NEXT GENERATION IMMUNOHISTOCHEMISTRY FOR SOFT TISSUE TUMORS:
FROM DIFFERENTIATION TO MOLECULAR GENETICS

Jason L Hornick, MD, PhD

Director of Surgical Pathology
and Immunohistochemistry
Brigham and Women's Hospital
Professor of Pathology
Harvard Medical School
Boston, MA, USA

Immunohistochemistry

20th Century

21st Century

DIFFERENTIATION (LINEAGE) → **MOLECULAR GENETICS**

Conventional Immunohistochemistry

Line of differentiation	IHC markers
Myofibroblastic	Smooth muscle actin
Smooth muscle	Smooth muscle actin, desmin
Skeletal muscle	Desmin, MyoD1, MYOG
Vascular	CD31, CD34, ERG
Nerve sheath (Schwann cell)	S100 protein, SOX10

21st Century Immunohistochemistry

- Protein correlates of molecular genetic alterations (amplifications, deletions, mutations)
- Protein products of gene fusions
- Protein markers identified by gene expression profiling

21st Century IHC Markers for Soft Tissue Tumors		
ALK	H3G34W	RB1
β-catenin	H3K27me3	ROS1
BCOR	H3K36M	SDHB
CAMTA1	MDM2	SMARCA4
CCNB3	MUC4	SMARCB1
CDK4	MYC	SS18::SSX
DDIT3	NKX2-2	TFE3
ETV4	PAX3	TLE1
FOSB	PDGFRA	pan-TRK

Protein Correlates of Molecular Genetic Alterations in Soft Tissue Tumors	
β-catenin	MYC
CDK4	PDGFRA
H3G34W	RB1
H3K27me3	SDHB
H3K36M	SMARCA4 (BRG1)
MDM2	SMARCB1 (INI1)

SMARCB1 (INI1, SNF5, BAF47)

- Member of SWI/SNF multi-subunit chromatin remodeling complex
- Mobilizes nucleosomes and exposes DNA to transcription factors
- Ubiquitously expressed in normal cells
- Tumor suppressor gene

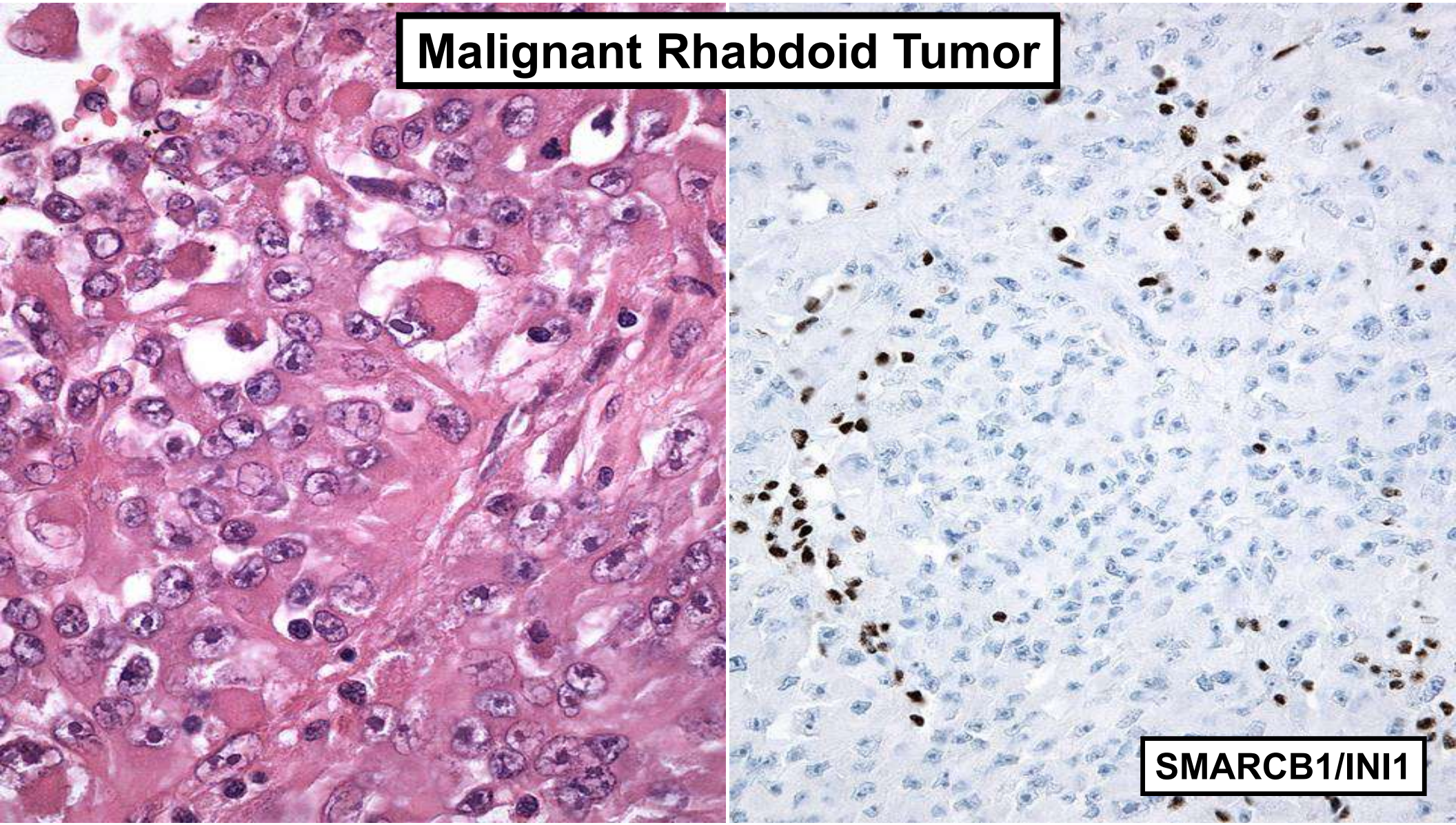
SMARCB1 in Malignant Rhabdoid Tumor

- **Biallelic inactivation (mutation/deletion) in 98% of malignant rhabdoid tumors of infancy (renal, soft tissue, atypical teratoid/ rhabdoid tumor of CNS)**
- **Loss of SMARCB1/INI1 protein expression by IHC useful to confirm diagnosis of MRT**

Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer

Isabella Versteege*, Nicolas Sévenet*, Julian Lange*, Marie-Françoise Rousseau-Merck*, Peter Ambros†, Rupert Handgretinger‡, Alain Aurias* & Olivier Delattre*

NATURE | VOL 394 | 9 JULY 1998


Malignant Rhabdoid Tumor
SMARCB1/INI1

SMARCB1 and Epithelioid Sarcoma

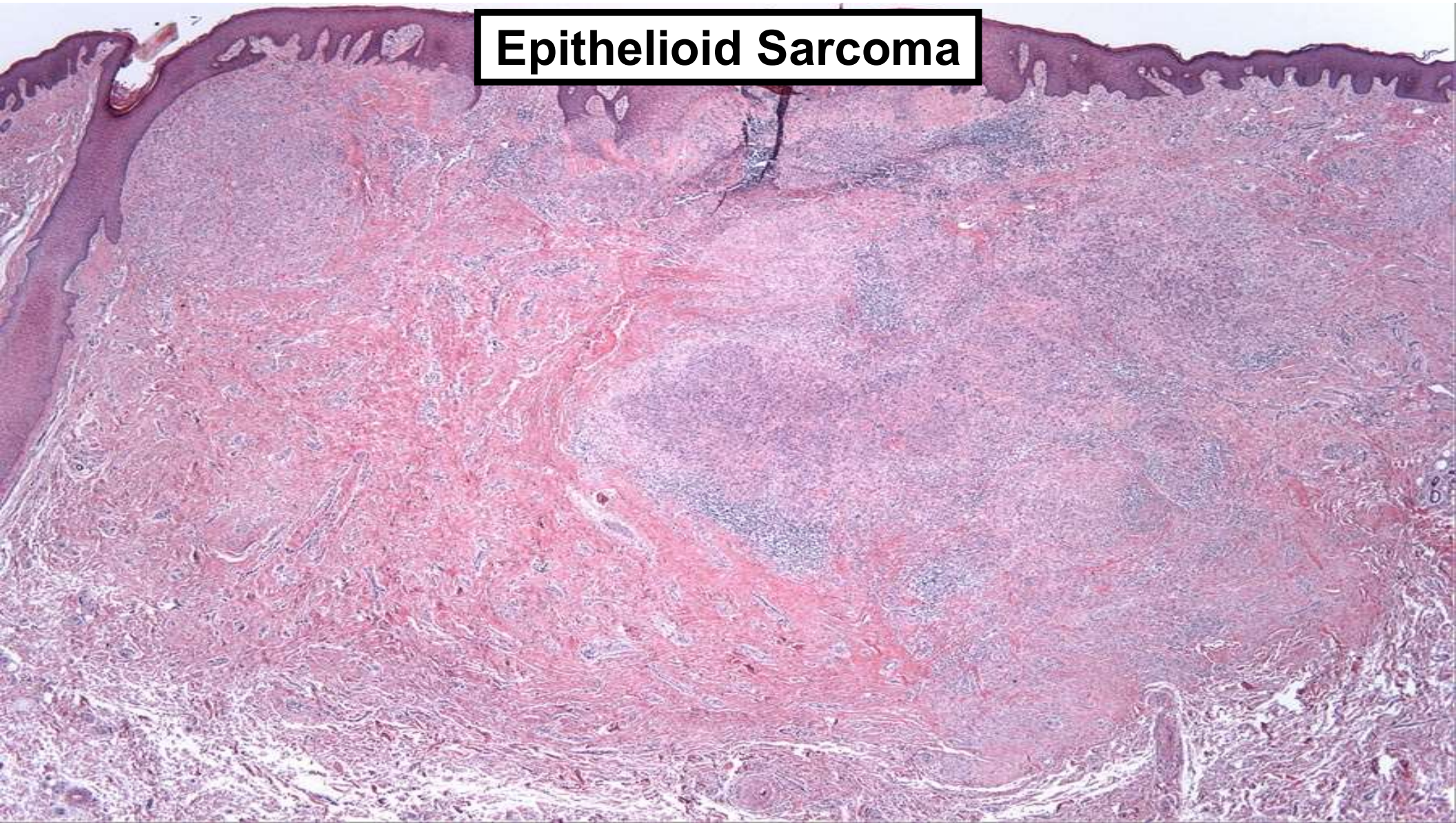
- **Most tumors show monoallelic or biallelic deletion of *SMARCB1* locus, along with expression of specific miRNAs (miR765)**
- **IHC: SMARCB1/INI1 expression lost in ~95% of epithelioid sarcomas**
- **Helpful in differential diagnosis (especially CD34-negative cases)**
- **Metastatic carcinomas and epithelioid vascular tumors (angiosarcoma, EHE) retain SMARCB1 expression**

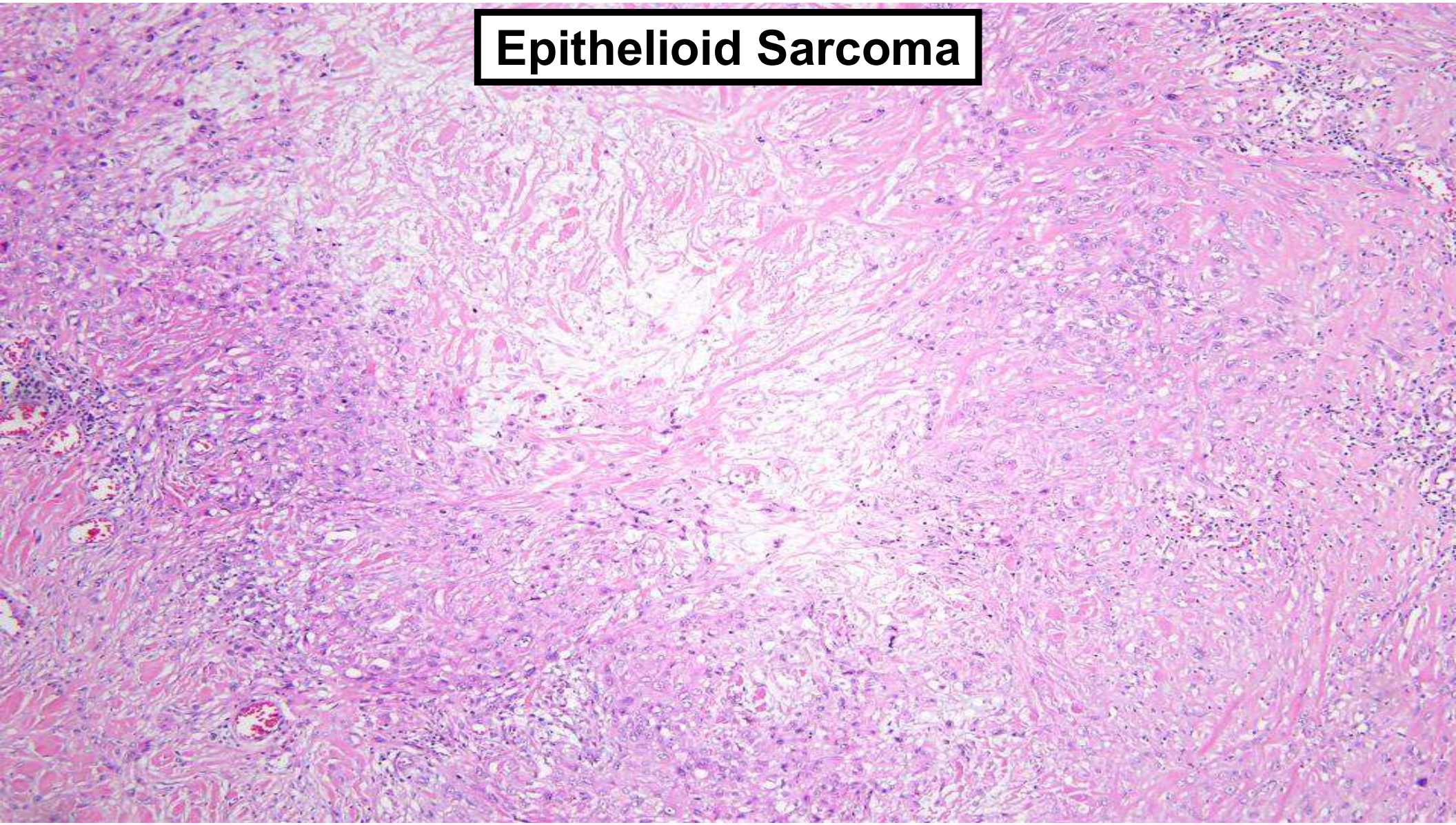
TABLE 1. Summary of INI1 Immunohistochemistry

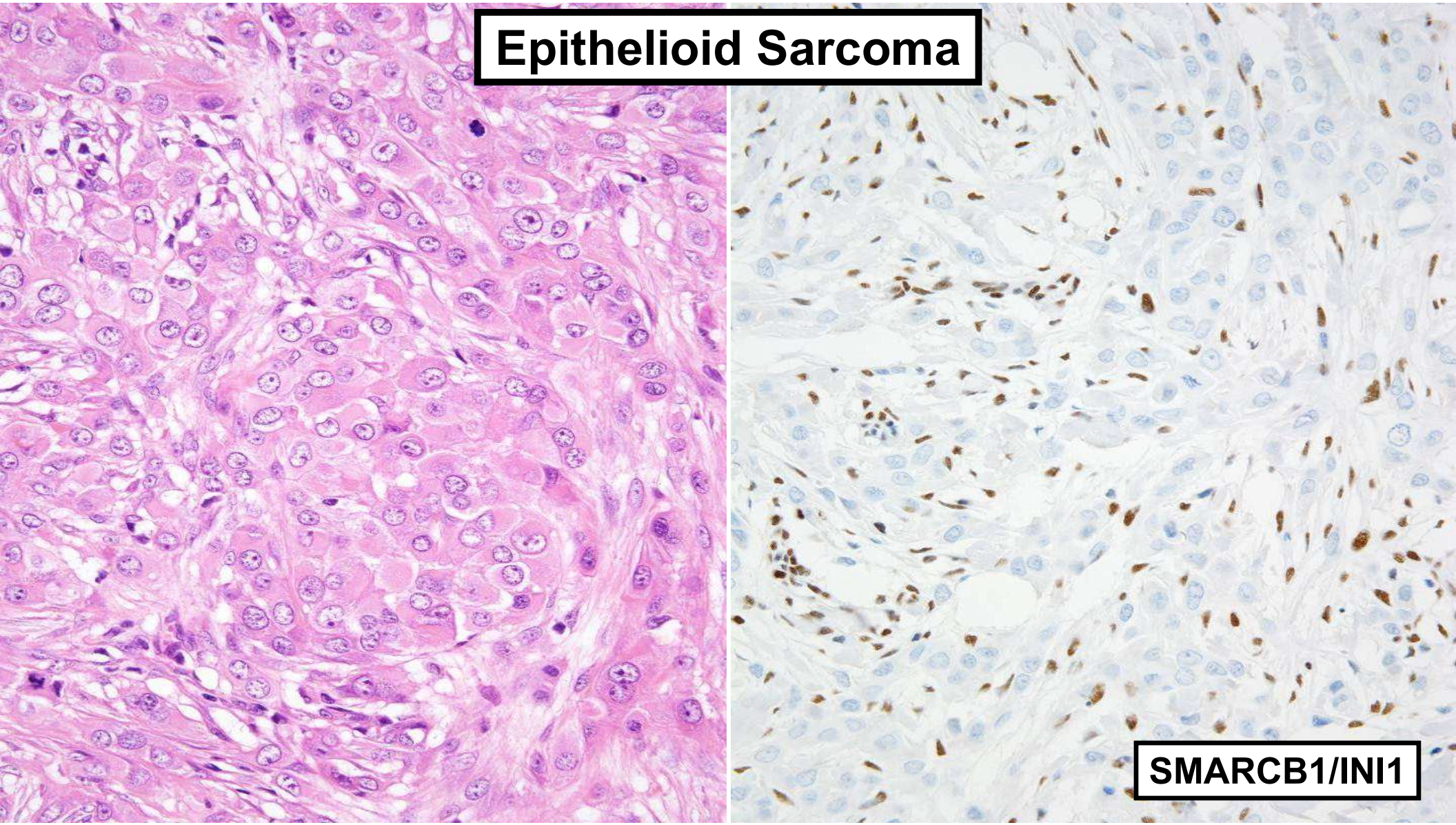
Tumor	Total Cases	Absence of INI1 (%)
Malignant rhabdoid tumor	10	10 (100)
Epithelioid sarcoma (total)	136	127 (93)
Conventional ("distal") type	64	58 (91)
Proximal type	64	61 (95)
Hybrid type	8	8 (100)
Epithelioid angiosarcoma	20	0 (0)
Epithelioid hemangioendothelioma	10	0 (0)
Epithelioid MPNST	24	12 (50)
Myoepithelial carcinoma of soft tissue	22	2 (9)
Histiocytic sarcoma	5	0 (0)
Anaplastic large cell lymphoma	7	0 (0)
Diffuse large B-cell lymphoma	10	0 (0)
Epithelioid mesothelioma	20	0 (0)
Metastatic melanoma	20	0 (0)
Metastatic carcinoma (total)	54	0 (0)
Nonsmall cell lung	22	0 (0)
Breast	6	0 (0)
Colorectum	5	0 (0)
Stomach	6	0 (0)
Kidney	5	0 (0)
Prostate	5	0 (0)
Pancreas	5	0 (0)
Metastatic embryonal carcinoma (testis)	12	0 (0)

Hornick et al. *Am J Surg Pathol* 2009

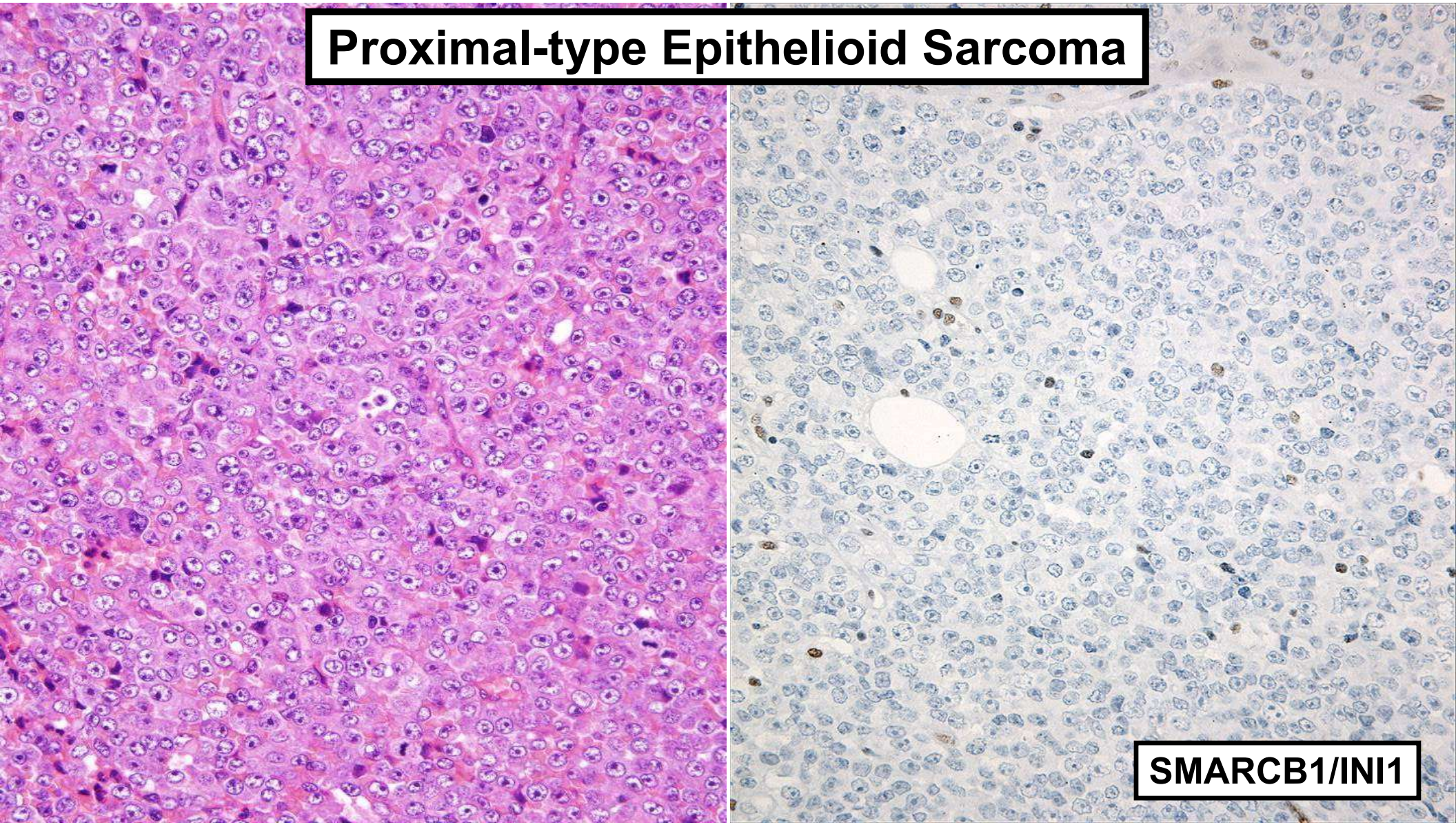
Epithelioid Sarcoma




Epithelioid Sarcoma


Epithelioid Sarcoma
SMARCB1/INI1

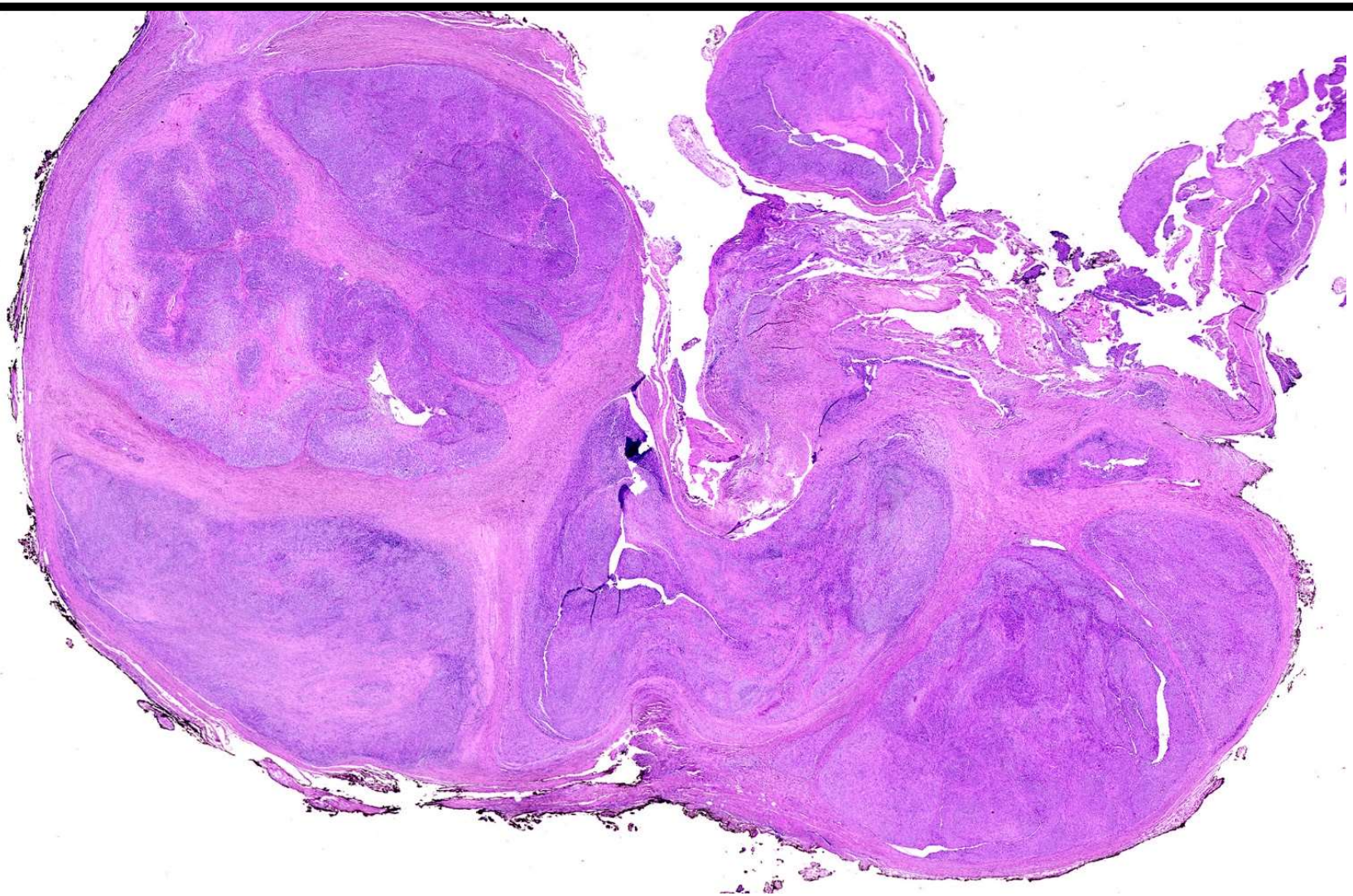
Proximal-type Epithelioid Sarcoma



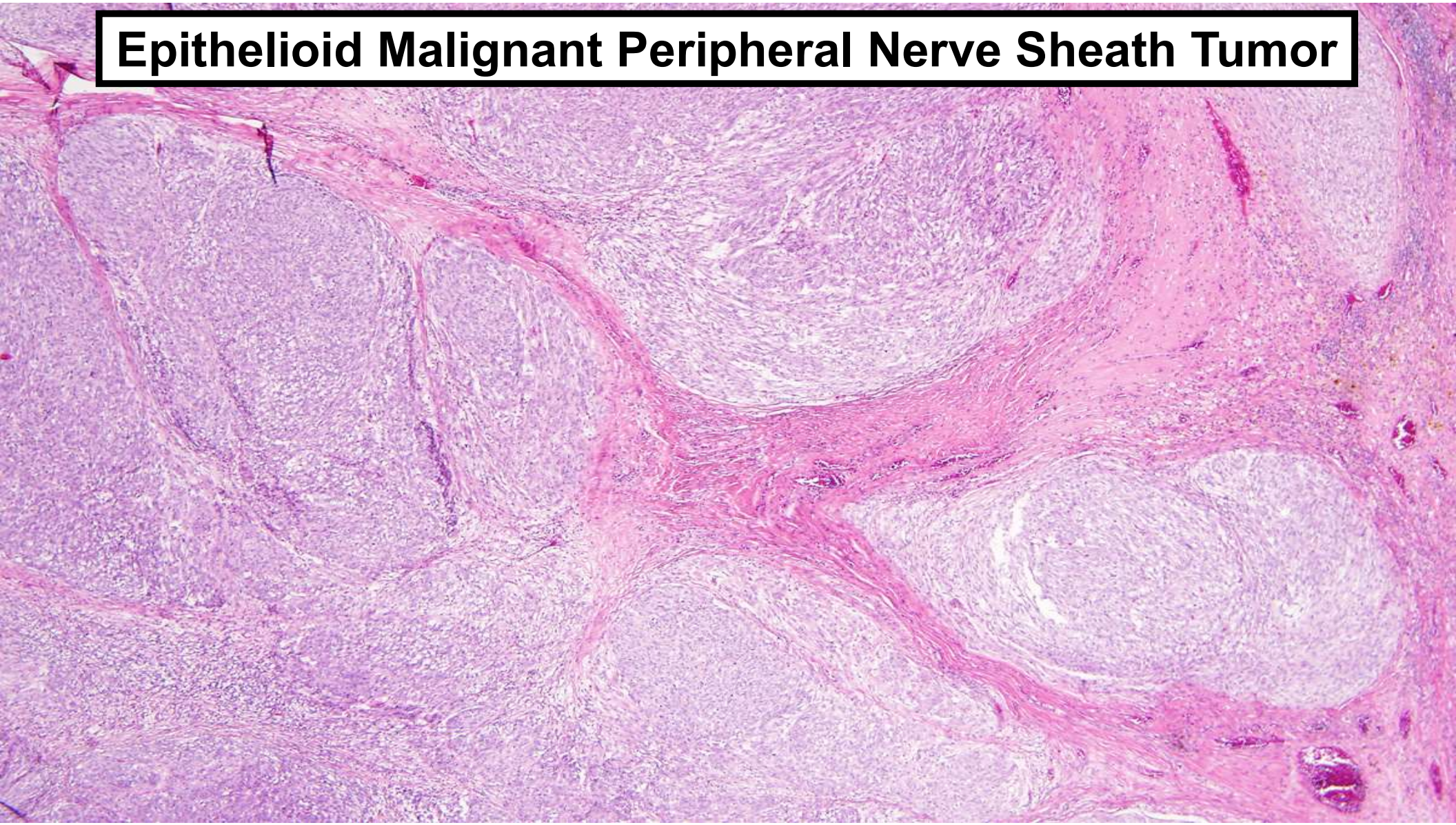
SMARCB1 Loss in Other Tumor Types

- Renal medullary carcinoma (100%)
- Poorly differentiated chordoma (100%)
- Epithelioid MPNST (70%)
- Soft tissue myoepithelial carcinoma (20%)
- Undifferentiated (rhabdoid) carcinomas (rare)

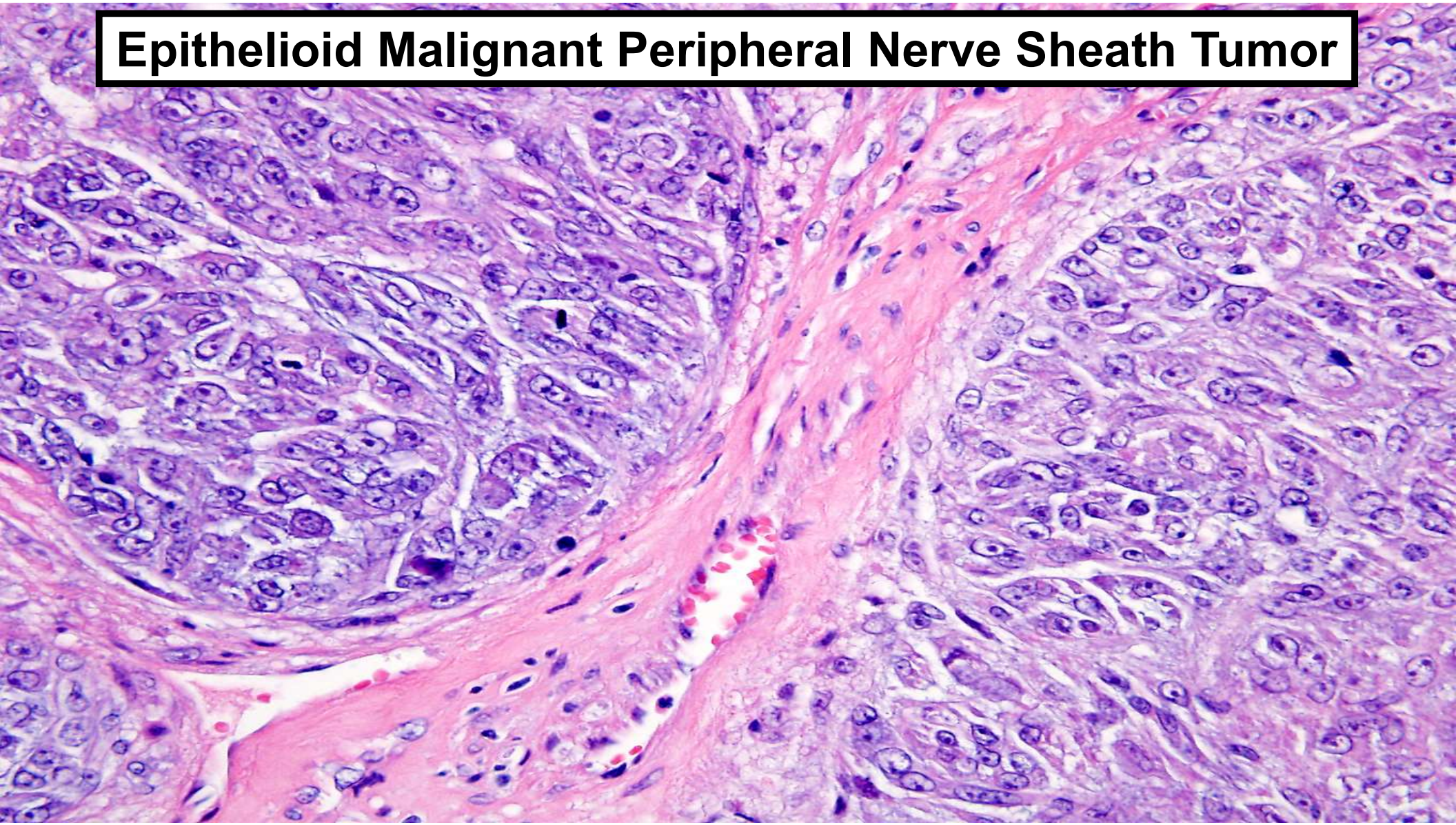
Epithelioid Malignant Peripheral Nerve Sheath Tumor



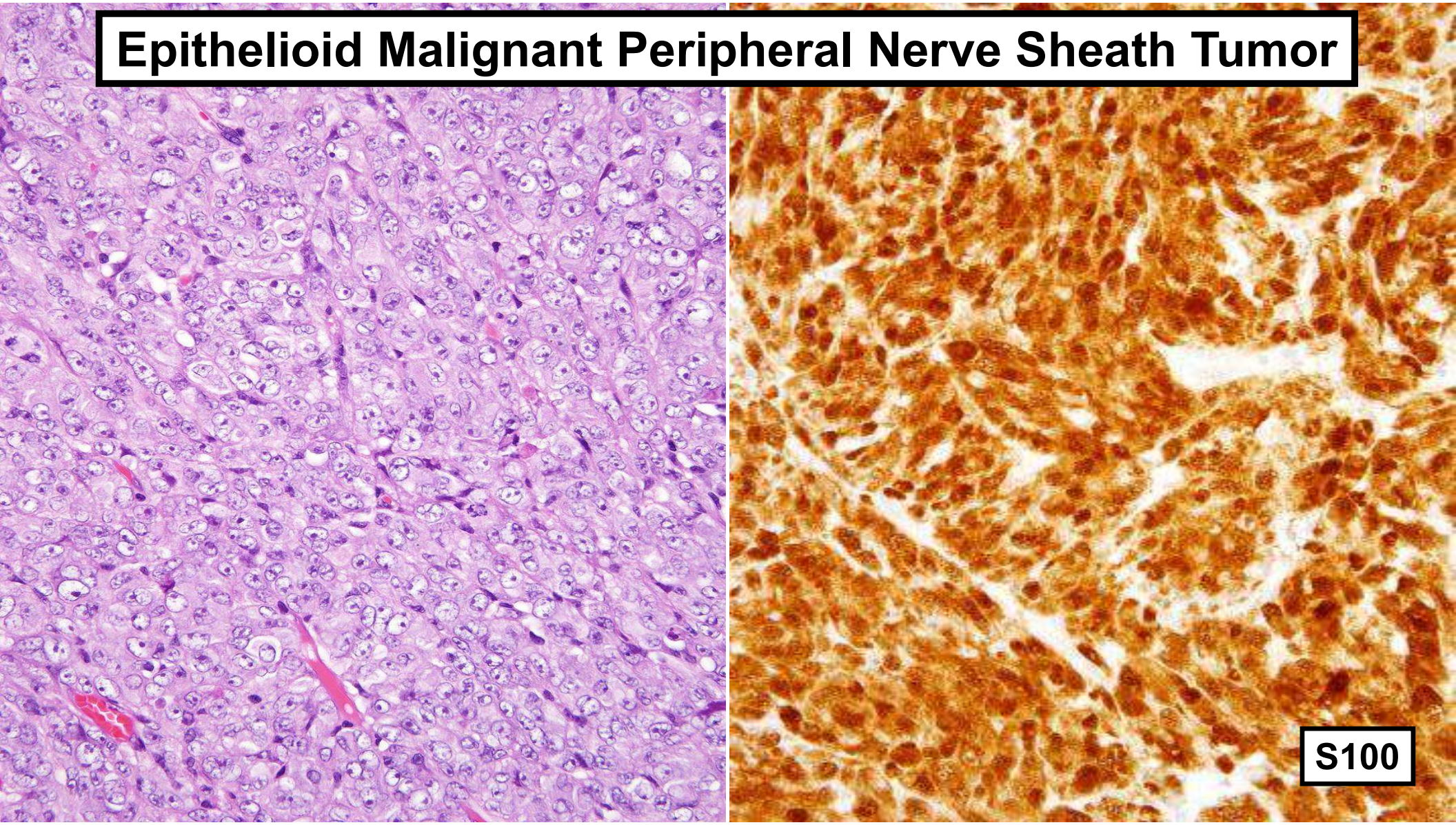
Epithelioid Malignant Peripheral Nerve Sheath Tumor



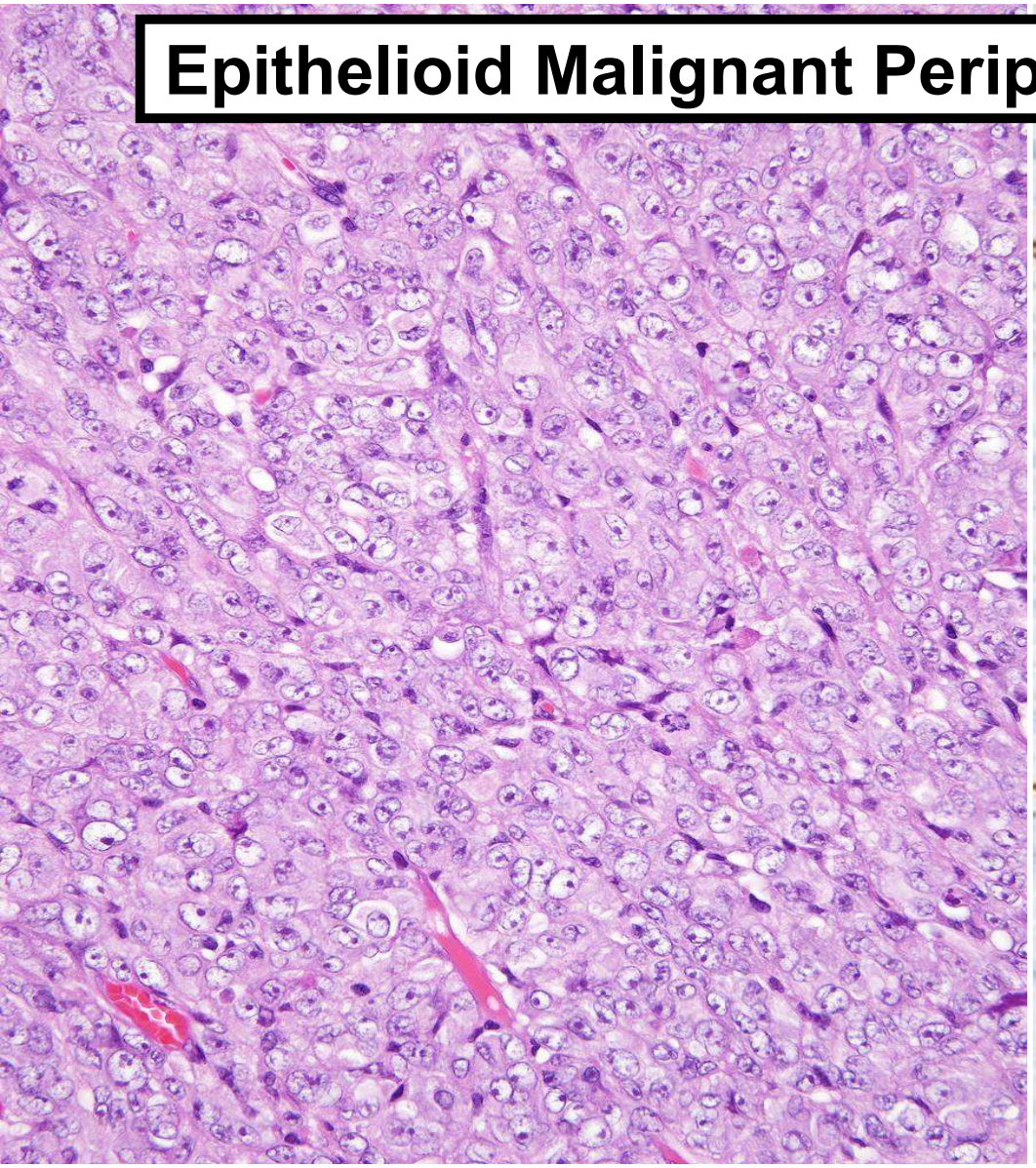
Epithelioid Malignant Peripheral Nerve Sheath Tumor

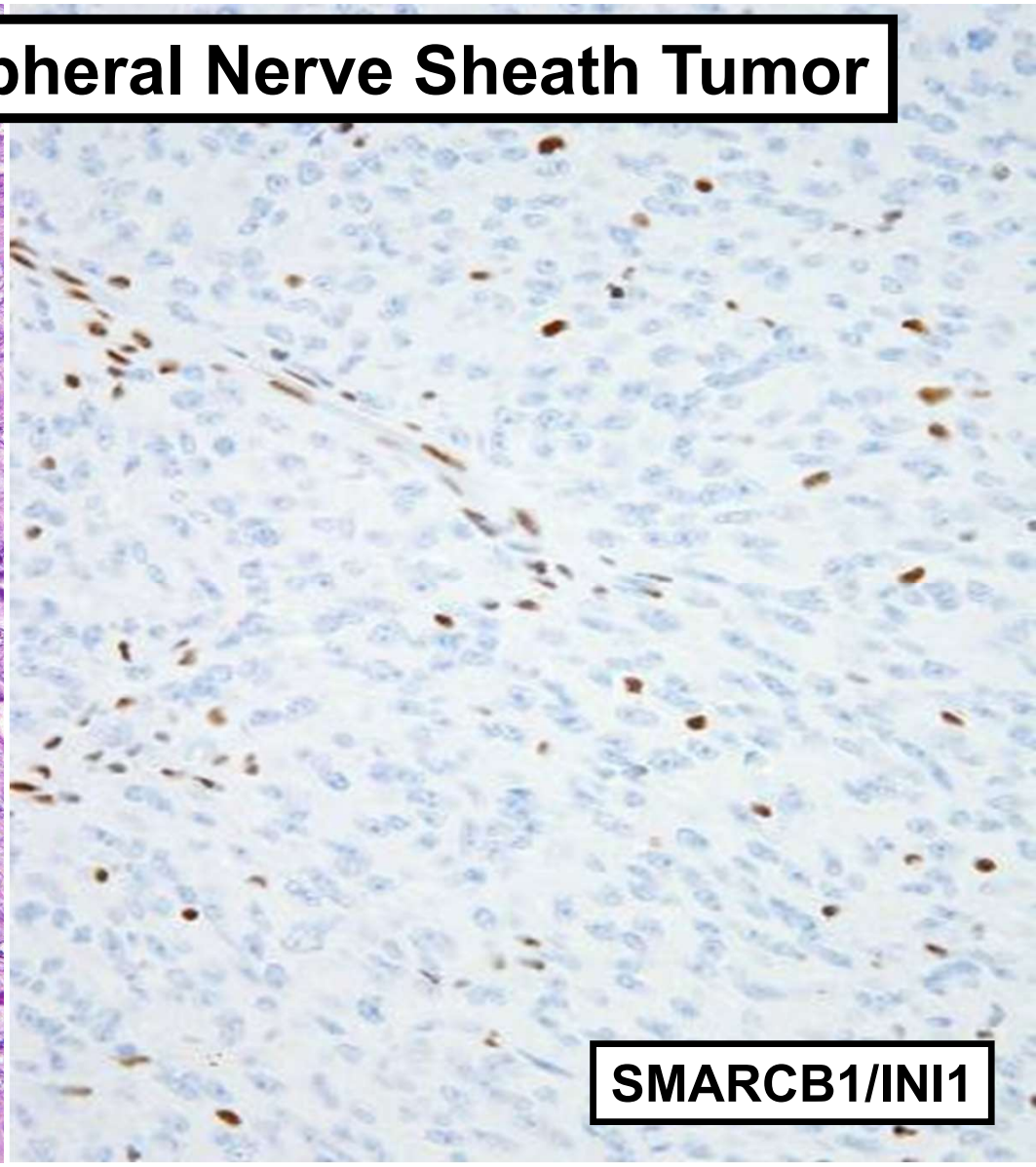


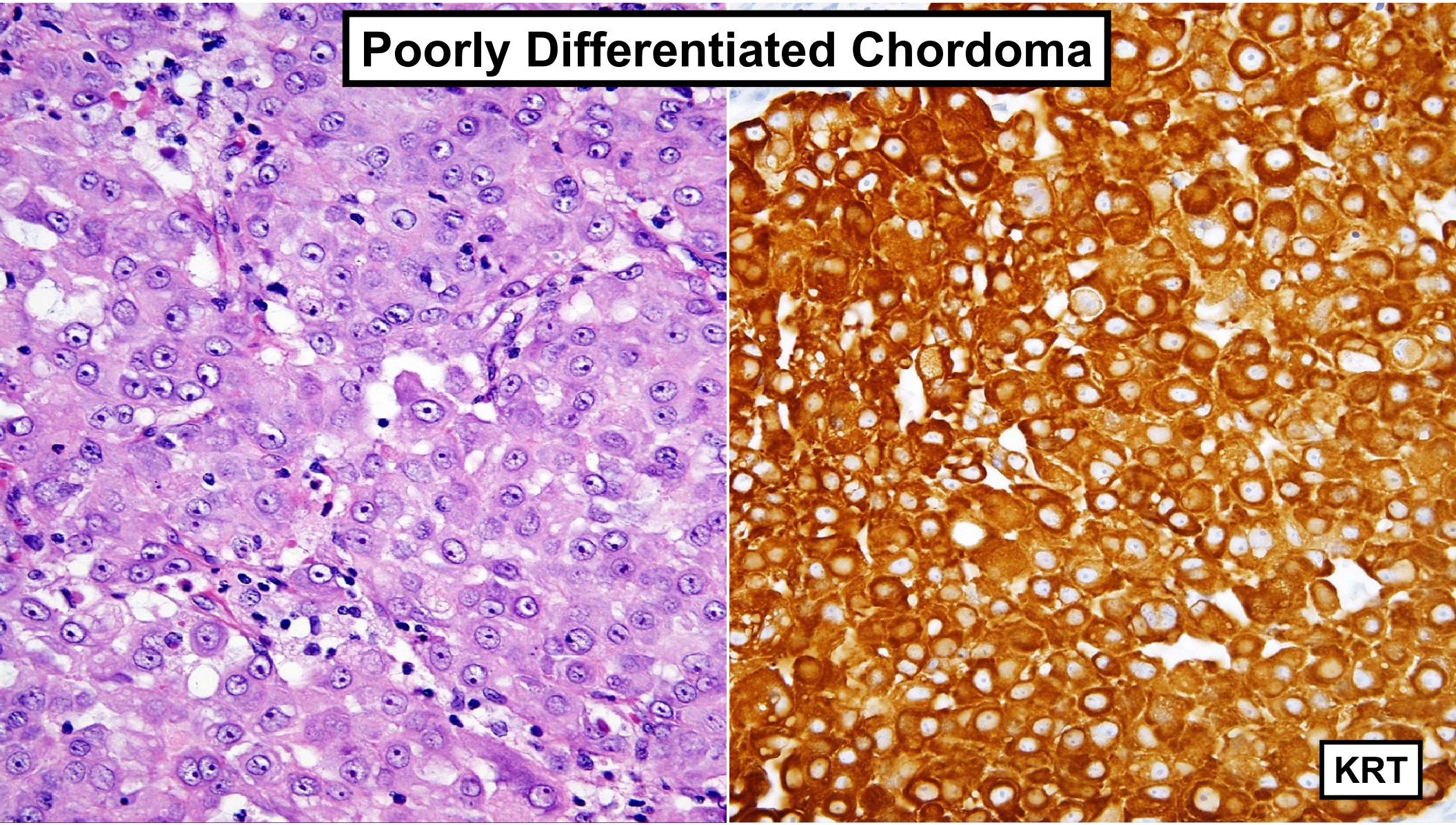
Epithelioid Malignant Peripheral Nerve Sheath Tumor

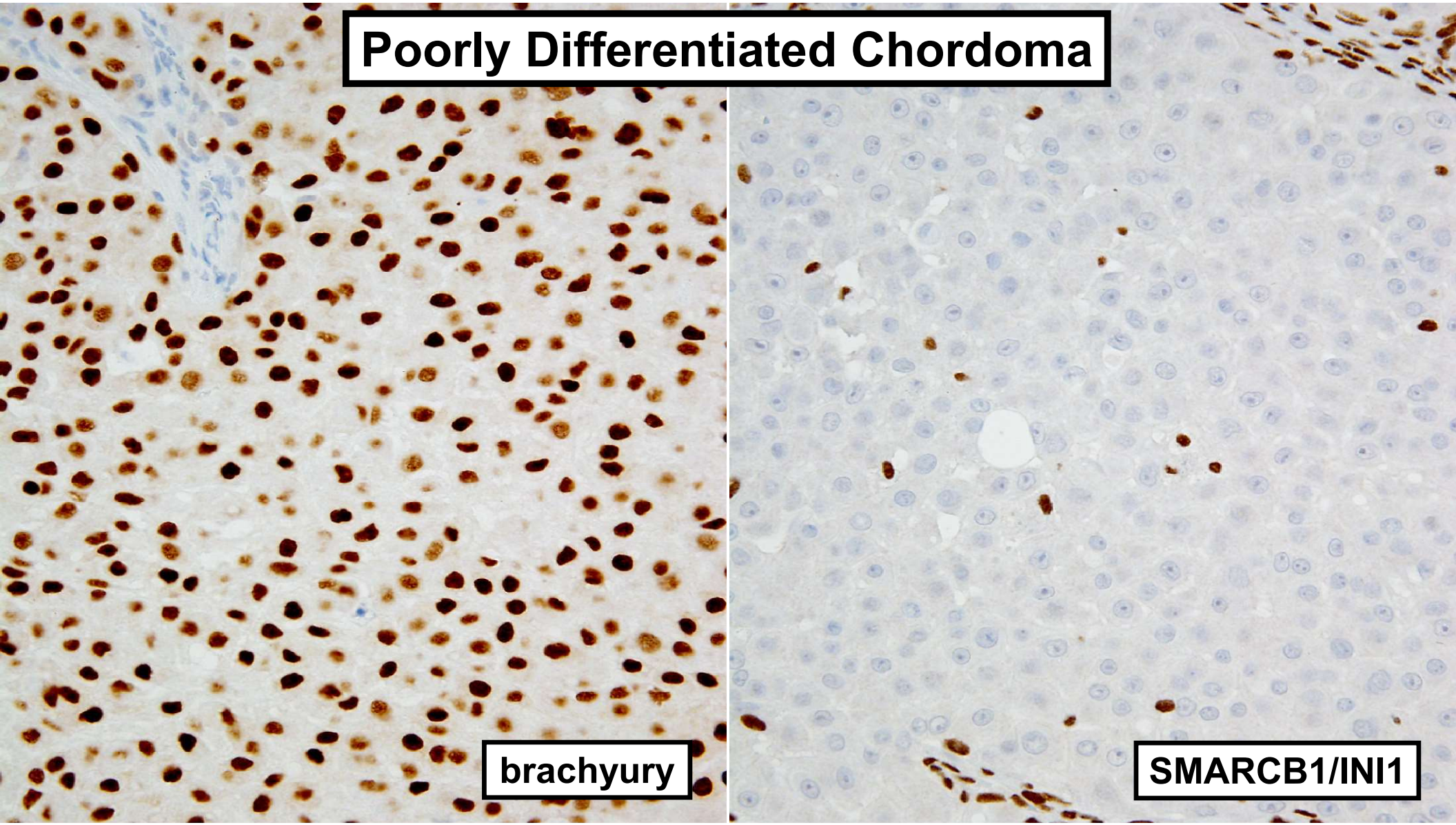


Epithelioid Malignant Peripheral Nerve Sheath Tumor



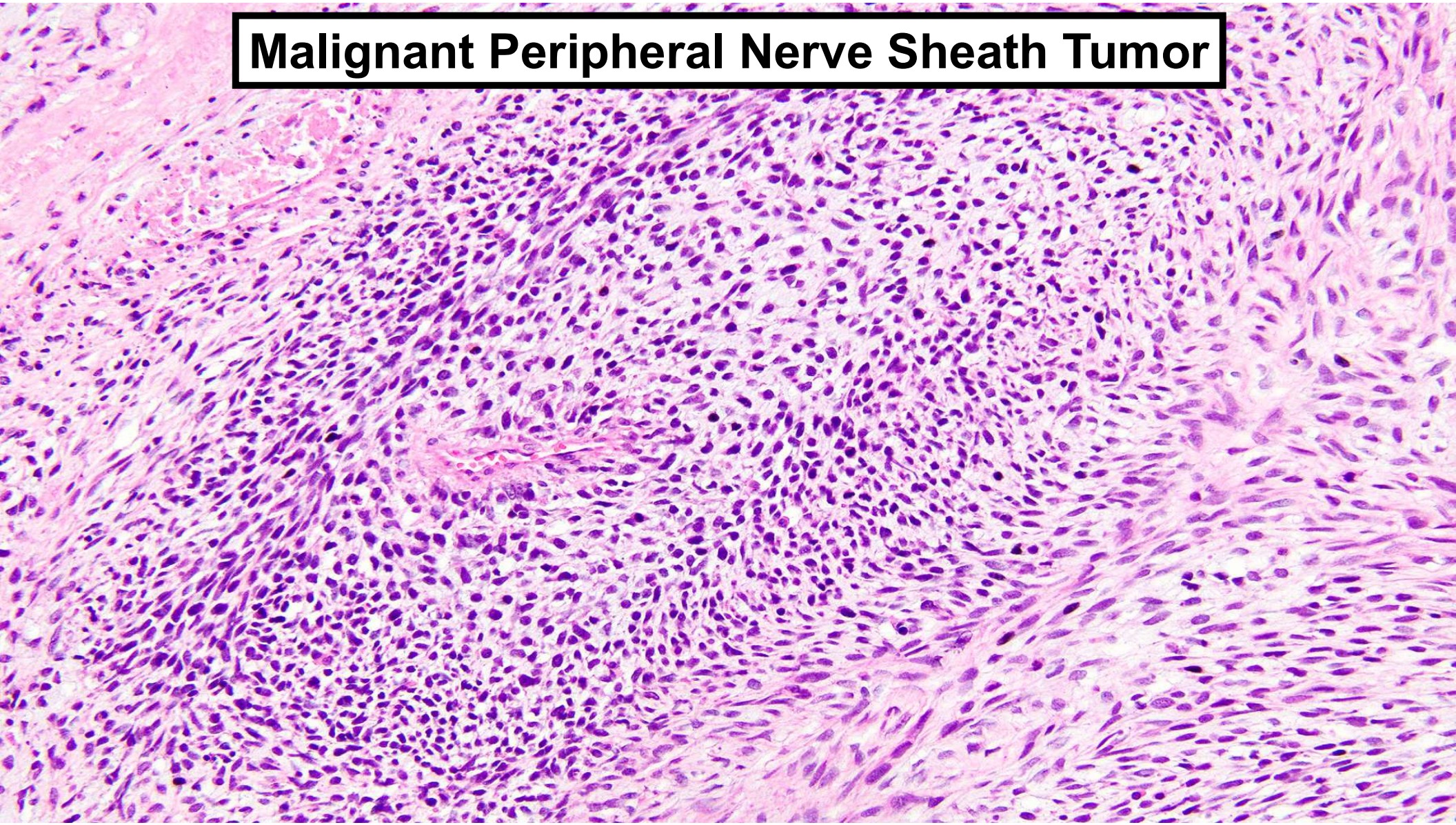



Poorly Differentiated Chordoma
KRT

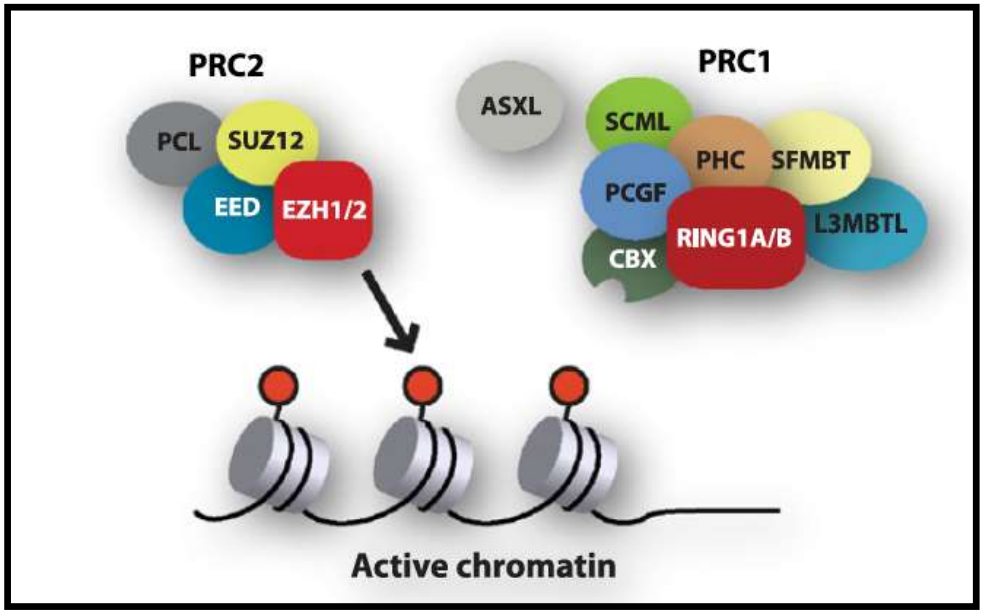

Poorly Differentiated Chordoma
brachyury
SMARCB1/INI1

Malignant Peripheral Nerve Sheath Tumor

- Arise in patients with NF1, sporadically, or following radiation therapy
- Challenging diagnosis
- Diagnostic criteria:
  1. Origin from a nerve or a neurofibroma
  2. Spindle cell sarcoma in a patient with NF1
  3. Evidence of Schwann cell differentiation by IHC or EM
     - » S100 protein and SOX10 only 30-50% sensitivity
- Diagnosis in sporadic setting relies on distinctive histology and exclusion of mimics


Malignant Peripheral Nerve Sheath Tumor

Polycomb Repressive Complexes



H3K27me3

Epigenetic modification of chromatin:

- **PRC2 recruits to chromatin and trimethylates histone H3 at lysine 27**

Physiologic regulation of cell fate and stem cell differentiation

Deregulation → cancer development

Modified from Sauvageau et al. *Cell Stem Cell* 2010

LETTER NATURE

doi:10.1038/nature13561

PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies

Thomas De Raedt[1,2,3], Eline Beert[4*†], Eric Pasmant[5,6*], Armelle Luscan[5,6], Hilde Brems[4], Nicolas Ortonne[5,6], Kristian Helin[7,8,9], Jason L. Hornick[10], Victor Mautner[11], Hildegard Kehrer-Sawatzki[12], Wade Clapp[13], James Bradner[2,14], Michel Vidaud[5,6], Meena Upadhyaya[15], Eric Legius[4,16] & Karen Cichowski[1,2,3]

Oct 2014

LETTERS

nature genetics

PRC2 is recurrently inactivated through *EED* or *SUZ12* loss in malignant peripheral nerve sheath tumors

William Lee[1,2,17], Sewit Teckie[2,3,17], Thomas Wiesner[3,17], Leili Ran[3,17], Carlos N Prieto Granada[4], Mingyan Lin[5], Sinan Zhu[3], Zhen Cao[3], Yupu Liang[3], Andrea Sboner[6–8], William D Tap[9,10], Jonathan A Fletcher[11], Kety H Huberman[12], Li-Xuan Qin[13], Agnes Viale[12], Samuel Singer[14], Deyou Zheng[5,15,16], Michael F Berger[3,4], Yu Chen[3,9,10], Cristina R Antonescu[4] & Ping Chi[3,9,10]

Nov 2014

BRIEF COMMUNICATIONS

nature genetics

Somatic mutations of *SUZ12* in malignant peripheral nerve sheath tumors

Ming Zhang[1,2], Yuxuan Wang[1,2], Sian Jones[3], Mark Sausen[3], Kevin McMahon[1,2], Rajni Sharma[4], Qing Wang[1,2], Allan J Belzberg[5], Kaisorn Chaichana[5], Gary L Gallia[5], Ziya L Gokaslan[5], Greg J Riggins[5], Jean-Paul Wolinksy[5], Laura D Wood[4], Elizabeth A Montgomery[4], Ralph H Hruban[4], Kenneth W Kinzler[1,2], Nickolas Papadopoulos[1,2], Bert Vogelstein[1,2] & Chetan Bettegowda[1,2,5]

Nov 2014

PRC2 and MPNST

- **PRC2 alterations (*SUZ12* or *EED* mutations) in 85-90% of MPNST**
- **Homozygous mutations result in loss of H3K27me3 (histone H3 lysine 27 trimethylation) in ~65% of MPNST**
- **Rate of H3K27me3 loss depends on grade**
- **IHC for H3K27me3 highly specific diagnostic marker**

Schaefer et al. *Mod Pathol* 2016

Prieto-Granada et al. *Am J Surg Pathol* 2016

IHC for H3K27me3 in MPNST

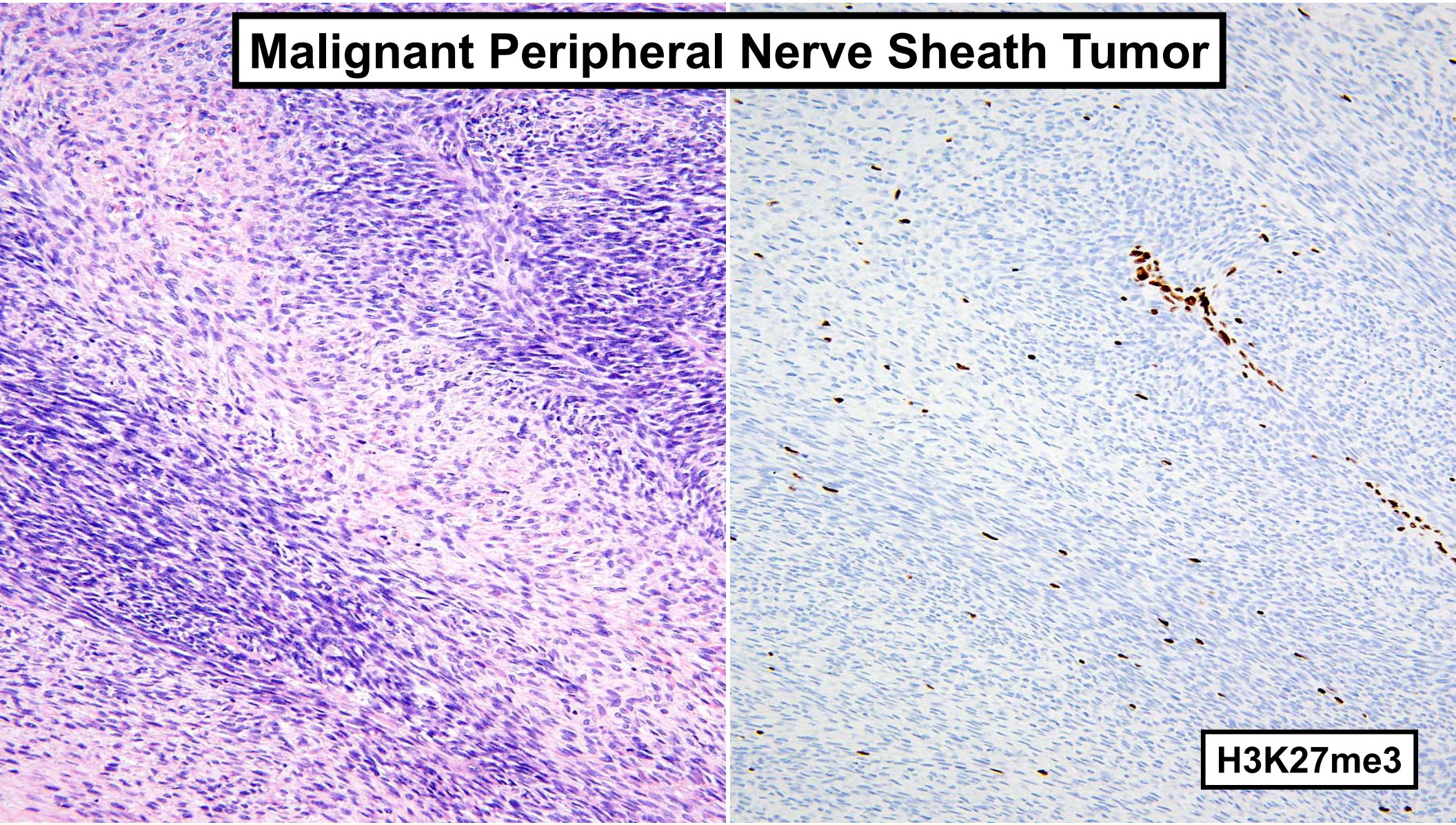
MPNST grade (or type)	H3K27me3 loss
Low grade	30%
Intermediate grade	60%
High grade	85%
Epithelioid	0%

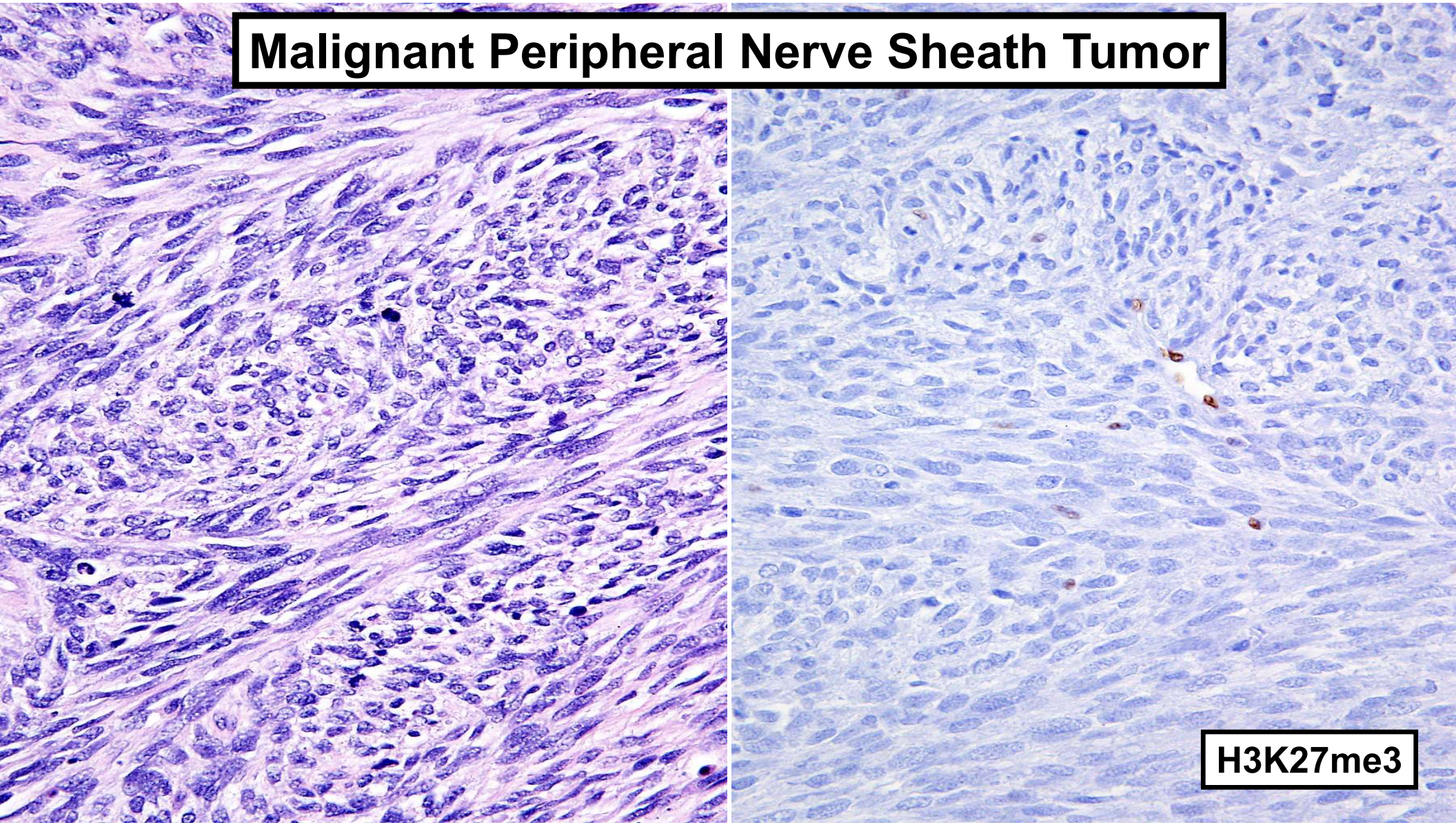
Schaefer et al. *Mod Pathol* 2016

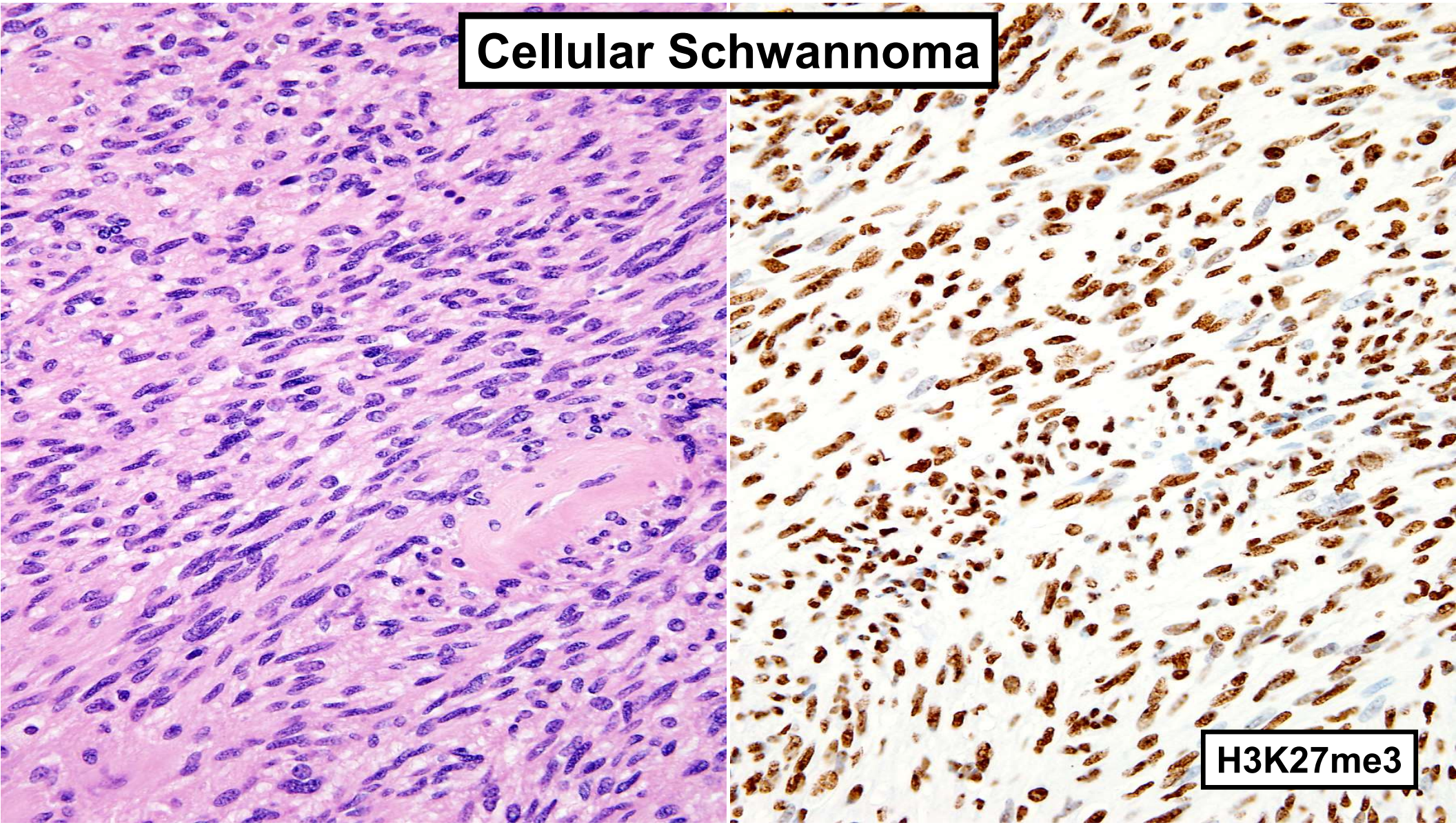
Prieto-Granada et al. *Am J Surg Pathol* 2016

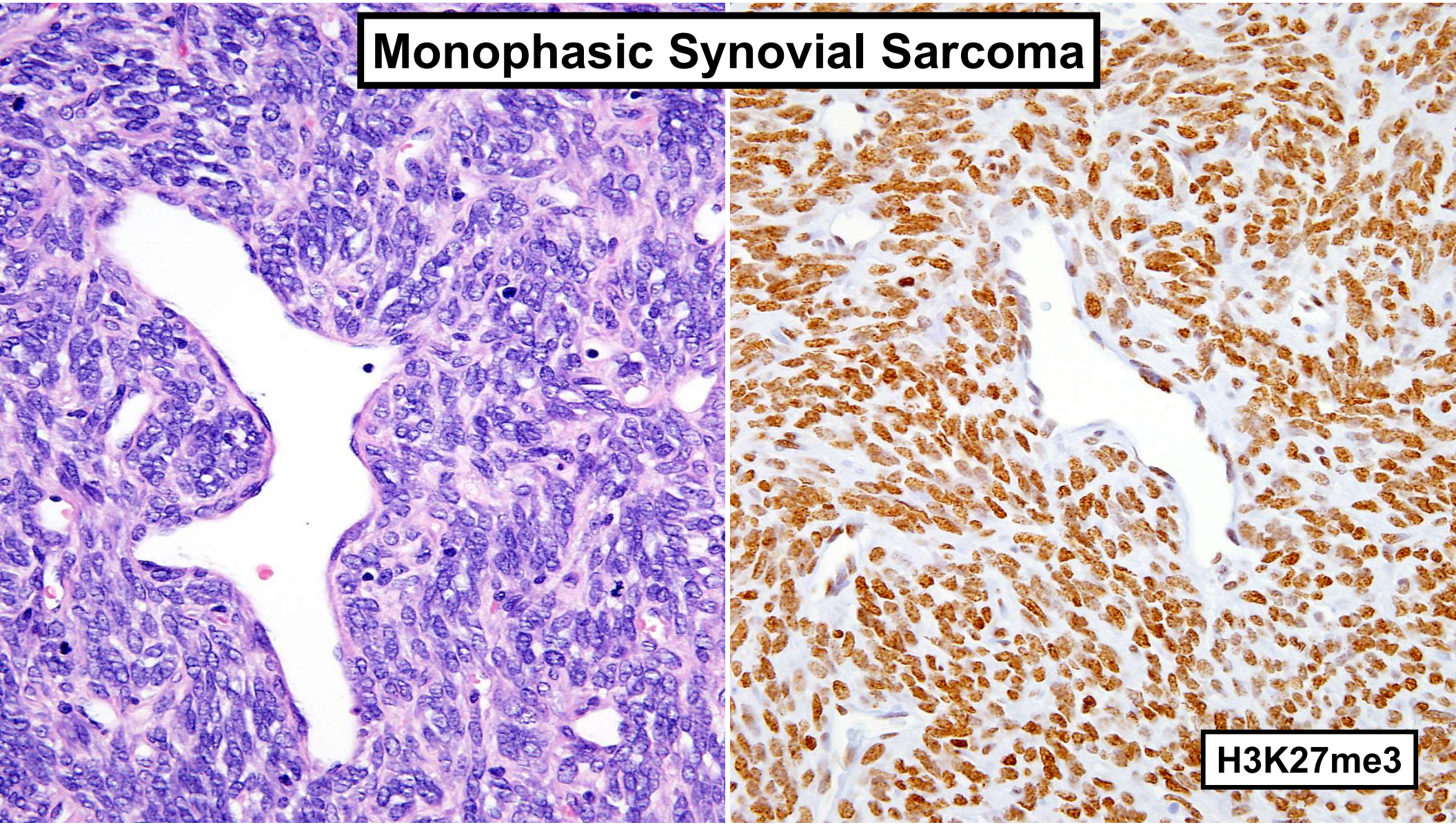
IHC for H3K27me3 in other spindle cell tumors

Tumor type	H3K27me3 loss
Cellular schwannoma	0%
Atypical neurofibroma	0%
Monophasic synovial sarcoma	0%
Leiomyosarcoma	0%
Myxofibrosarcoma	0%
Malignant solitary fibrous tumor	0%
Low-grade fibromyxoid sarcoma	0%
Spindle cell rhabdomyosarcoma	0%
Gastrointestinal stromal tumor	0%
Dedifferentiated liposarcoma	6%
Spindle cell melanoma	7%


Malignant Peripheral Nerve Sheath Tumor
H3K27me3


Malignant Peripheral Nerve Sheath Tumor
H3K27me3


Cellular Schwannoma
H3K27me3


Monophasic Synovial Sarcoma
H3K27me3

Protein Products of Gene Fusions	
ALK	ROS1
BCOR	SS18::SSX
CAMTA1	STAT6
CCNB3	TFE3
DDIT3	Pan-TRK
FOSB	WT1

Synovial Sarcoma

- **Relatively common soft tissue sarcoma: 8% overall**
- **Peak in young adults; predilection for extremities**
- **Aggressive: 5-yr and 10-yr survival 60% and 50%**
- **Harbors pathognomonic t(X;18)(p11;q11)**
- **Results in *SS18::SSX1* >> *SS18::SSX2* (rarely *SS18::SSX4*)**

- **Monophasic, biphasic, and poorly differentiated variants**
- **Considerable overlap with other tumor types**
- **Currently available IHC markers lack specificity**

TABLE 1. Summary of IHC Staining With SS18-SSX Fusion-specific and SSX C-terminus Antibodies

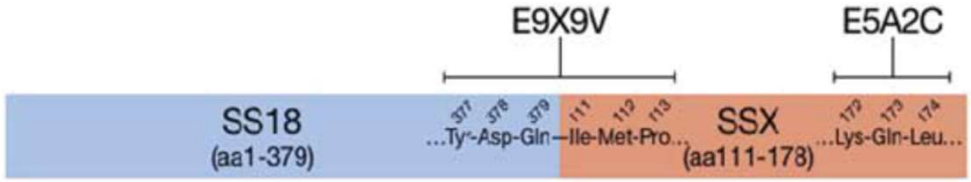
Tumor Type	Total Cases	n (%) SS18-SSX Positive	n (%) SSX C-terminus Positive
SS	100	95 (95)	100 (100)
Monophasic SS	41	39 (95)	41 (100)
Biphasic SS	18	18 (100)	18 (100)
PD SS	41	38 (93)	41 (100)
Non-SS tumors	300	0 (0)	13 (4)
MPNST	20	0 (0)	2 (10)
SFT	20	0 (0)	0 (0)
Dedifferentiated liposarcoma	20	0 (0)	2 (10)
Leiomyosarcoma	20	0 (0)	0 (0)
Fibrosarcomatous variant of DFSP	20	0 (0)	0 (0)
Ewing sarcoma	20	0 (0)	0 (0)
CIC sarcoma	20	0 (0)	0 (0)
Spindle cell rhabdomyosarcoma	20	0 (0)	0 (0)
Alveolar rhabdomyosarcoma	20	0 (0)	1 (5)
Embryonal rhabdomyosarcoma	20	0 (0)	1 (5)
Mesenchymal chondrosarcoma	20	0 (0)	2 (10)
Desmoplastic small round cell tumor	20	0 (0)	2 (10)
Clear cell sarcoma	20	0 (0)	0 (0)
Biphenotypic sinonasal sarcoma	10	0 (0)	1 (10)
BCOR-rearranged sarcoma	10	0 (0)	0 (0)
Sarcomatoid mesothelioma	10	0 (0)	2 (20)
Biphasic mesothelioma	10	0 (0)	0 (0)

ORIGINAL ARTICLE

Am J Surg Pathol • Volume 44, Number 7, July 2020

A Novel SS18-SSX Fusion-specific Antibody for the Diagnosis of Synovial Sarcoma

Esther Baranov, MD, Matthew J. McBride, PhD,† Andrew M. Bellizzi, MD,‡ Azra H. Ligon, PhD,* Christopher D.M. Fletcher, MD, FRCPath,* Cigall Kadoch, PhD,† and Jason L. Hornick, MD, PhD**



Antibody	Sensitivity	Specificity
SS18::SSX	95%	100%
SSX (C-term)	100%	96%

IHC with SS18::SSX fusion-specific antibody

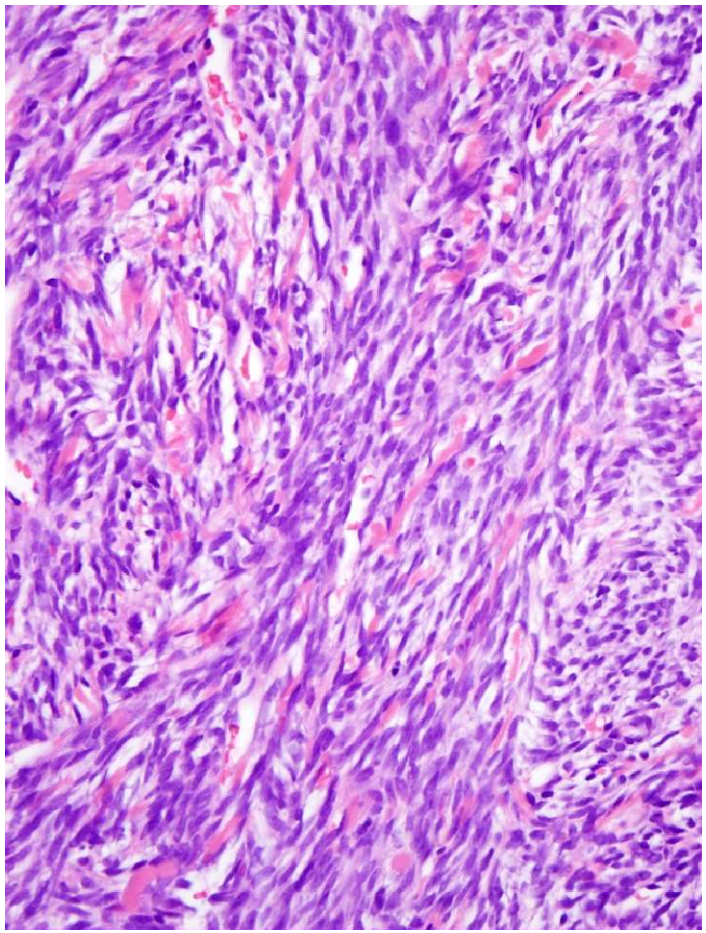
Tumor type	Total cases	SS18-SSX +
Synovial sarcoma	233	94%
Malignant peripheral nerve sheath tumor	128	0%
Solitary fibrous tumor	52	0%
Dedifferentiated liposarcoma	87	0%
Leiomyosarcoma	64	0%
Ewing sarcoma	35	0%
Mesothelioma (sarcomatoid)	24	0%
Sarcomatoid carcinoma	19	0%

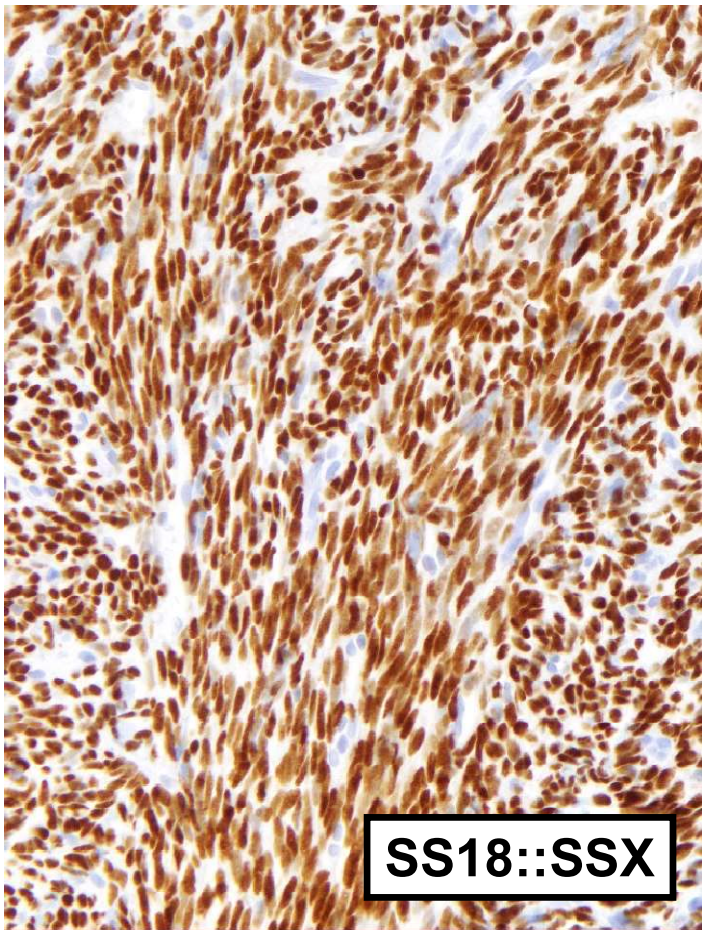
Baranov et al. *Am J Surg Pathol* 2020

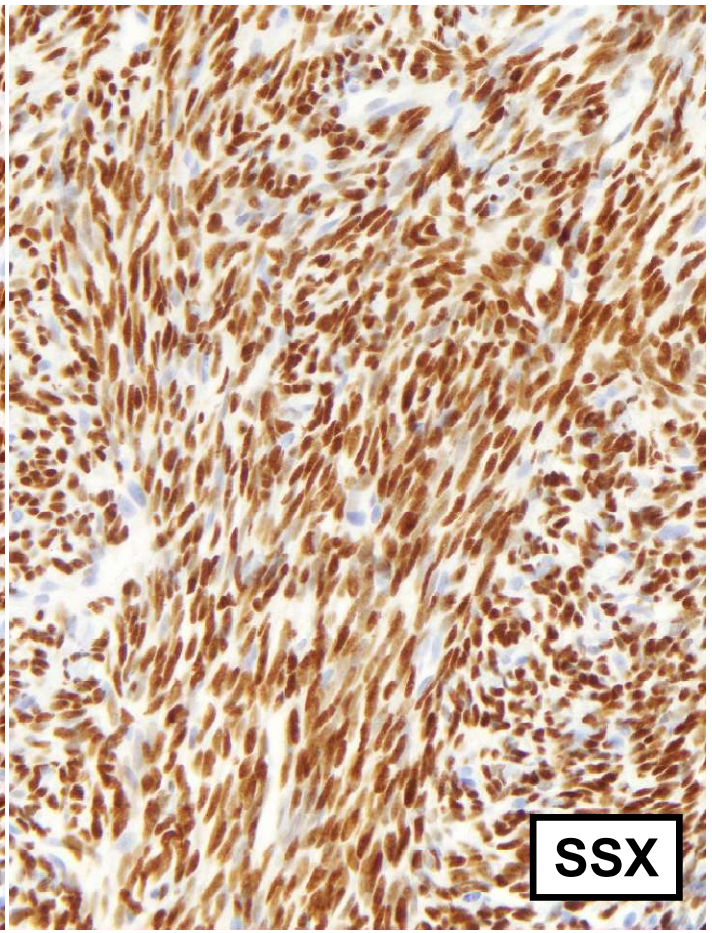
Zaborowksi et al. *Histopathology* 2020

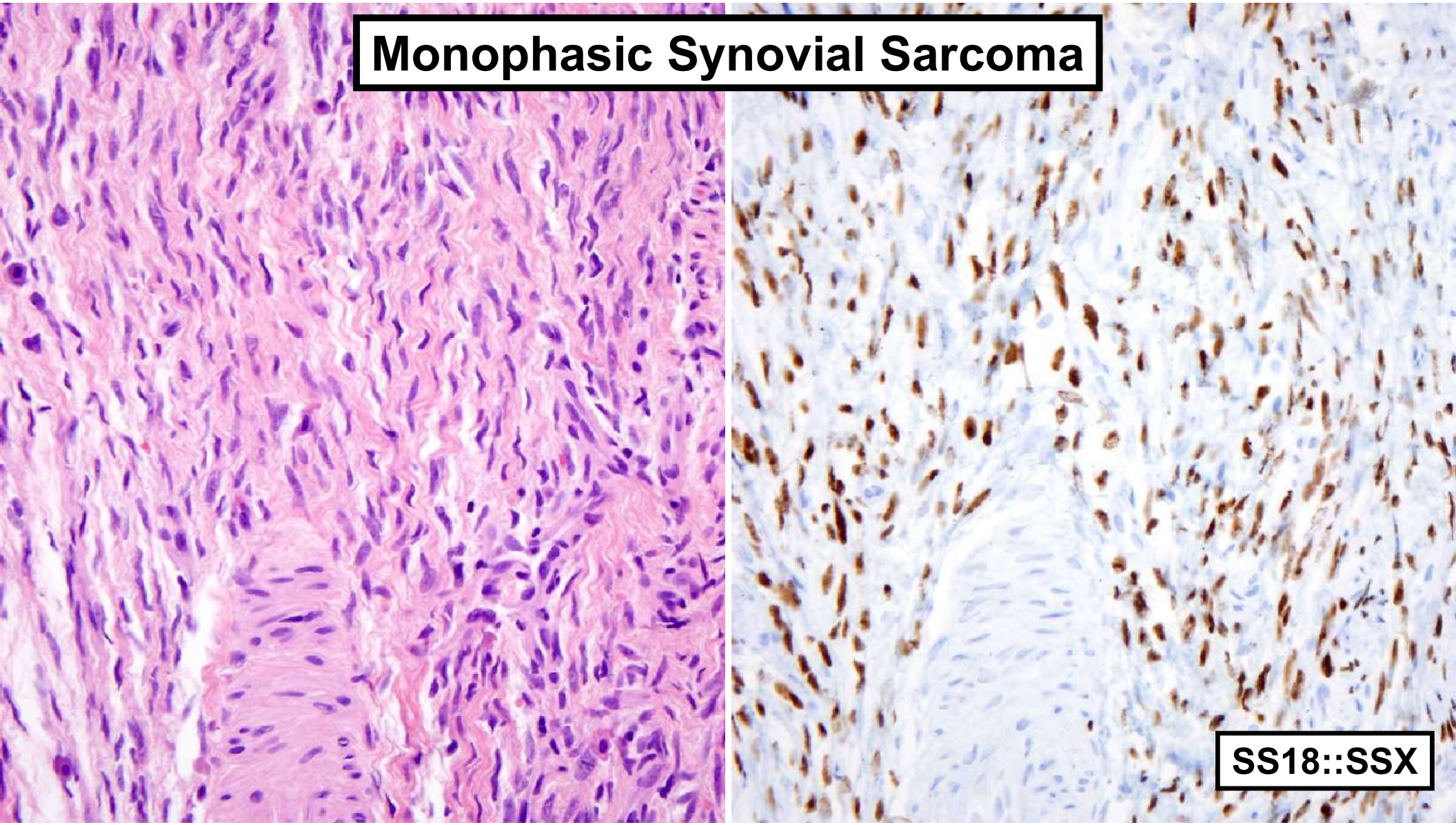
Perret et al. *Am J Surg Pathol* 2021

Monophasic Synovial Sarcoma

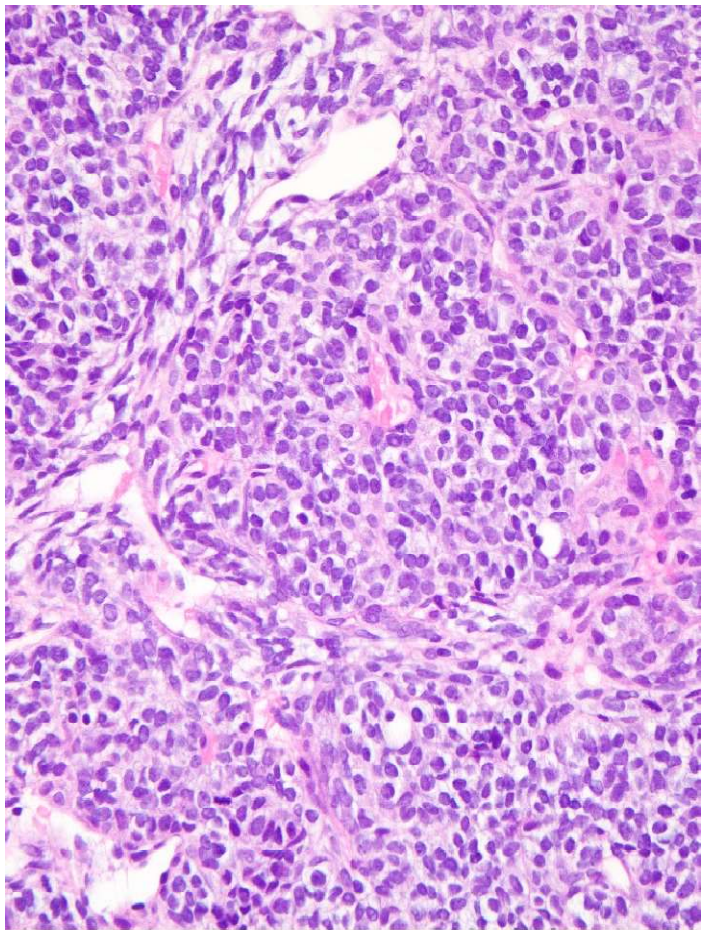


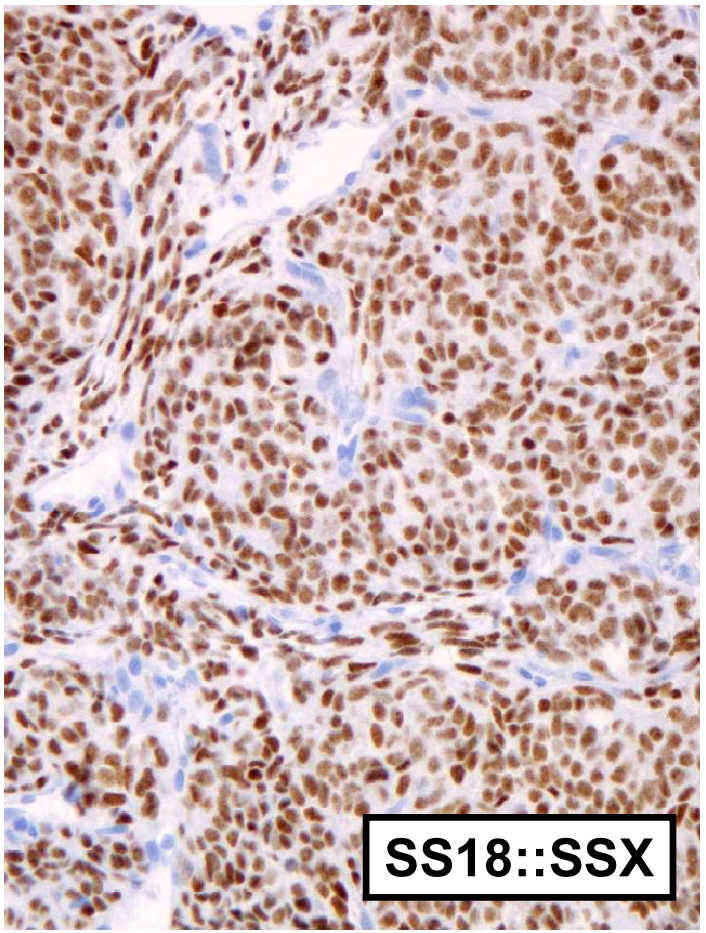


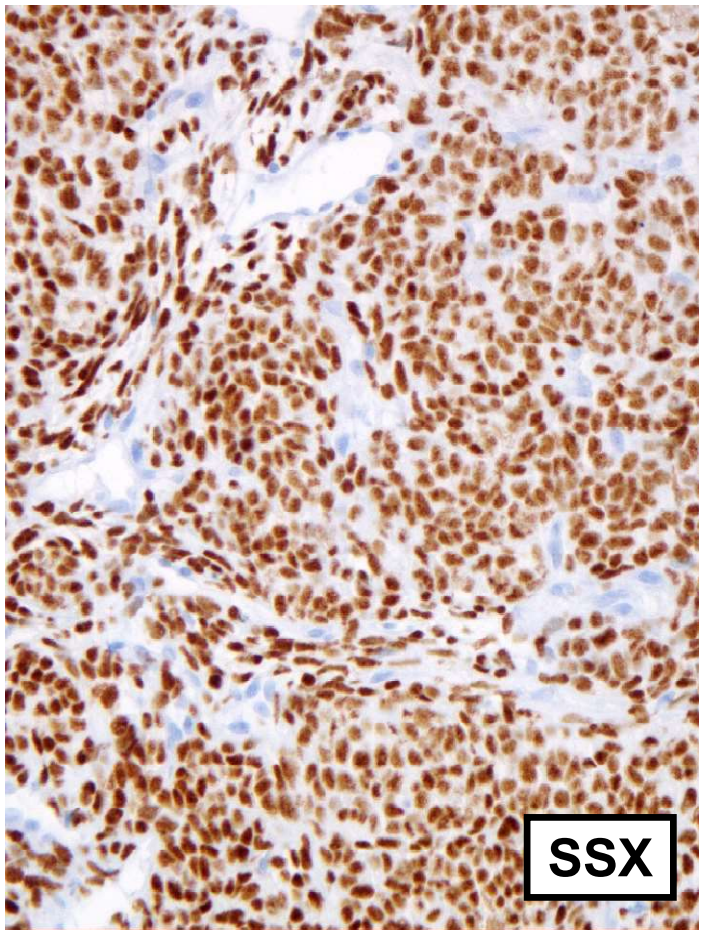



Monophasic Synovial Sarcoma
SS18::SSX

Poorly Differentiated Synovial Sarcoma

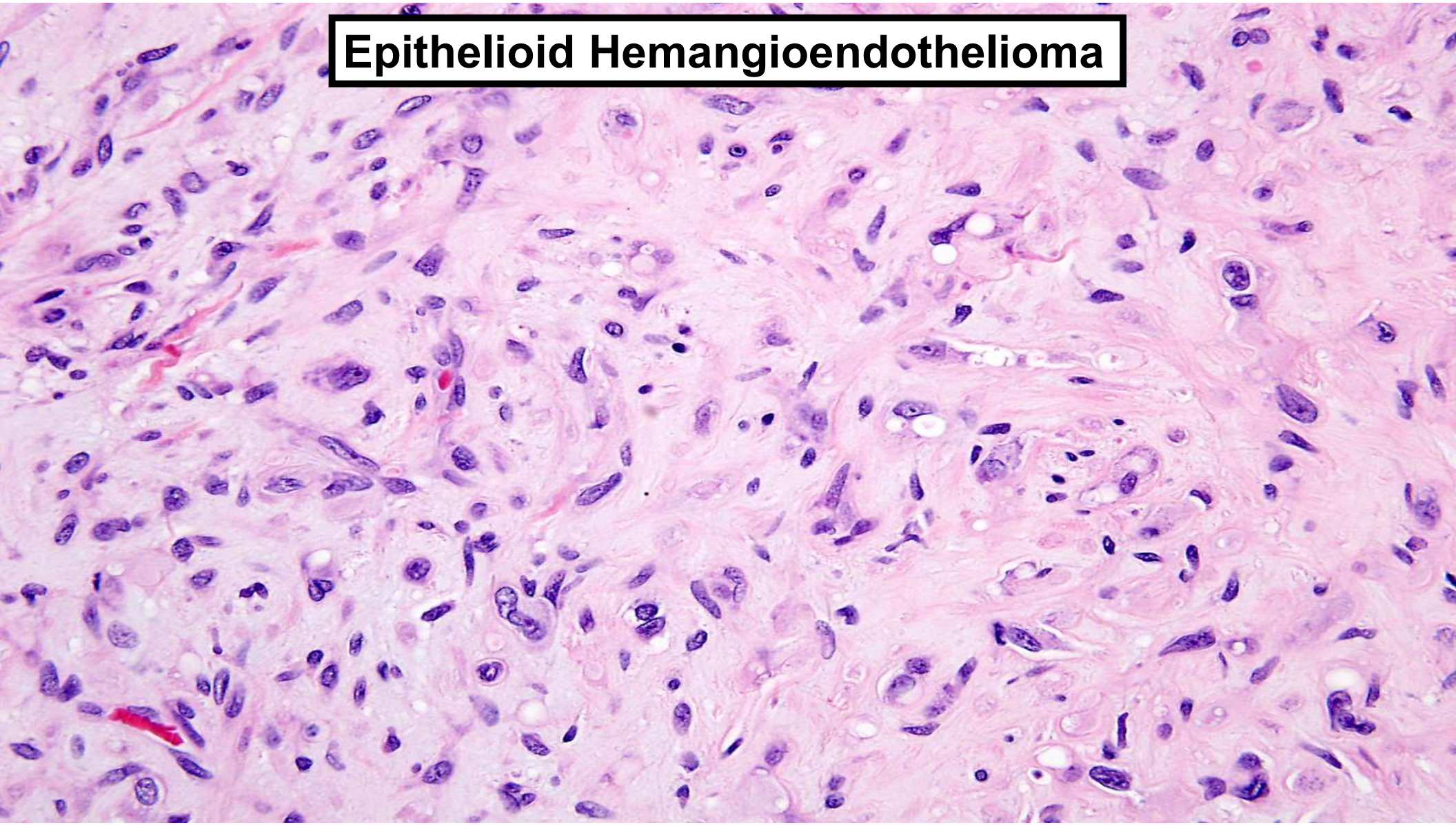


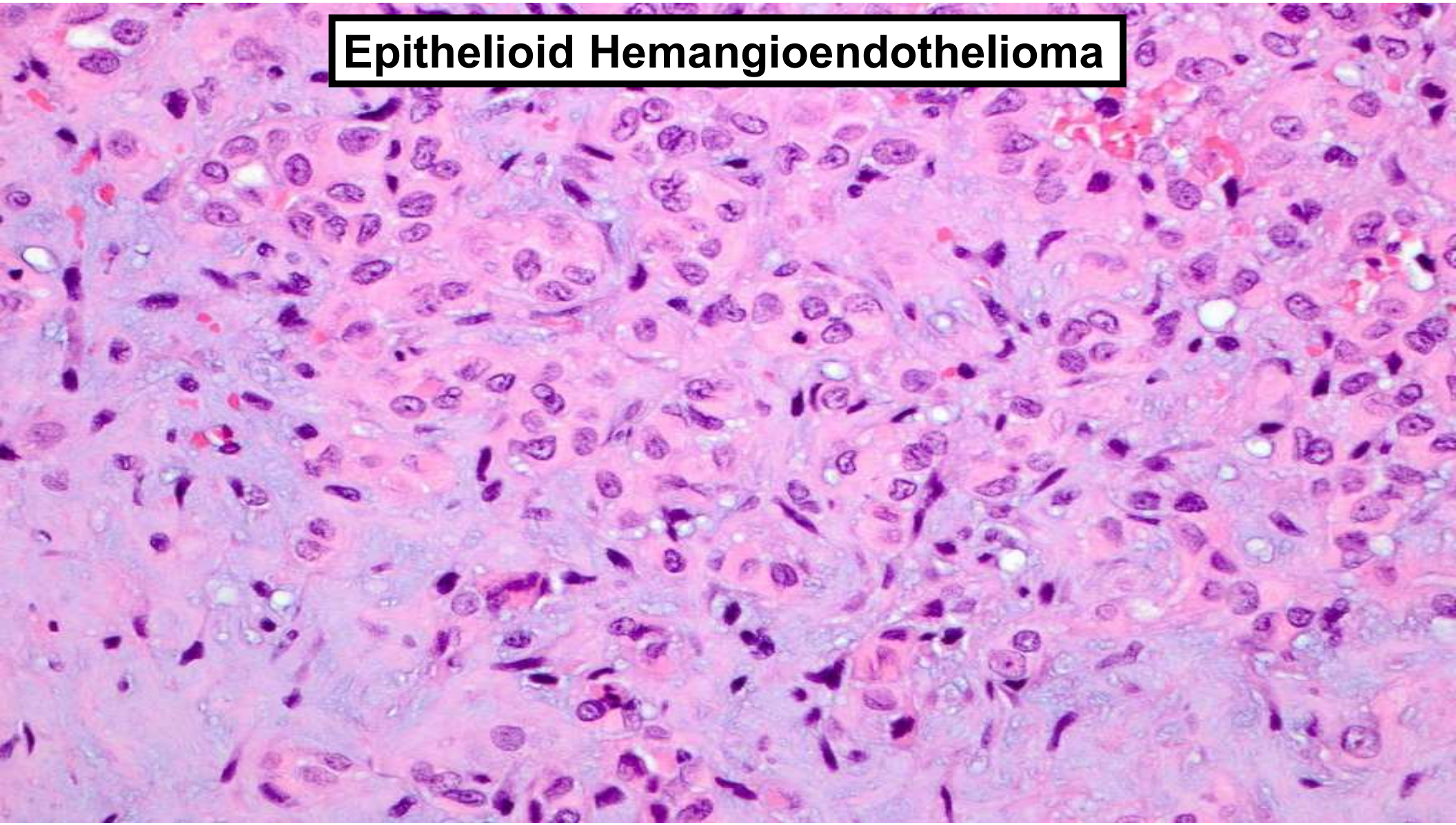




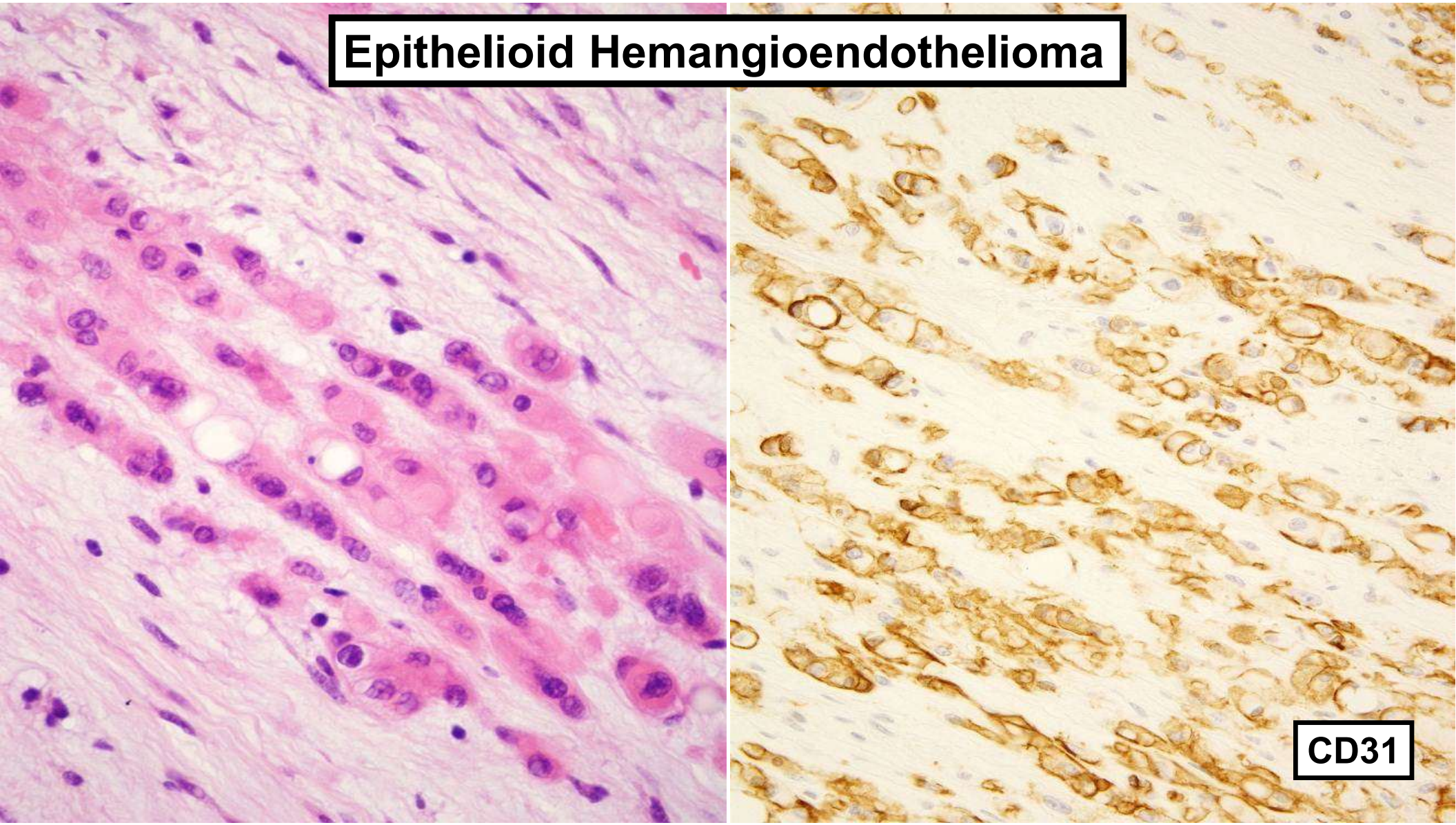
Epithelioid Hemangioendothelioma

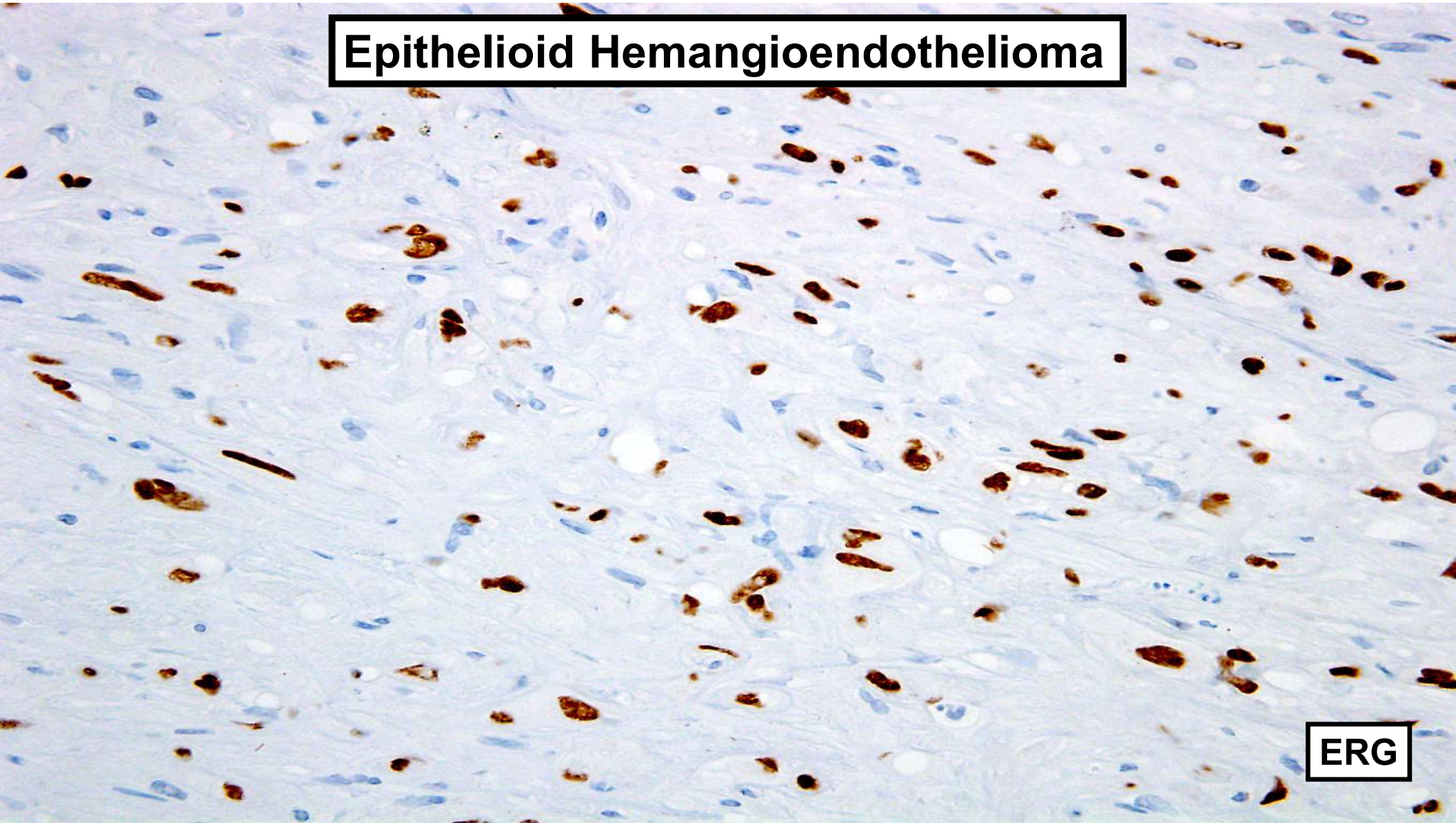
- Distinctive sarcoma showing endothelial differentiation; less aggressive than angiosarcoma
- Epithelioid cells arranged in cords and nests
- Myxohyaline stroma typical
- Occasional cytoplasmic vacuoles
- Keratin expression common
- May be confused with metastatic carcinoma, especially lobular breast and signet-ring-cell gastric


Epithelioid Hemangioendothelioma


Epithelioid Hemangioendothelioma

Epithelioid Hemangioendothelioma




Epithelioid Hemangioendothelioma
ERG

The American Journal of Surgical Pathology *25(5): 684–687, 2001*

Translocation t(1;3)(p36.3;q25) Is a Nonrandom Aberration in Epithelioid Hemangioendothelioma

Matthew R. Mendlick, B.A., Marilu Nelson, B.S., CLSp (CG), CLSp (MB), Diane Pickering, B.S., CLSp (CG), Sonny L. Johansson, M.D., Ph.D., Thomas A. Seemayer, M.D., James R. Neff, M.D., Gerardo Vergara, M.D., Howard Rosenthal, M.D., and Julia A. Bridge, M.D.

www.ScienceTranslationalMedicine.org 31 August 2011 Vol 3 Issue 98 98ra82

Identification of a Disease-Defining Gene Fusion in Epithelioid Hemangioendothelioma

Munir R. Tanas,[1] Andrea Sboner,[2] Andre M. Oliveira,[3] Michele R. Erickson-Johnson,[3] Jessica Hespelt,[1] Philip J. Hanwright,[1] John Flanagan,[4] Yuling Luo,[4] Kerry Fenwick,[5] Rachael Natrajan,[5] Costas Mitsopoulos,[5] Marketa Zvelebil,[5] Benjamin L. Hoch,[6] Sharon W. Weiss,[7] Maria Debiec-Rychter,[8] Raf Sciot,[9] Rob B. West,[10] Alexander J. Lazar,[11] Alan Ashworth,[5] Jorge S. Reis-Filho,[5] Christopher J. Lord,[5] Mark B. Gerstein,[2,12] Mark A. Rubin,[13] Brian P. Rubin[1]*

GENES, CHROMOSOMES & CANCER 50:644–653 (2011)

A Novel *WWTR1-CAMTA1* Gene Fusion Is a Consistent Abnormality in Epithelioid Hemangioendothelioma of Different Anatomic Sites

Costantino Errani,[1,2†‡] Lei Zhang,[1†] Yun Shao Sung,[1] Mihai Hajdu,[1] Samuel Singer,[3] Robert G. Maki,[4] John H. Healey,[2] and Cristina R. Antonescu[1*]

IHC for CAMTA1

- Nuclear staining in most cases of EHE
- Negative in epithelioid hemangioma and epithelioid angiosarcoma
- Negative in other epithelioid mesenchymal tumors
- Negative in carcinomas
- Useful diagnostic marker for EHE

Shibuya et al. *Histopathology* 2015

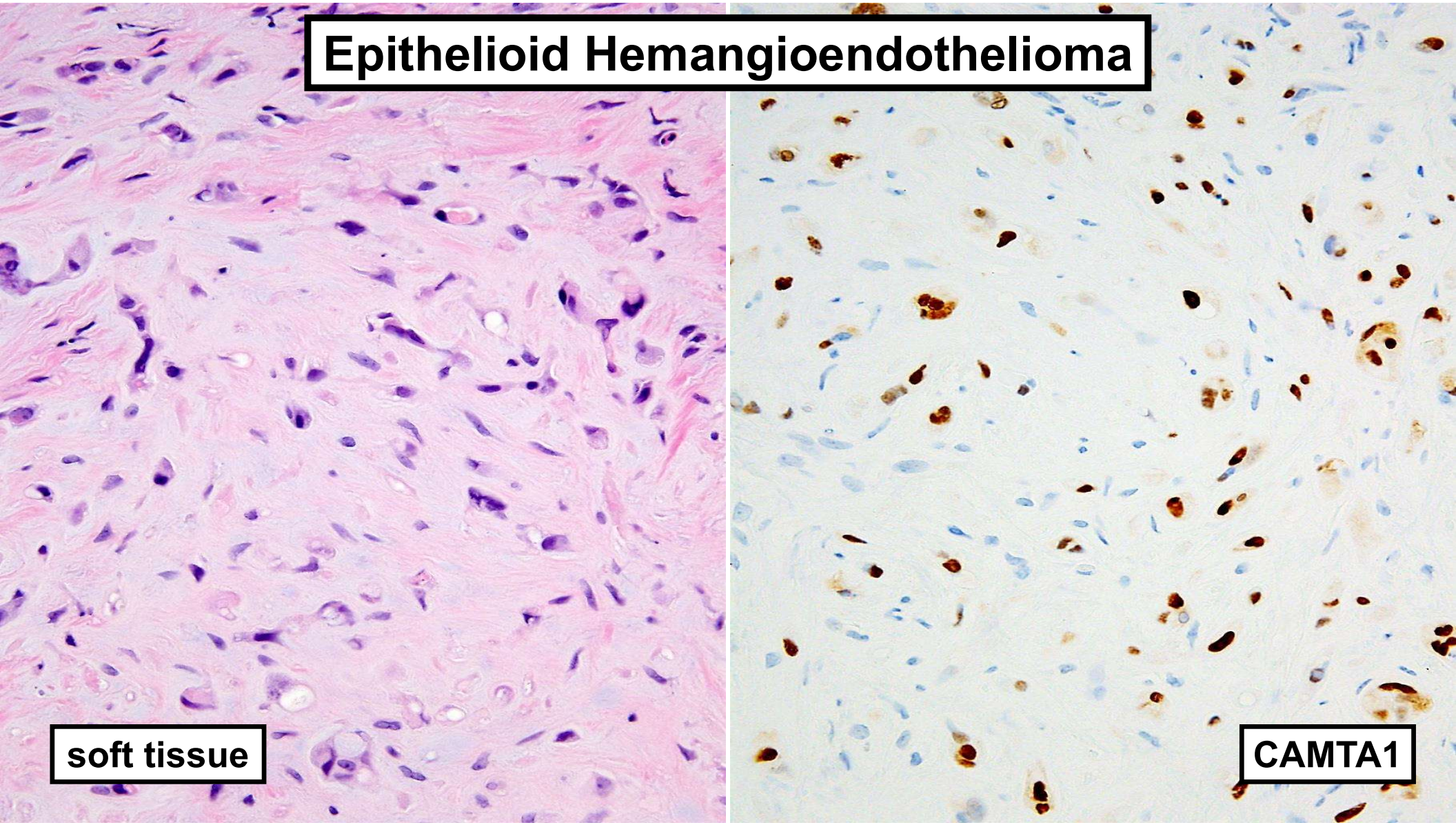
Doyle et al. *Am J Surg Pathol* 2016

TABLE 1. Summary of IHC Staining for CAMTA1 in EHE and Other Epithelioid Mesenchymal Tumors

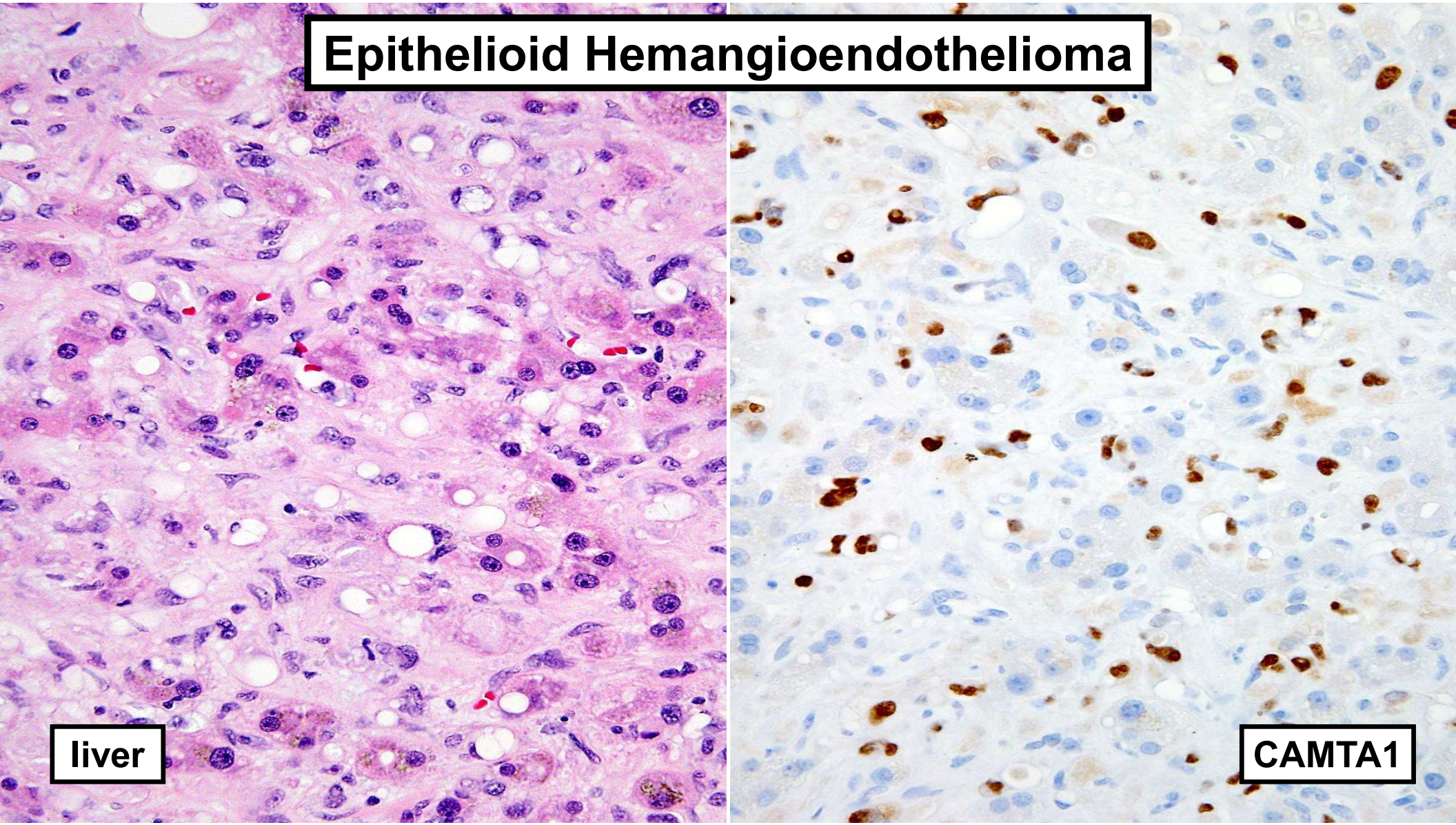
Tumor Type	Total Cases	CAMTA1 Positive (n [%])
EHE	59	51 (86)
Epithelioid hemangioma	20	0 (0)
Epithelioid angiomatous nodule	10	0 (0)
Epithelioid angiosarcoma	25	1 (4)
Composite hemangioendothelioma	5	0 (0)
Pseudomyogenic hemangioendothelioma	10	0 (0)
Epithelioid sarcoma	25	0 (0)
Sclerosing epithelioid fibrosarcoma	10	0 (0)
Myoepithelial neoplasms of soft tissue	10	0 (0)
PEComa	10	0 (0)
Alveolar soft part sarcoma	10	0 (0)
Ossifying fibromyxoid tumor	10	0 (0)

Doyle et al. *Am J Surg Pathol* 2016

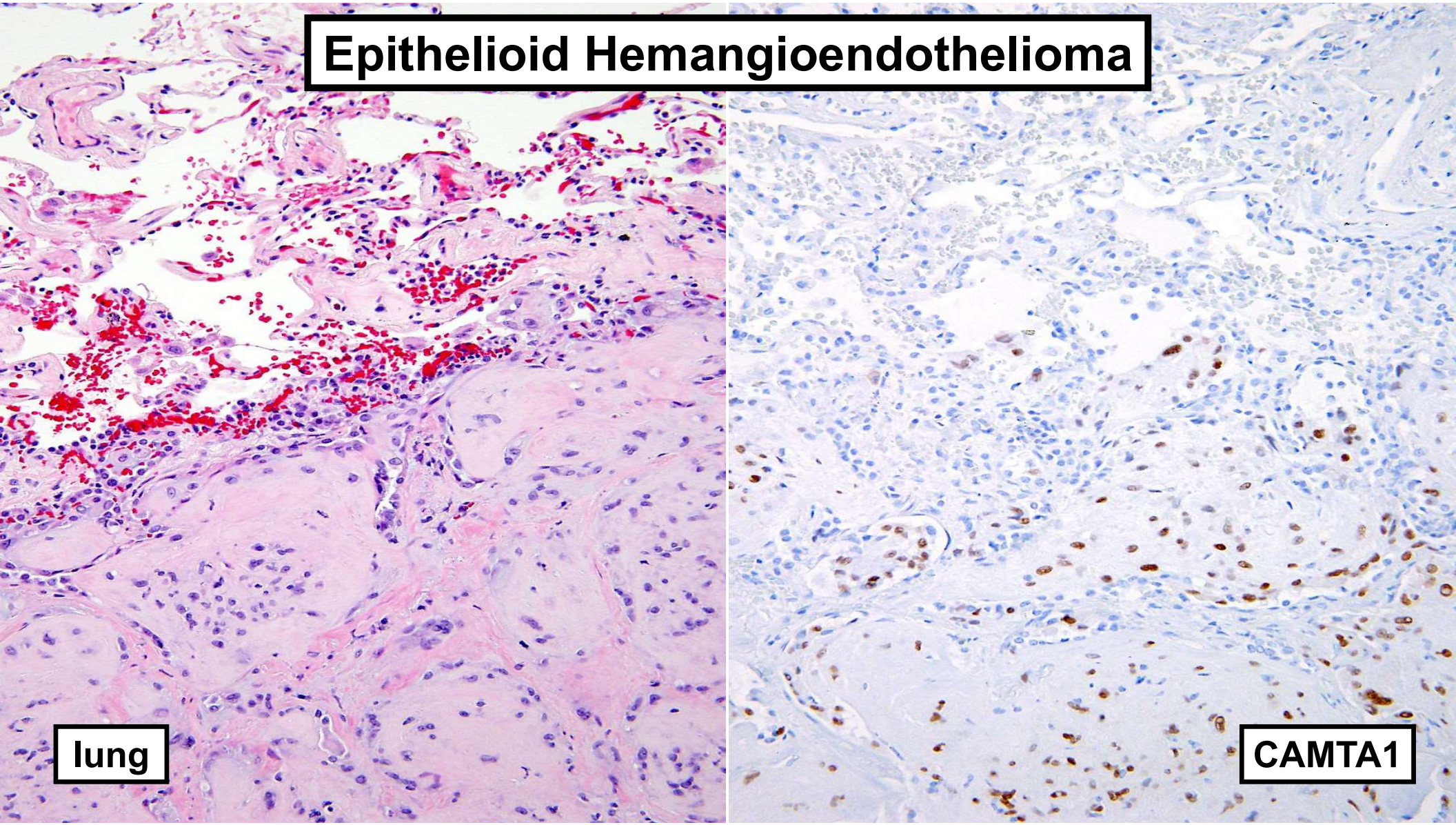
Epithelioid Hemangioendothelioma

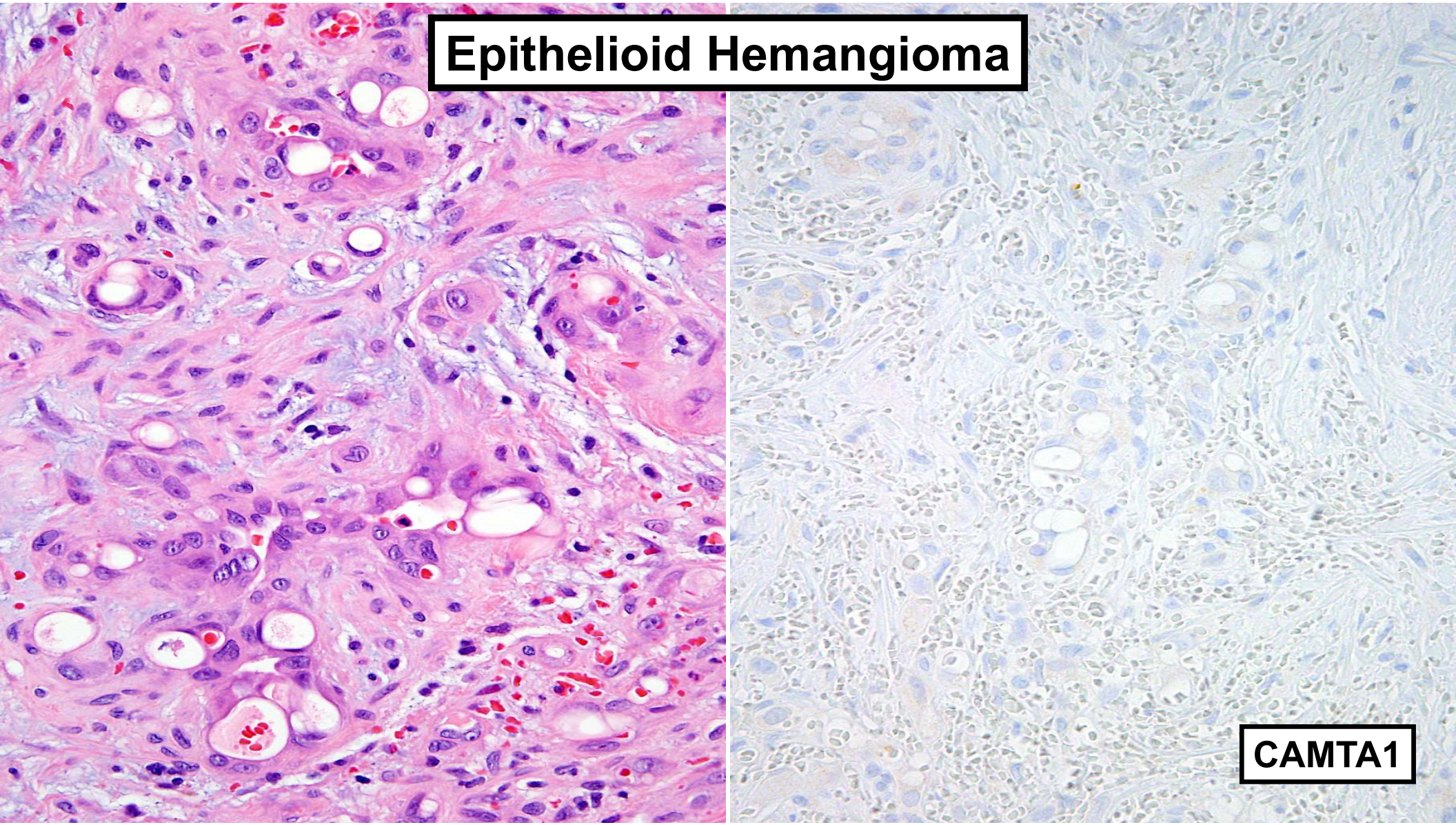


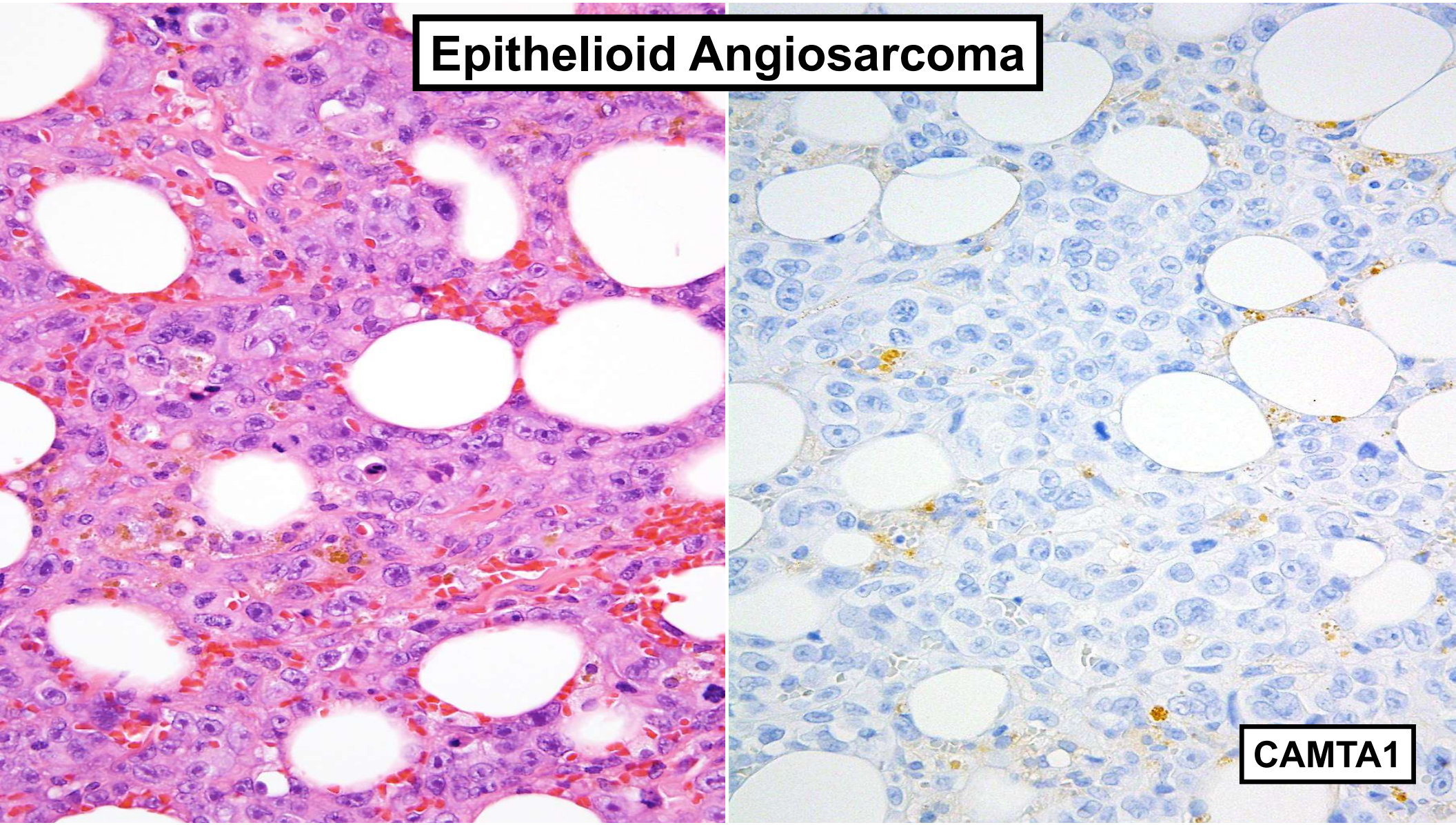
Epithelioid Hemangioendothelioma



Epithelioid Hemangioendothelioma




Epithelioid Hemangioma
CAMTA1


Epithelioid Angiosarcoma
CAMTA1

Diagnostic Markers Identified by Gene Expression Profiling	
DOG1 (ANO1)	NKX2-2
ETV4	SATB2
MUC4	TLE1

NKX2-2

- **Homeobox transcription factor involved in neuronal development and glial/ neuroendocrine differentiation**
- **Gene expression profiling: NKX2-2 downstream target of *EWSR1::FLI1* fusion**
- **NKX2-2 required for oncogenic transformation**

Expression profiling of EWS/FLI identifies *NKX2.2* as a critical target gene in Ewing's sarcoma

Richard Smith,[1,6] Leah A. Owen,[2,6] Deborah J. Trem,[1] Jenny S. Wong,[3] Jennifer S. Whangbo,[3] Todd R. Golub,[3,4] and Stephen L. Lessnick[1,2,5,*]

CANCER CELL 9, 405–416, MAY 2006

NKX2-2

- **IHC: diffuse nuclear NKX2-2 sensitive marker for Ewing sarcoma (95%)**
- **Also positive in Ewing sarcoma with *EWSR1::ERG***
- **Imperfect specificity: mesenchymal chondrosarcomas often positive (also olfactory neuroblastomas)**

NKX2.2 is a Useful Immunohistochemical Marker for Ewing Sarcoma

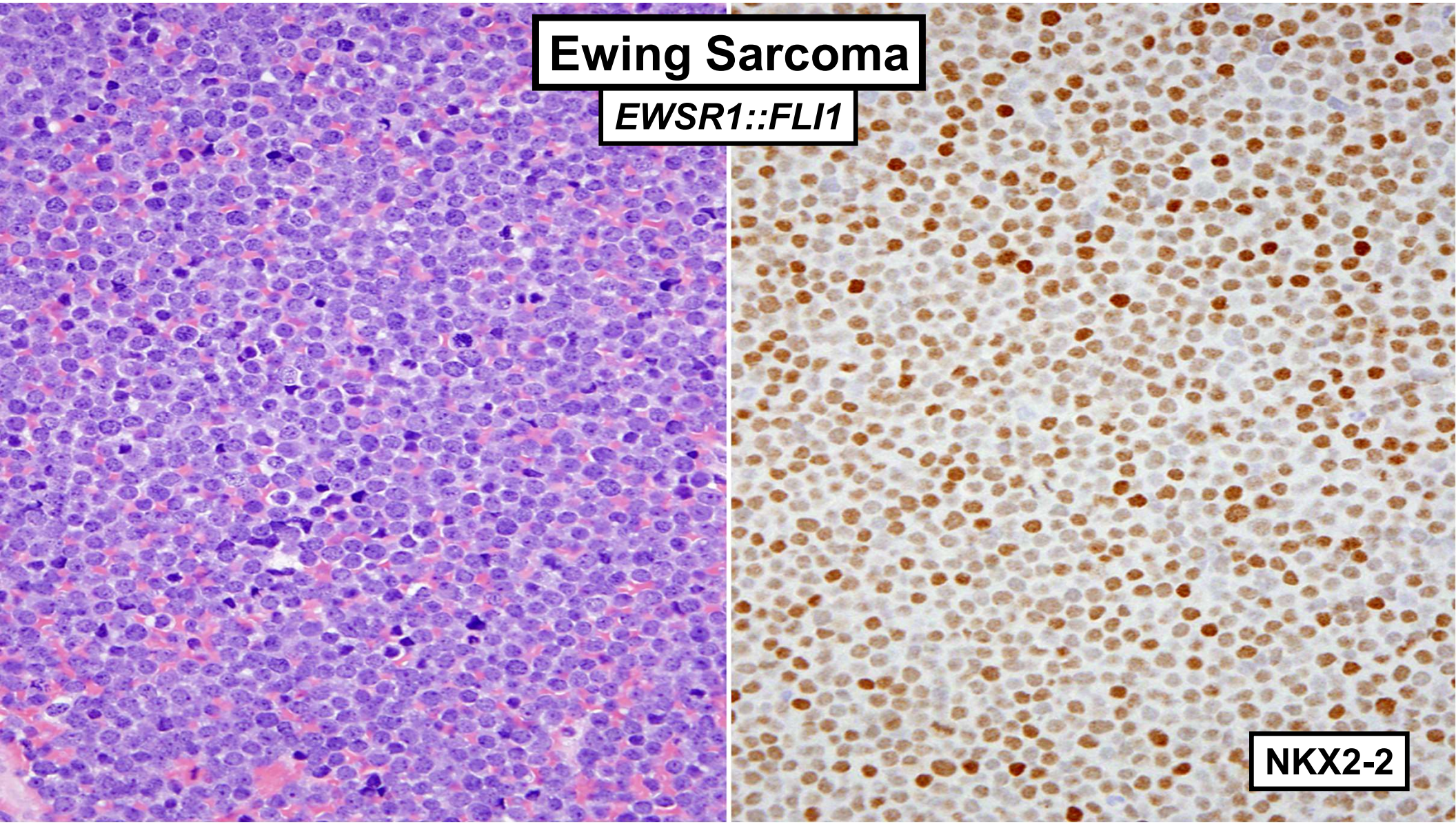
Akihiko Yoshida, MD,† Shigeki Sekine, MD, PhD,‡ Koji Tsuta, MD, PhD,* Masashi Fukayama, MD, PhD,† Koh Furuta, MD, PhD,* and Hitoshi Tsuda, MD, PhD**

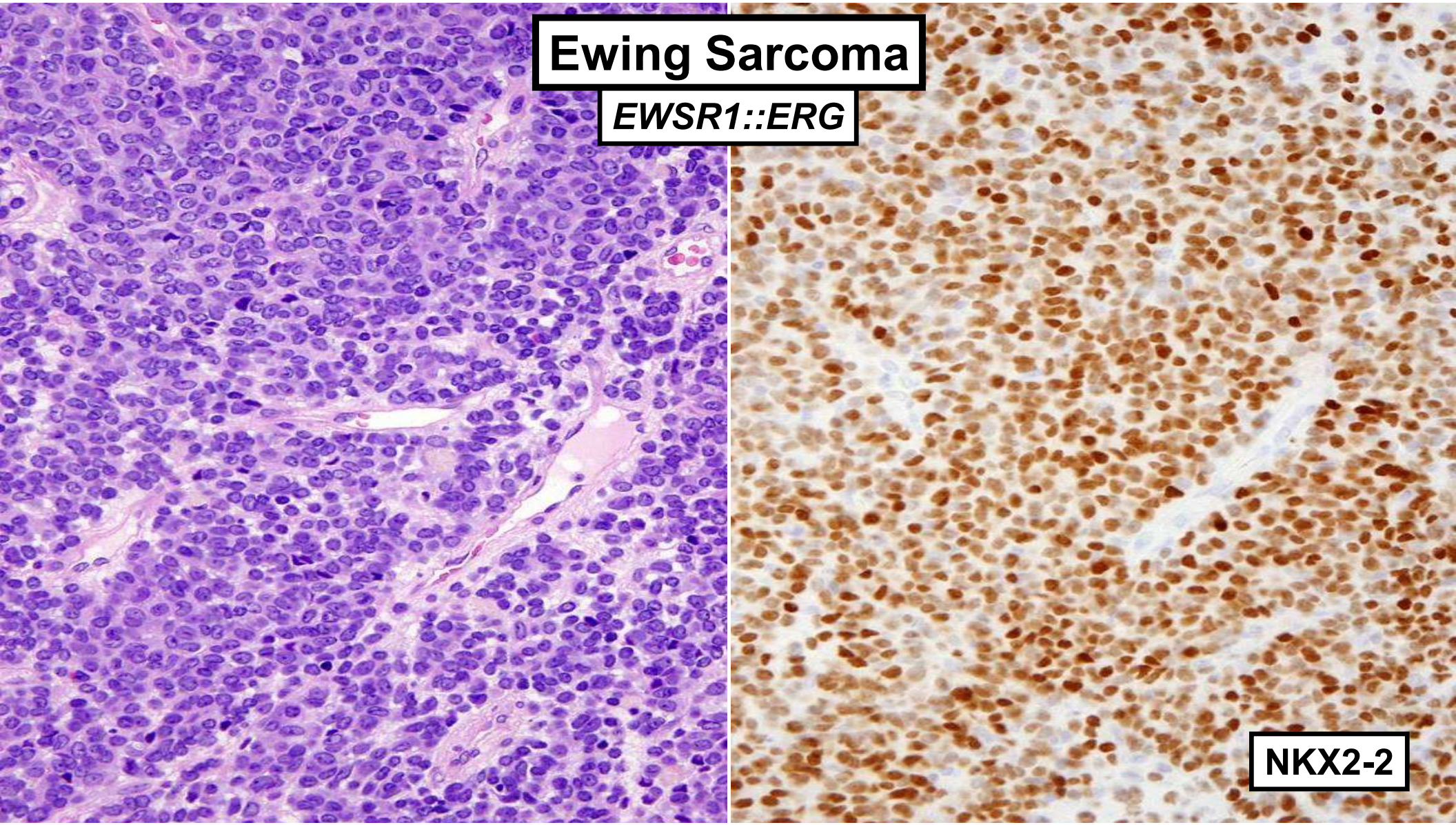
Am J Surg Pathol • Volume 36, Number 7, July 2012

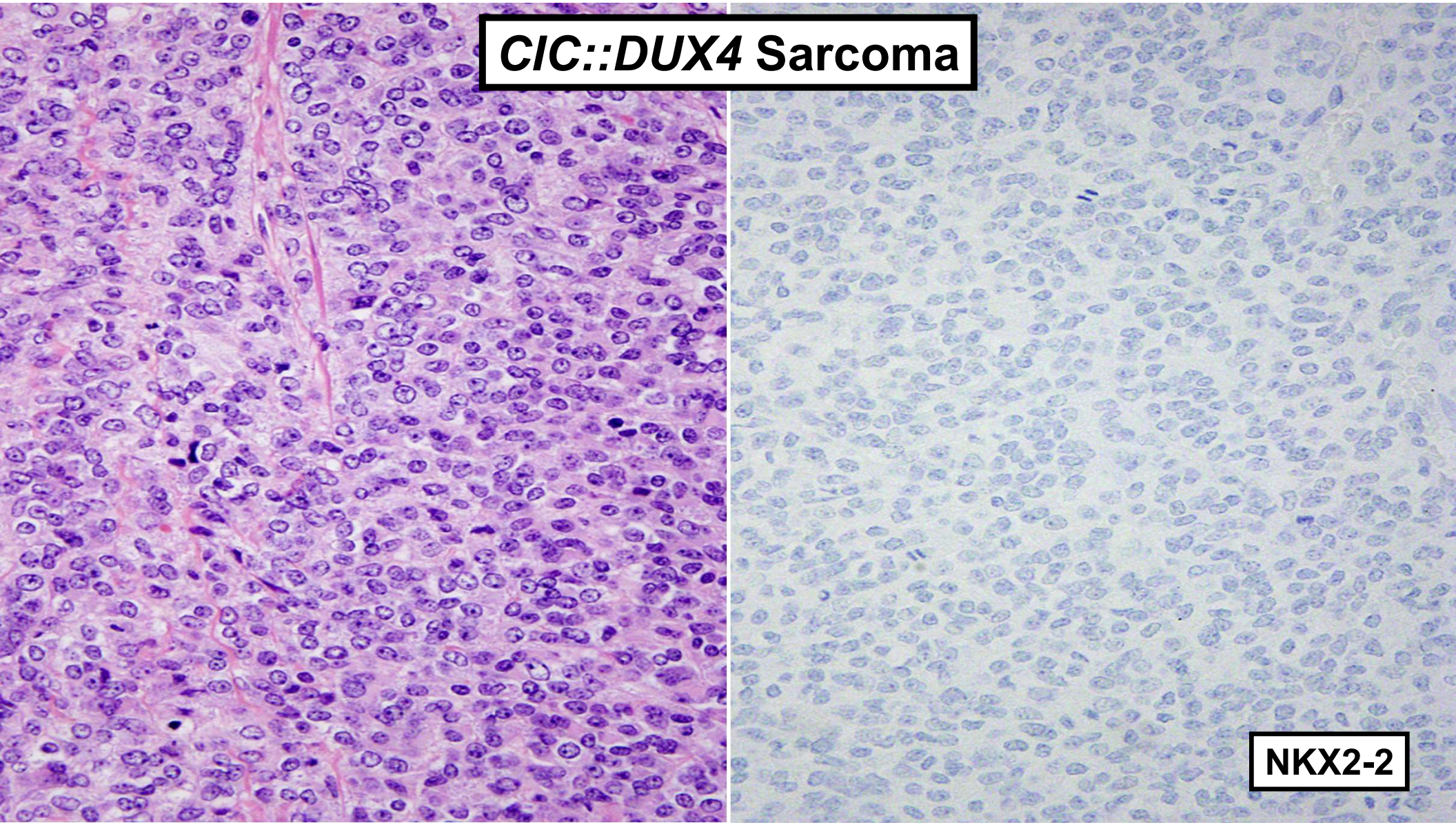
Table 1 Summary of immunohistochemical staining for NKX2-2

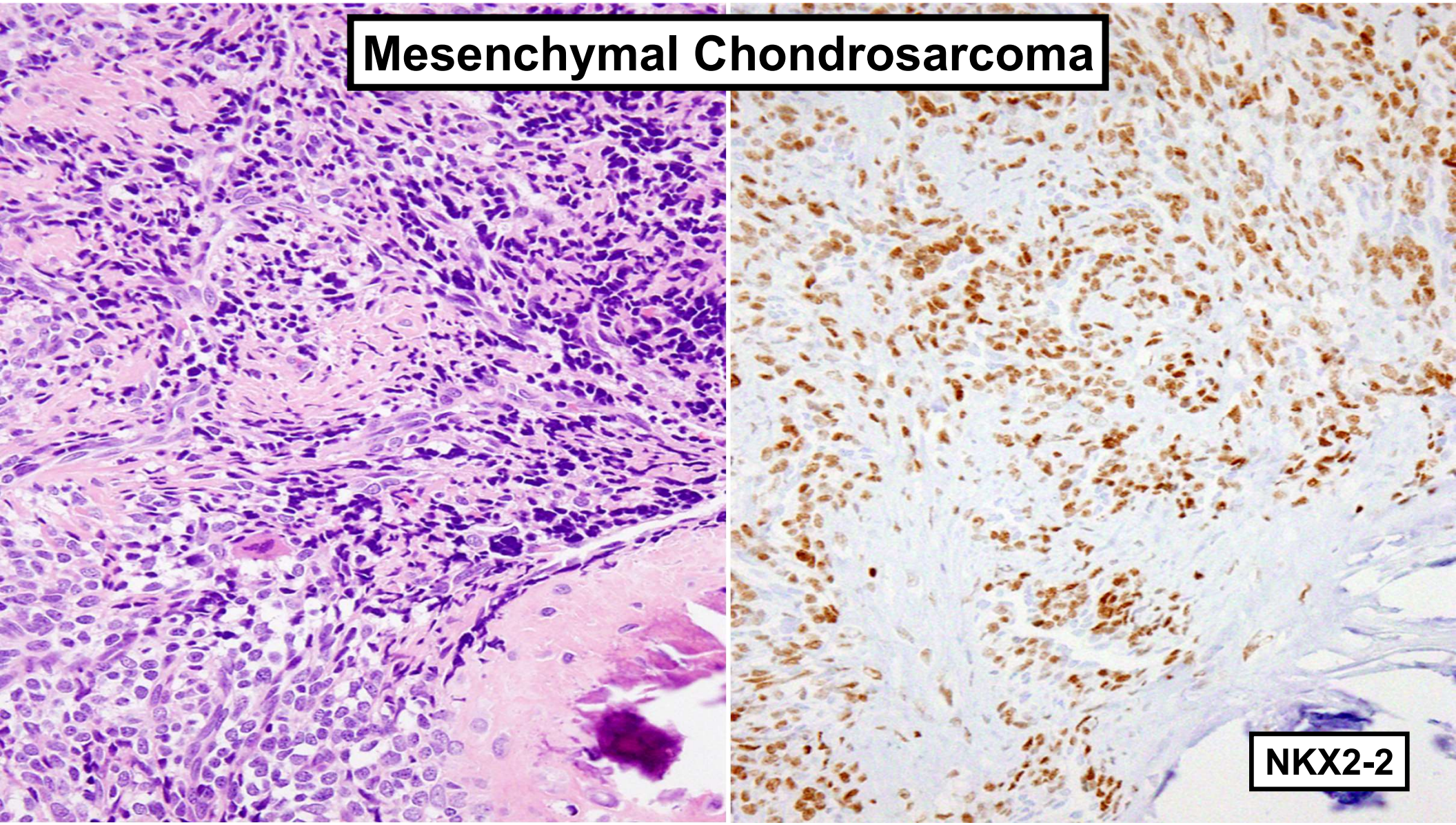
Tumor type	*Total cases*	*NKX2-2 positive (%)*
Ewing sarcoma	40	37 (93)
Non-Ewing small round blue cell tumors		
CIC-DUX4 sarcoma	20	1 (5)
BCOR-CCNB3 sarcoma	5	0 (0)
Unclassified round cell sarcoma	9	2 (22)
Synovial sarcoma, poorly differentiated	10	1 (10)
Lymphoblastic lymphoma	10	0 (0)
Alveolar rhabdomyosarcoma	10	0 (0)
Embryonal rhabdomyosarcoma	10	0 (0)
NUT midline carcinoma	5	0 (0)
Wilms tumor	10	0 (0)
Merkel cell carcinoma	10	0 (0)
Melanoma	20	0 (0)
Small cell carcinoma	10	3 (30)
Neuroblastoma	10	1 (10)
Olfactory neuroblastoma	10	8 (80)
Mesenchymal chondrosarcoma	12	9 (75)

Hung et al. *Mod Pathol* 2016


Ewing Sarcoma
EWSR1::FLI1
NKX2-2

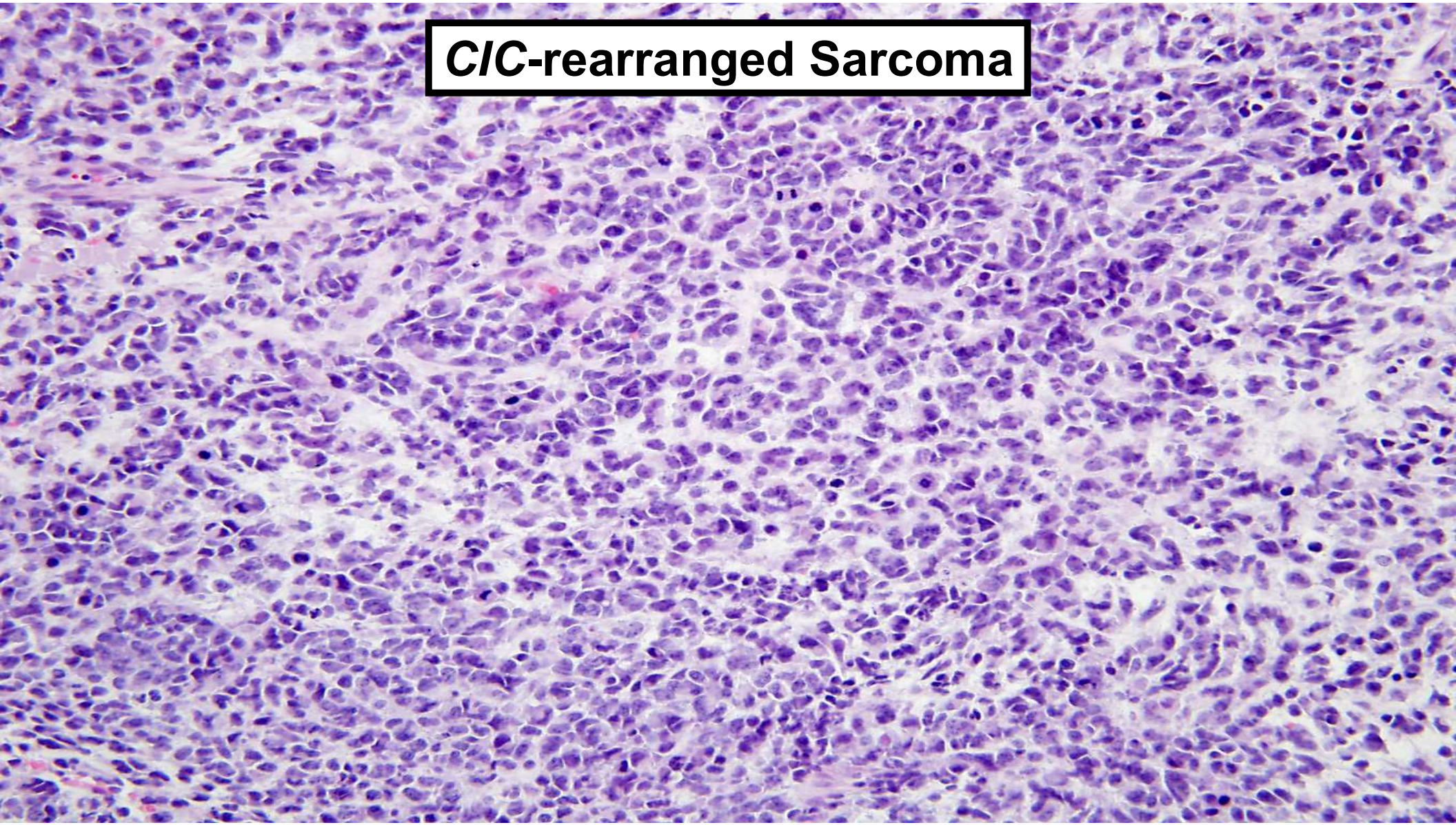

Ewing Sarcoma
EWSR1::ERG
NKX2-2

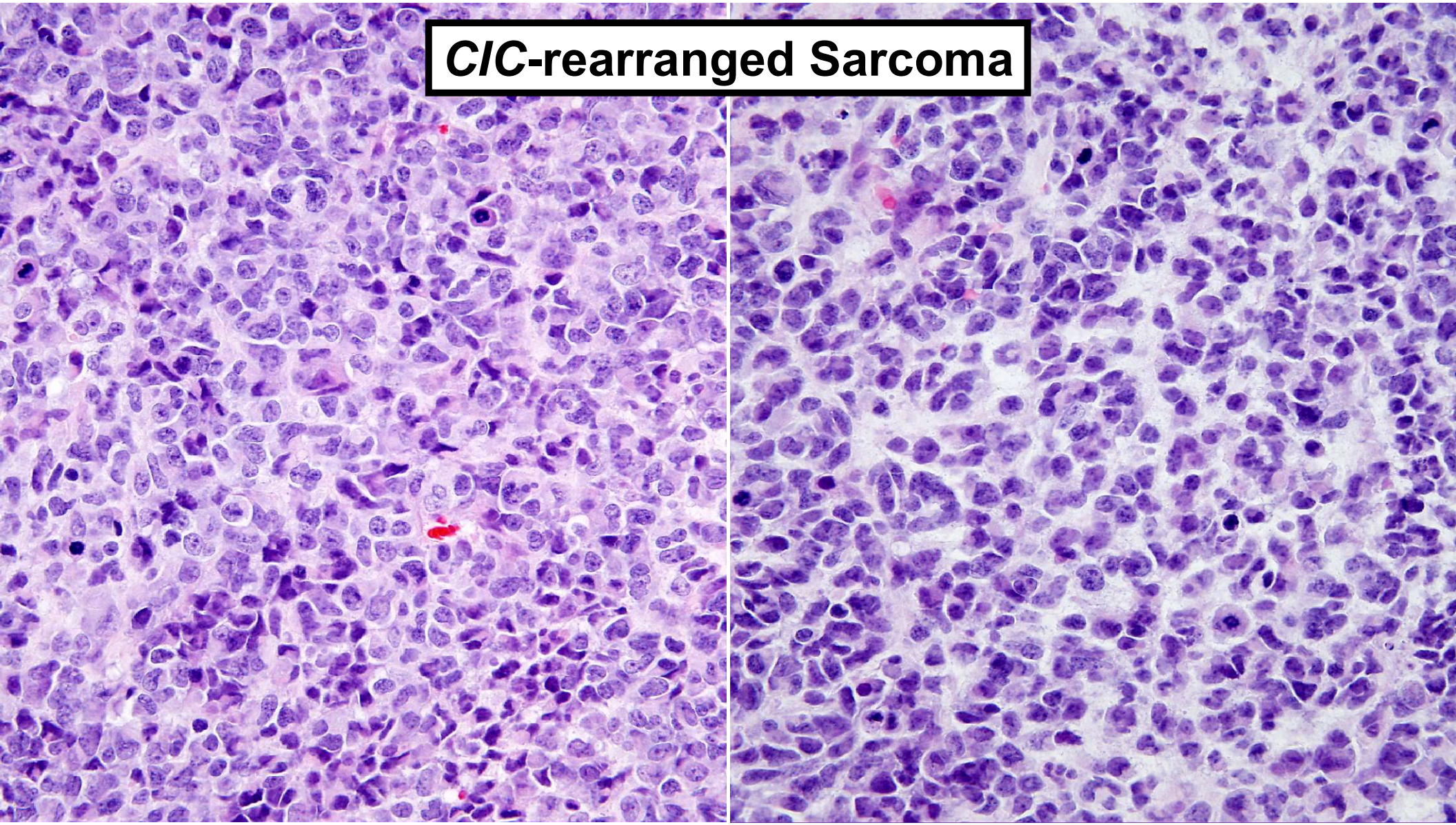

CIC::DUX4 Sarcoma
NKX2-2

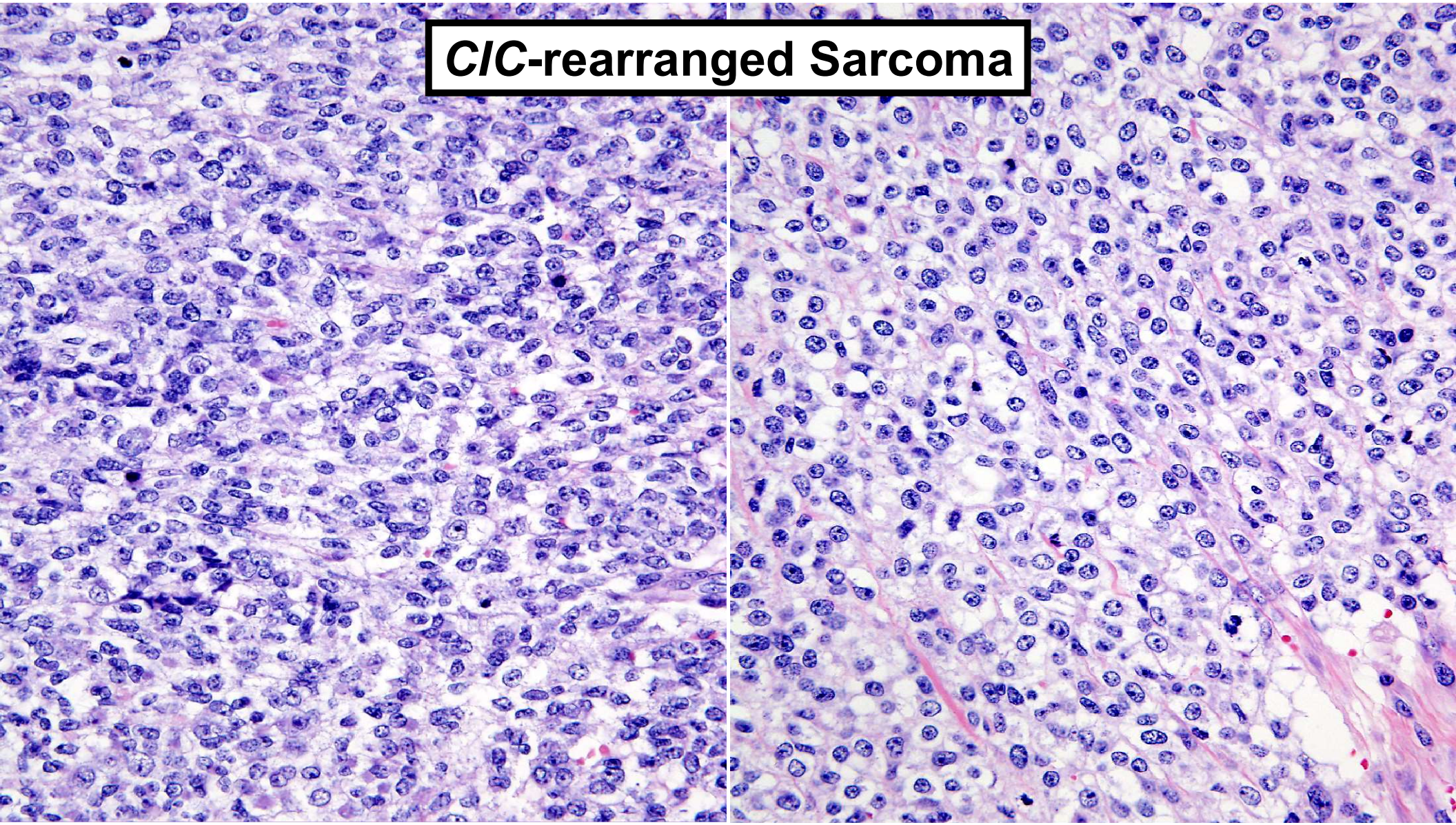

Mesenchymal Chondrosarcoma
NKX2-2

CIC-rearranged sarcoma

- **Most common "Ewing-like" ("undifferentiated") round cell sarcoma that lacks *EWSR1* gene fusions (more than 70%)**
- **Majority with *CIC::DUX4* fusions (also known as *CIC::DUX4* sarcoma)**
- **Wide age range; peak in young adults**
- **Deep soft tissue of extremities and trunk most frequent**
- **Bone and visceral sites rare**
- **Much more aggressive clinical course and worse survival than Ewing sarcoma; currently treated similarly**


CIC-rearranged Sarcoma

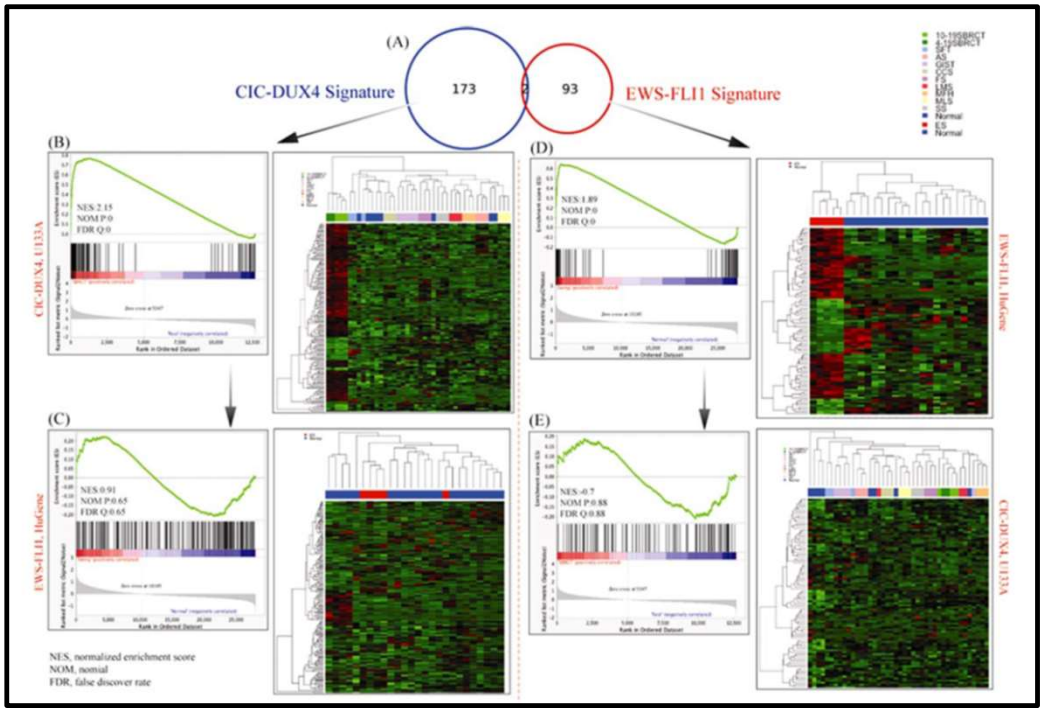

CIC-rearranged Sarcoma


CIC-rearranged Sarcoma

GENES, CHROMOSOMES & CANCER 53:622–633 (2014)

Distinct Transcriptional Signature and Immunoprofile of *CIC-DUX4* Fusion–Positive Round Cell Tumors Compared to *EWSR1*-Rearranged Ewing Sarcomas: Further Evidence Toward Distinct Pathologic Entities

Katja Specht,[1] Yun-Shao Sung,[2] Lei Zhang,[2] Günther H. S. Richter,[3] Christopher D. Fletcher,[4]* and Cristina R. Antonescu[2]*



MODERN PATHOLOGY (2015) 28, 57–68

CIC-DUX sarcomas demonstrate frequent MYC amplification and ETS-family transcription factor expression

Steven Christopher Smith[1,2,6,7], Darya Buehler[3,6], Eun-Young Karen Choi[1], Jonathan B McHugh[1], Brian P Rubin[4], Steven D Billings[4], Bonnie Balzer[2], Dafydd G Thomas[1], David R Lucas[1], John R Goldblum[4] and Rajiv M Patel[1,5]

MODERN PATHOLOGY (2016) 29, 1324–1334

Evaluation of ETV4 and WT1 expression in *CIC*-rearranged sarcomas and histologic mimics

Yin P Hung, Christopher DM Fletcher and Jason L Hornick

MODERN PATHOLOGY (2016) 29, 1523–1531

ETV4 is a useful marker for the diagnosis of *CIC*-rearranged undifferentiated round-cell sarcomas: a study of 127 cases including mimicking lesions

Sophie Le Guellec[1,2], Valérie Velasco[3], Gaëlle Pérot[2,3], Sarah Watson[4], Franck Tirode[4] and Jean-Michel Coindre[2,3,5]

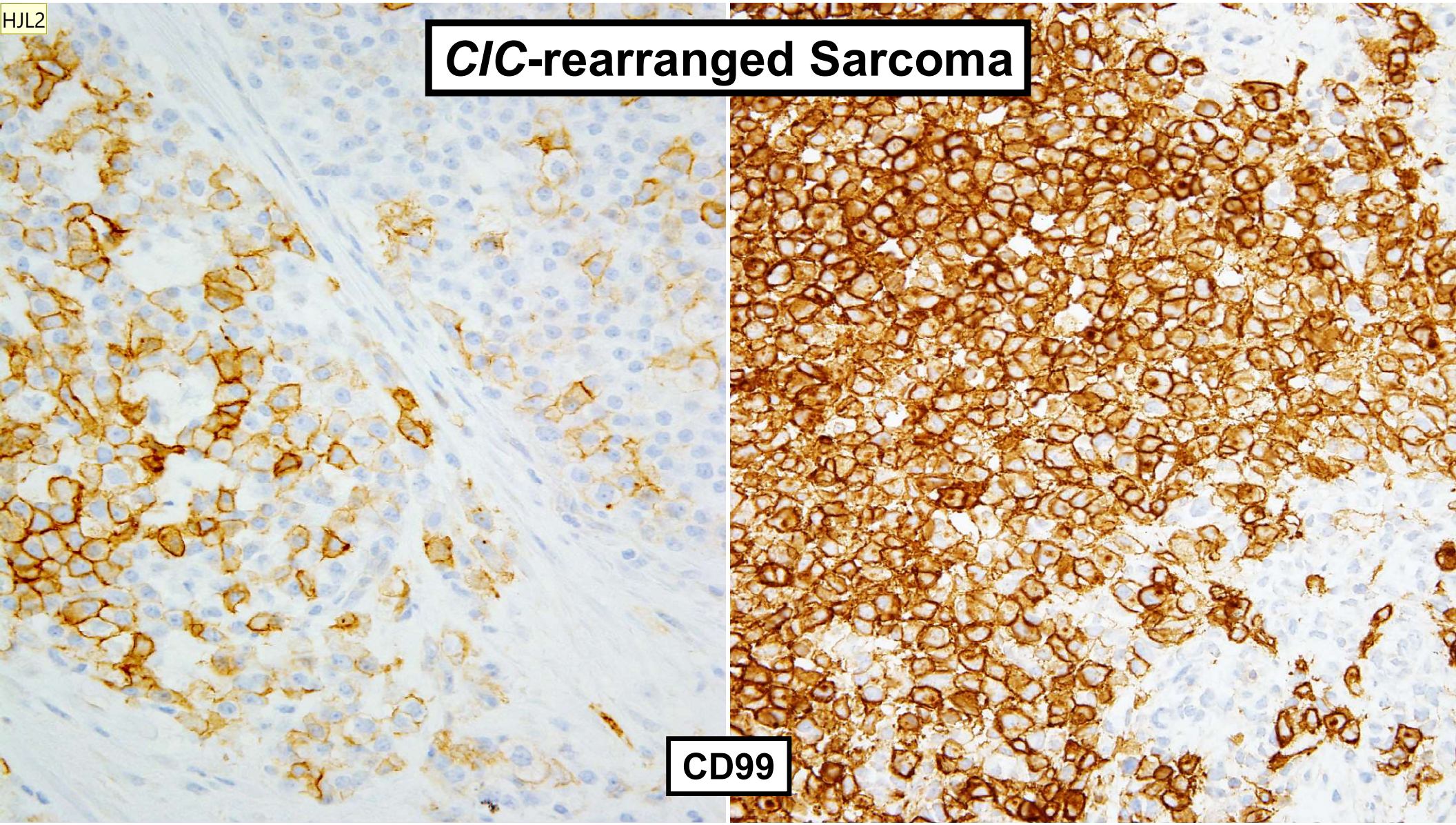
CIC-rearranged Sarcoma: IHC

Marker	Positive	Comments
CD99	85%	Usually patchy; 20% diffuse
WT1	90%	Nuclear +/- cytoplasmic
ETV4	95%	Nuclear
Keratins	15%	Focal

Hung et al. *Mod Pathol* 2016

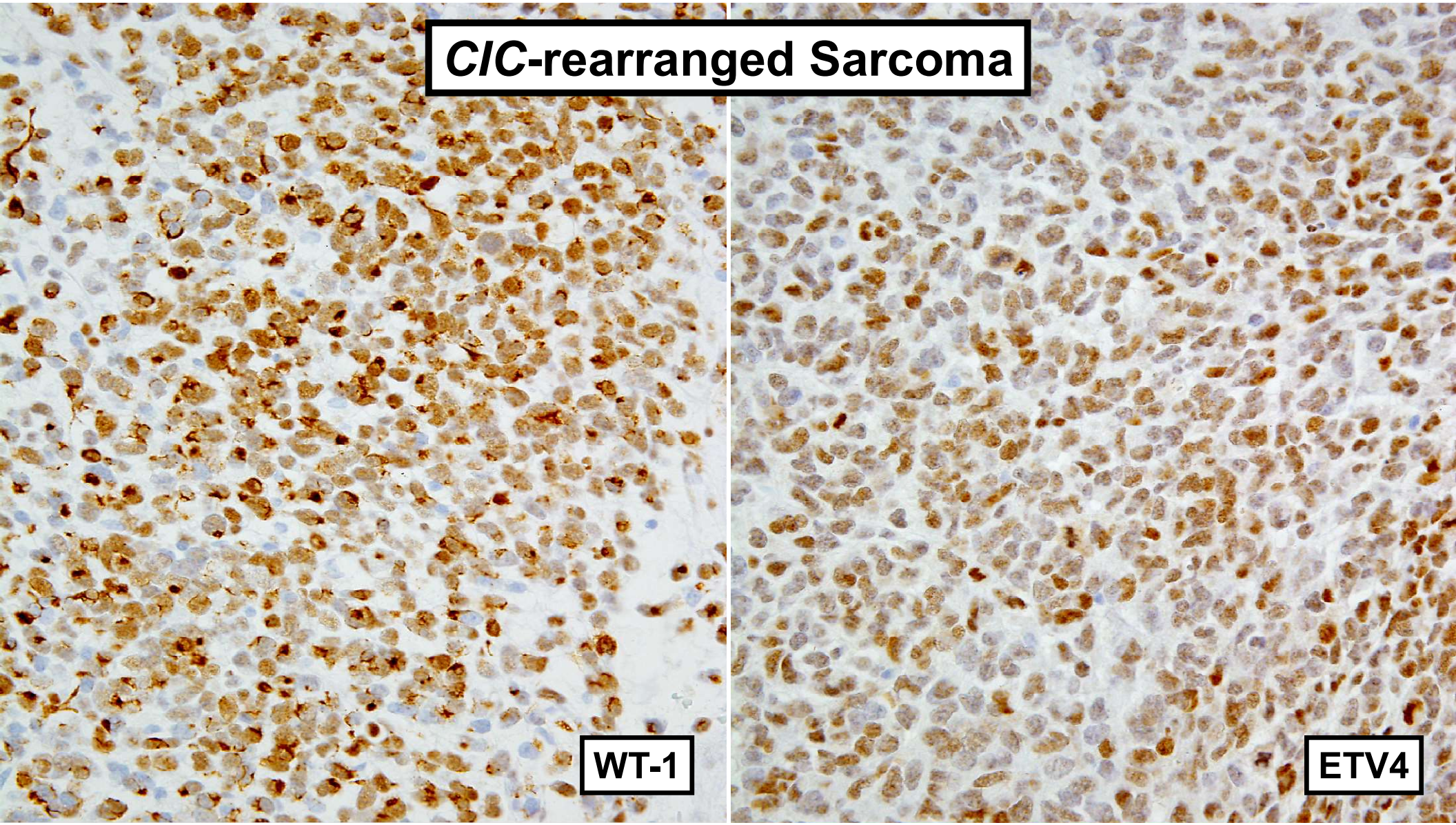
Le Guellec et al. *Mod Pathol* 2016

Antonescu et al. *Am J Surg Pathol* 2017


HJL2
CIC-rearranged Sarcoma
CD99

Slide 71

HJL2 Hornick, Jason L.,M.D.,Ph.D., 2/3/2019


CIC-rearranged Sarcoma
WT-1
ETV4

Histopathology 2017, **71**, 461–469.

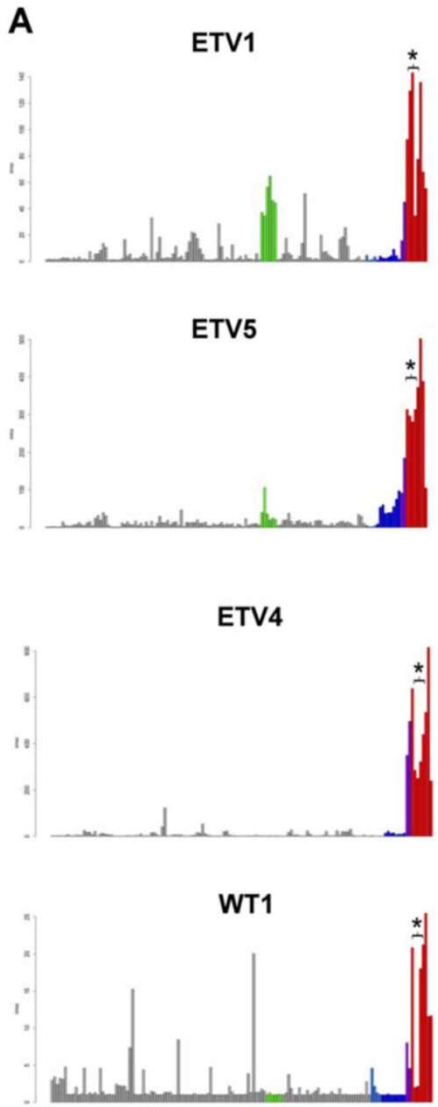
CIC break-apart fluorescence *in-situ* hybridization misses a subset of *CIC–DUX4* sarcomas: a clinicopathological and molecular study

Akihiko Yoshida,[1,2,*] Yasuhito Arai,[3,*] Eisuke Kobayashi,[2,4] Kan Yonemori,[2,5] Koichi Ogura,[3] Natsuko Hama,[3] Wakako Mukai,[3] Toru Motoi,[6] Akira Kawai,[2,4] Tatsuhiro Shibata[3] & Nobuyoshi Hiraoka[1]

Genes Chromosomes Cancer. 2017;56:501–510

ETV transcriptional upregulation is more reliable than RNA sequencing algorithms and FISH in diagnosing round cell sarcomas with *CIC* gene rearrangements

Yu-Chien Kao[1,2] | Yun-Shao Sung[1] | Chun-Liang Chen[1] | Lei Zhang[1] | Brendan C Dickson[3] | David Swanson[3] | Sumathi Vaiyapuri[4] | Farida Latif[5] | Abdullah Alholle[6] | Shih-Chiang Huang[7] | Jason L. Hornick[8] | Cristina R Antonescu[1]



CIC-rearranged sarcoma: Genetics

- ***CIC::DUX4*** **in most cases (95%)**
- ***CIC::FOXO4, CIC::LEUTX, CIC::NUTM1, CIC::NUTM2A*** **in rare cases**
- **FISH negative in 15% (cryptic rearrangement)**
- **Next-generation sequencing can also miss gene fusions**

MUC4

- **High-molecular-weight transmembrane glycoprotein**
- **Expressed in colonic epithelium, among others**
- **Gene expression profiling: MUC4 excellent discriminator of low-grade fibromyxoid sarcoma from histologic mimics**

FUS-CREB3L2/L1*–Positive Sarcomas Show a Specific Gene Expression Profile with Upregulation of *CD24* and *FOXL1

Emely Möller[1], Jason L. Hornick[4], Linda Magnusson[1], Srinivas Veerla[3], Henryk A. Domanski[2], and Fredrik Mertens[1]

Clin Cancer Res; 17(9) May 1, 2011

MUC4 in Low-Grade Fibromyxoid Sarcoma

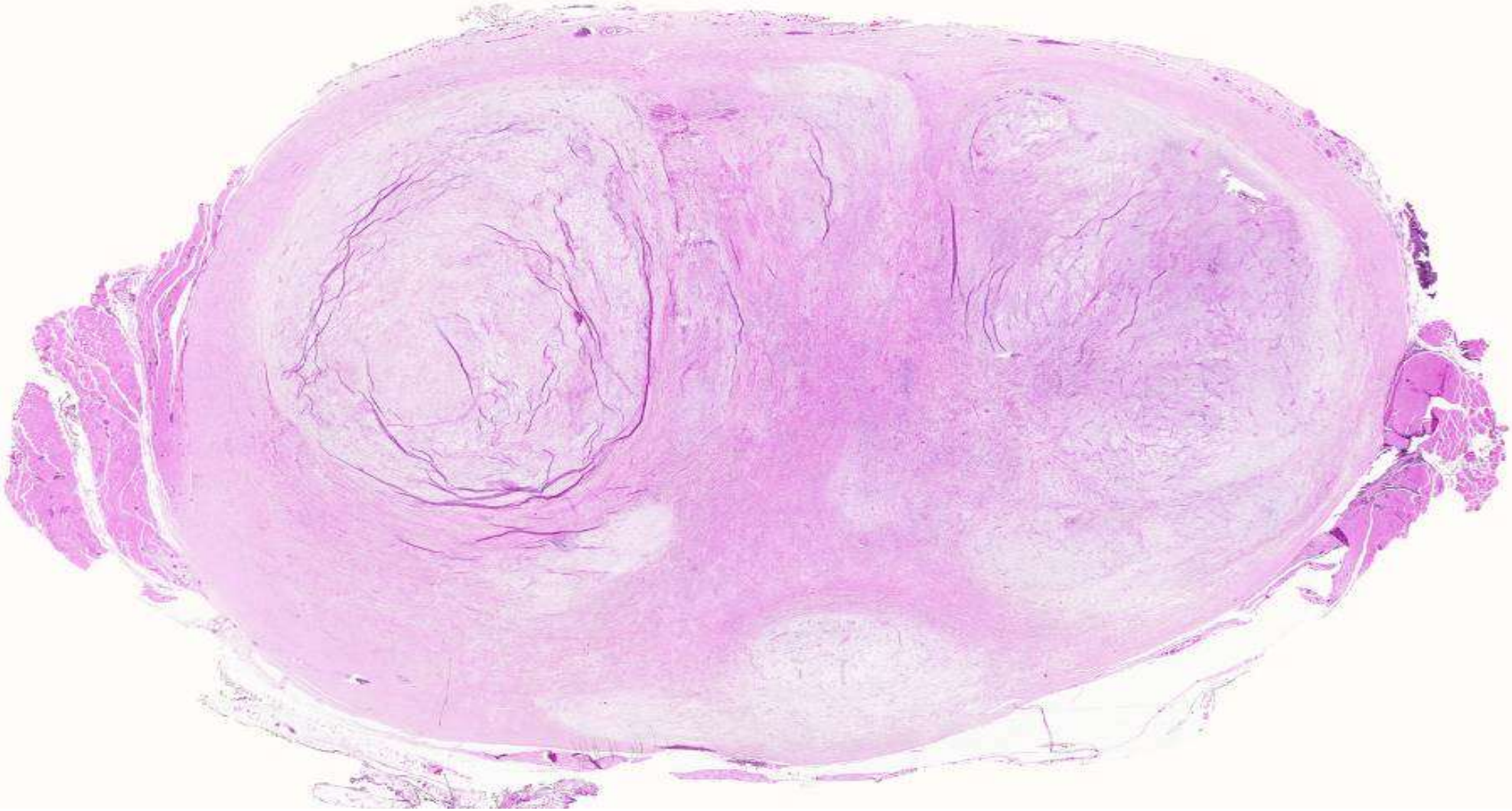
- **IHC for MUC4 helpful in differential diagnosis:**
  - **Positive in >99% of LGFMS**
  - **Negative in soft tissue perineurioma, MPNST, myxofibrosarcoma, solitary fibrous tumor, desmoid fibromatosis, intramuscular/cellular myxoma**

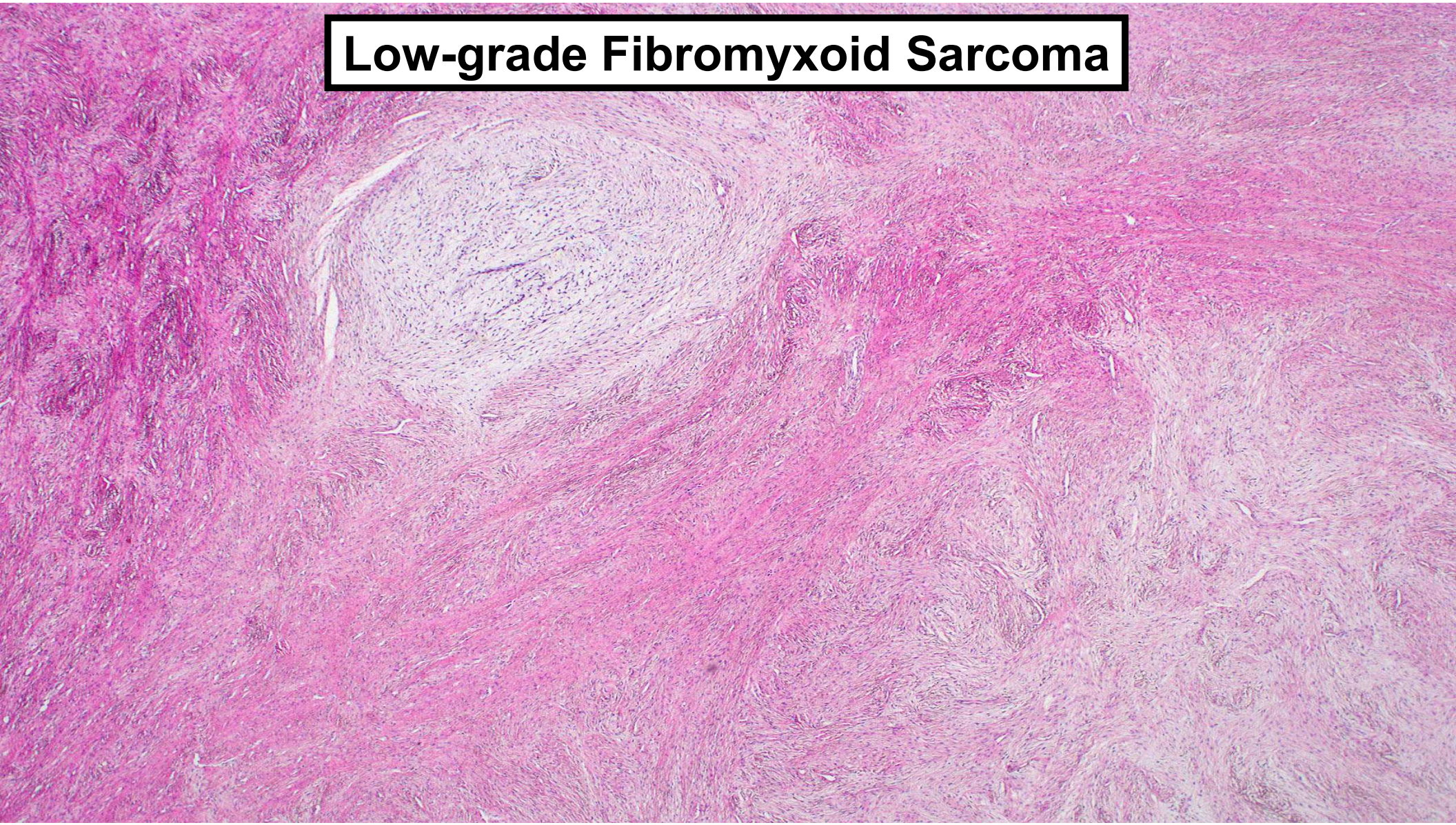
MUC4 Is a Highly Sensitive and Specific Marker for Low-grade Fibromyxoid Sarcoma

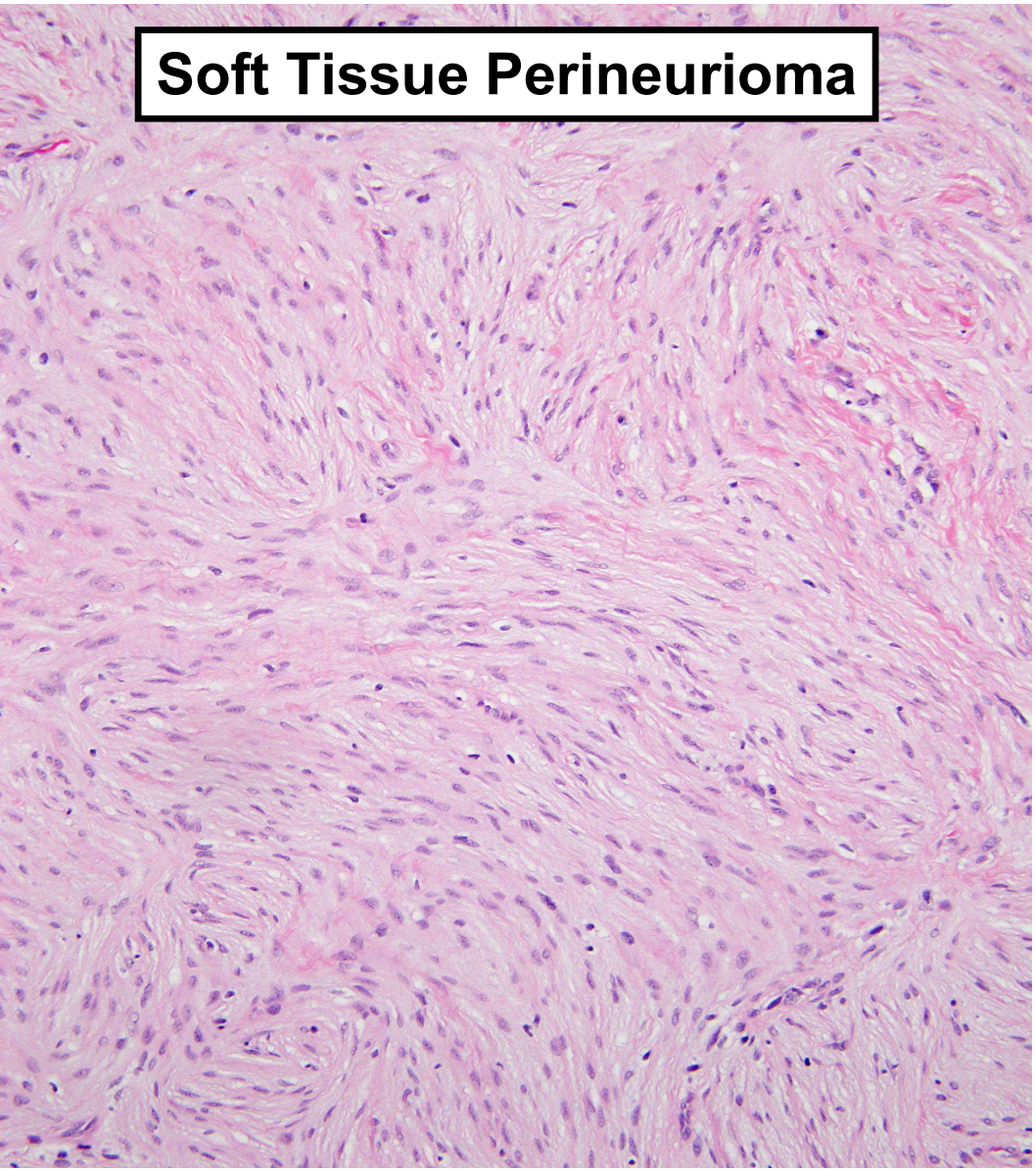
Leona A. Doyle, MD, Emely Möller, PhD,† Paola Dal Cin, PhD,* Christopher D.M. Fletcher, MD, FRCPath,* Fredrik Mertens, MD, PhD,† and Jason L. Hornick, MD, PhD**

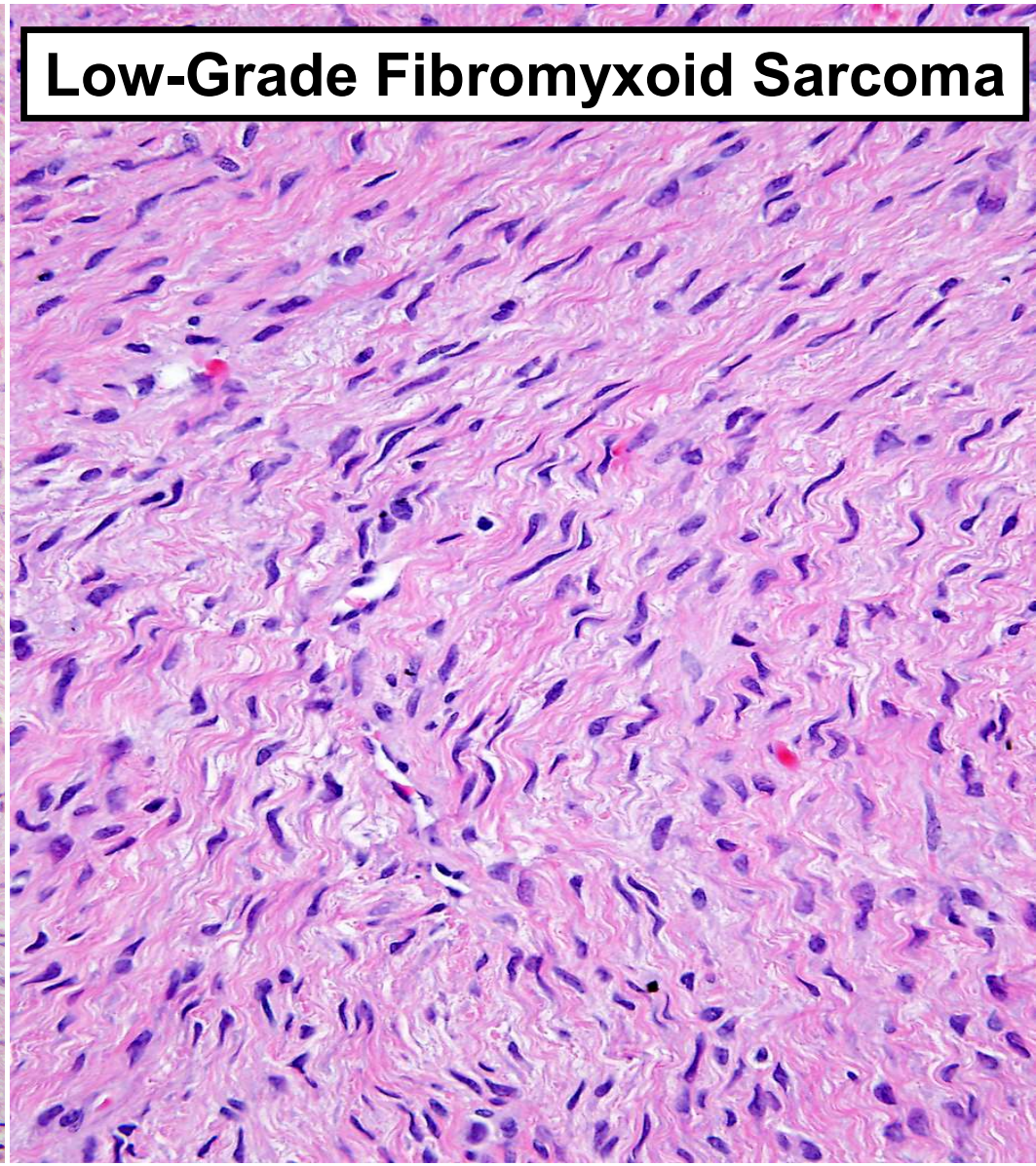
Am J Surg Pathol • Volume 35, Number 5, May 2011

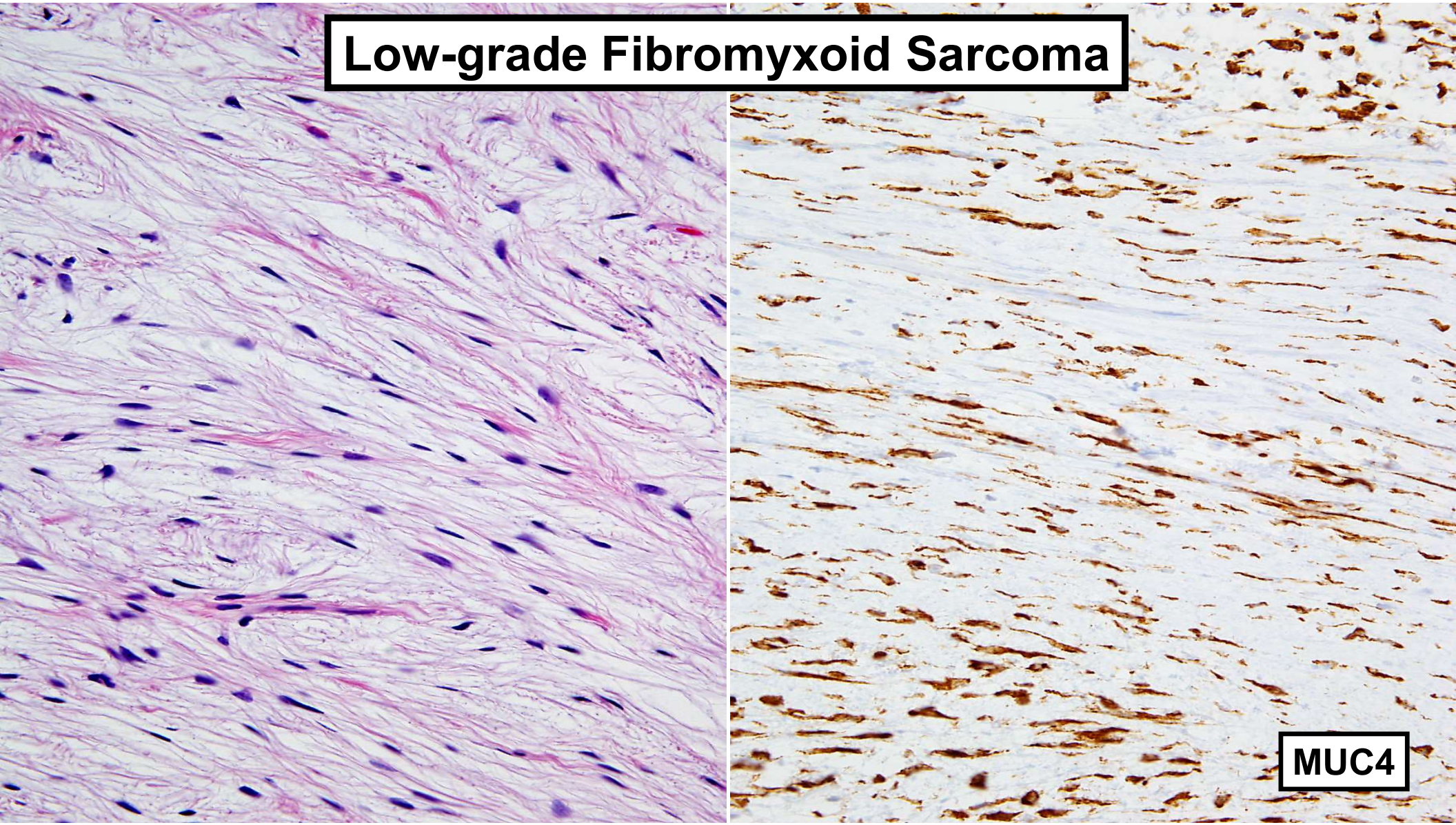
Low-grade Fibromyxoid Sarcoma

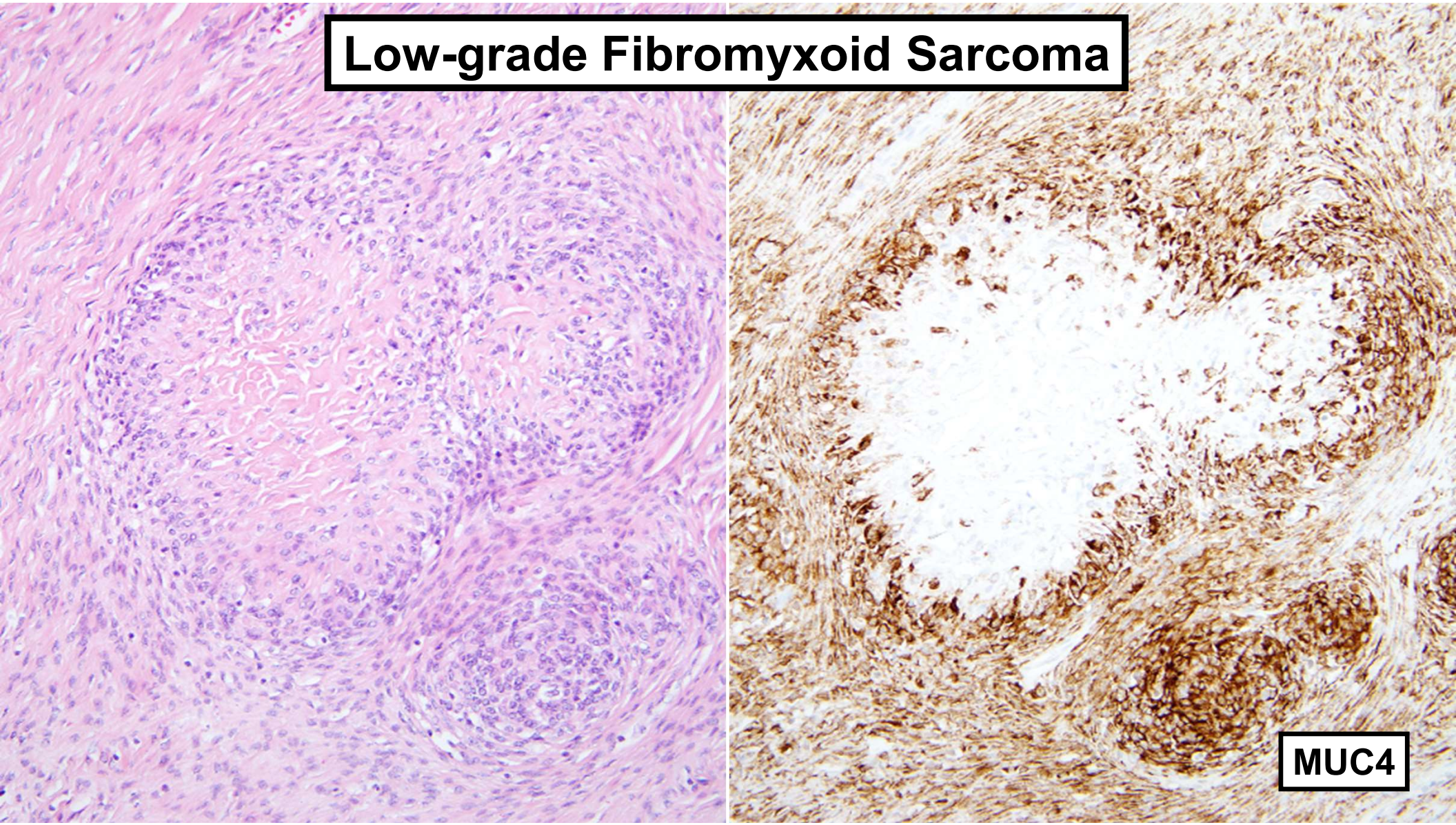


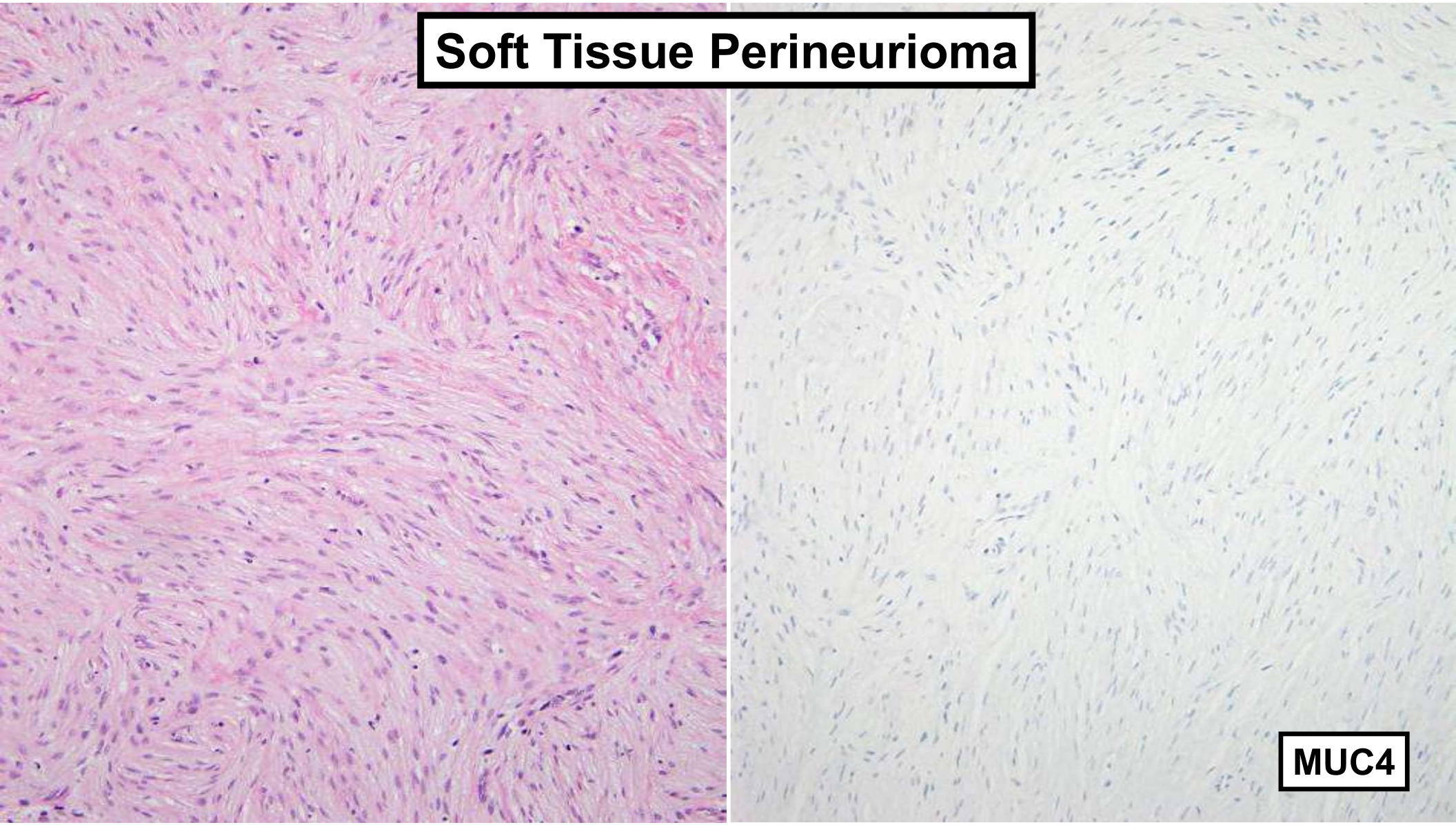

Low-grade Fibromyxoid Sarcoma

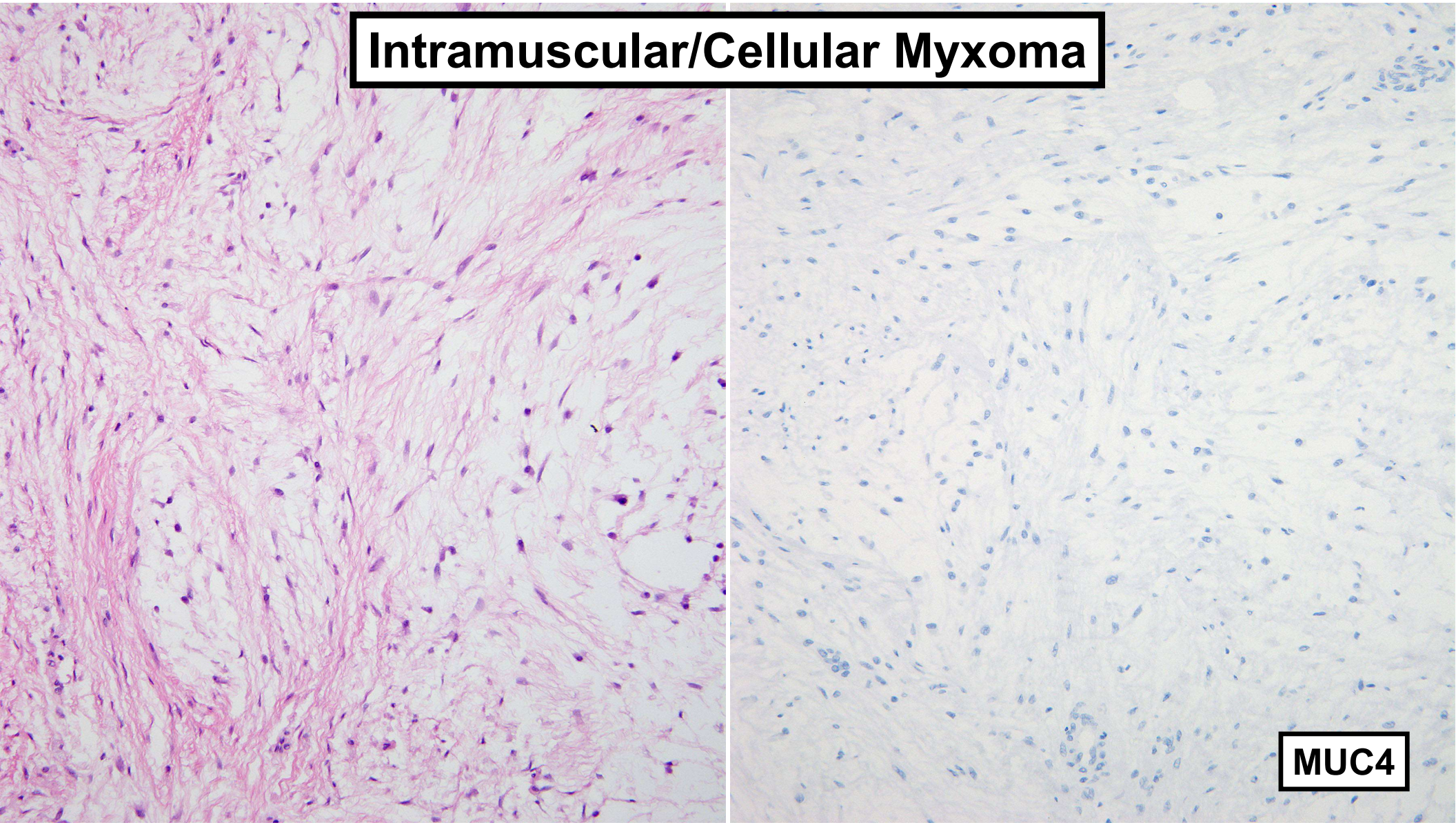

Soft Tissue Perineurioma


Low-Grade Fibromyxoid Sarcoma


Low-grade Fibromyxoid Sarcoma
MUC4


Low-grade Fibromyxoid Sarcoma
MUC4


Soft Tissue Perineurioma
MUC4


Intramuscular/Cellular Myxoma
MUC4

Practice Points

- Rapid evolution in understanding of genetics of soft tissue tumors
- Molecular genetic findings lead to highly specific IHC markers
- Gene expression profiling provides novel markers to discriminate among classes of histologically similar tumors
- Should lead to more reproducible and accurate diagnosis of rare tumor types

@JLHornick

THANK YOU!