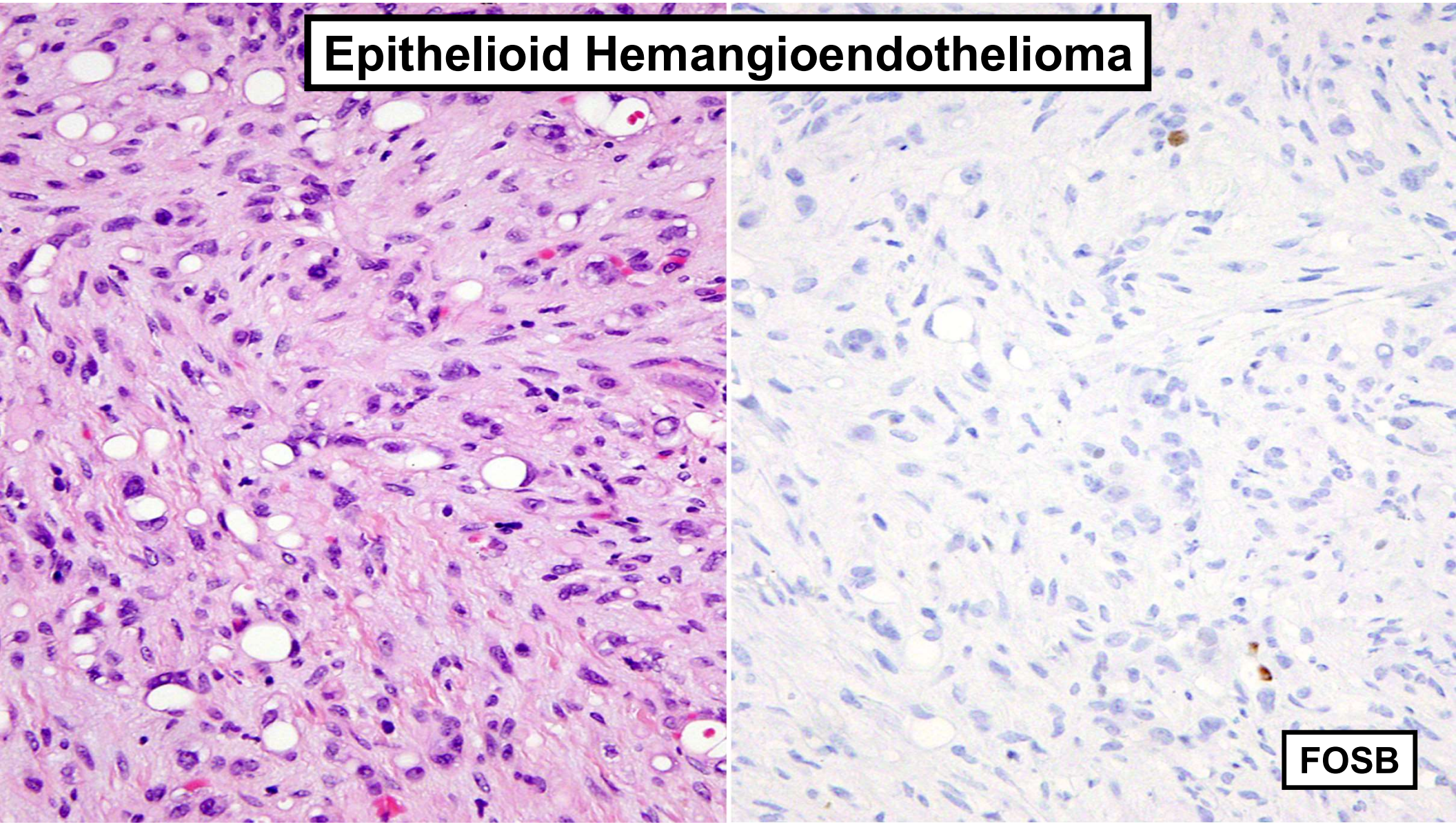
Yin P. Hung, MD, PhD, Christopher D.M. Fletcher, MD, FRCPath, and Jason L. Hornick, MD, PhD

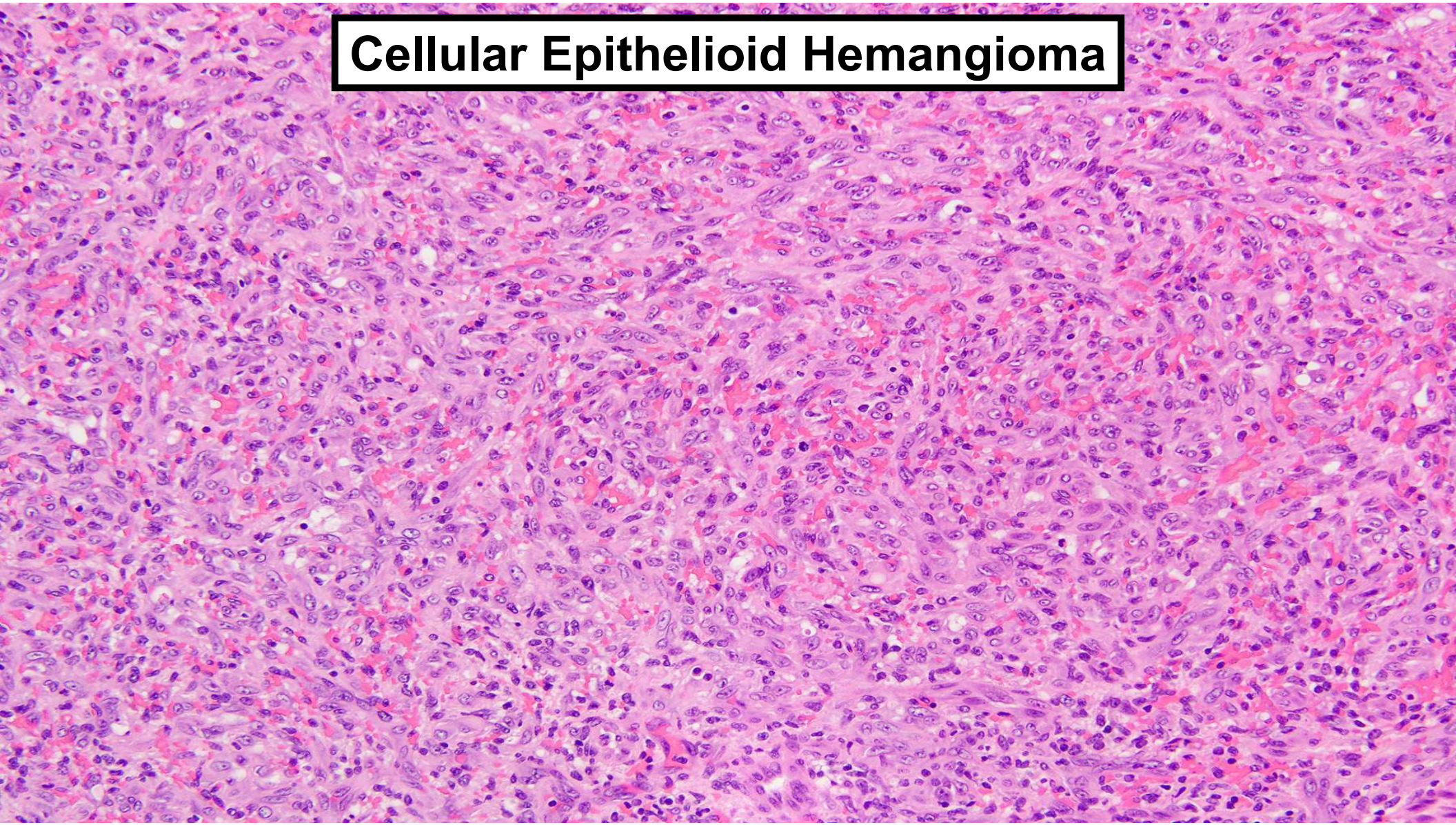
Am J Surg Pathol • Volume 41, Number 5, May 2017

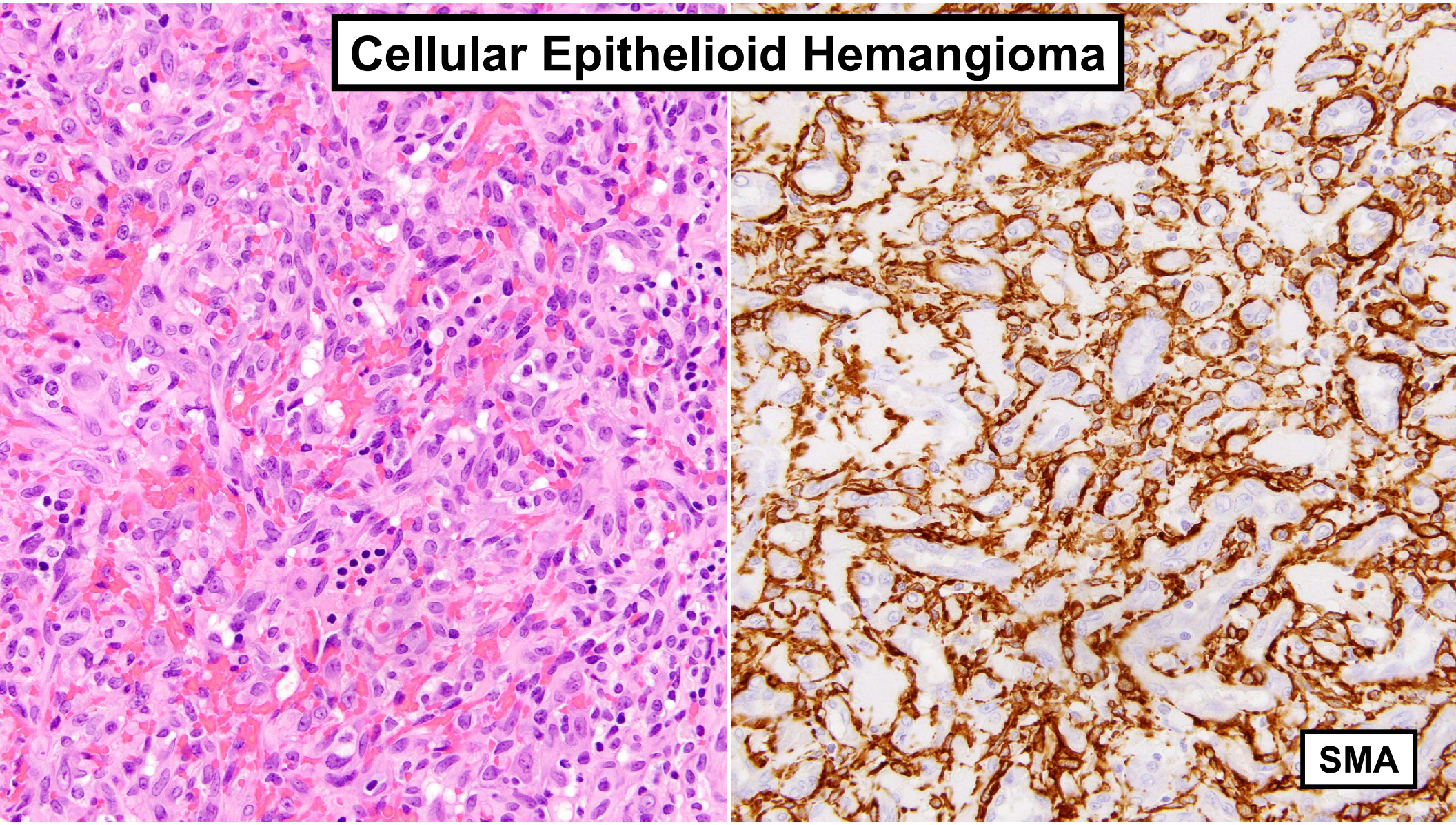
TABLE 1. Summary of Immunohistochemical Staining for FOSB

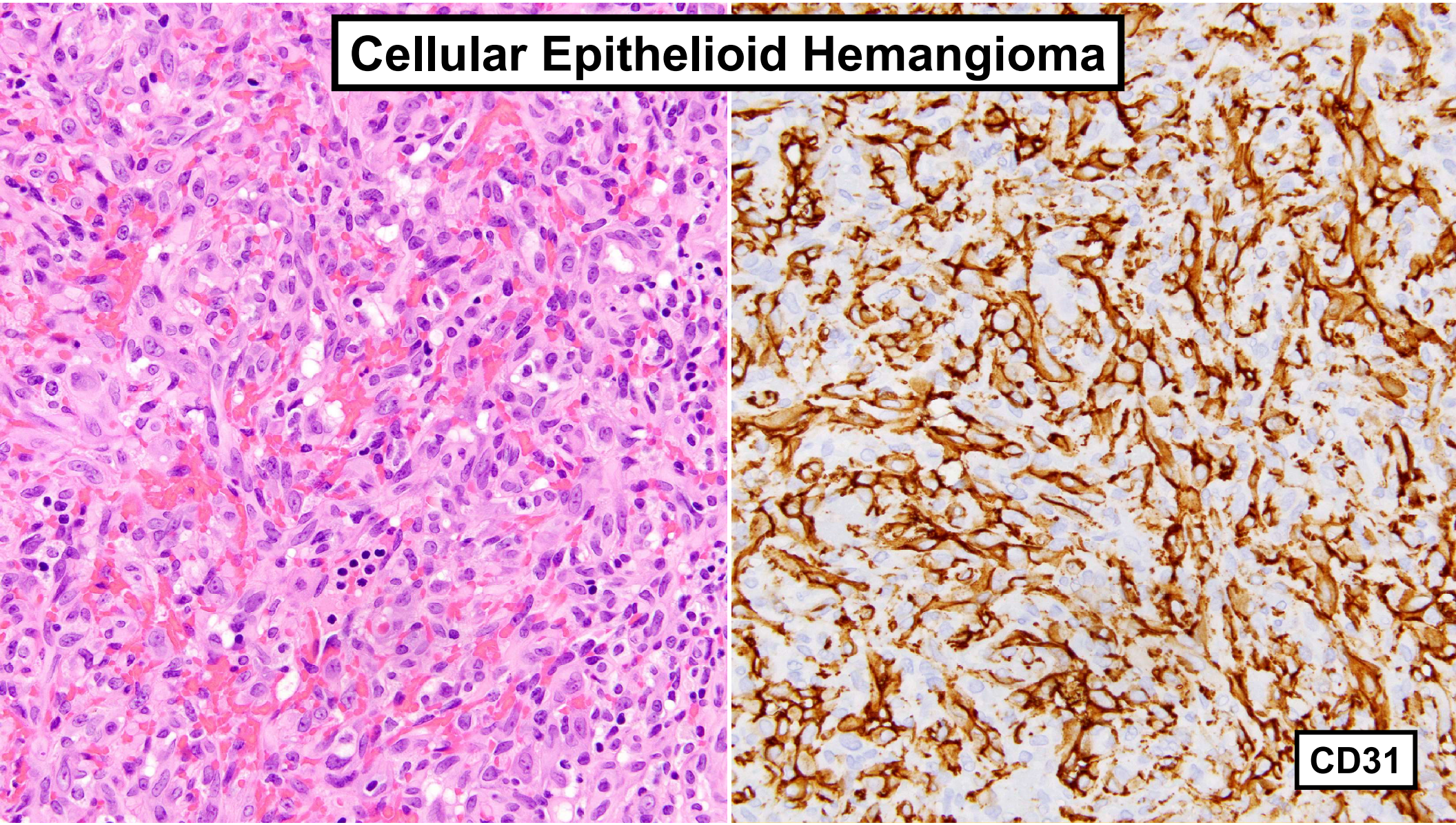
Tumor Type	Total Cases	FOSB Positive (%)*	0	1+	2+	3+	4+
Pseudomyogenic hemangioendothelioma	50	48 (96)	2	0	0	1	47
Epithelioid hemangioma	24	13 (54)	6	4	1	6	7
Conventional	8	6 (75)	0	1	1	4	2
Cellular	10	1 (10)	6	3	0	0	1
Angiolymphoid hyperplasia with eosinophilia	6	6 (100)	0	0	0	2	4
Other endothelial neoplasms and histologic mimics	200	7 (4)	142	42	9	4	3
Epithelioid angiosarcoma	20	1 (5)	11	7	1	0	1
Spindle-cell angiosarcoma	10	1 (10)	9	0	0	1	0
Epithelioid hemangioendothelioma	20	1 (5)	15	4	0	1	0
Epithelioid angiomatous nodule	10	0	9	1	0	0	0

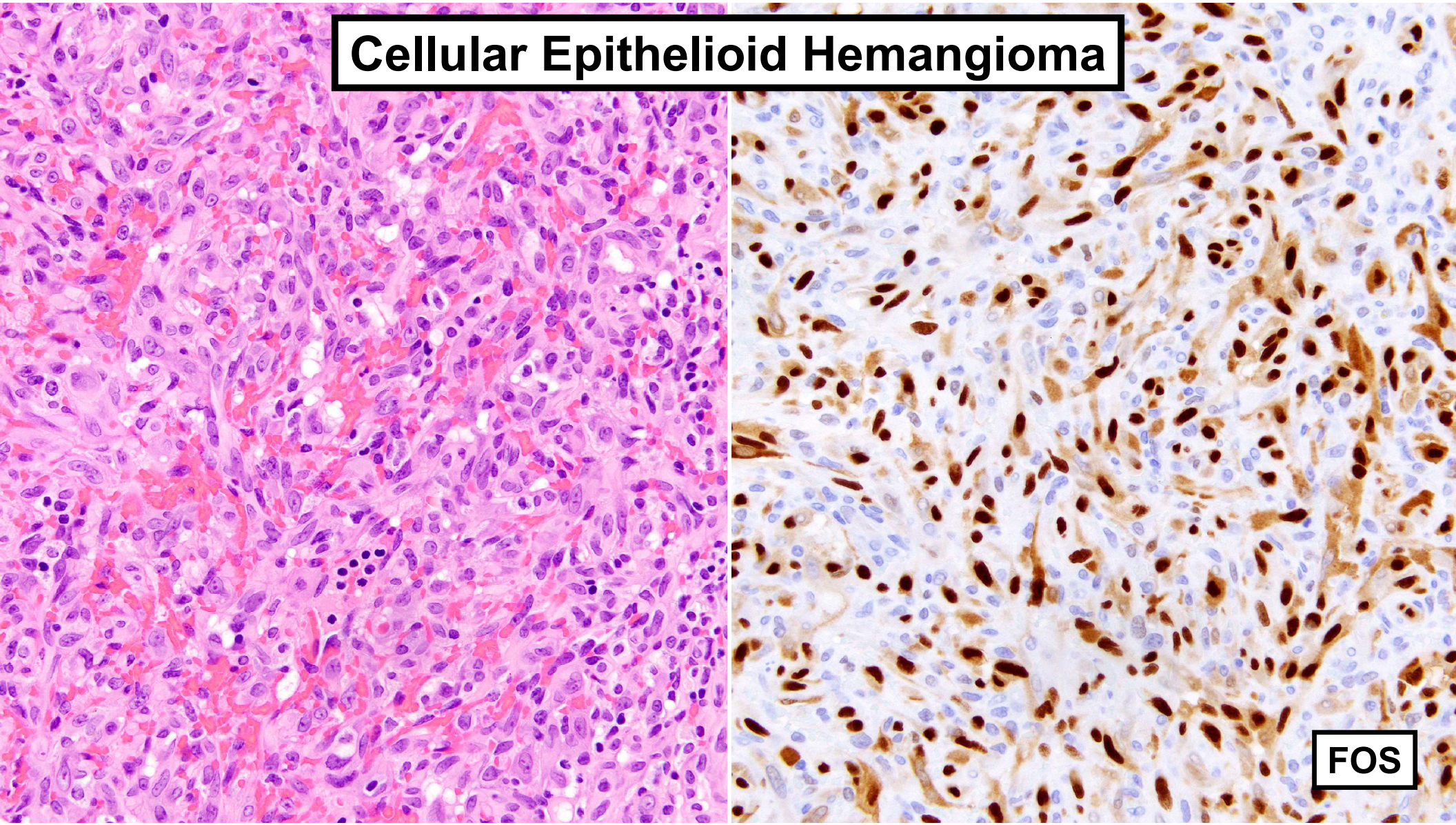

Epithelioid Hemangioma
FOSB


Epithelioid Hemangioendothelioma
FOSB


Cellular Epithelioid Hemangioma


Cellular Epithelioid Hemangioma
SMA


Cellular Epithelioid Hemangioma
CD31


Cellular Epithelioid Hemangioma
FOS

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Peripheral nerve sheath tumors

Tumor type	New genetic alterations
Epithelioid schwannoma	*SMARCB1* mutations
Granular cell tumor	*ATP6AP1* or *ATP6AP2* mutations
Benign triton tumor (neuromuscular choristoma)	*CTNNB1* mutations
Malignant peripheral nerve sheath tumor	*SUZ12* or *EED* mutations (loss of H3K27me3)

Tumors of uncertain differentiation

Tumor type	New genetic alterations
Phosphaturic mesenchymal tumor	*FN1::FGFR1*, *FN1::FGF1* (rare)

Summary

- **“New” soft tissue tumor types continue to be defined, through a combination of clinicopathologic studies and molecular genetic investigations**
- **Large studies of rare soft tissue tumor types enables the development of risk stratification models to aid in prognostication**
- **Discoveries in molecular genetics and the development of correlative markers for IHC make diagnosis of soft tissue tumors more straightforward and reproducible**

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THANK YOU!