PATHOLOGY AND GENETICS OF SOFT TISSUE TUMOURS: THE STATE OF THE ART

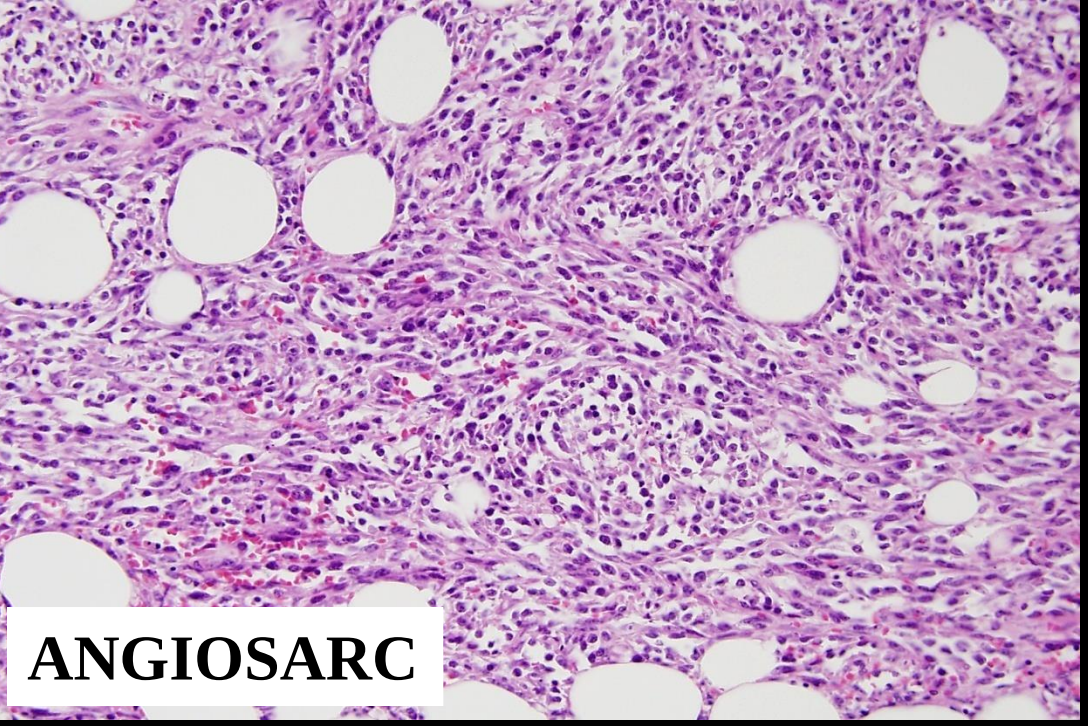
Christopher D.M. Fletcher M.D. FRCPath
Brigham and Women's Hospital
and Harvard Medical School
Boston, MA

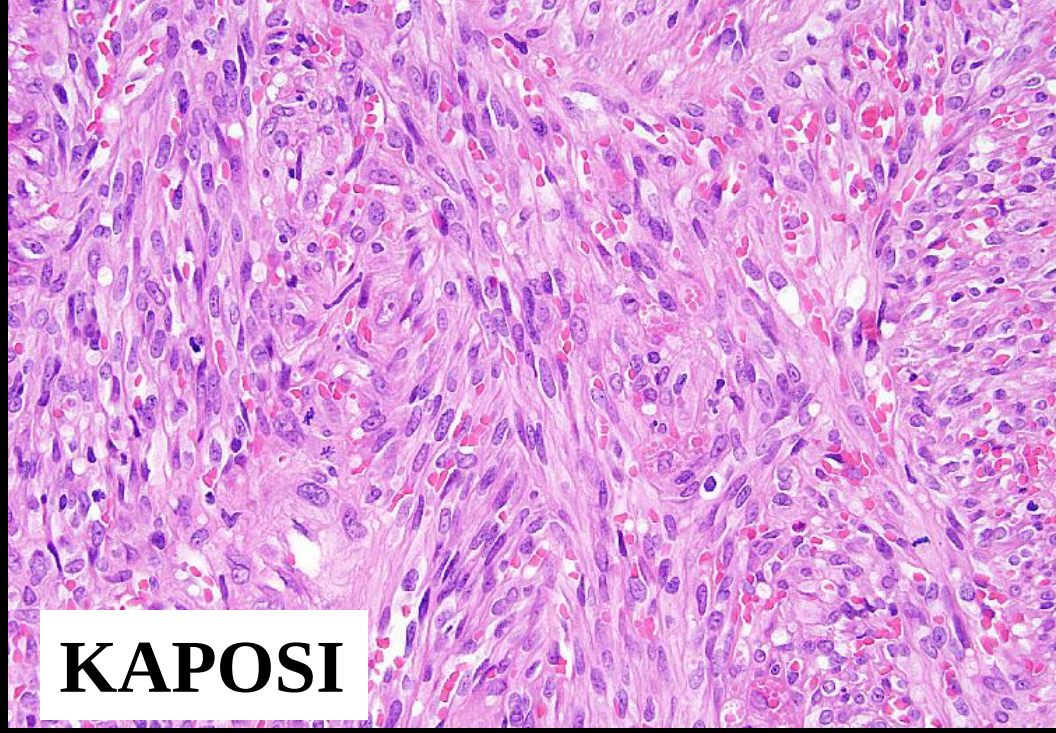
SOFT TISSUE SARCOMAS
ONCOLOGISTS' MAIN QUESTIONS

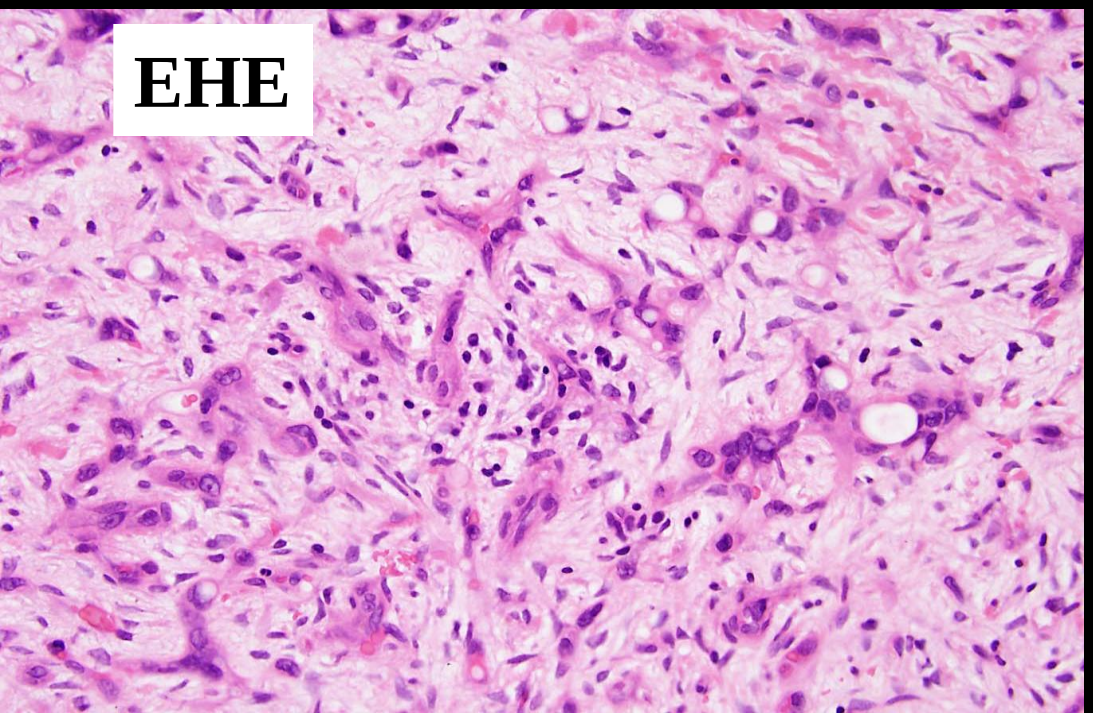
What is the diagnosis ?
What is the grade ?
(Is grade meaningful in this tumor type ?)
Is there a validated protocol ?
Is there a target ?
Is there a clinical trial ?
(Status of margins)

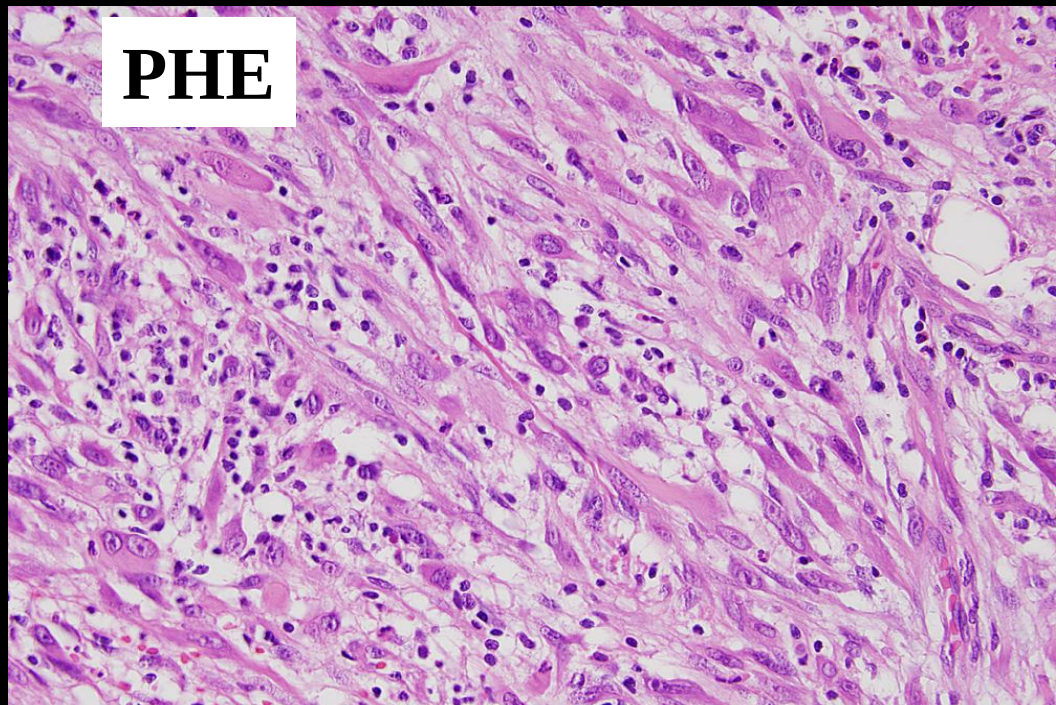
SOFT TISSUE SARCOMAS
TREATMENT SELECTION

- Ewing sarcoma
- Rhabdomyosarcoma
- Angiosarcoma
- GIST
- Synovial sarcoma
- Myxoid liposarcoma


ANGIOSARC


KAPOSI


EHE


PHE

SOFT TISSUE TUMORS
ROLE OF PATHOLOGY

- Diagnosis / histotype
- Status of excision margins
- Prognosis + any other implications
- Prediction of treatment response
- Assessment of treatment response
- Target identification (where relevant)
- Definition of new subtypes
- Refined classification

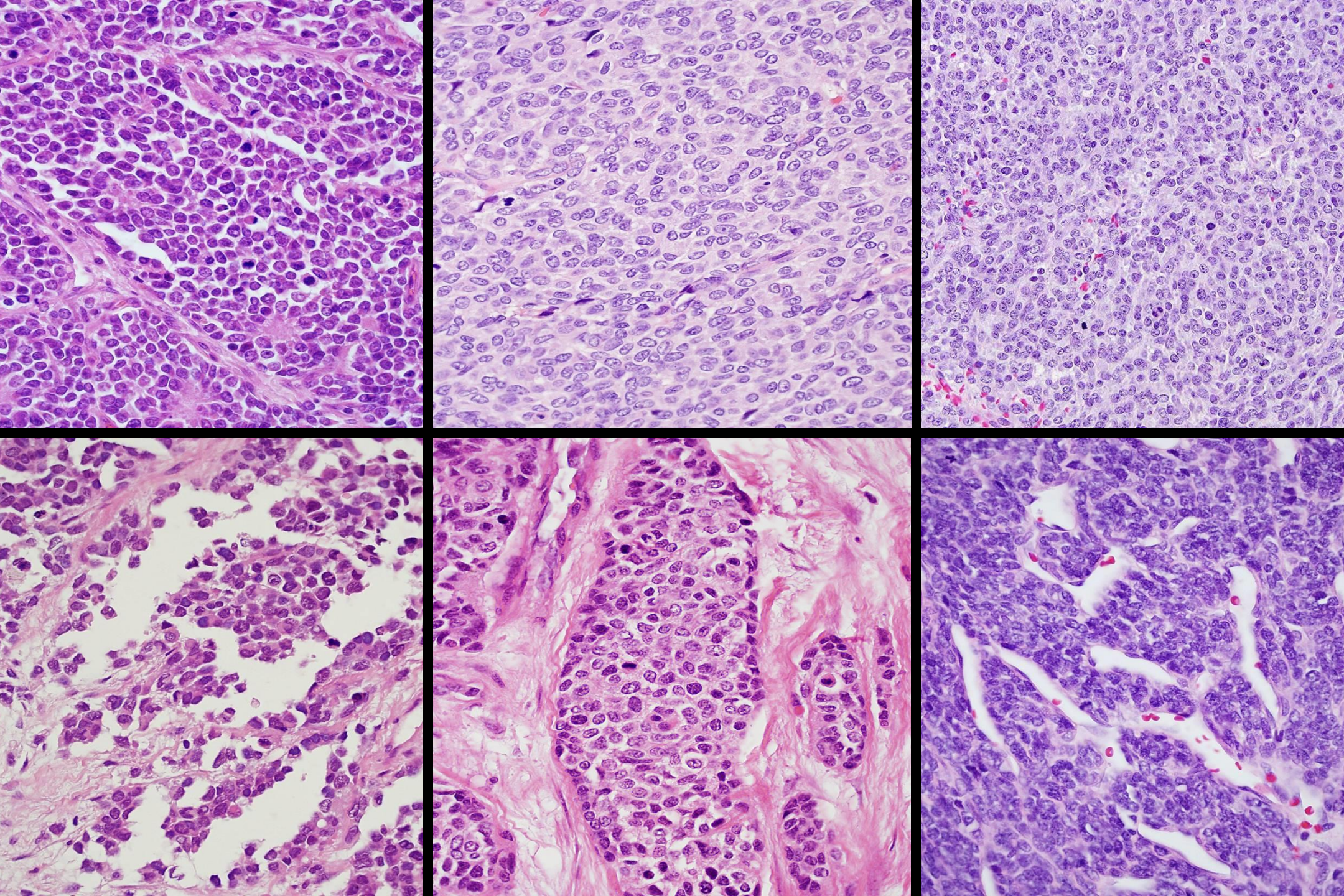
DIAGNOSIS OF SOFT TISSUE SARCOMAS

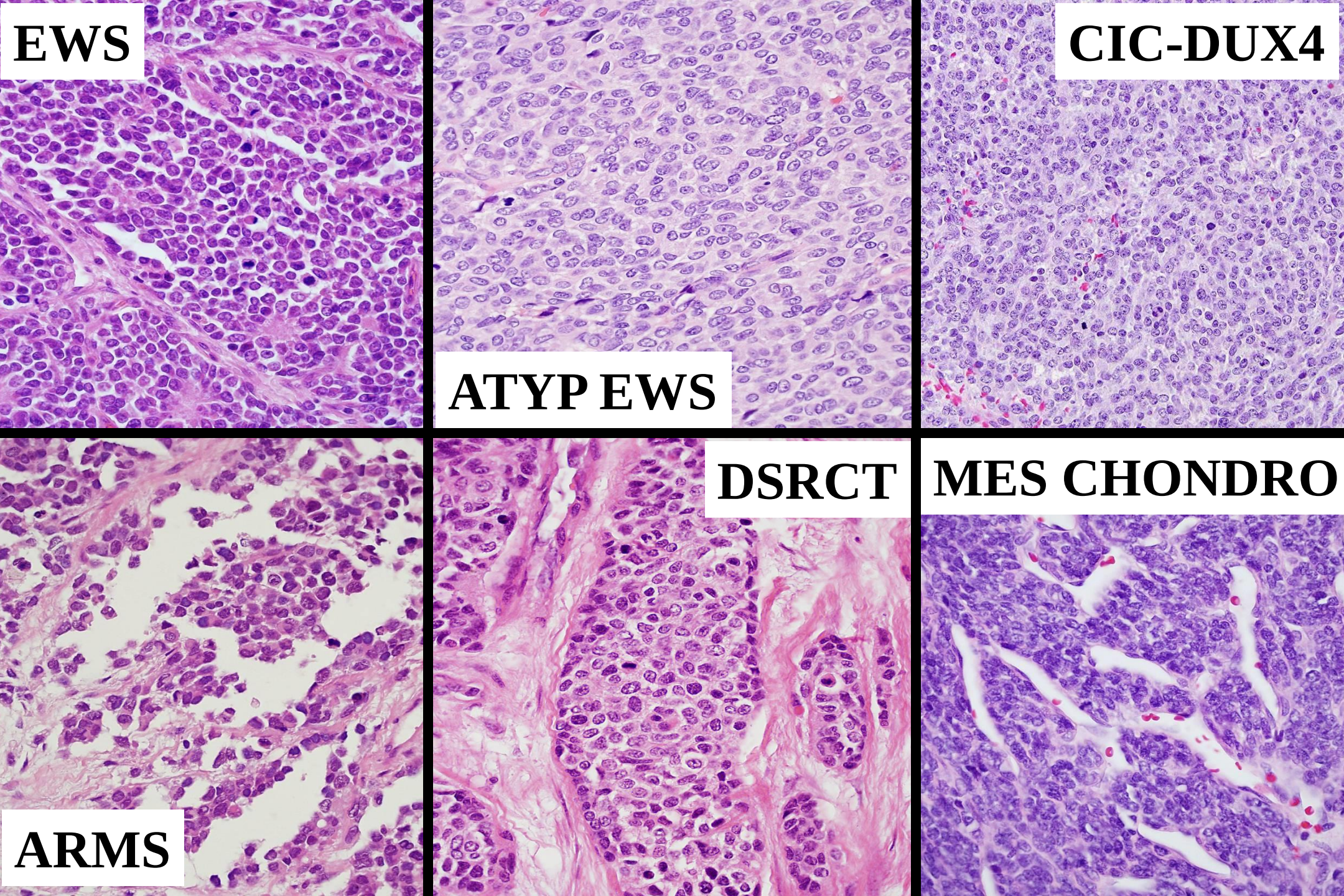
PRACTICAL ROLE OF PATHOLOGY

- **Benign ? Malignant ? Reactive ?**
  - or did the biopsy miss ?...
- **Is the tissue sufficient for diagnosis and any additional relevant testing ?**
- **Diagnosis / histotype**
- **Status of excision margins**
- **Grade/Prognosis/Other implications**
- **Prediction of treatment response**
- **Assessment of treatment response**
- **Target identification (where relevant)**

SOFT TISSUE SARCOMAS
TREATMENT SELECTION

- **Ewing sarcoma**
- **Rhabdomyosarcoma**
- **Poorly diff synovial sarcoma**
- **DSCRCT**
- **Mesenchymal chondrosarcoma**
- **Round cell sarcoma with *CIC-DUX4***

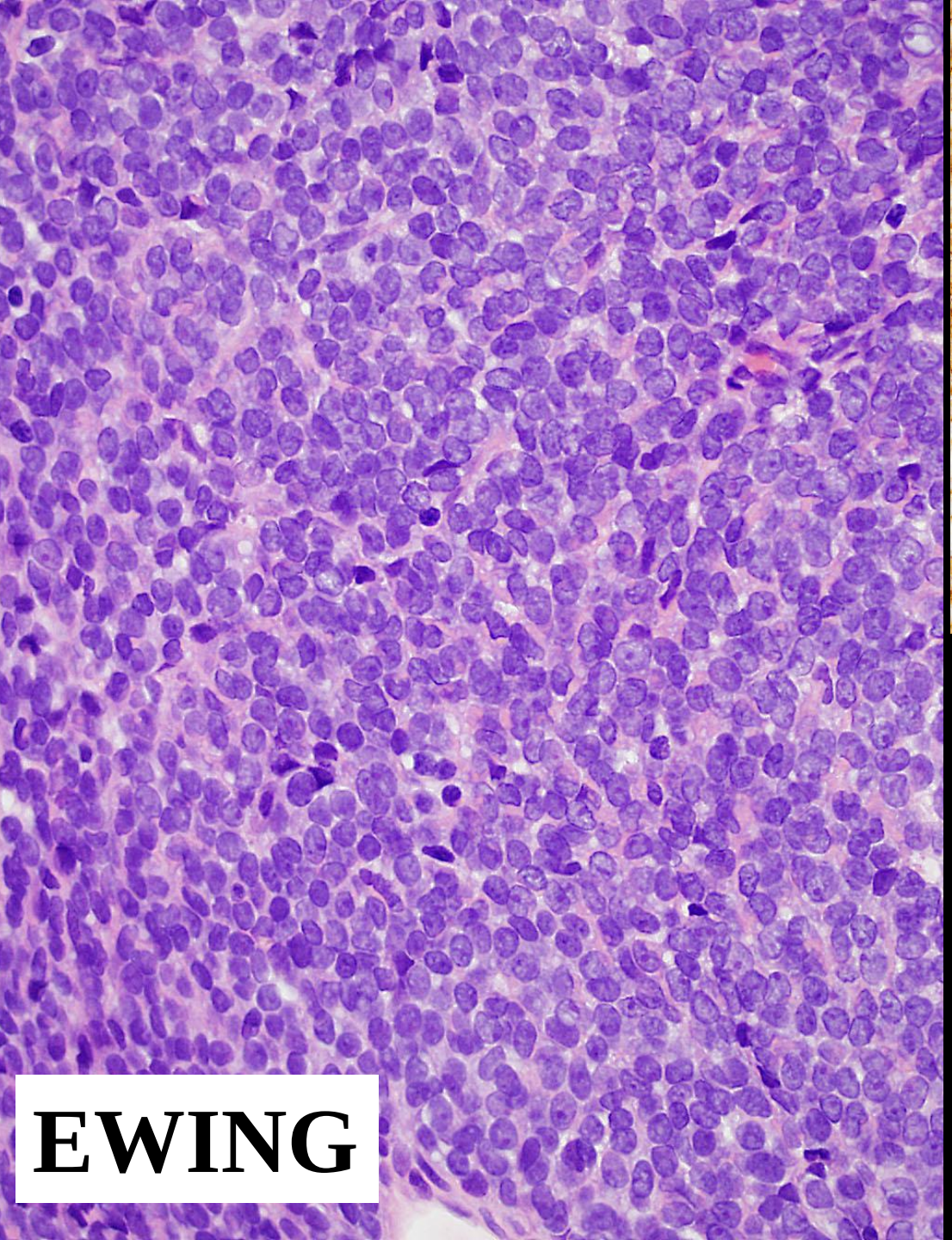


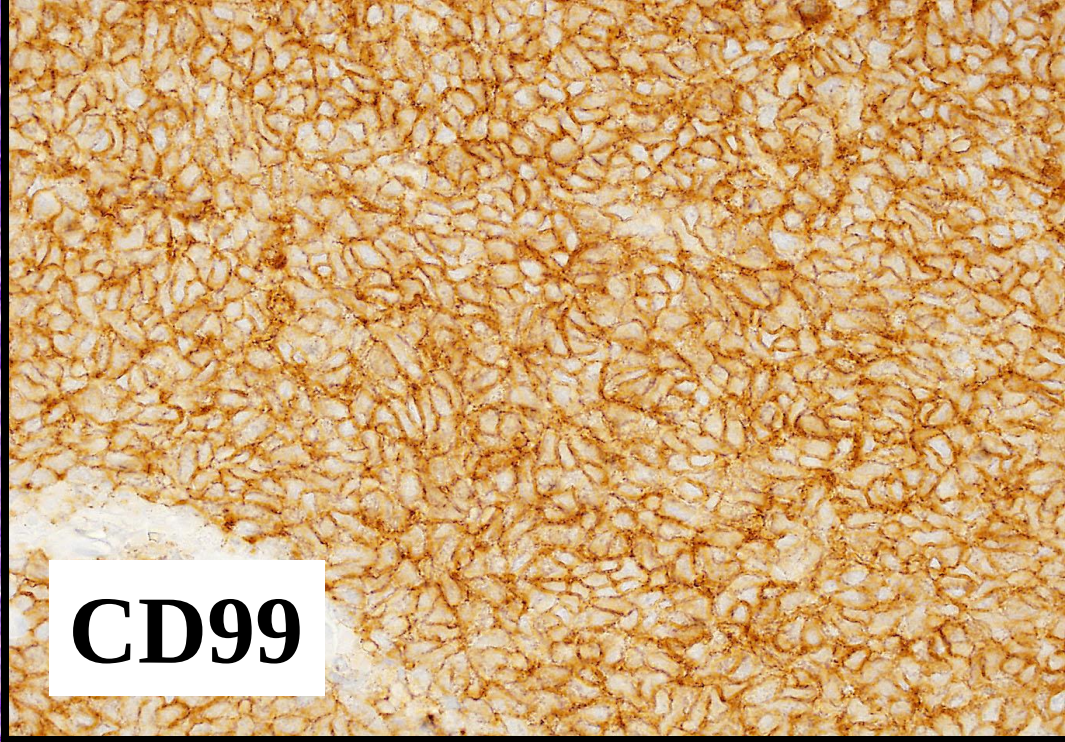

EWS
ATYP EWS
CIC-DUX4
ARMS
DSRCT
MES CHONDRO

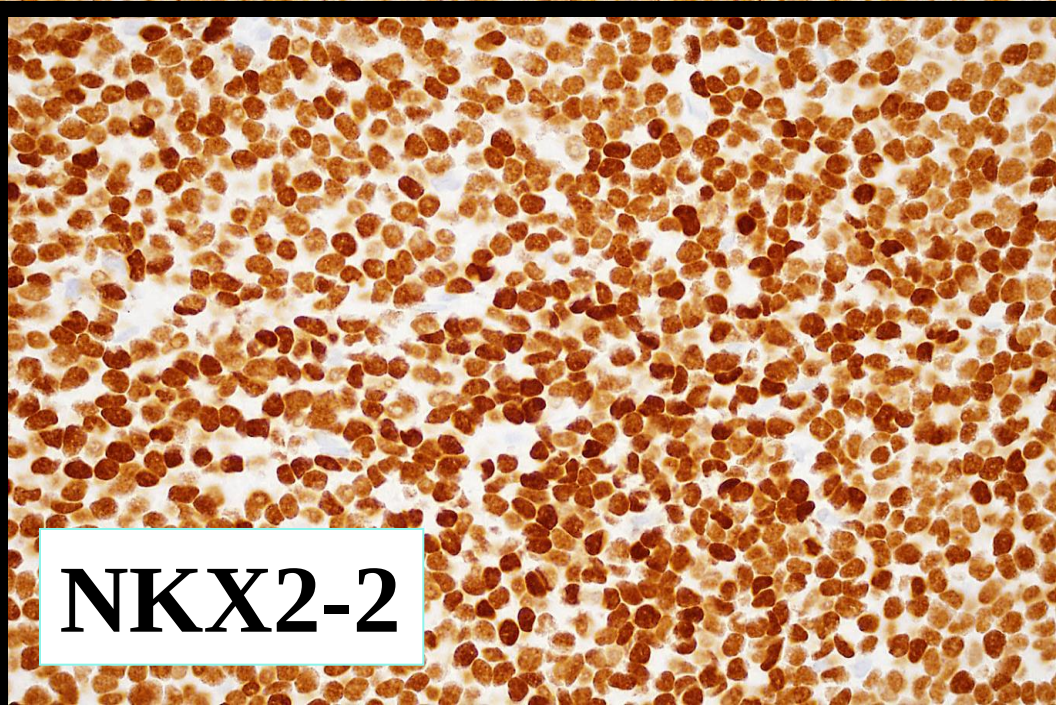
SOFT TISSUE SARCOMAS
APPLICABLE TECHNOLOGIES

Histology
Immunohistochemistry
(Electron microscopy)
Cytogenetics
Molecular diagnostics
DNA sequencing/Genomics

Which is truly useful ?

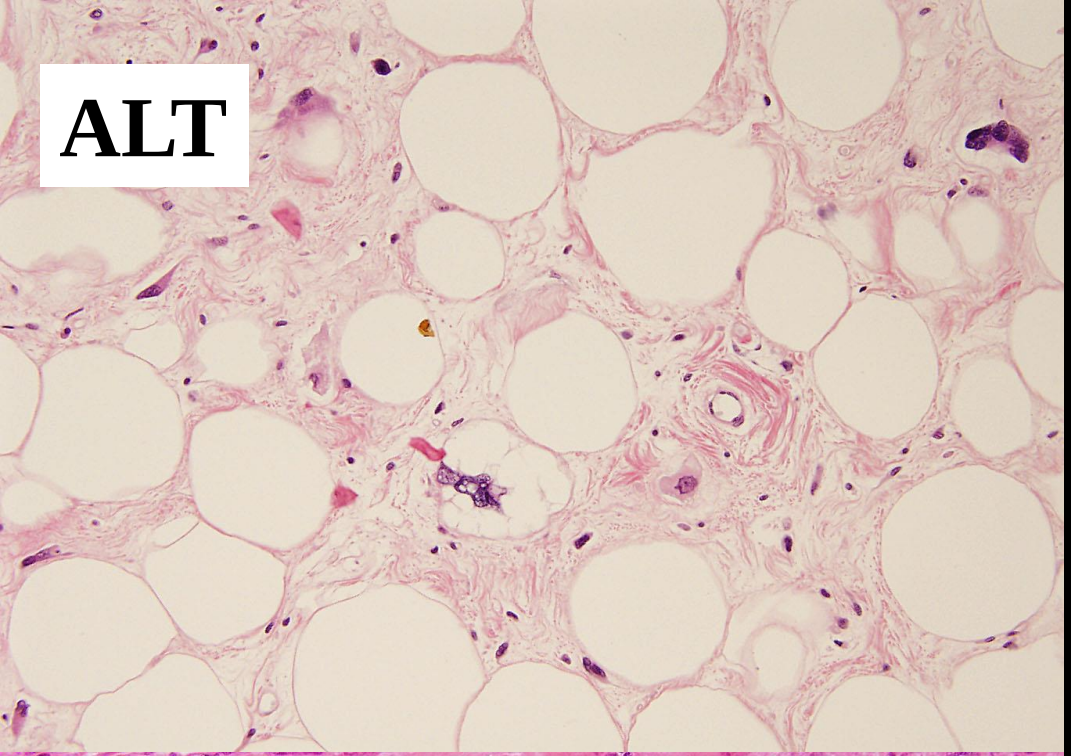

EWING

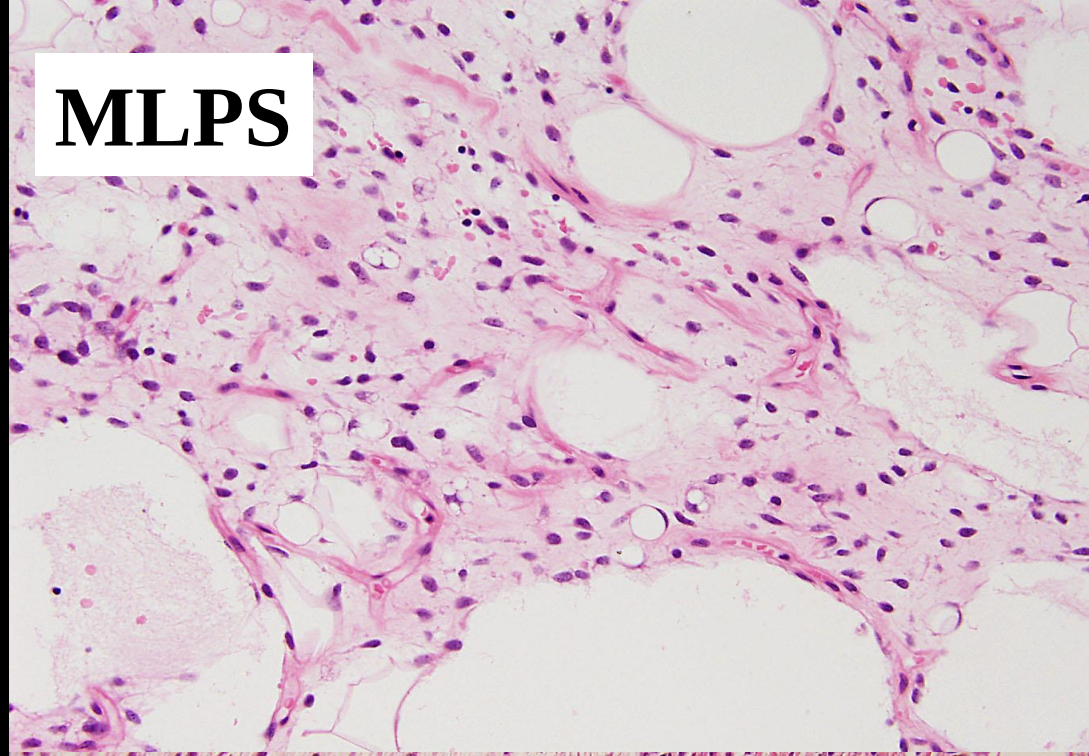

CD99

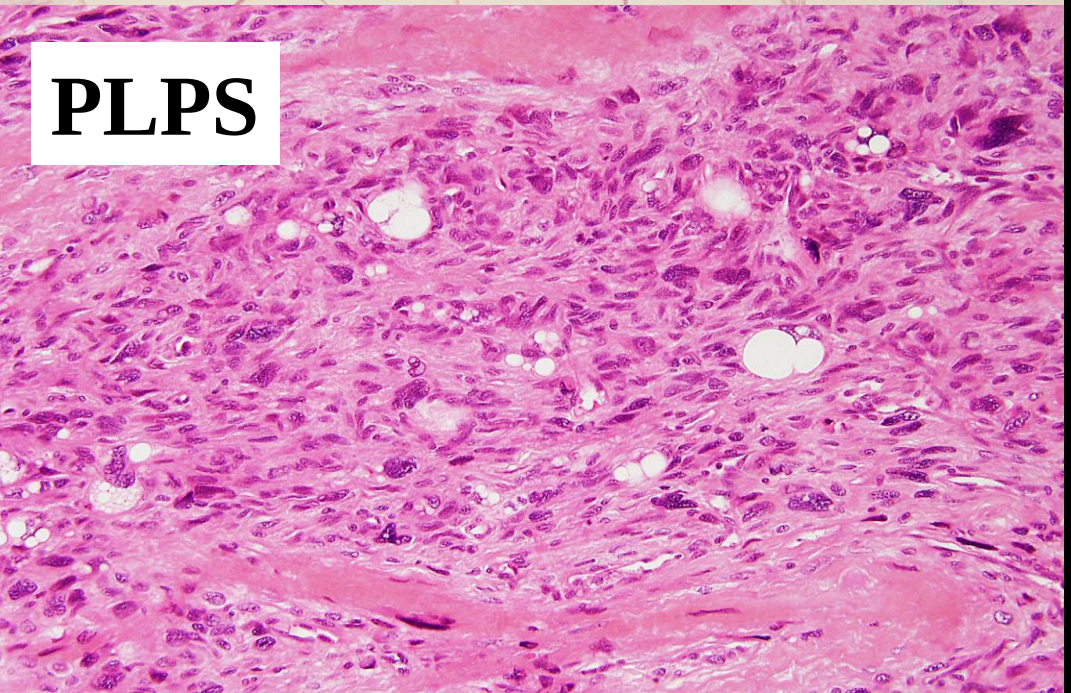

NKX2-2

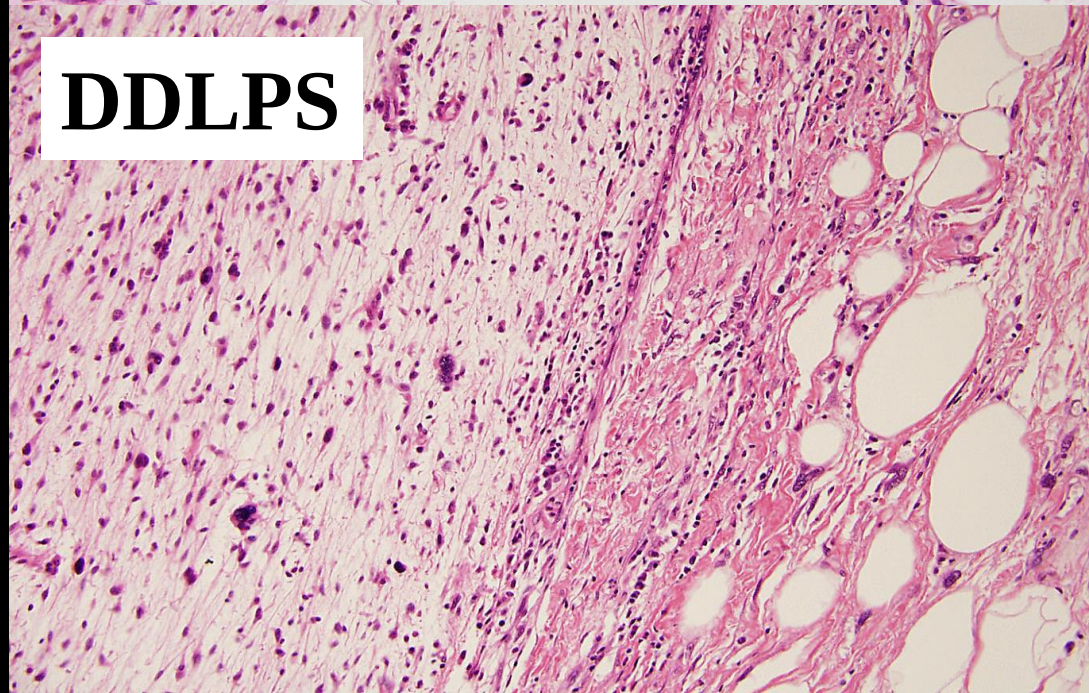
LIPOSARCOMA….

…. Is not one single disease…


ALT

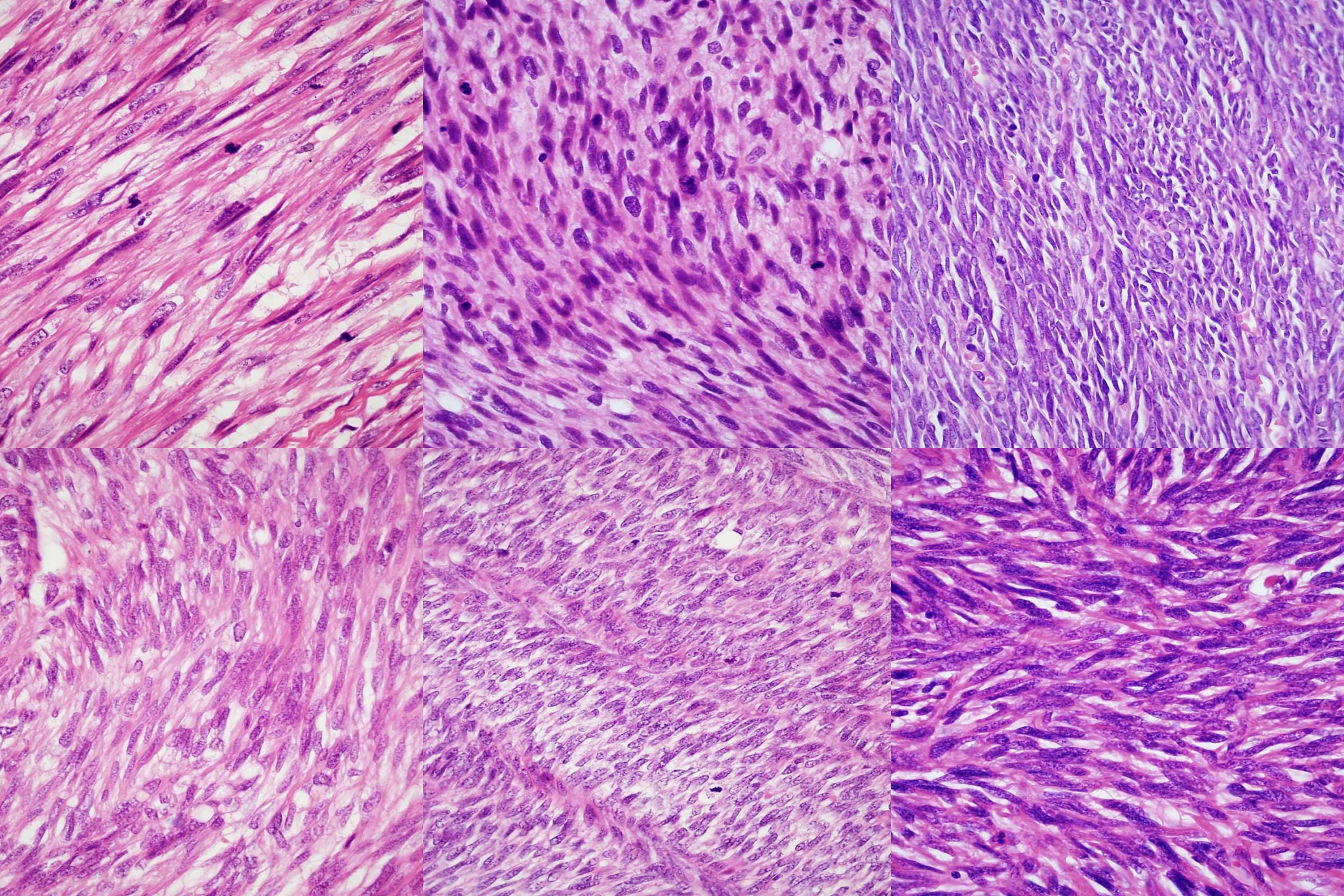

MLPS

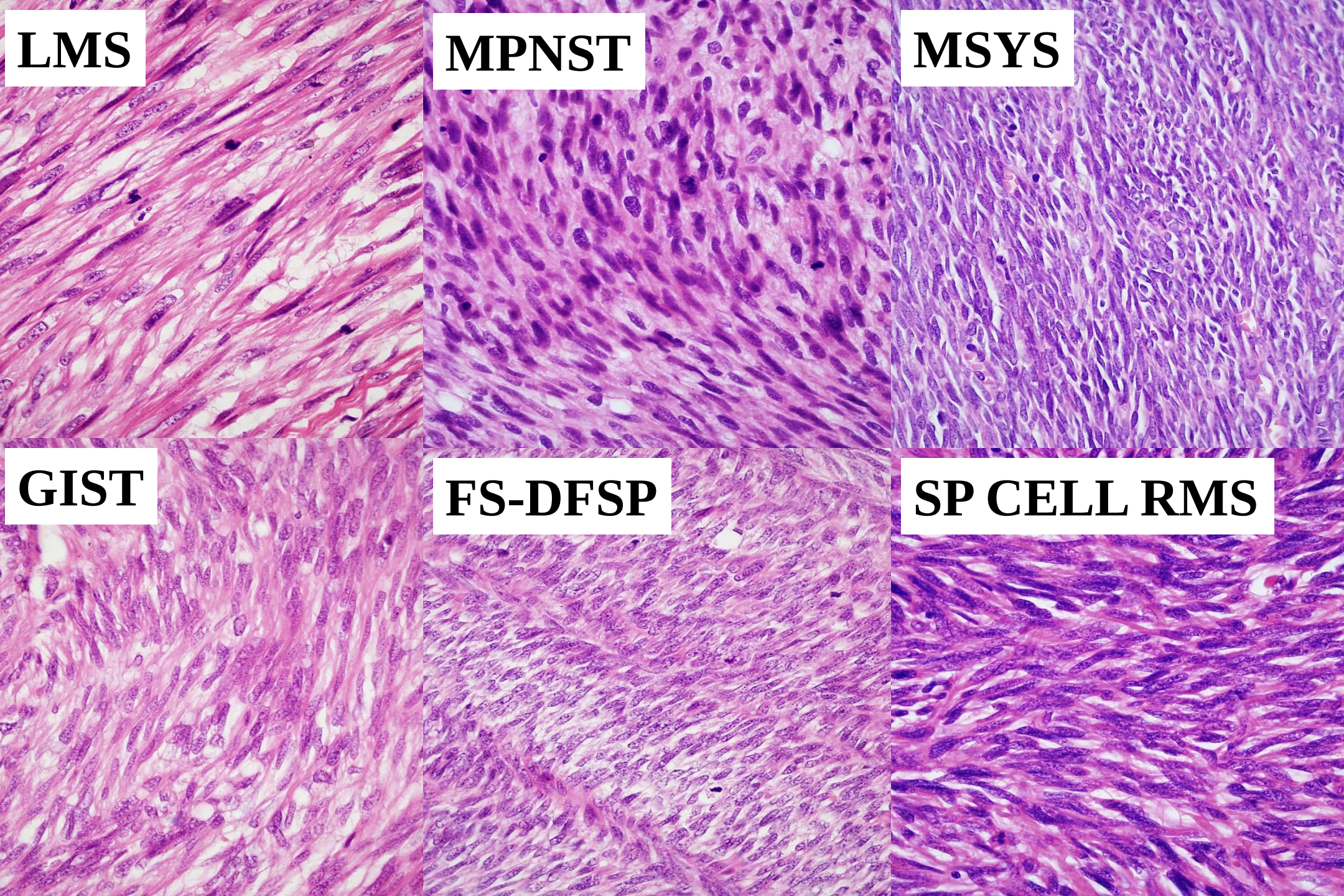

PLPS

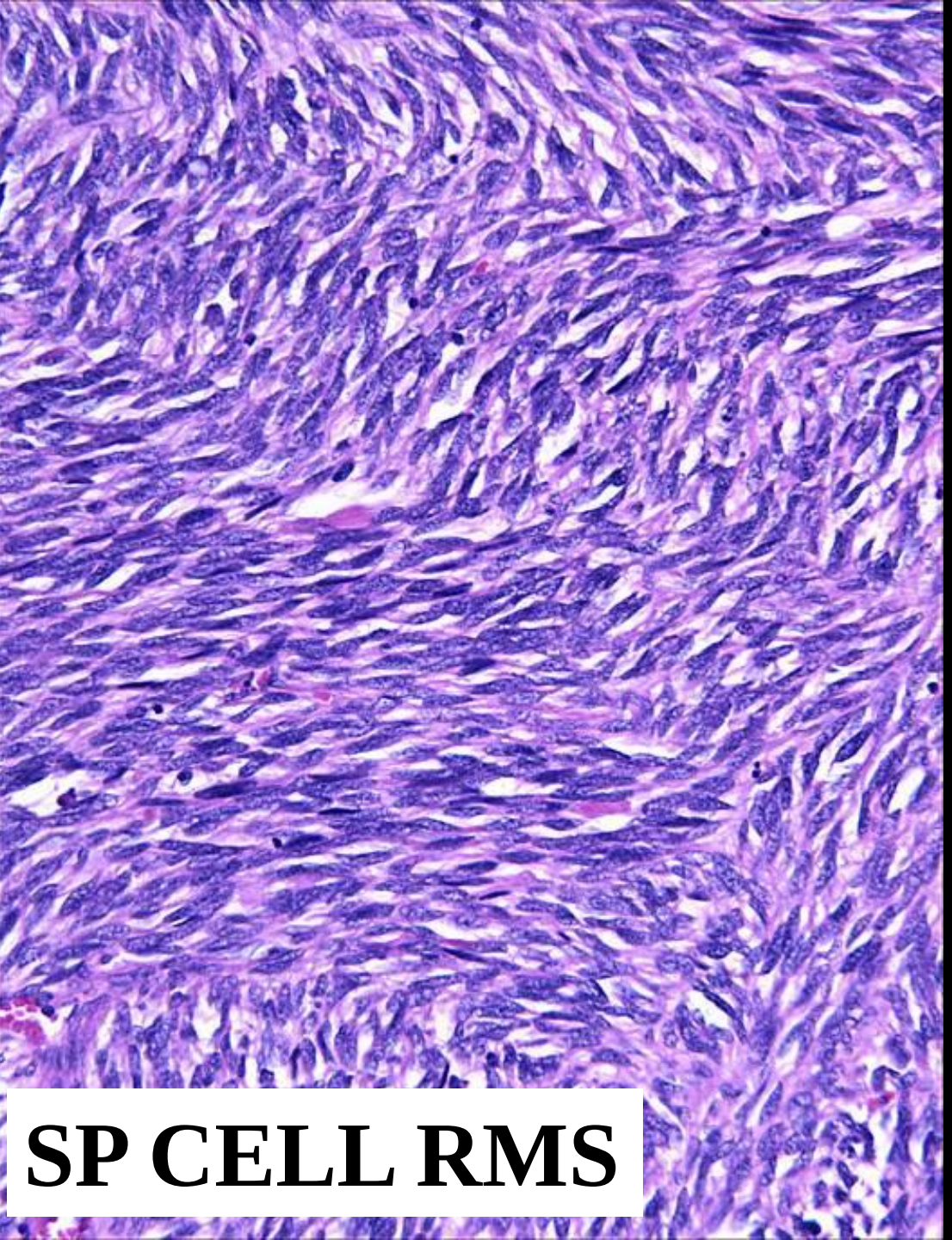

DDLPS

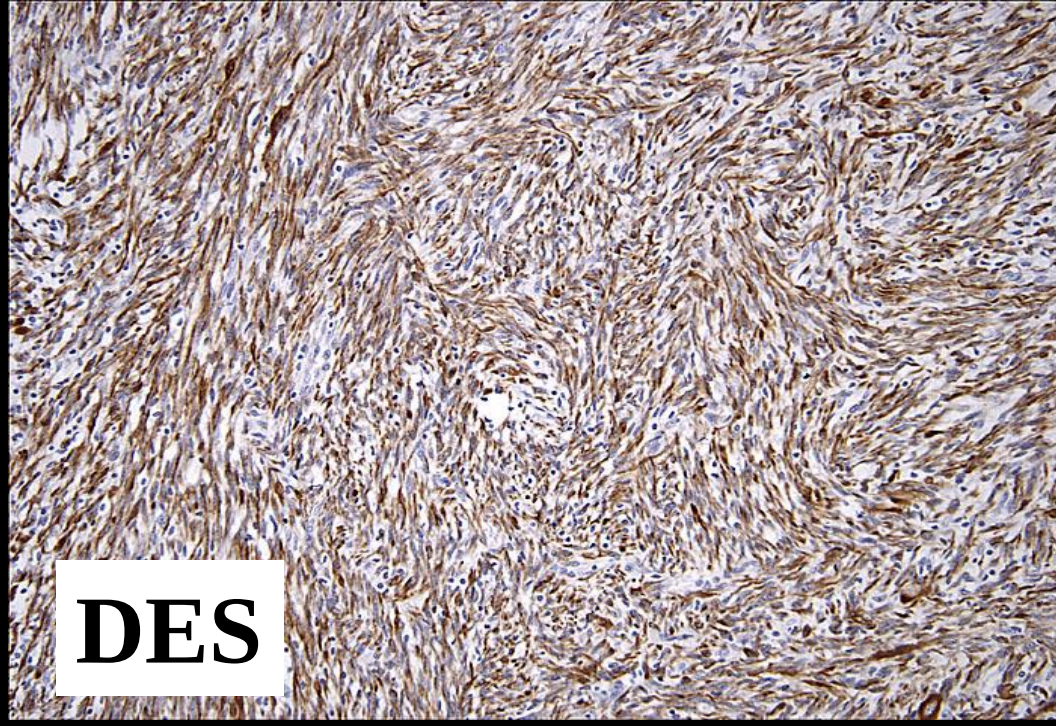
SOFT TISSUE SARCOMAS
TREATMENT SELECTION

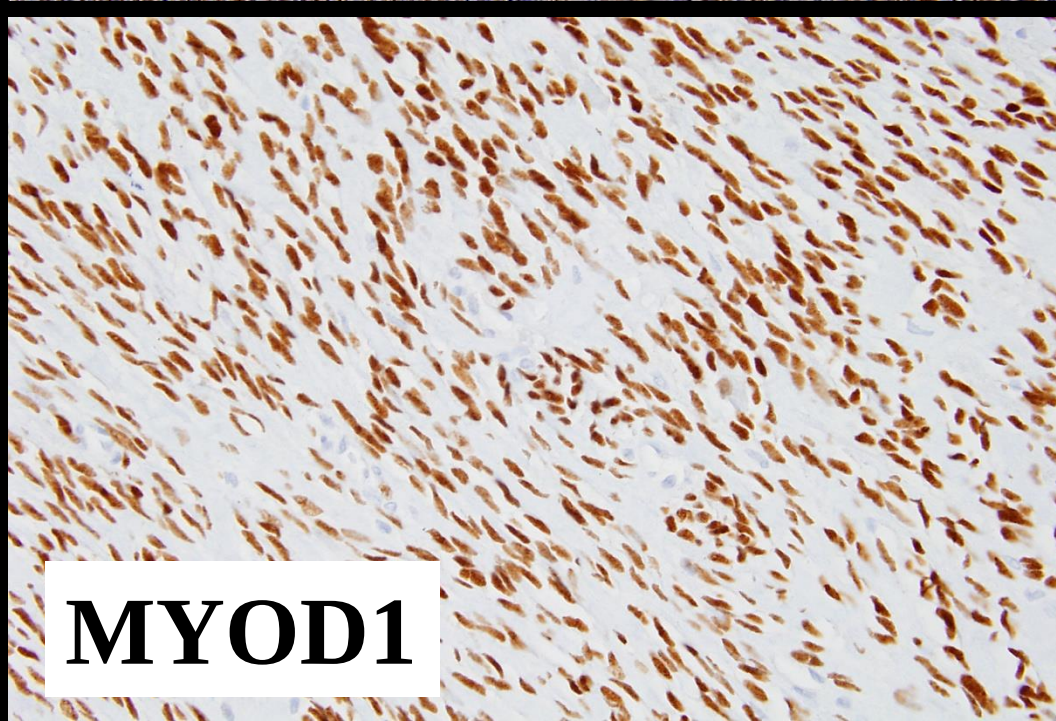
- MPNST
- Synovial sarcoma
- Leiomyosarcoma
- Dediff liposarcoma
- Fibrosarcomatous DFSP




LMS
MPNST
MSYS
GIST
FS-DFSP
SP CELL RMS


SP CELL RMS

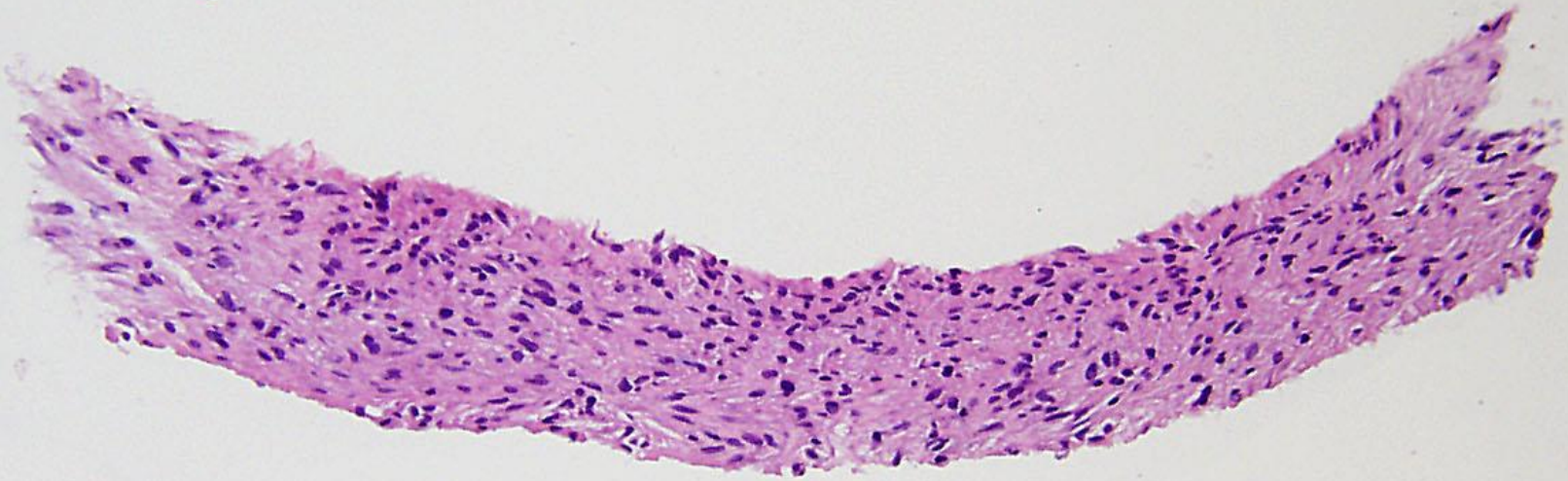

DES


MYOD1

SOFT TISSUE SARCOMAS
PATHOLOGIC CLASSIFICATION 2016

- **More accurate than ever**
- **More detailed than ever**
- **More reliable than ever**
- **More reproducible than ever**

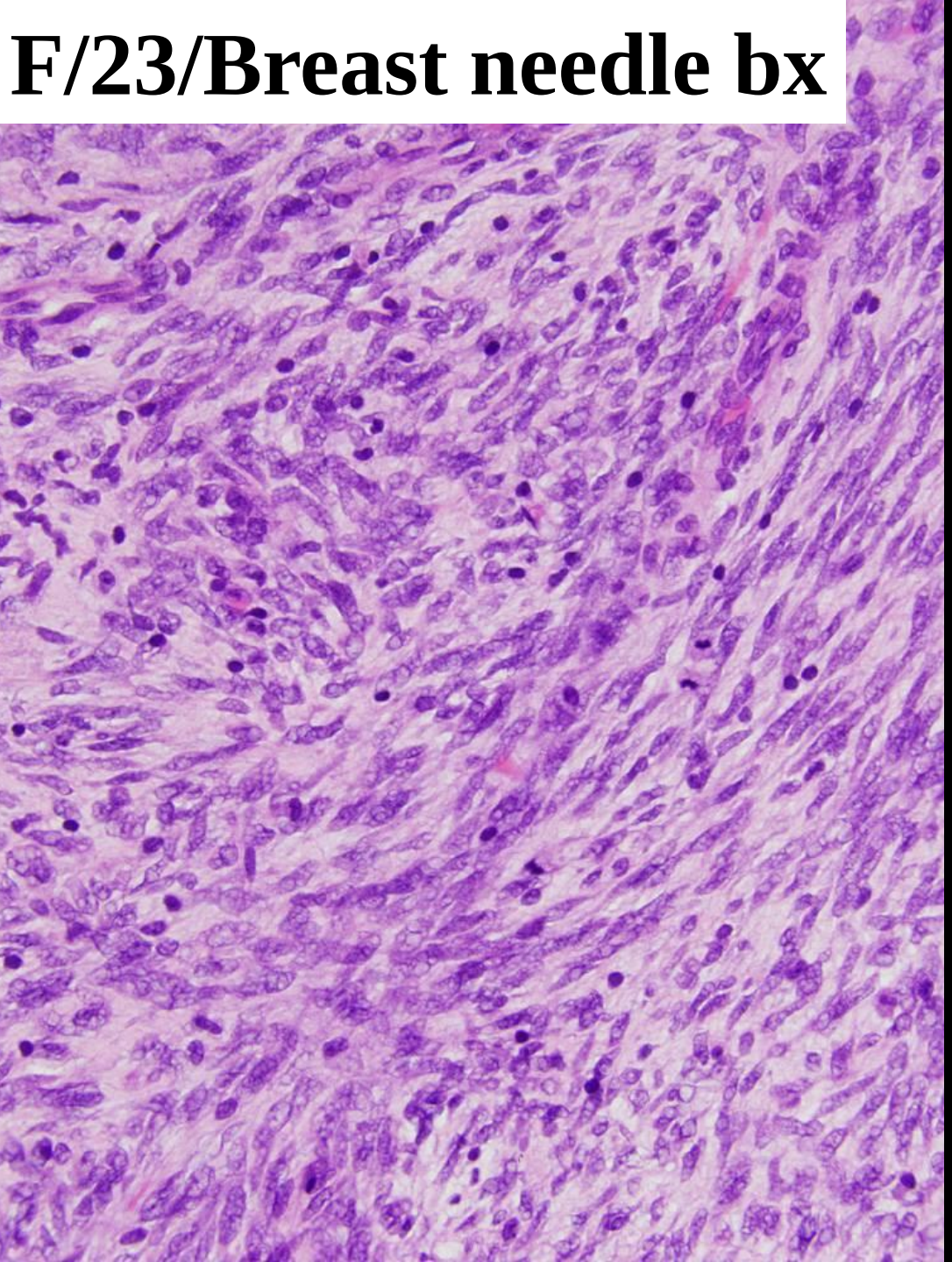
BUT TOTALLY DEPENDS ON QUALITY OF SPECIMEN….

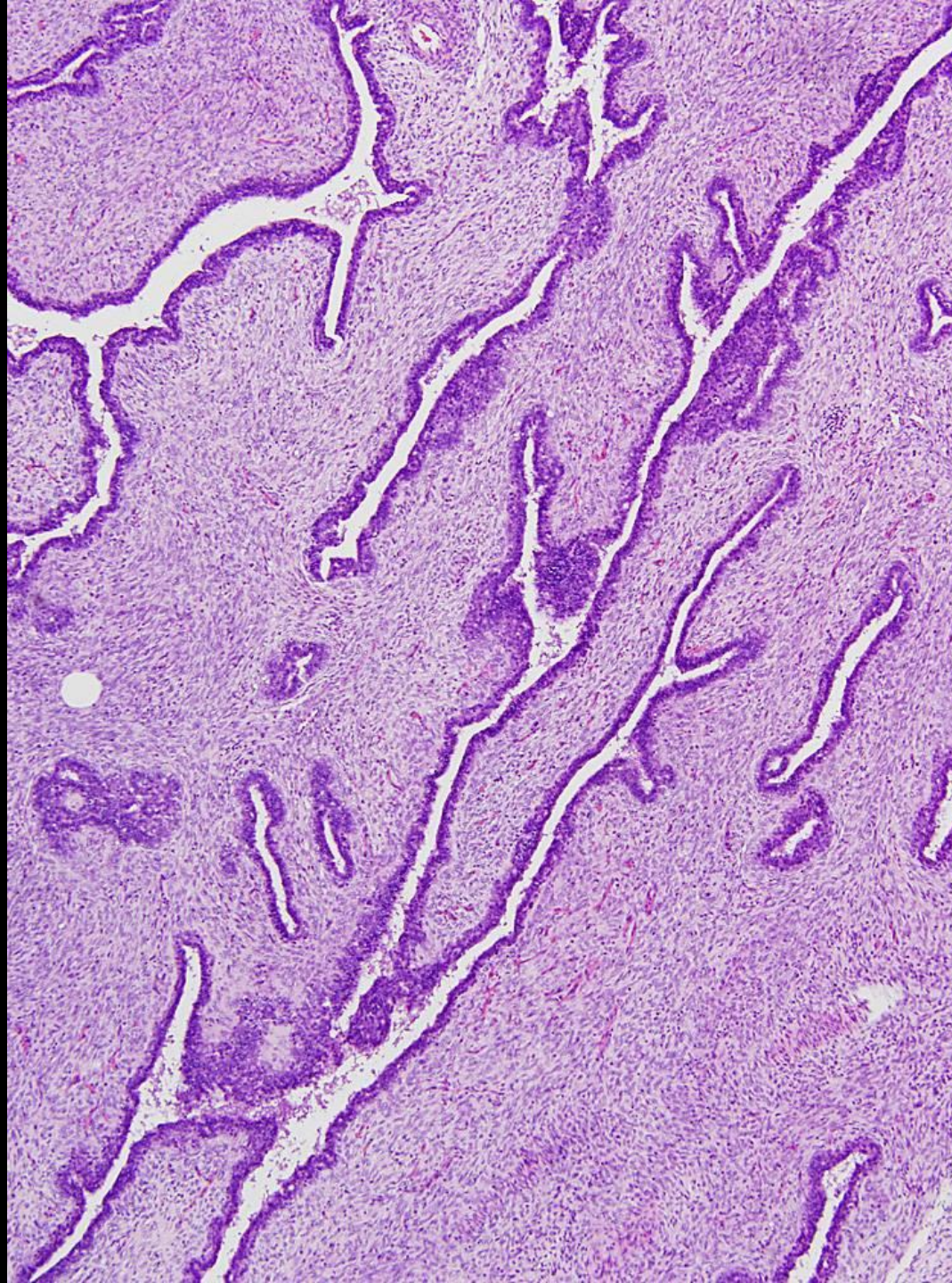


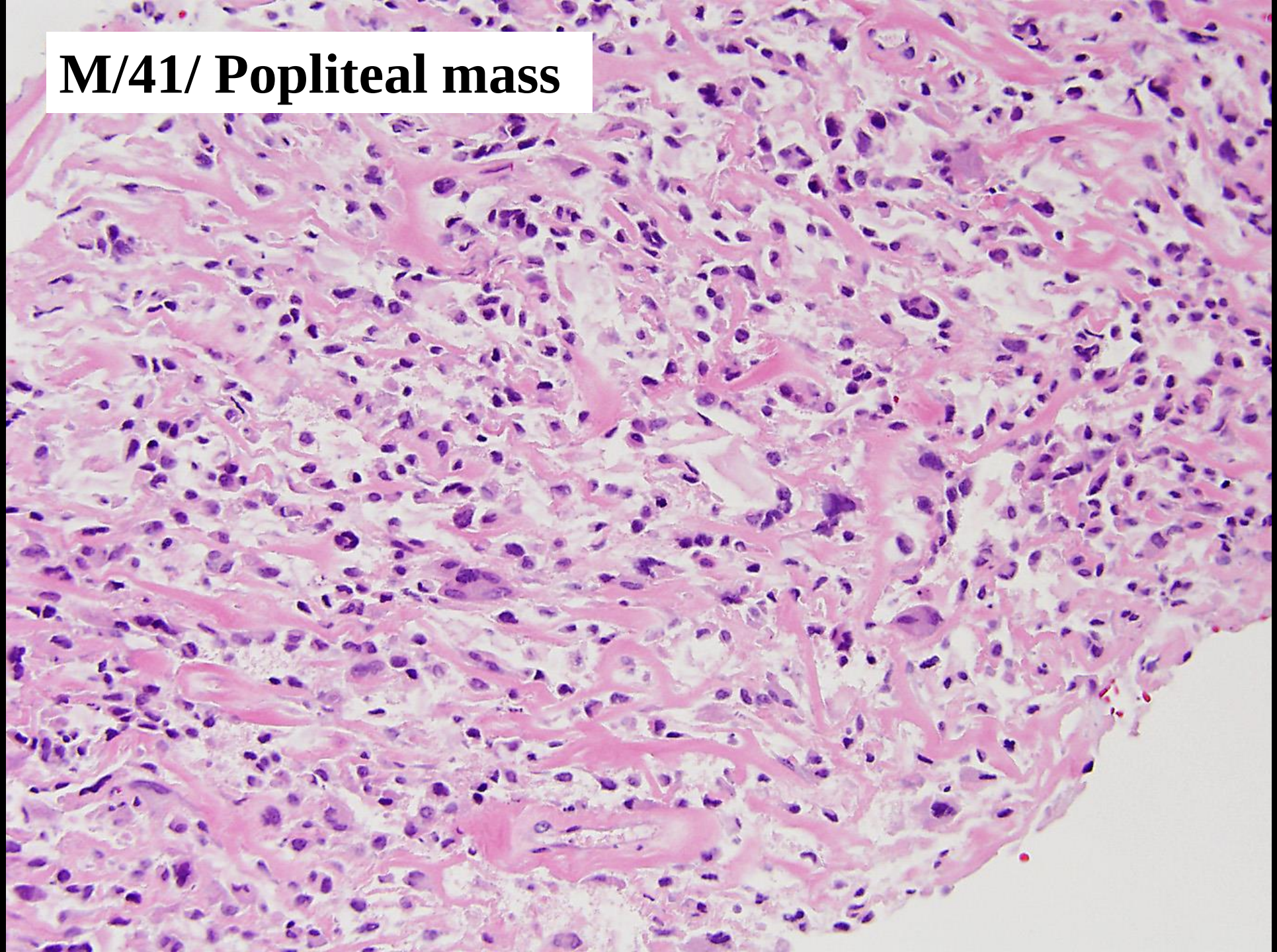
MAIN ISSUES WITH SMALL NEEDLE BIOPSIES

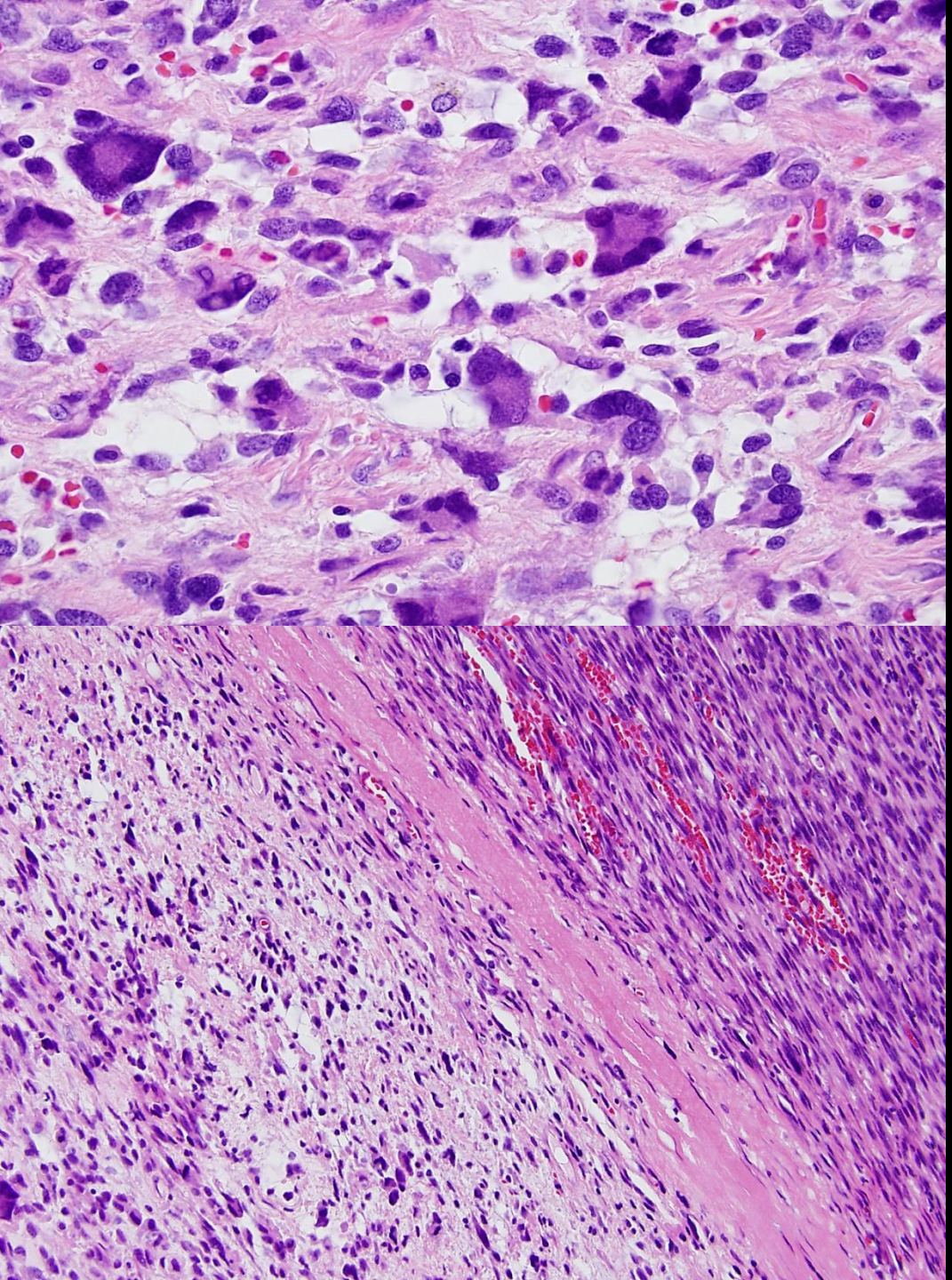
- Failure to sample diagnostic area
- Tissue too limited to allow recognition
- Under-representation of malignant features
- Under-estimation of histologic grade

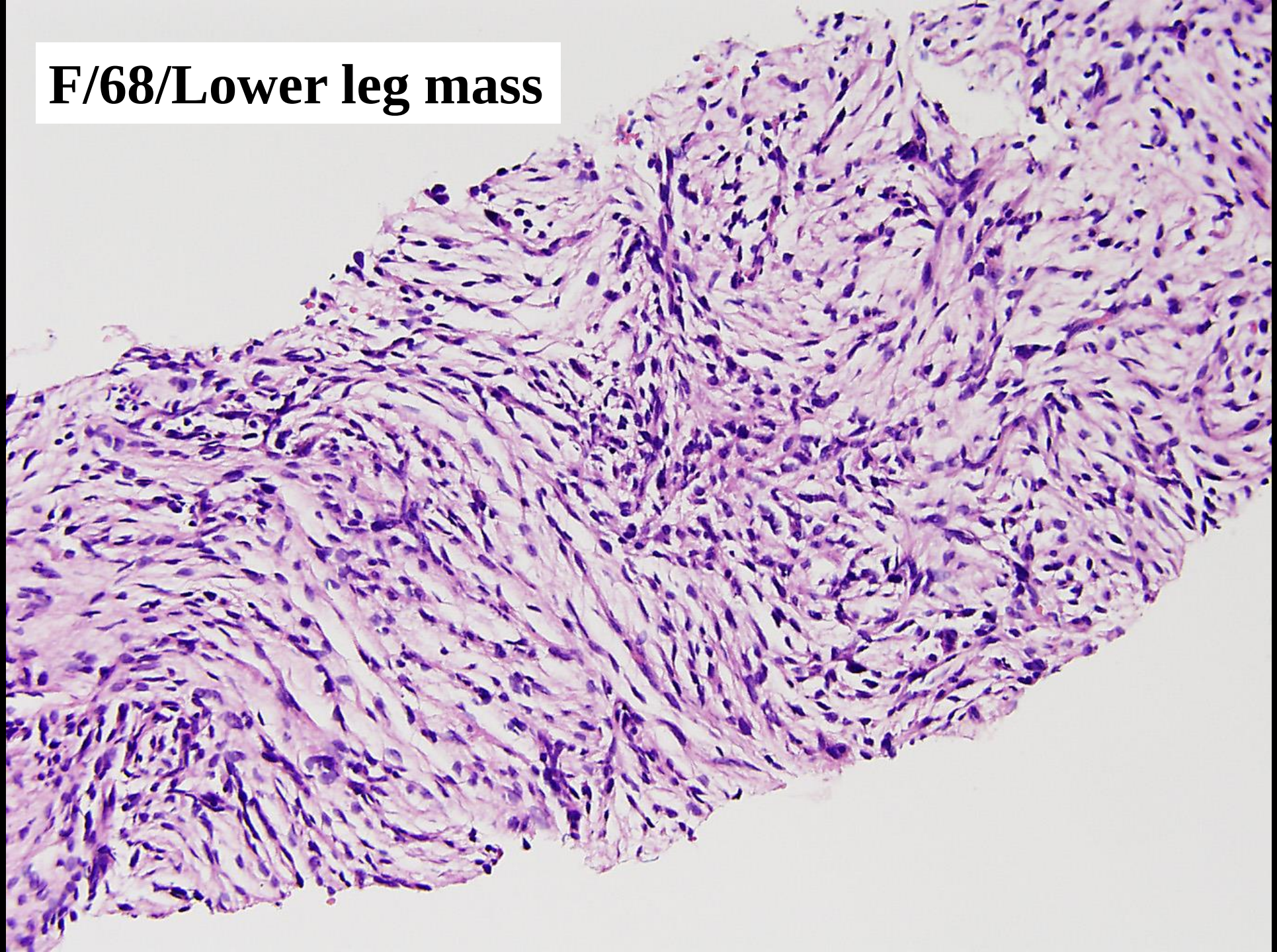
F/23/Breast needle bx

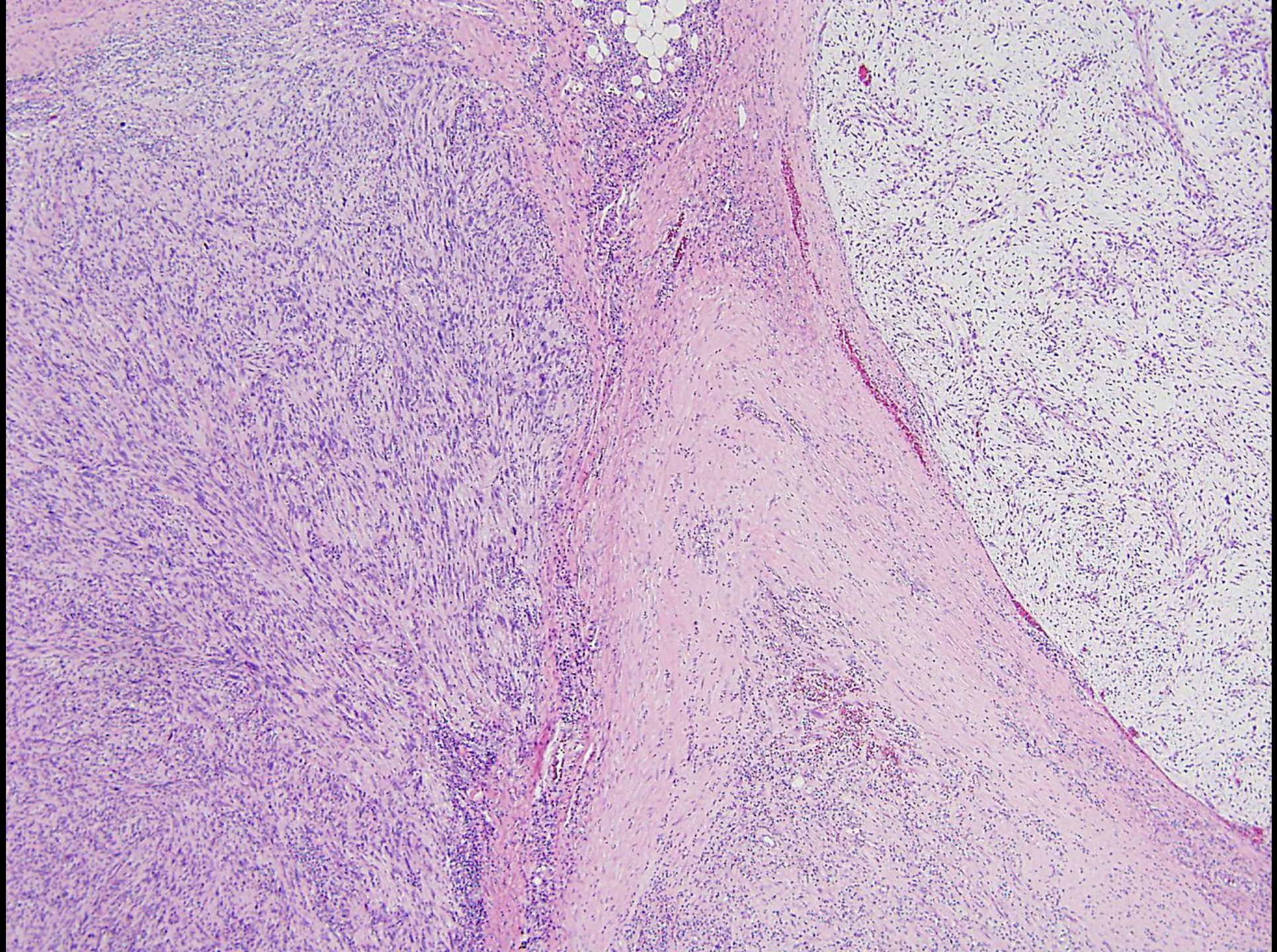


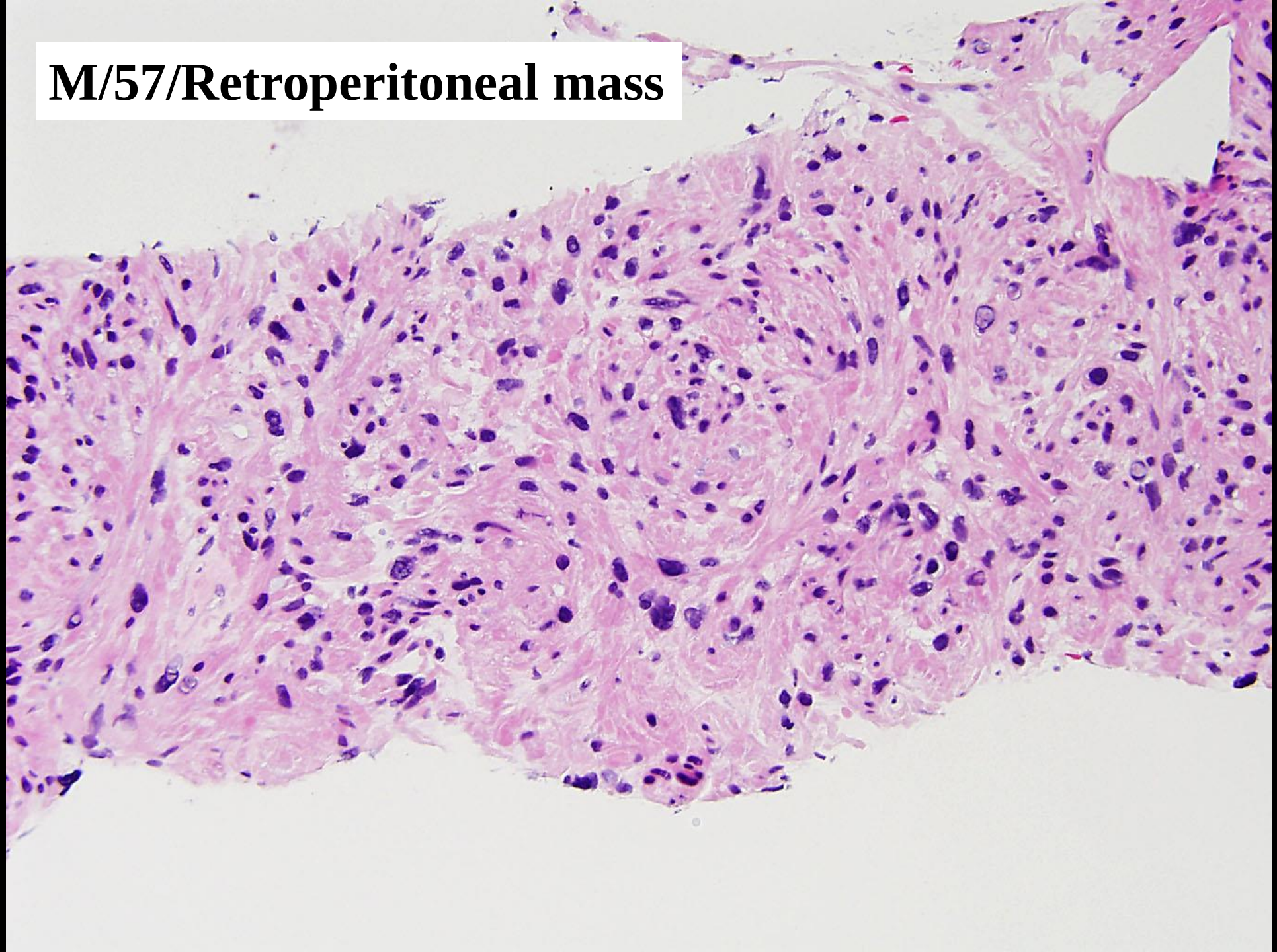


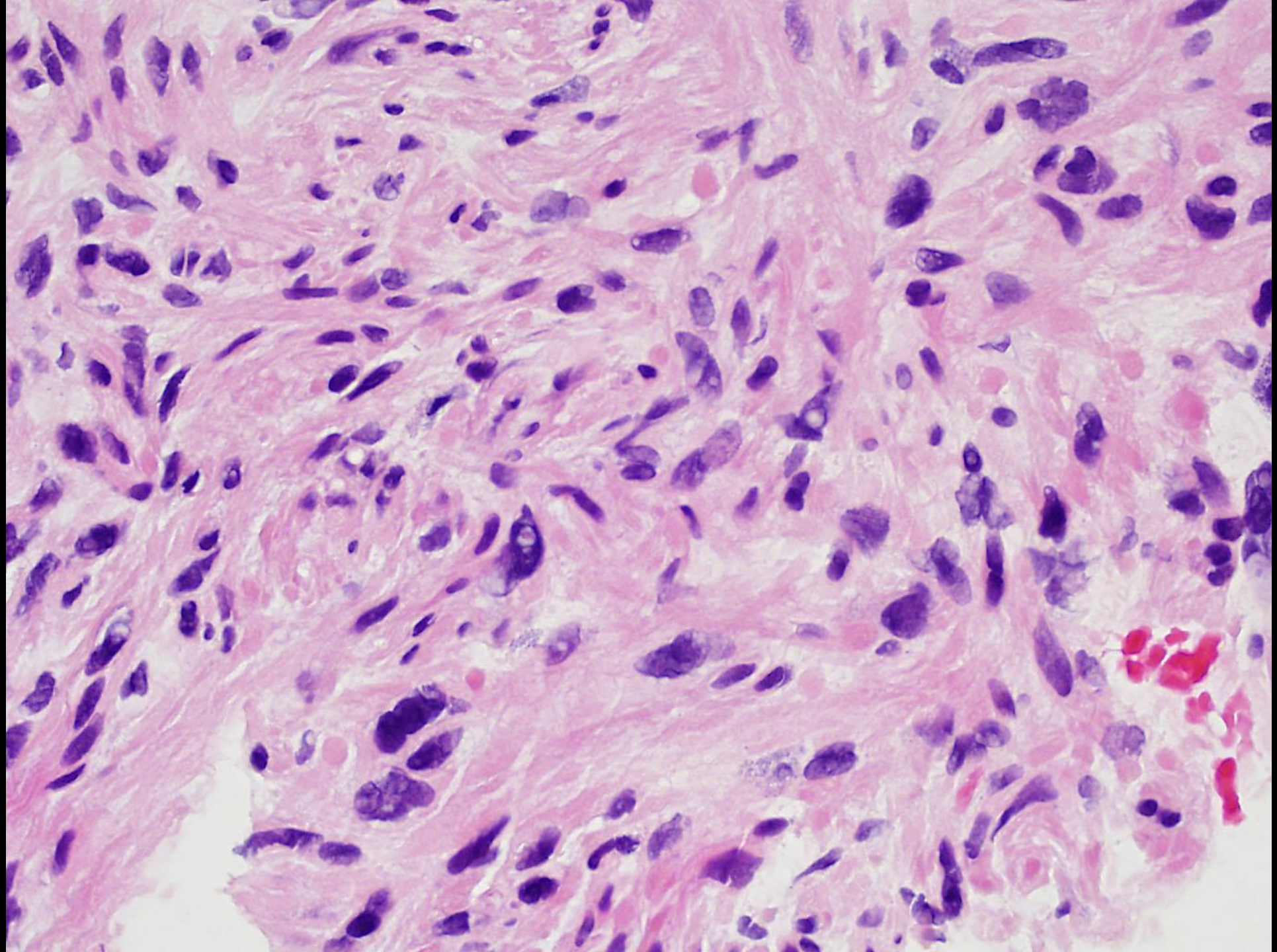

M/41/ Popliteal mass

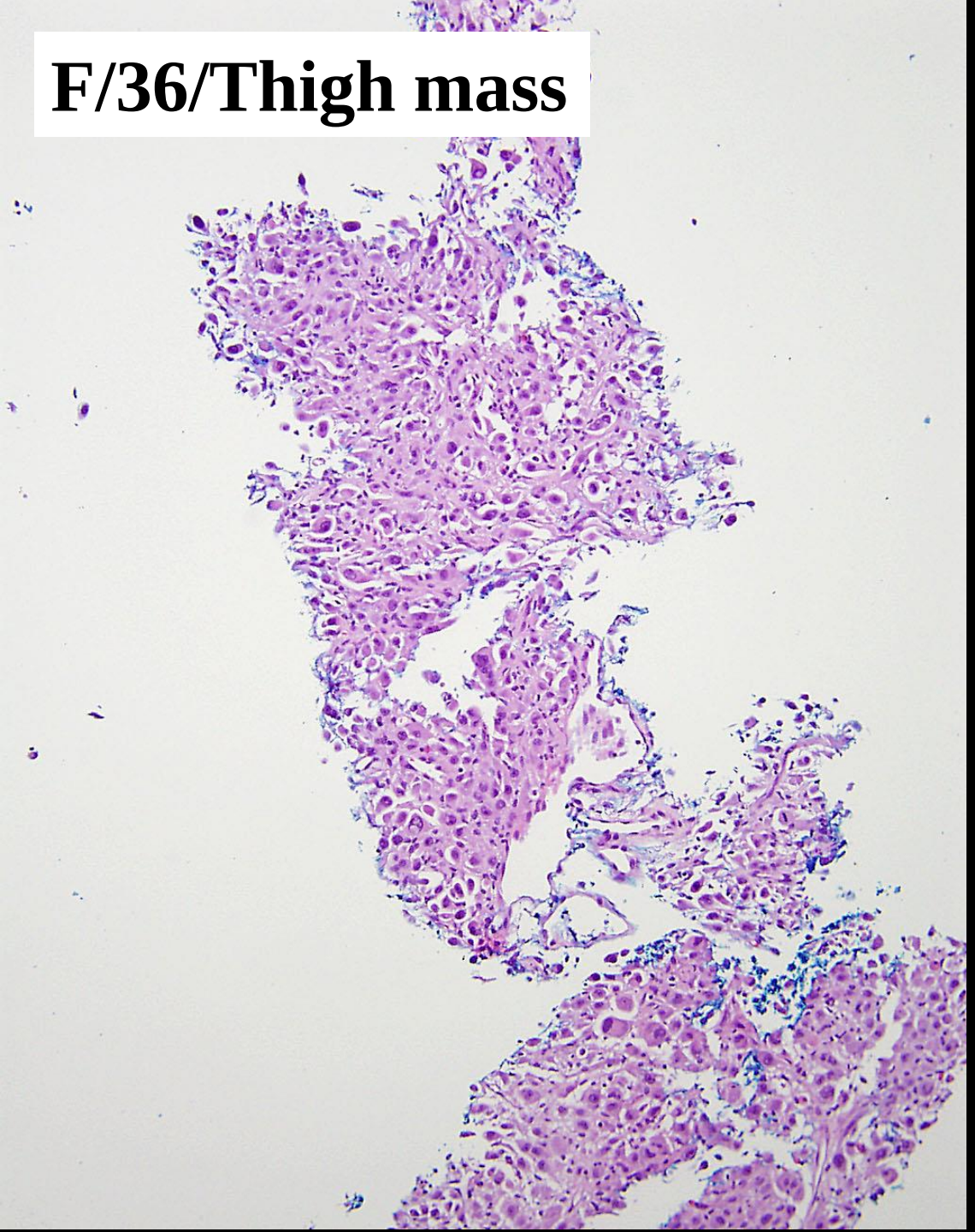


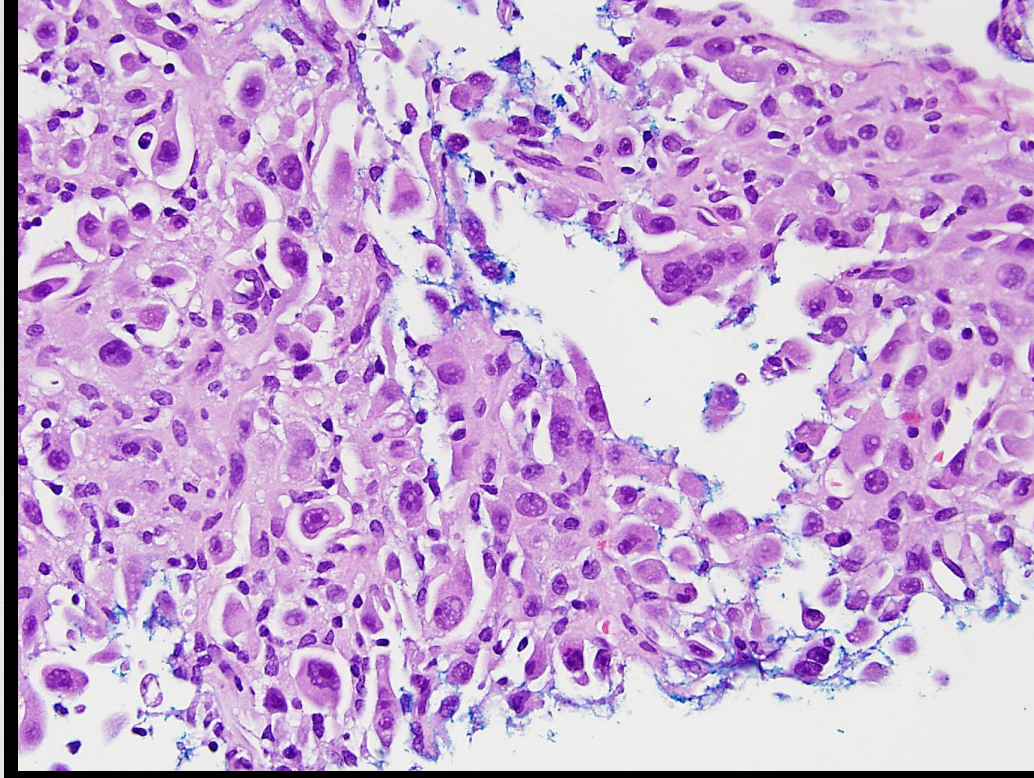

F/68/Lower leg mass

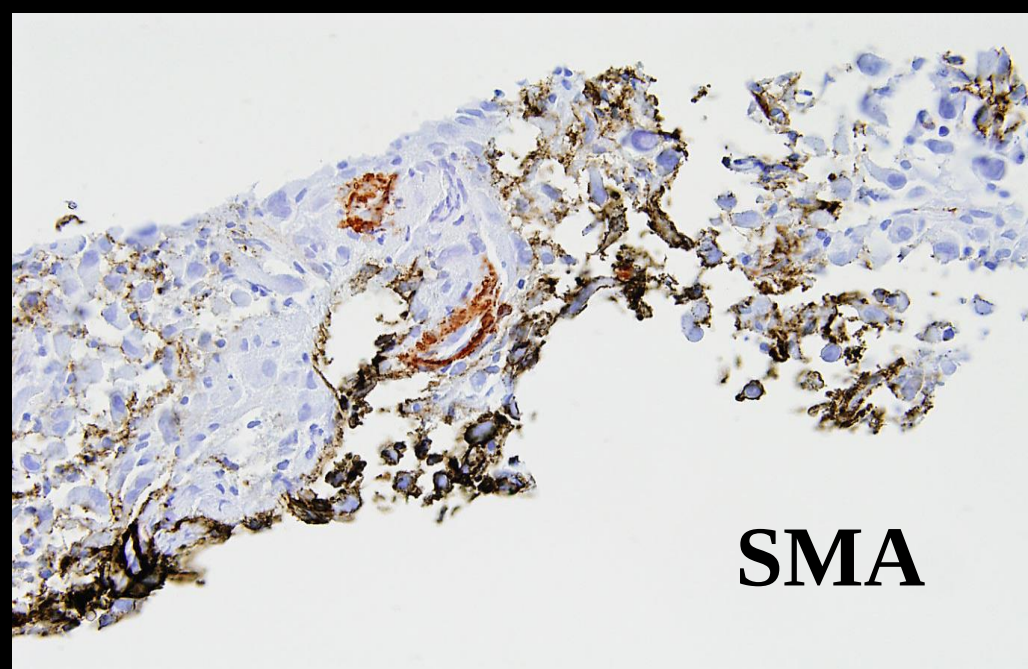



M/57/Retroperitoneal mass




F/36/Thigh mass




SMA

SOFT TISSUE SARCOMAS
CLASSIFICATION IN 2016

- **More extensive molecular characterization**
- **Predominance of chromosomal translocations in almost all lineages**
- **Gradual disappearance of histogenetic concept**

CYTOGENETIC ABERRATIONS IN SOFT TISSUE SARCOMAS

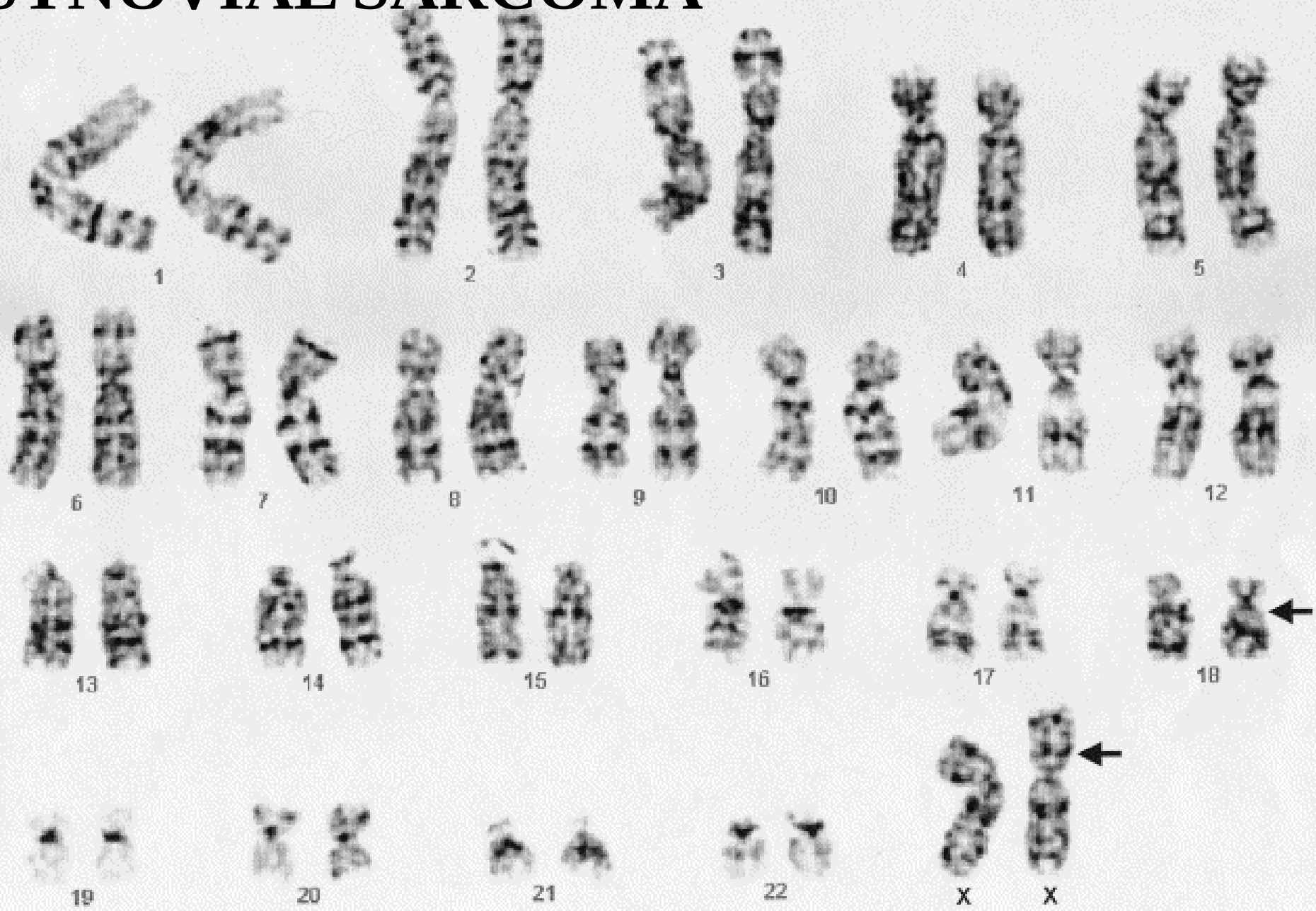
Tumor type	Cytogenetic changes	Gene fusion
Ewing's sarcoma/primitive neuroectodermal tumor	t(11;22)(q24;q12)	*FLI-1-EWSR1*
	t(21;22)(q22;q12)	*ERG-EWSR1*
	t(7;22)(p22;q12)	*ETV1-EWSR1*
	t(17;22)(q12;q12)	*EIAF-EWSR1*
	t(2;22)(q33;q12)	*FEV-EWSR1*
	t(16;21)(p11;q22)	*FUS-ERG*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FOXO1A*
	t(1;13)(p36;q14)	*PAX7-FOXO1A*
Myxoid/round cell liposarcoma	t(12:16)(q13;q11)	*DDIT3-FUS*
	t(12;22)(q13;q11-12)	*DDIT3-EWSR1*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*WT1-EWSR1*
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SSX1-SS18*
		SSX2-SS18
Clear cell sarcoma/ so-called angiomatoid 'MFH'	t(12;22)(q13;q12)	*ATF-1-EWSR1*
	t(2;22)(q33;q12)	*CREB1-EWSR1*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*NR4A3-EWSR1*
	t(9;17)(q22;q11)	*NR4A3-TAF15*
Dermatofibrosarcoma protuberans/ giant cell fibroblastoma	t(17;22)(q22;q13)	*PDGFB-COL1A1*
Infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*ASPL-TFE3*
Low grade fibromyxoid sarcoma	t(7;16)(q33;p11)	*FUS-CREB3L2*
	t(11;16)(p13;p11)	*FUS-CREB3L1*
Myxoinflammatory fibrobl. sarcoma	t(1;10)(p22;q24)	*TGFBR3-MGEA5*

MORE RECENTLY IDENTIFIED SPECIFIC CYTOGENETIC / MOLECULAR GENETIC ABERRATIONS IN SOFT TISSUE TUMORS

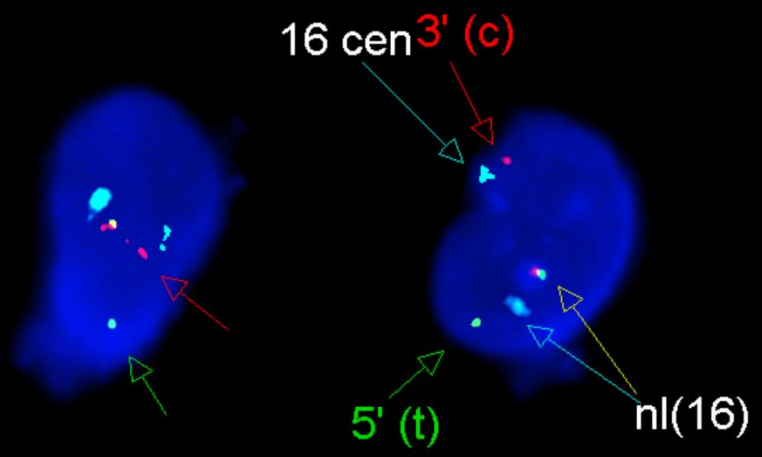
Myoepithelial tumors	***EWSR1* and various fusion partners**	
Nodular fasciitis	**t(17;22)(p13;q12.3)**	***USP6-MYH9***
Mesenchymal chondrosarc	**t(8;8)(q21.1;q13.3)**	***HEY1-NCOA2***
Epithelioid h' endothelioma	**t(1;3)(p36.3;q25)**	***WWTR1-CAMTA1***
		YAP1-TFE3
Pseudomyogenic hemangioendothelioma	**t(7;19)(q22;q13)**	***SERPINE1-FOSB***
Soft tissue angiofibroma	**t(5;8)(p15;q13)**	***AHRR-NCOA2***
Undiff[d] (Ewing-like) sarcoma	**t(4;19)(q35;q13.1)**	***CIC-DUX4***
	t(4;10)(q35;q26)	***CIC-DUX4***
Ossifying fibromyxoid tumor	**Rearrangement of *PHF1* at 6p21**	
Solitary fibrous tumor	**inv12 (q13;q13)**	***NAB2-STAT6***
Spindle cell/sclerosing rhabdo		***MYOD1* mutations**

More to come.....

SYNOVIAL SARCOMA



LOW GRADE FIBROMYXOID SARCOMA



FUS - 16p11

3' (c)

5' (t)

CEP 16

SOFT TISSUE SARCOMAS
BENEFITS OF IMPROVED CLASSIFICATION

- **Better prediction of behavior**
- **Better prediction of overall outcome**
- **Clearer communication with patient**
- ***Possibly* better treatment selection and prediction of treatment response**

SOFT TISSUE SARCOMAS
BENEFITS OF IMPROVED CLASSIFICATION

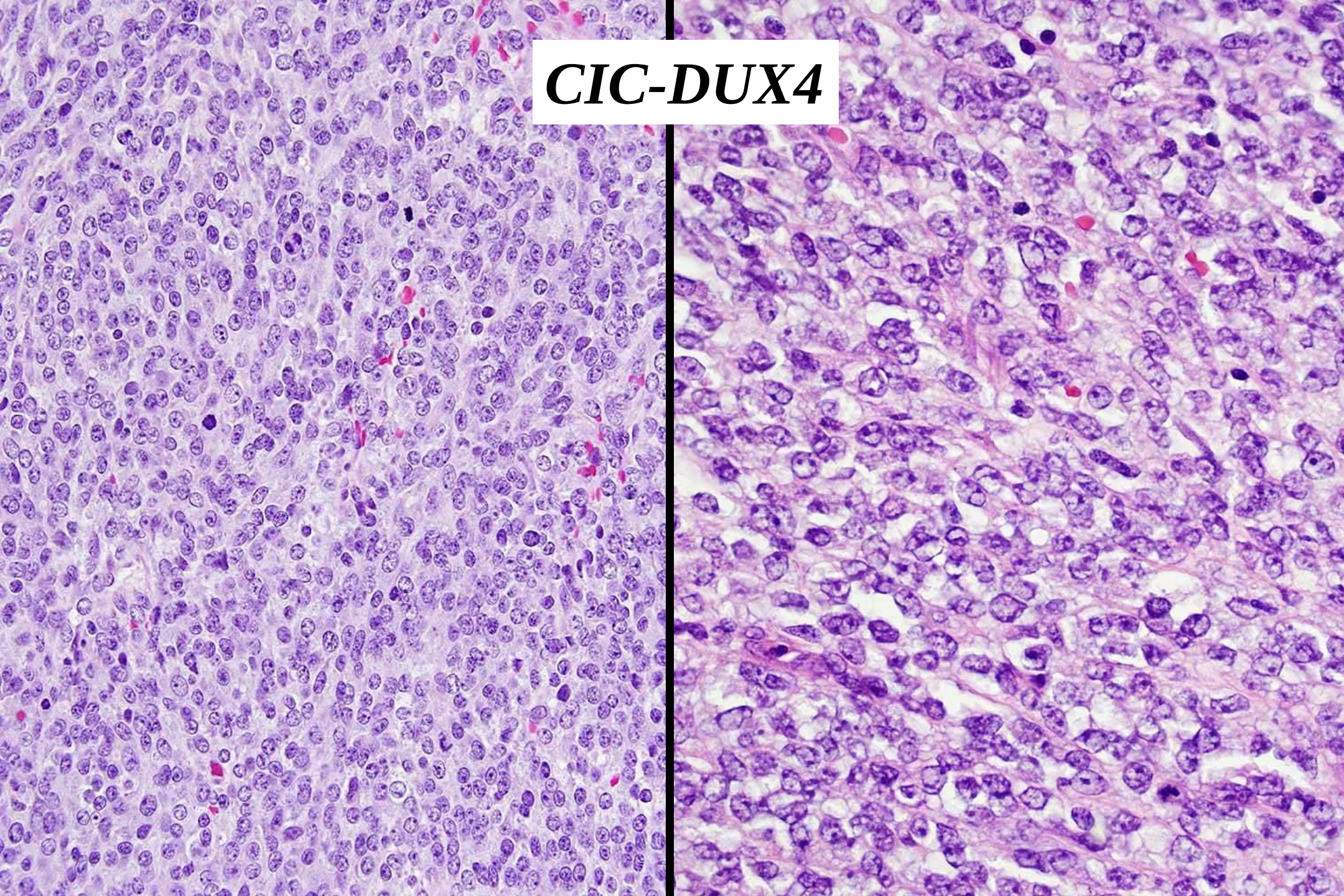
- **Better prediction of behavior**
- **Better prediction of overall outcome**
- **Clearer communication with patient**
- ***Possibly* better treatment selection and prediction of treatment response**

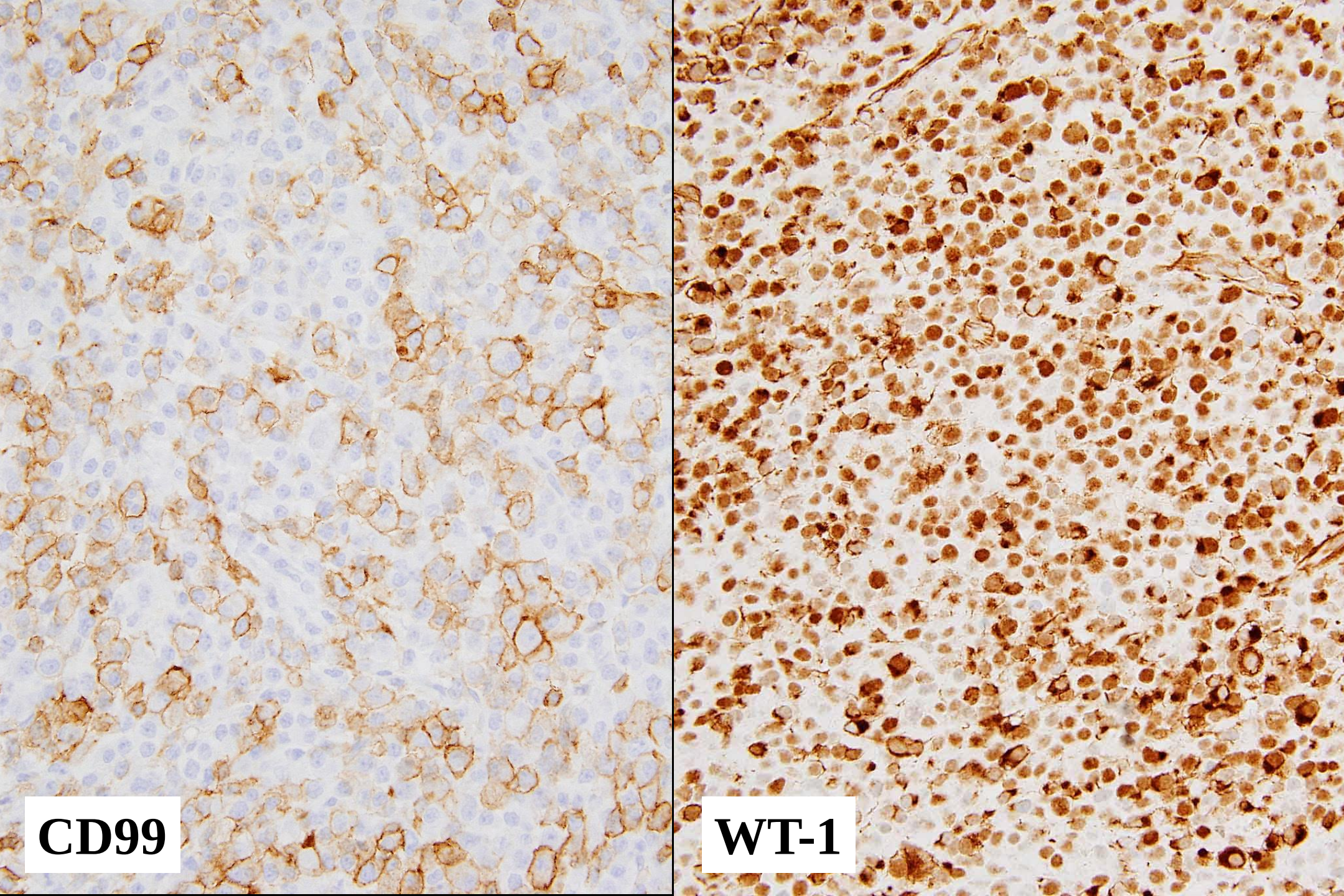
Modern, more ‘granular’ subclassification often exceeds treatment options – but may help to uncover the latter

ROUND CELL SARCOMA WITH *CIC-DUX4*
CLUES AND SIGNIFICANCE

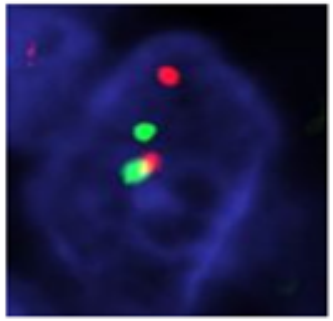
Mostly young adults, M>F
Extremities +++
Aggressive/most often fatal
-less reliably chemosensitive than Ewing
Less uniform than Ewing sarcoma
-round/ovoid/focal spindle cells
Often prominent nucleoli/necrosis ++
CD99 variable/less diffuse; WT-1 often pos

Can only prove molecularly

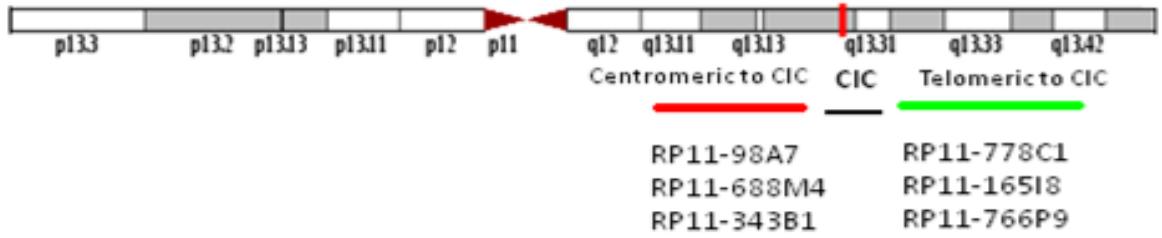

CIC-DUX4

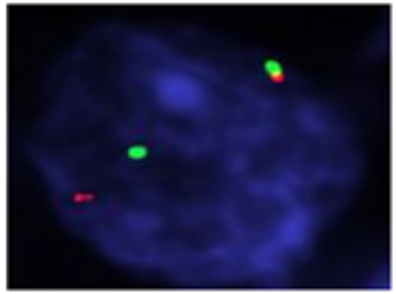

CD99
WT-1

CIC-DUX4 fusions



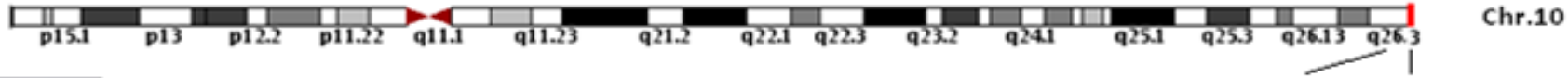
breakapart of CIC

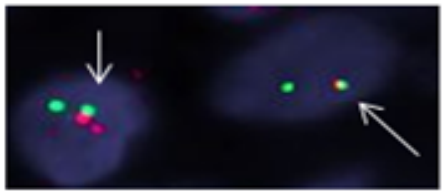




t(4;19)

fusion of T-CIC (in green) on chr.19 and C-DUX4 (in red) on chr.4





t(10;19)

fusion of T-CIC (in green) on Chr.19 and C-DUX4 (in red) on Chr.10

Italiano A, Genes Chrom Cancer 2012

SOFT TISSUE SARCOMAS
PROGNOSTICATION

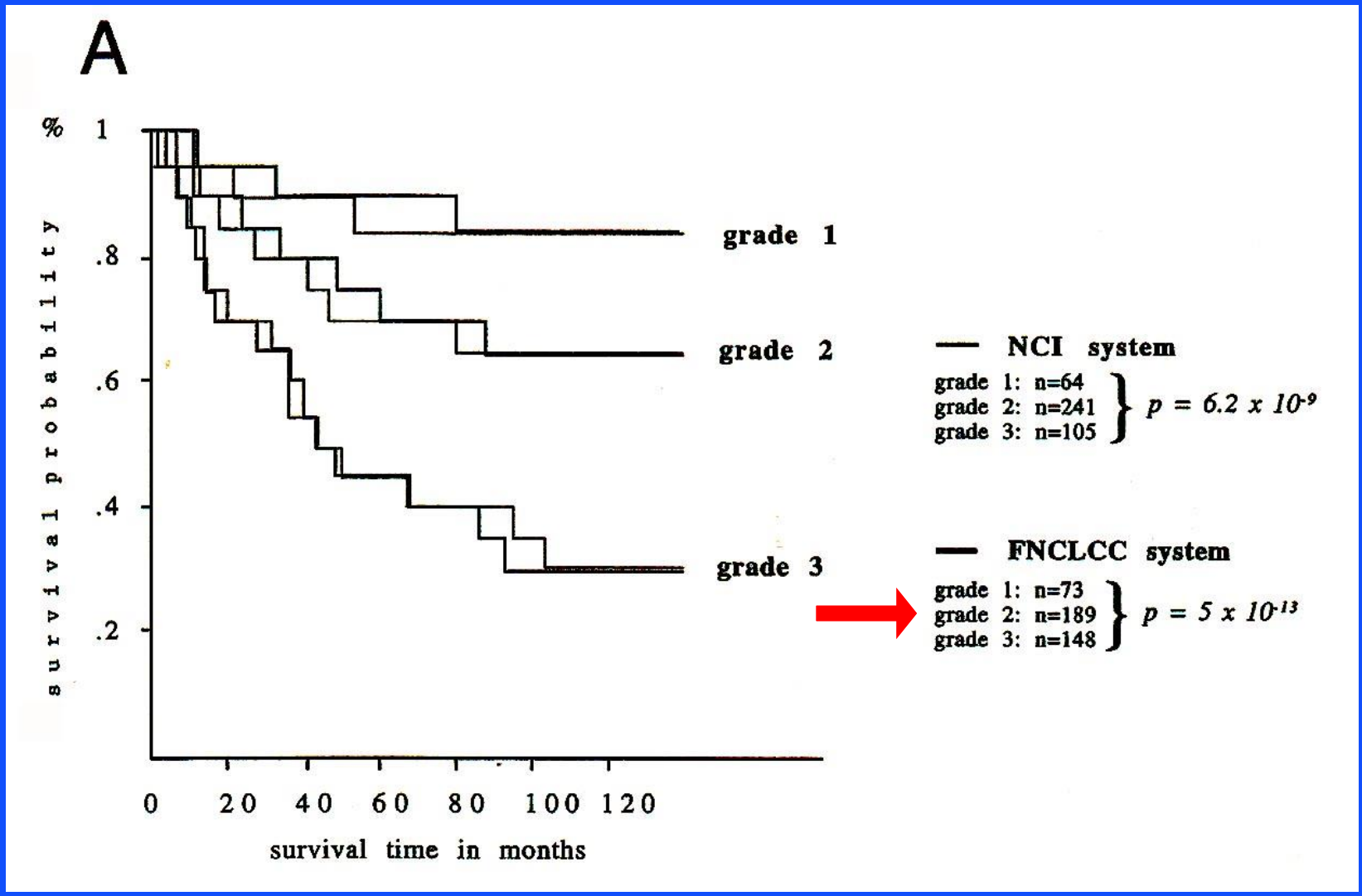
Histologic grading
- FNCLCC, NCI
AJCC staging
Risk assessment
Prognostic nomograms
Genomic profiling

How useful for individual patients?

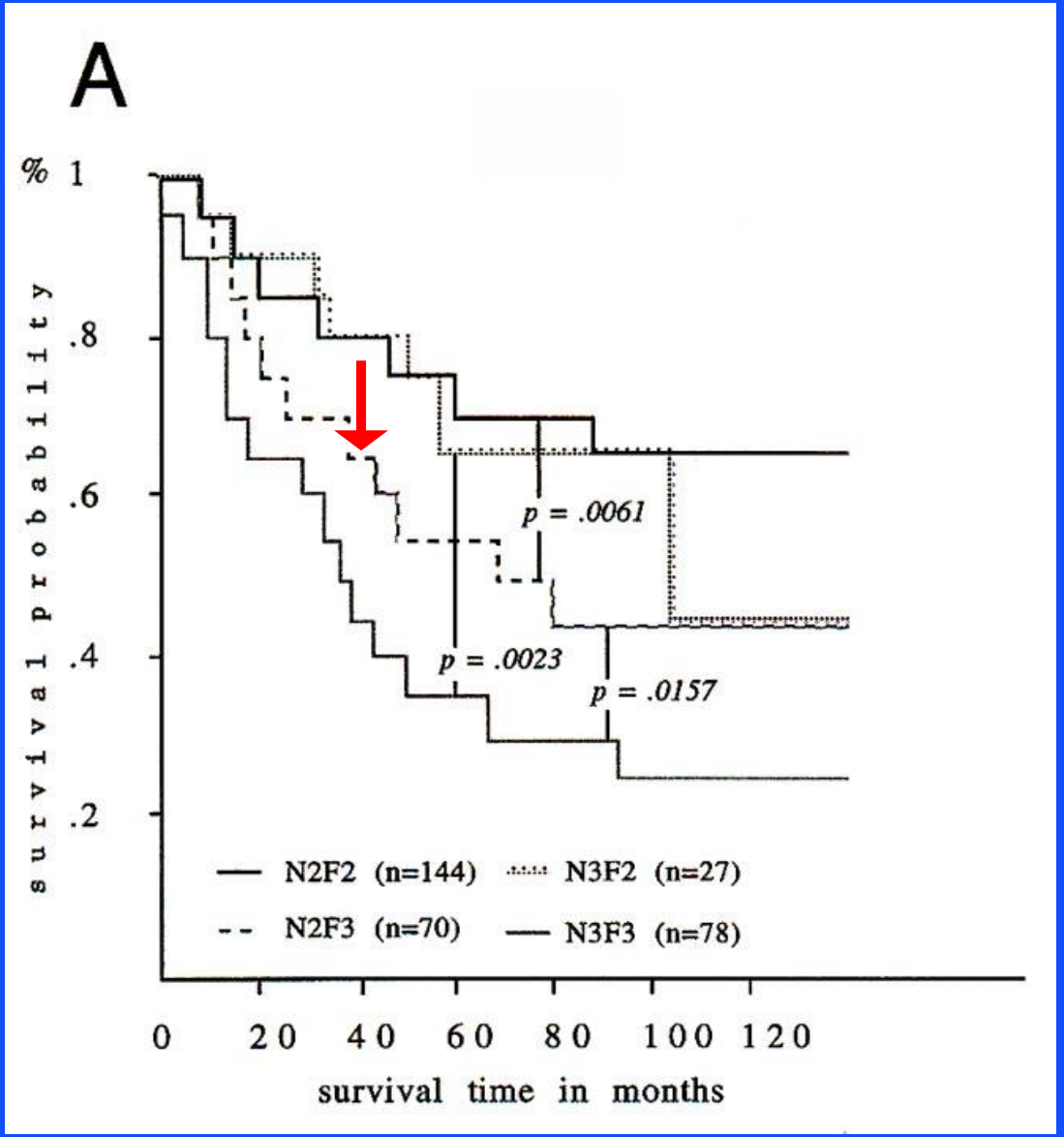
SOFT TISSUE SARCOMAS
KEY ELEMENTS IN CURRENTLY ACCEPTED GRADING SCHEMES

Histotype / differentiation
Mitoses
Necrosis

- **French (FNCLCC) & NCI systems best known and best validated**
- **French system is more discriminatory**



Guillou et al. *J Clin Oncol* 1997; 15:350-362

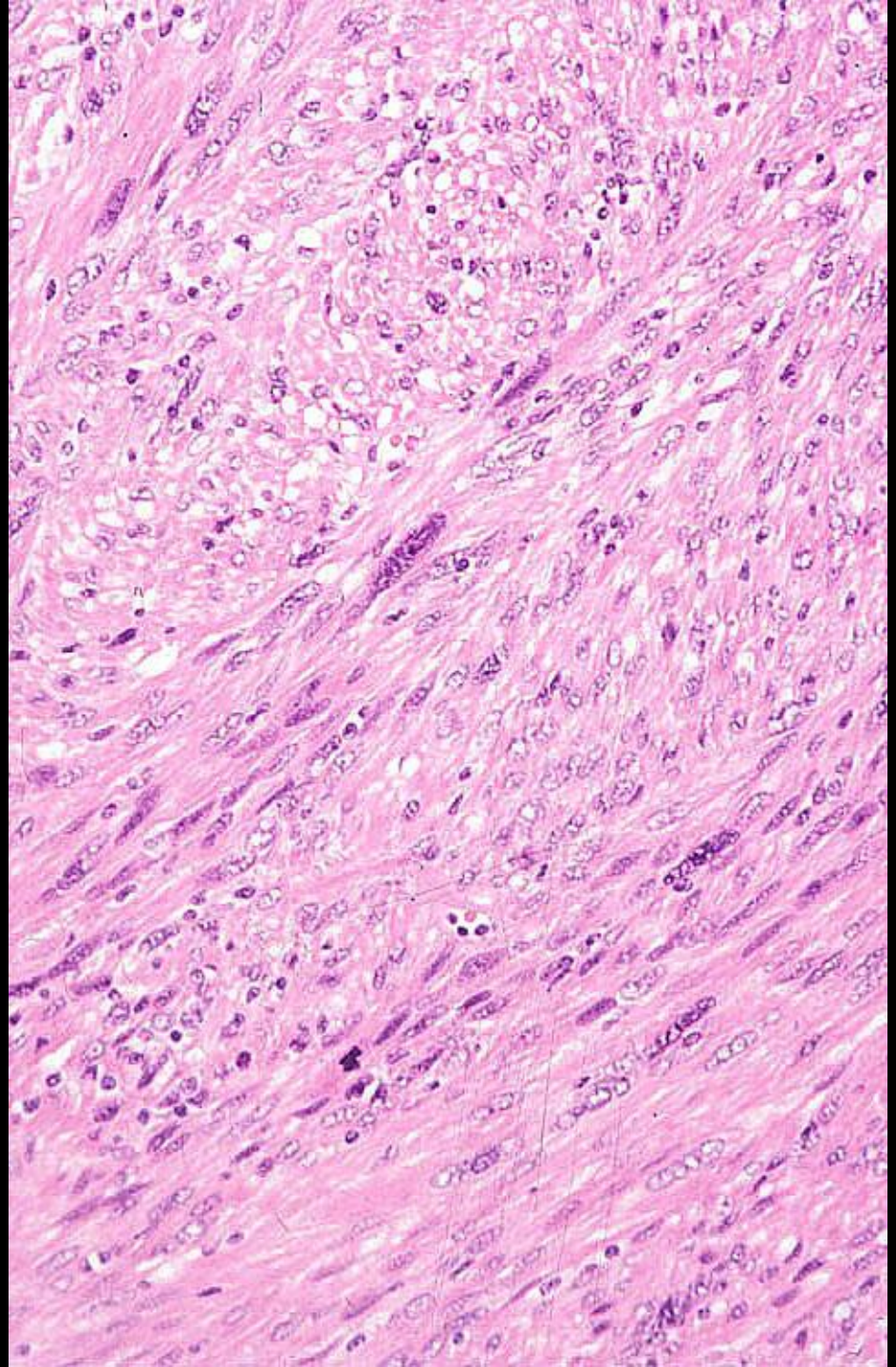


Guillou et al. *J Clin Oncol* 1997; 15:350-362

HISTOLOGIC GRADING OF SOFT TISSUE SARCOMAS
WHEN DOES IT WORK ?

- **In tumours which show a morphologic spectrum that correlates with outcome**
- **In the context of an accurate histologic diagnosis**

e.g. leiomyosarcoma, myxofibrosarcoma



TUMOUR TYPES IN WHICH FNCLCC SYSTEM DOES NOT WORK

MPNST (?)
Angiosarcoma
Epithelioid sarcoma
Clear cell sarcoma
Extraskeletal myxoid chondrosarcoma
Alveolar soft part sarcoma

Table 1-12

GUIDELINES FOR GRADING SOFT TISSUE SARCOMAS*

Tumors which are definitionally high grade
- Ewing's sarcoma/MPNET
- Rhabdomyosarcoma (all types)
- Angiosarcoma
- Pleomorphic liposarcoma
- Soft tissue osteosarcoma
- Mesenchymal chondrosarcoma
- Desmoplastic small cell tumor
- Extra-renal rhabdoid tumor

Tumors which are definitionally low grade
- Well-differentiated liposarcoma/atypical lipomatous tumor
- Dermatofibrosarcoma protuberans
- Infantile fibrosarcoma
- Angiomatoid "MFH"

Tumors which are not gradable but which often metastasize within 10–20 years of follow-up
- Alveolar soft part sarcoma
- Clear cell sarcoma
- Epithelioid sarcoma
- Synovial sarcoma
- "Low-grade" fibromyxoid sarcoma

Tumors of varying behavior for which grading may be prognostically useful
- Myxoid liposarcoma
- Leiomyosarcoma
- Malignant peripheral nerve sheath tumor
- Fibrosarcoma
- Myxofibrosarcoma (myxoid MFH)

Tumors of varying behavior for which grading parameters are not yet established
- Hemangiopericytoma
- Myxoid chondrosarcoma
- Malignant granular cell tumor
- Malignant mesenchymoma

*Table 3 from Association of Directors of Anatomic Pathology. Recommendations for reporting soft tissue tumors (2a).

Tumors of the soft tissues, Atlas of Tumor Pathology, 3rd Series, RL Kempson et al, eds. Washington DC: AFIP 2001

HISTOLOGIC GRADING OF SOFT TISSUE SARCOMAS

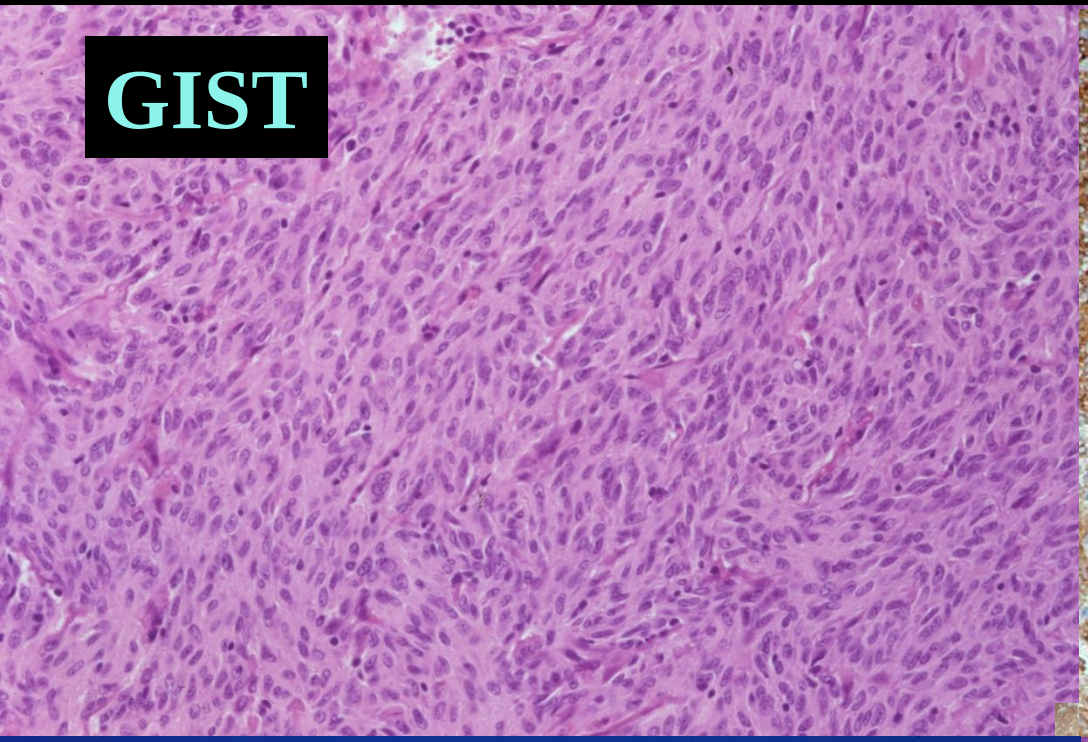
No reason to believe or expect that prognostic parameters would be same in all tumour types

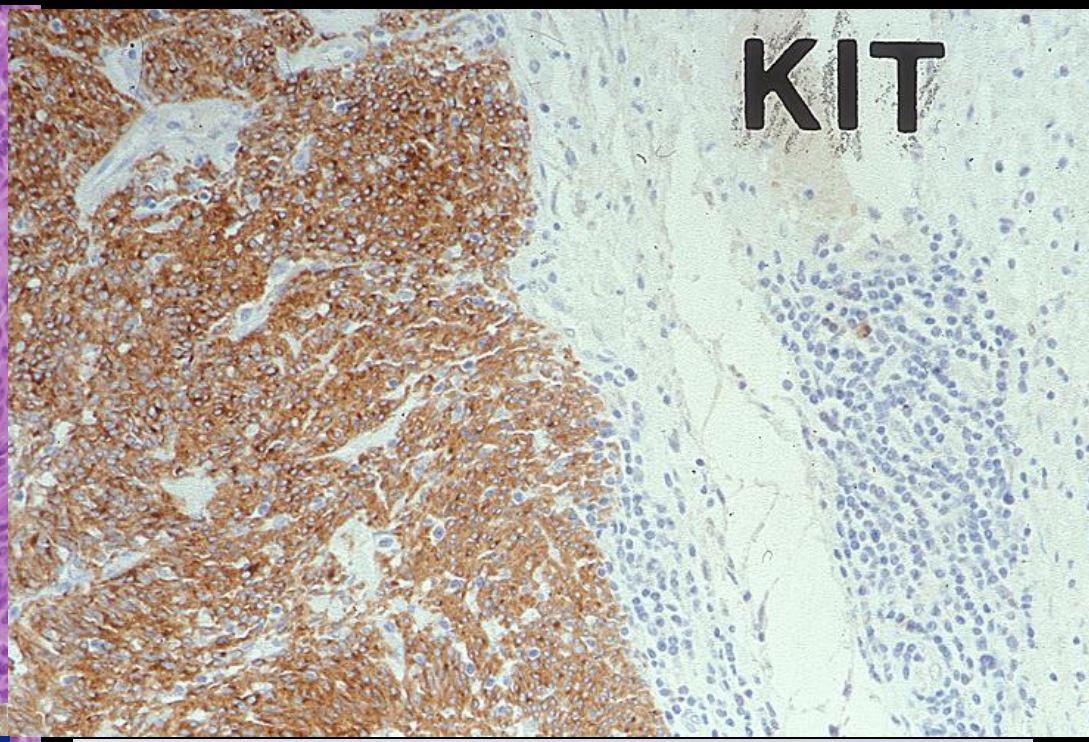
Grade	**-**	**Myxofibrosarcoma**
Cellularity	**-**	**Myxoid liposarcoma**
Size	**-**	**Myxoid chondrosarcoma**
Location	**-**	**Dedifferentiated liposarcoma**
Genotype	**-**	**Alveolar rhabdomyosarcoma**
Clinical stage	**-**	**Embryonal rhabdomyosarcoma**
Patient age	**-**	**Alveolar soft part sarcoma**

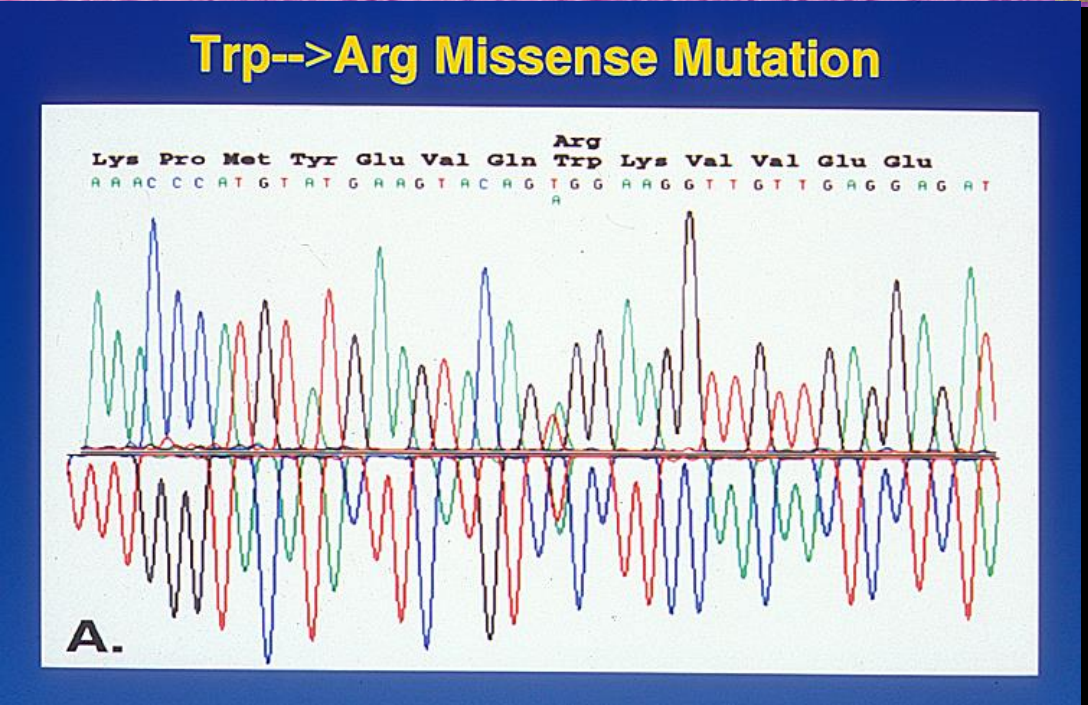
Table 1 Risk Stratification of Primary GIST by Mitotic Index, Size, and Site

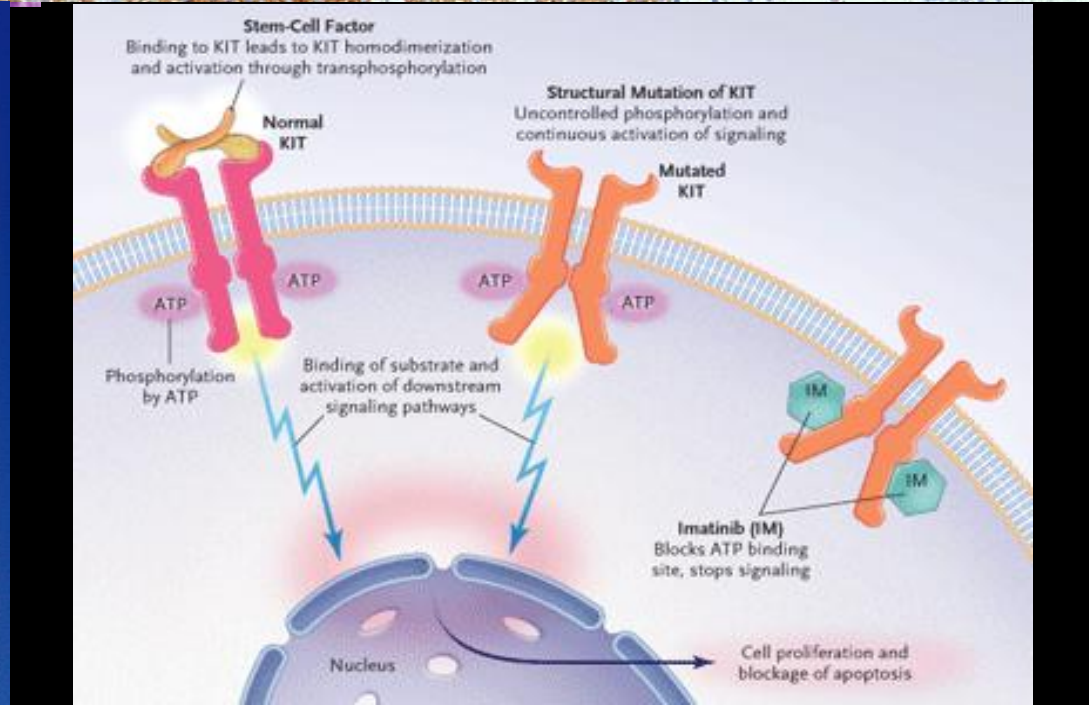
Tumor Parameters		Risk for Progressive Disease*(%), Based on Site of Origin			
Mitotic Rate	Size	Stomach	Jejunum/Ileum	Duodenum	Rectum
≤ 5 per 50 HPF	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	> 2, ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
	> 5, ≤ 10 cm	Low (3.6%)	Moderate (24%)	Insufficient data	Insufficient data
	> 10 cm	Moderate (10%)	High (52%)	High (34%)	High (57%)
> 5 per 50 HPF	≤ 2 cm	None†	High†	Insufficient data	High (54%)
	> 2, ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
	> 5, ≤ 10 cm	High (55%)	High (85%)	Insufficient data	Insufficient data
	> 10 cm	High (86%)	High (90%)	High (86%)	High (71%)

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.
Abbreviations: GIST, gastrointestinal stromal tumor; HPF, high-power field.
*Defined as metastasis or tumor-related death.
†Denotes small numbers of cases.
Adapted from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diagn Pathol 2006;23:70–83.


GIST


KIT


Trp-->Arg Missense Mutation
Lys Pro Met Tyr Glu Val Gln Arg Trp Lys Val Val Glu Glu
A.


Stem-Cell Factor
Binding to KIT leads to KIT homodimerization and activation through transphosphorylation
Normal KIT
Structural Mutation of KIT
Uncontrolled phosphorylation and continuous activation of signaling
Mutated KIT
ATP
Phosphorylation by ATP
Binding of substrate and activation of downstream signaling pathways
IM
Imatinib (IM)
Blocks ATP binding site, stops signaling
Nucleus
Cell proliferation and blockage of apoptosis

GASTROINTESTINAL STROMAL TUMOURS
MUTATIONAL ANALYSIS

- Approx. 75-80% have *KIT* mutations and 5-7% have *PDGFRA* mutations, irrespective of type/size

	% of cases	Gleevec response
KIT exon 11	60-65	80-85%
KIT exon 9	10-15	45-50%
KIT exon 13	< 5%	Too few data
KIT exon 17	< 5%	Too few data
PDGFRA (exons 12/18)	~ 6%	Variable

- Tumors with *PDGFRA* mutations seem more indolent
- Tumours lacking either *KIT* or *PDGFRA* mutations still show 40-45% response – but progress sooner
- Gleevec response, predicted by mutation type, correlates with survival (resistance due to 2º mutations)

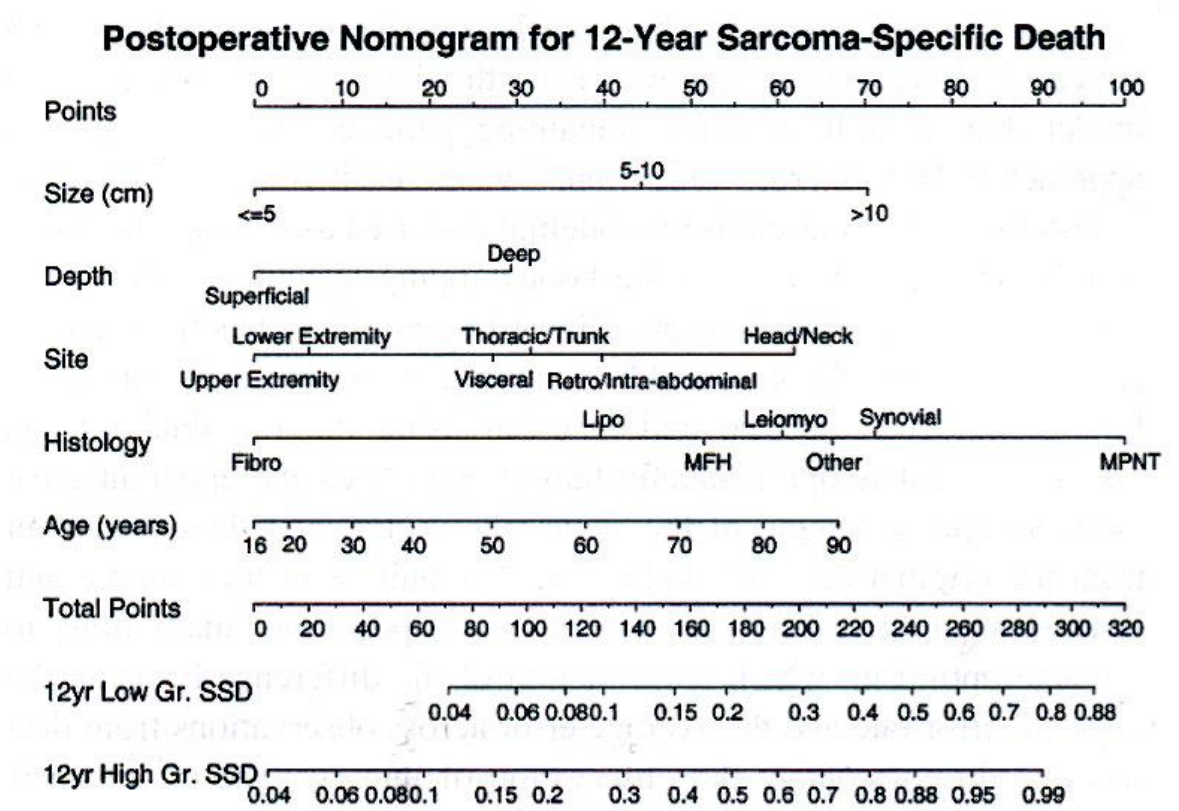


Fig 2. Postoperative nomogram for 12-year sarcoma-specific death based on 2,163 patients treated at Memorial Sloan-Kettering Cancer Center. Abbreviations: Fibro indicates fibrosarcoma; Lipo, liposarcoma; Leiomyo, leiomyosarcoma; MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral-nerve tumor; GR, grade; SSD, sarcoma-specific death.

Kattan et al. *J Clin Oncol* 2002; 20:791-796

GENE EXPRESSION FOR PROGNOSIS - THE WAY FORWARD ? (1)

Large study by French Sarcoma Group
183 1º non-translocation-type sarcomas
- **validated in independent cohort of 127 cases**

Genomic profiling → 3 groups
- **simple amplification type (DDLPS) (16%)**
- **few alterations, whole arm / chromosome (23%)**
- **high level of complexity (UPS/LMS) (61%)**

Genomic complexity ∝ histologic grade

GENE EXPRESSION FOR PROGNOSIS - THE WAY FORWARD ? (2)

Then selected genes reflecting (1) greatest CGH imbalance, (2) grade 3 vs 2, (3) chromosome instability → final 67 gene set (CINSARC)

1) **CINSARC better than FNCLCC grade**
2) **CINSARC also works in GIST, breast Ca, DLBCL**

Chibon et al, *Nature Med* 2010; 16:781-788

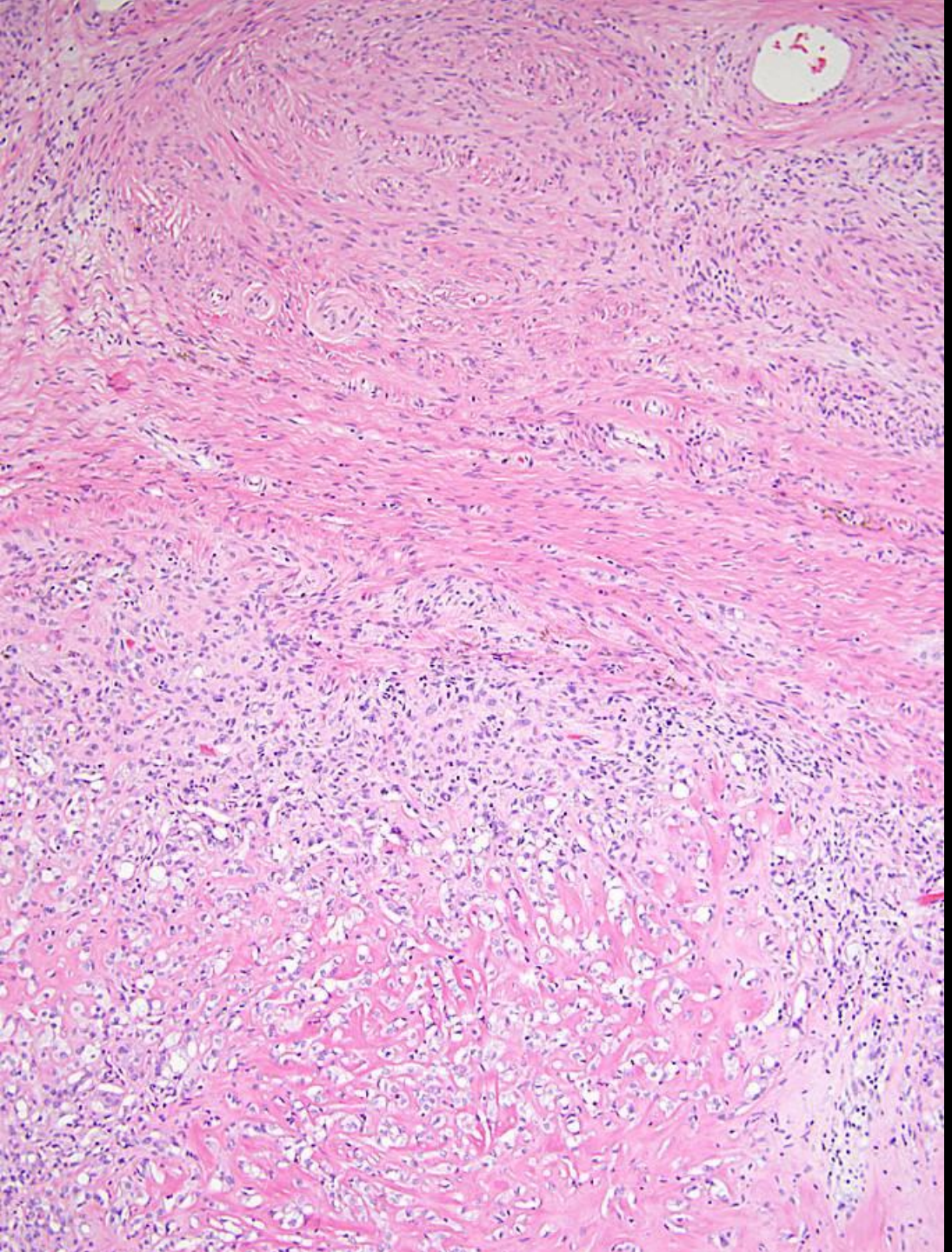
Still needs independent validation

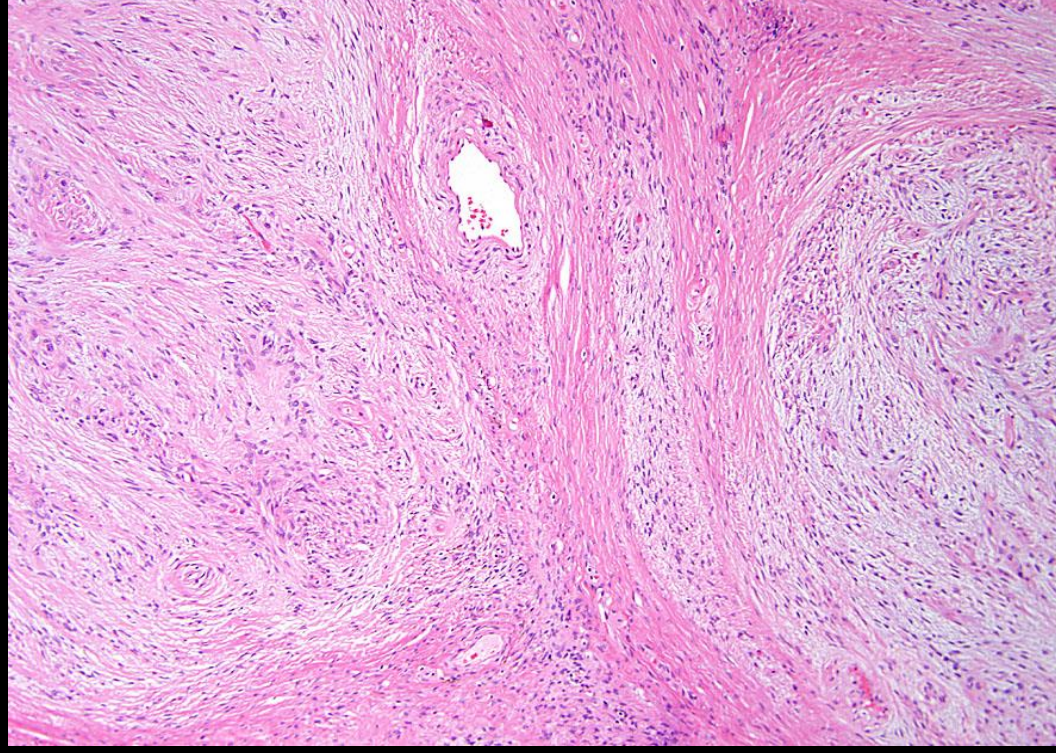
SOFT TISSUE TUMORS WITH GENETIC OVERLAP

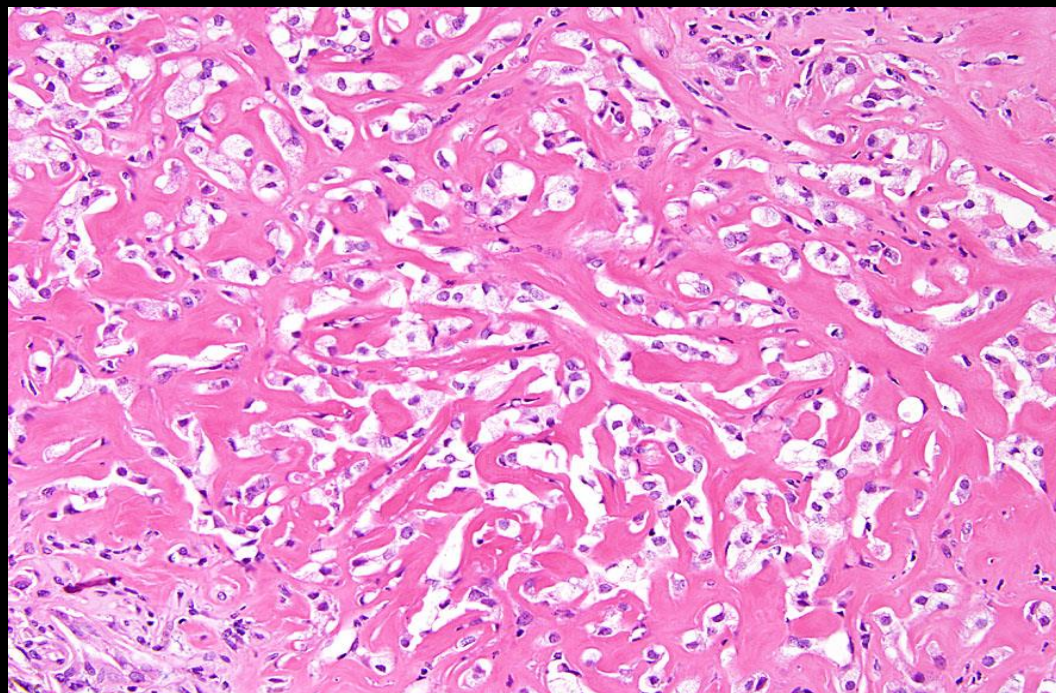
- **Evidence of relationship?**
- **Biologic / mechanistic significance ?**
- **Impact on classification schemes?**
- **Variants of a single ‘molecular’ entity?**
- **Potential impact on diagnosis**
- **Potential impact on treatment**

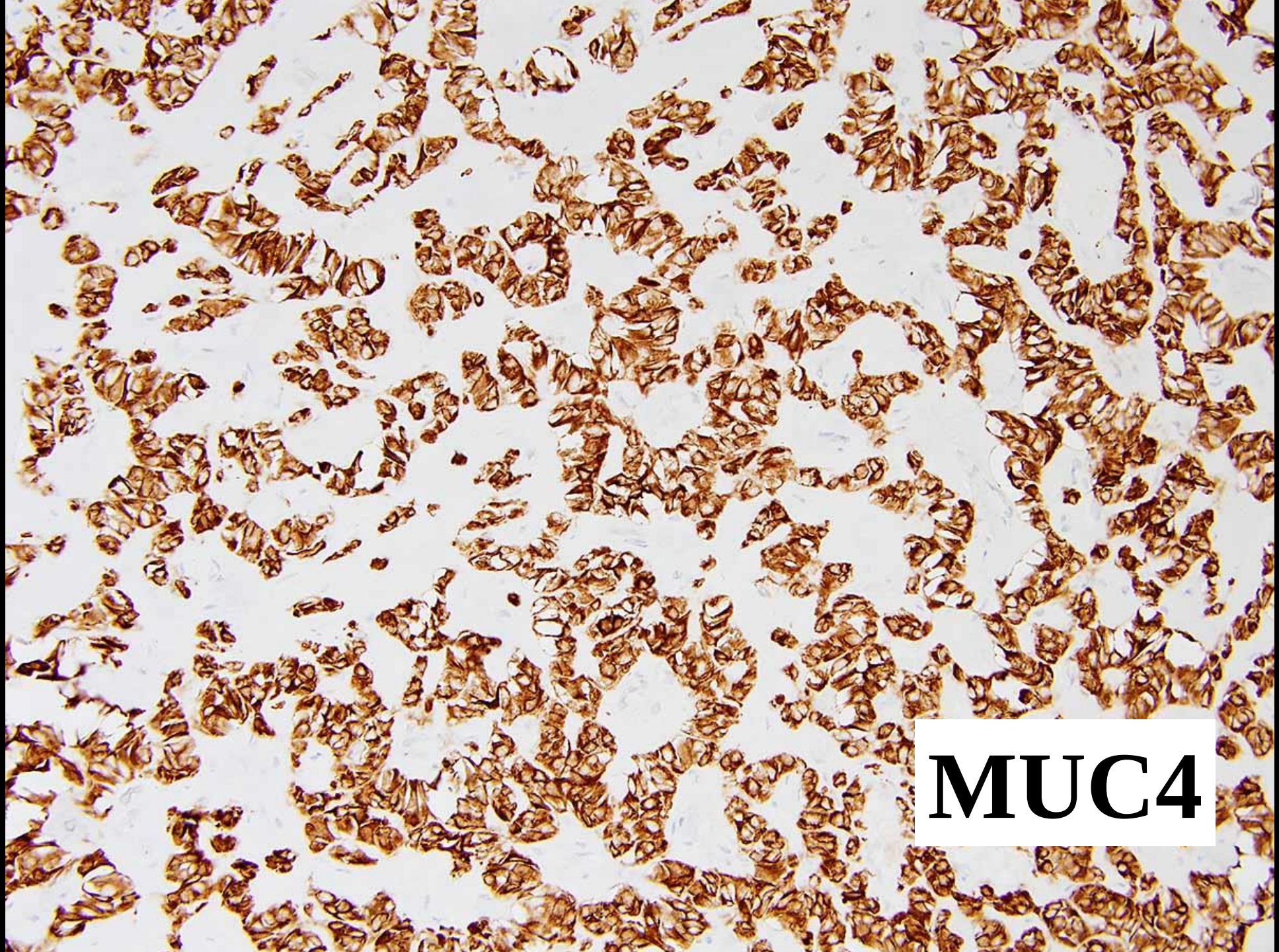
SOFT TISSUE TUMORS
EXAMPLES OF GENETIC OVERLAP

- **Tumors with similar morphology**
- **Tumors that may show hybrid morphology**
- **Seemingly totally unrelated tumors**
- **Tumors of different lineages**








MUC4

SCLEROSING EPITHELIOID FIBROSARCOMA
MOLECULAR GENETICS

PURE SEF

Most are MUC4 +ve – **? Up to 90% have *EWSR1-CREB3L1***
? 30-40% have *FUS* rearrangement
(some with *CREB3L1* or *CREB3L2*)

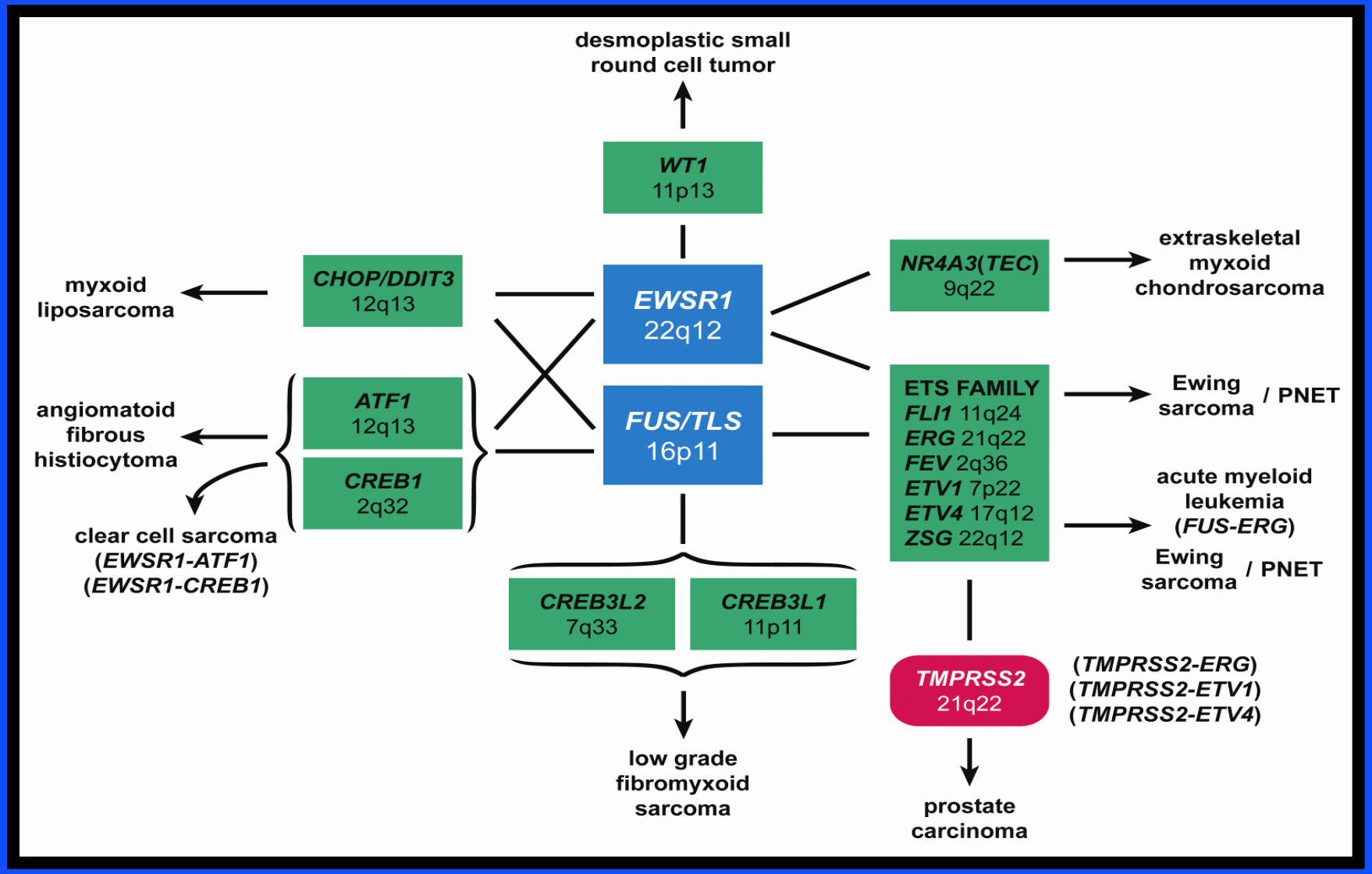
MUC4 -ve – Usually lack *FUS* or *EWSR1* alteration

HYBRID LGFMS/SEF

All are MUC4 +ve – Most have either *FUS* or *EWSR1* rearrangement
(usually with *CREB3L2* – similar to LGFMS)

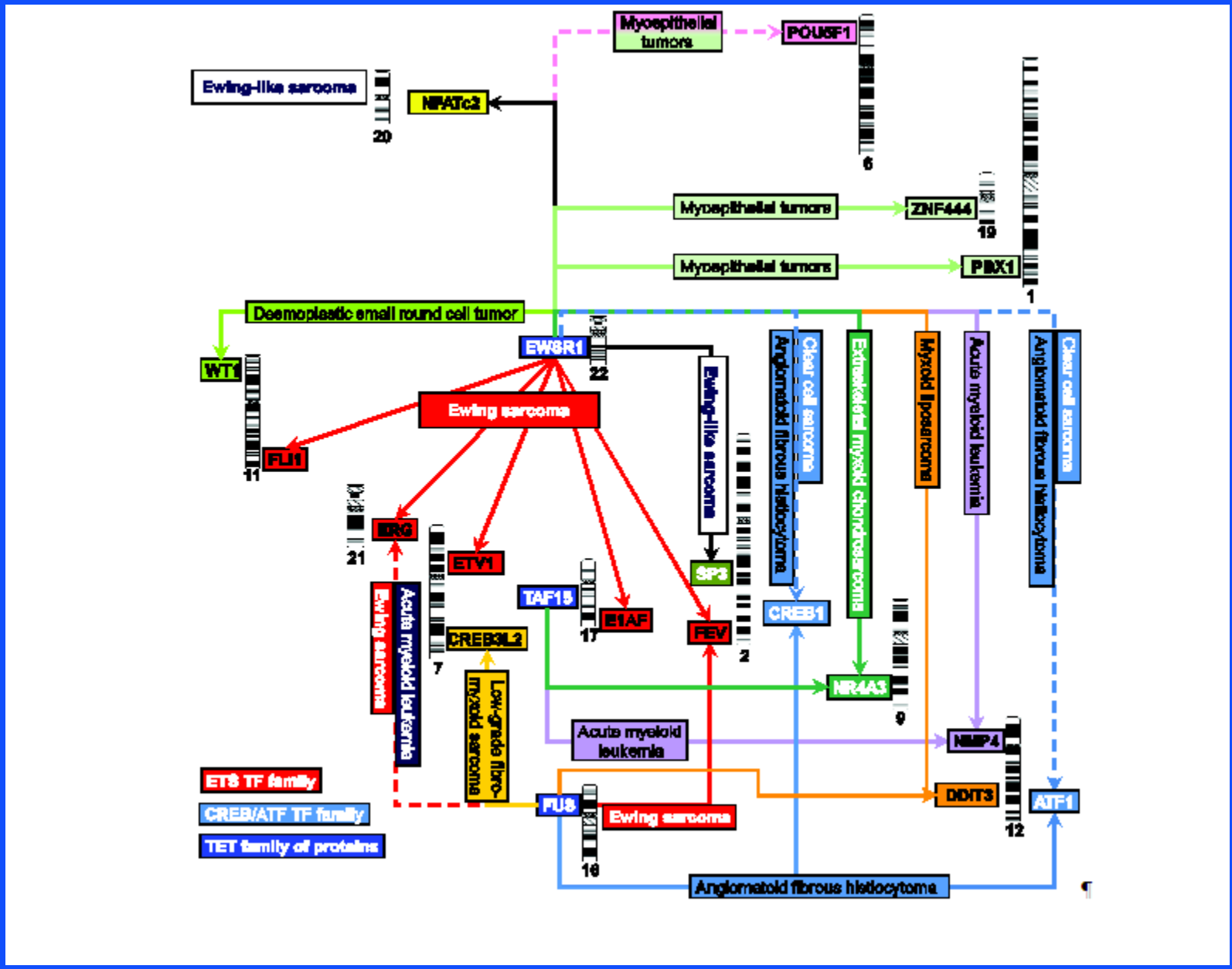
SOFT TISSUE TUMORS
TYPES OF GENETIC OVERLAP

- **Frequently involved genes in multiple different tumor types, e.g. *EWSR1*, *HMGA2***
- **Interchangeable genes in multiple distinct tumor types, e.g. *EWSR1* and *FUS***
- **Shared fusion genes in tumors thought to be distinct entities, e.g. *TGFBR3-MGEA5***
- **Shared fusion genes in tumors which appear totally unrelated, e.g. *EWSR1-ATF1***



Courtesy of Dr. Alex Lazar, MDACC (2008)

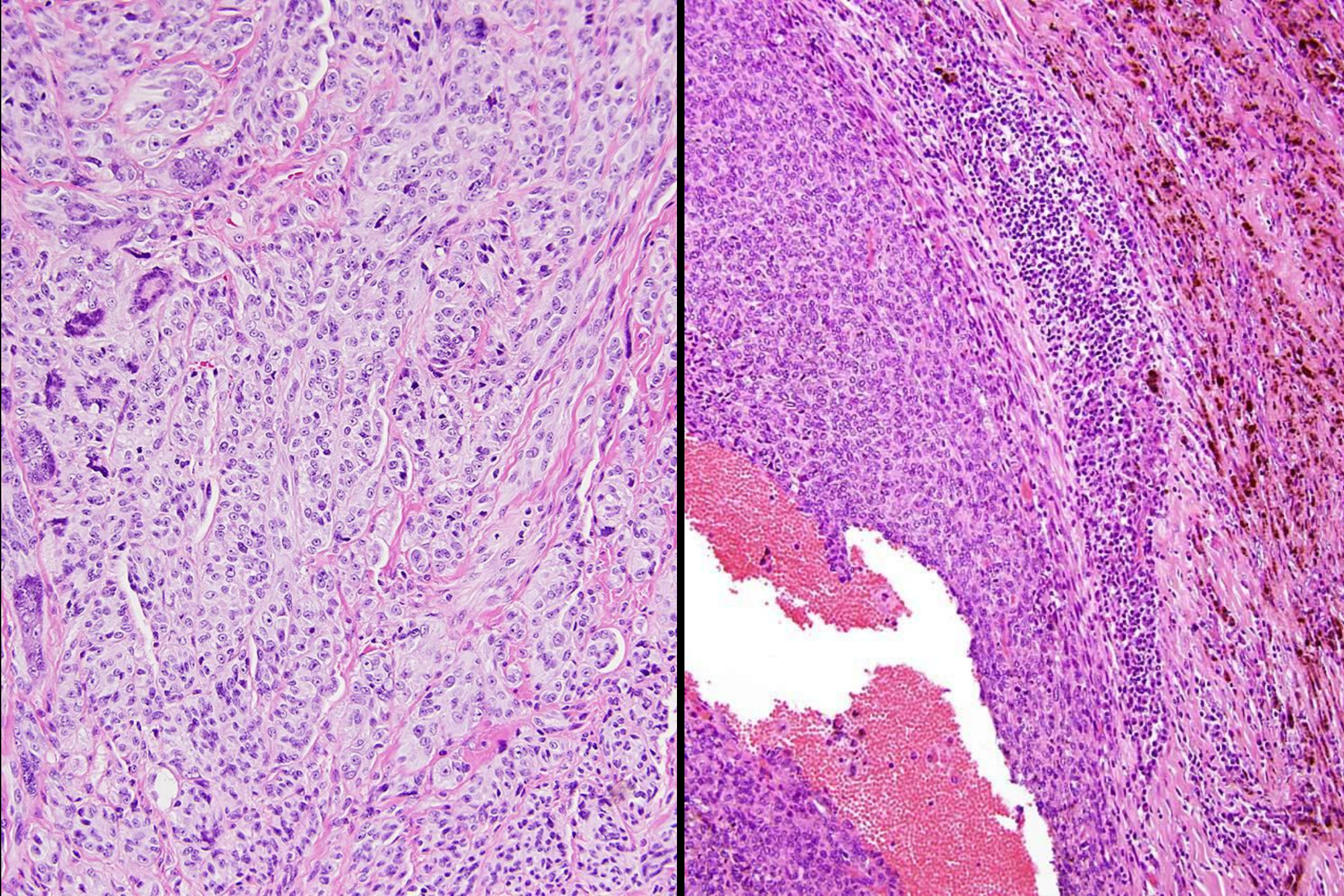
SHARED FUSION GENES IN SOFT TISSUE SARCOMAS



Szuhai & Bovee, 2012

ETV6-NTRK3

- **Infantile fibrosarcoma**
- **Cellular mesoblastic nephroma**
- **Secretory carcinoma of breast (and salivary gland)**
- **Rare cases of AML, CML &ALL**
- **Radiation-assoc^{d} thyroid carcinomas**



EWSR1-ATF1
EWSR1-CREB1

- **Clear cell sarcoma**

- **“Melanocytic”**
- **Deep soft tissue/GI**
- **Adults (mainly young)**
- **> 50% metastasise**

- **Angiomatoid “MFH”**

- **Lineage unknown**
- **?? dendritic cell**
- **Mostly subcutaneous**
- **Commonest < 20 years**
- **< 2% metastasise**

SOFT TISSUE SARCOMAS
WHAT ARE THE REAL ISSUES ?

- **Low case numbers except in major centers**
- **Rare/‘orphan’ disease - funding implications**
- **Many (~ 50) distinct tumor types**
- **Still often 1st treated by non-specialists (USA is worse than Europe in this regard)**
- **Treating metastatic disease is tough**

SOFT TISSUE SARCOMAS
WHAT ARE THE OTHER CURRENT ISSUES?

- Societal expectations (mainly USA)
- Target hunting/NGS hype
- Proliferation of unvalidated lab testing
- “Personalized/genomic medicine”
- Definitions of improved survival
- Uneducated patient demands/mass delusion
- Cost

Original specimen collection date - 05/30/2014

Original pathologic diagnosis - Pleomorphic Malignant Spindle Cell Neoplasm

Estimated percentage of neoplastic cells in submitted specimen - 80%

RESULTS:

There are 5685143 unique, aligned, high-quality reads for this specimen with a mean of 136 reads across all targeted exons and 95% of all exons having more than 30 reads.

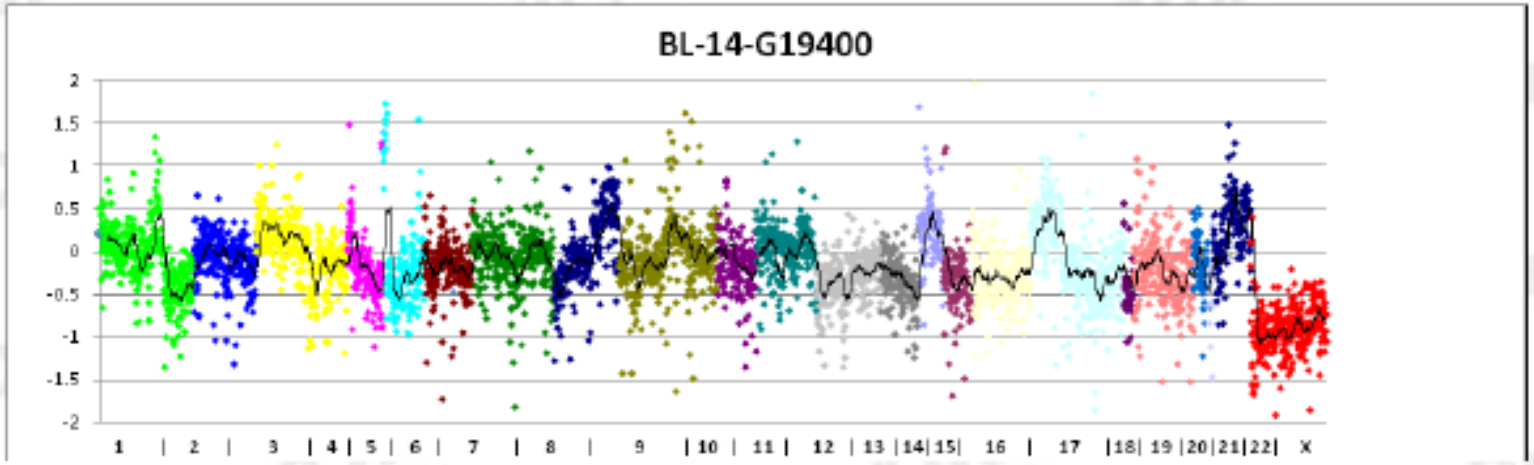


Figure legend: Plot of copy number variation by chromosomes which are color-coded. Sex chromosomes are excluded from the analysis. The vertical axis is the ratio of number of reads for this specimen and a panel of normals in log base 2 scale. A value of 0 denotes no difference from normal (diploid). When the sample contains 100% tumor cells, a value of -1 equals to 1 copy loss and 0.58 is 1 copy gain. The sensitivity and specificity of copy number variation evaluation by next-generation sequencing is affected by several factors, including the tumor percentage, ploidy, clonal heterogeneity, and the GC content of the gene of interest. For example, a sample with 20% tumor cells having a 5-copy amplification of a gene is indistinguishable from a sample with 100% tumor cells with 1 copy gain of the same gene. Confirmation of the copy number variation findings by Next-Gen Sequencing with a different testing platform is recommended.

DNA VARIANTS:

See Background section for tier definitions

Tier 1 variants: None identified.

Tier 2 variants:

CDKN2A c.172C>T (p.R58), exon 2* - in 41% of 29 reads *

TP53 c.527G>T (p.C176F), exon 5 - in 53% of 242 reads *

Tier 3 variants: None identified.

Tier 4 variants:

ABL1 c.1879C>T (p.Q627), exon 11* - in 36% of 98 reads ***
ALOX12B c.1657T>C (p.F553L), exon 13 - in 14% of 116 reads ***
ARID1A c.4337G>A (p.R1446Q), exon 18 - in 24% of 129 reads ***
B2M c.218_223ACTTGT>A (p.D73fs), exon 2 - in 38% of 214 reads ***
BCL6 c.739T>A (p.L247M), exon 5 - in 47% of 155 reads ***
CARD11 c.3398G>A (p.R1133H), exon 25 - in 51% of 130 reads ***
CDK5 c.649C>T (p.R217), exon 9* - in 12% of 73 reads ***
CRTC2 c.1561G>A (p.G521S), exon 12 - in 10% of 88 reads ***
EPHA5 c.1823C>T (p.S608F), exon 9 - in 21% of 70 reads ***
EPHA7 c.2560C>T (p.R854C), exon 15 - in 27% of 159 reads ***
EXT1 c.622_623GG>AA (p.G208K), exon 1 - in 47% of 269 reads ***
FANCA c.2443C>T (p.P815S), exon 26 - in 42% of 100 reads ***
FLCN c.49C>T (p.R17C), exon 4 - in 46% of 82 reads ***
FLT4 c.3308T>A (p.L1103H), exon 24 - in 32% of 52 reads ***
KDM6B c.2591C>T (p.S864F), exon 11 - in 15% of 45 reads ***
KDR c.271C>T (p.P91S), exon 3 - in 19% of 134 reads ***
MLH1 c.2141G>T (p.W714L), exon 19 - in 62% of 230 reads ***
MYC c.131C>T (p.A44V), exon 2 - in 47% of 160 reads ***
NBN c.1604C>T (p.S535F), exon 11 - in 22% of 341 reads ***
NF1 c.1682G>A (p.W561), exon 15* - in 23% of 94 reads ***
NOTCH1 c.1093C>T (p.R365C), exon 6 - in 26% of 42 reads ***
NOTCH1 c.3145C>T (p.Q1049), exon 19* - in 57% of 19 reads ***
NOTCH1 c.6950G>A (p.G2317D), exon 34 - in 18% of 64 reads ***
NTRK1 c.2203G>A (p.E735K), exon 16 - in 54% of 98 reads ***
PIK3C2B c.1417C>T (p.R473W), exon 7 - in 24% of 113 reads ***
PMS1 c.2686G>A (p.D896N), exon 13 - in 35% of 186 reads ***
PRKCZ c.1490_1491CC>TT (p.P497L), exon 16 - in 17% of 52 reads ***
PRKCZ c.1653G>C (p.Q551H), exon 17 - in 33% of 133 reads ***
RAD21 c.1570G>C (p.E524Q), exon 12 - in 45% of 267 reads ***
SETD2 c.6314A>C (p.K2105T), exon 15 - in 65% of 139 reads ***
STK11 c.1072G>A (p.D358N), exon 8 - in 12% of 83 reads ***
SUZ12 c.620C>T (p.P207L), exon 7 - in 25% of 125 reads ***
TERT c.2915G>A (p.R972H), exon 12 - in 4% of 224 reads ***

NEGATIVE for mutations in the following genes with clinical relevance for this tumor type: *APC*, *BRAF*, *EGFR*, *KRAS*, *MET*

COPY NUMBER VARIATIONS:

1q25.1	RFWD2	Single copy deletion
1q31.2	CDC73	Single copy deletion
1q32.1	PIK3C2B	Single copy deletion
1q32.1	MDM4	Single copy deletion
1q42.12	H3F3A	Single copy deletion
1q43	FH	Single copy deletion
1q43	AKT3	Single copy deletion
5p15.33	TERT	Low copy number gain
10q21.2	CDK1	Low copy number gain
10q22.1	PRF1	Low copy number gain
22q12.2	EWSR1	Low copy number gain
22q12.2	NF2	Low copy number gain
22q13.2	EP300	Low copy number gain

Chromosomal Rearrangement:

No structural variants were detected in any of the genes tested. Note that many structural rearrangements are associated with DNA changes in introns, and the ability of this test to detect these rearrangements is limited to selected portions of selected introns of only 30 genes (see list below). Therefore, the absence of a rearrangement by this method is not a definitive result, and requires confirmation by an alternative method (e.g., FISH or karyotype) in the appropriate clinicopathologic context.

SOFT TISSUE SARCOMAS
VALIDATED THERAPEUTIC TARGETS

KIT

ALK

MDM2/CDK4

IGF1R

? MTOR

? MET

AND...

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators

Summary

Background Molecularly targeted agents have been reported to have anti-tumour activity for patients whose tumours harbour the matching molecular alteration. These results have led to increased off-label use of molecularly targeted agents on the basis of identified molecular alterations. We assessed the efficacy of several molecularly targeted agents marketed in France, which were chosen on the basis of tumour molecular profiling but used outside their indications, in patients with advanced cancer for whom standard-of-care therapy had failed.

Lancet Oncol 2015

Published Online
September 3, 2015
http://dx.doi.org/10.1016/S1470-2045(15)00188-6

See Online/Comment

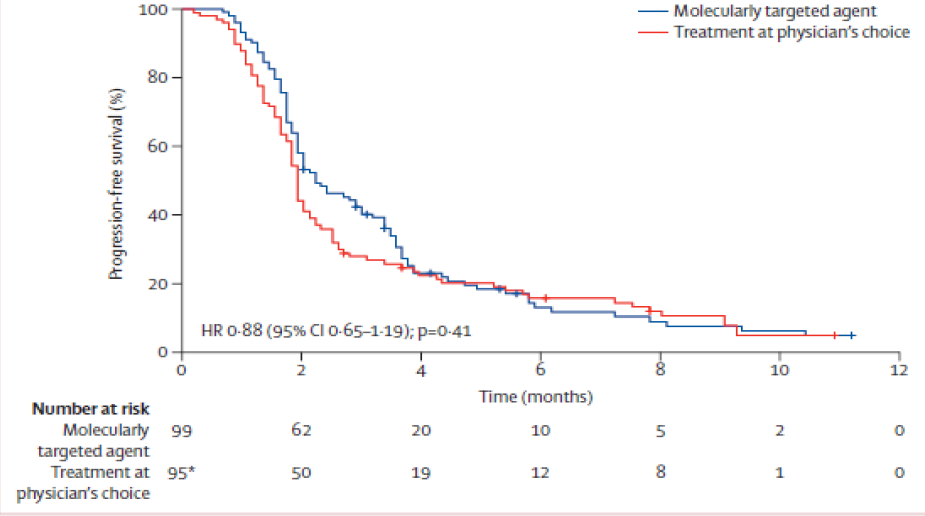


Figure 3: **Progression-free survival**
*One patient had a follow-up of zero days so is not shown here.

JAMA Oncology

Original Investigation | July 2015

Whole-Exome Sequencing of Metastatic Cancer and Biomarkers of Treatment Response FREE

Himisha Beltran, MD[1,2,3]; Kenneth Eng, MS[1,4]; Juan Miguel Mosquera, MD[1,5]; Alexandros Sigaras, MS[1]; Alessandro Romanel, PhD[6]; Hanna Rennert, MD[5]; Myriam Kossai, MD[1,5]; Chantal Pauli, MD[1,5]; Bishoy Faltas, MD[2]; Jacqueline Fontugne, MD[1,5]; Kyung Park, MD[5]; Jason Banfelder, MCh.E[1,4]; Davide Prandi, PhD[6]; Neel Madhukar, BS[1,4]; Tuo Zhang, PhD[1,4]; Jessica Padilla, MA[1]; Noah Greco, MBA[1]; Terra J. McNary, BA[1]; Erick Herrscher, BA[1]; David Wilkes, PhD[1]; Theresa Y. MacDonald, BS[5]; Hui Xue, PhD[7]; Vladimir Vacic, PhD[8]; Anne-Katrin Emde, PhD[8]; Dayna Oschwald, PhD[8]; Adrian Y. Tan, MD[1]; Zhengming Chen, PhD, MPH[9]; Colin Collins, PhD[6]; Martin E. Gleave, MD[6]; Yuzhuo Wang, PhD[6]; Dimple Chakravarty, PhD[5]; Marc Schiffman, MD[10]; Robert Kim, BS[1,4]; Fabien Campagne, PhD[4,11]; Brian D. Robinson, MD[1,6]; David M. Nanus, MD[2]; Scott T. Tagawa, MD[2]; Jenny Z. Xiang, MD[1]; Agata Smogorzewska, MD, PhD[12]; Francesca Demichelis, PhD[5,6]; David S. Rickman, PhD[1,5]; Andrea Sboner, PhD[1,4,5]; Olivier Elemento, PhD[1,4]; Mark A. Rubin, MD[1,5]

[+] Author Affiliations

JAMA Oncol. 2015;1(4):466-474. doi:10.1001/jamaoncol.2015.1313.

“A gene recurrently altered in a sarcoma subtype does not necessarily play a role in initiation or progression… identification of recurrent (genetic) lesions far outstrips our ability to test their importance. To determine involvement of a gene in sarcoma biology and credential it as a therapeutic target, systematic biologic validation in genetically defined models must follow.”

SOFT TISSUE SARCOMAS : WHAT IS THE GOLD STANDARD ?

SOFT TISSUE SARCOMAS : WHAT IS THE GOLD STANDARD ?

PATHOLOGY

SOFT TISSUE SARCOMAS
FUTURE GOALS

- **Better understand biology**
- **Better understand pathogenetic mechanisms**
- **Larger collaborative studies of single histotypes**
- **Prognostic schemes for individual histotypes**
- **More targeted therapies (hopefully…)**
- **Affordable, effective care**