The Pathology of GIST

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Relevance of Correct Classification

- Rationale of clinical decision making
- Prognosis
- Prediction of response
- Conventional morphology = powerful tool
- Integration with immunohistochemistry is a diagnostic standard
- Molecular genetics increasingly helpful in selected situations

Diagnostic Errors in Pathology of Sarcomas

- Clinical trials
  - 7-10%
- Second opinion
  - 15-35%
- Rare Cancer Networks
  - 5-40%

Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based study within three European regions

I. Ray-Coquard[1,2], M. C. Montesco[3], J. M. Coindre[4,5], A. P. Dei Tos[6], A. Lurkin[1,2], D. Ranchère-Vince[2], A. Vecchiato[3], A. V. Decouvelaere[2], S. Mathoulin-Pélissier[4,5,7], S. Albert[7], P. Cousin[2], D. Cellier[8], L. Toffolatti[6], C. R. Rossi[3,9] & J. Y. Blay[2,10] for the Conticanet group

[1]University Lyon, EAM 4129 Health Individual Society, Hôtel Dieu, Lyon; [2]Centre Léon Bérard, Lyon, France; [3]Veneto Institute of Oncology (IOV), IRCCS, Padova, Italy; [4]University Bordeaux Segalen; [5]INSERM U916, Bordeaux, France; [6]General Hospital of Treviso, Italy; [7]INSERM CIC-EC7 and Clinical and Epidemiological Research Unit, Institut Bergonié, Bordeaux; [8]Merck Serono, Lyon, France; [9]University of Padova, Italy; [10]NSERM U590 Cytokine and Cancer, Centre Léon Bérard, Lyon, France

Concordance	Zero	Partial	Full	*P*
Included tumors[a]	104	515	814	
Type of laboratory				
Public	40 (5%)	241 (32%)	477 (63%)	**<0.001**
Private	64 (9%)	274 (41%)	337 (50%)	
Included tumors[b]	119	518	820	
Type of tumor sample				
Biopsy	26 (9%)	110 (38%)	154 (53%)	0.47
Surgical specimen	93 (8%)	408 (35%)	666 (57%)	
Included tumors	51	409	449	
Grade				
I	18 (7%)	77 (30%)	164 (63%)	**<0.001**
II–III	33 (5%)	332 (51%)	285 (44%)	
Included tumors[c]	116	515	821	
Type of sarcoma				
Soft tissue	82 (9%)	323 (36%)	502 (55%)	**0.004**
Visceral	34 (6%)	192 (35%)	319 (59%)	
Included tumors	121	518	824	
Region				
Aquitaine	34 (10%)	148 (42%)	170 (48%)	**<0.001**
Rhone-Alpes	65 (10%)	252 (38%)	345 (52%)	
Veneto	22 (5%)	118 (26%)	309 (69%)	
Included tumors	121	518	824	
Subgroup analysis				
SO requested	71 (13%)	263 (47%)	230 (40%)	**<0.001**
No SO requested	50 (6%)	255 (28%)	594 (66%)	

Ann Oncol 2012;23:2442

Main challenges

- Correct diagnosis
  - Clinical findings
  - Morphology
  - Immunostains
  - Molecular analysis
- Differential diagnosis
- Interpretation of molecular results

Identification of KIT Gain-of-Function Mutations

Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

Science 279:577-580, 1998

- KIT staining was positive in 46 of 49 GIST (94%)
- 5 of 6 GIST had mutations in KIT gene
- Mutant forms of KIT are constitutively active

Hirota et al. Science. 1998;279:577.

The New England Journal of Medicine

Established in 1812 as The New England Journal of Medicine and Surgery

VOLUME 344 APRIL 5, 2001 NUMBER 14

Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

*Jaap Verweij, Paolo G Casali, John Zalcberg, Axel LeCesne, Peter Reichardt, Jean-Yves Blay, Rolf Issels, Allan van Oosterom, Pancras C W Hogendoorn, Martine Van Glabbeke, Rossella Bertulli, Ian Judson, for the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group**

Lancet 2004; 364: 1127–134

See **Comment** page 1101

*Study investigators listed at end f report

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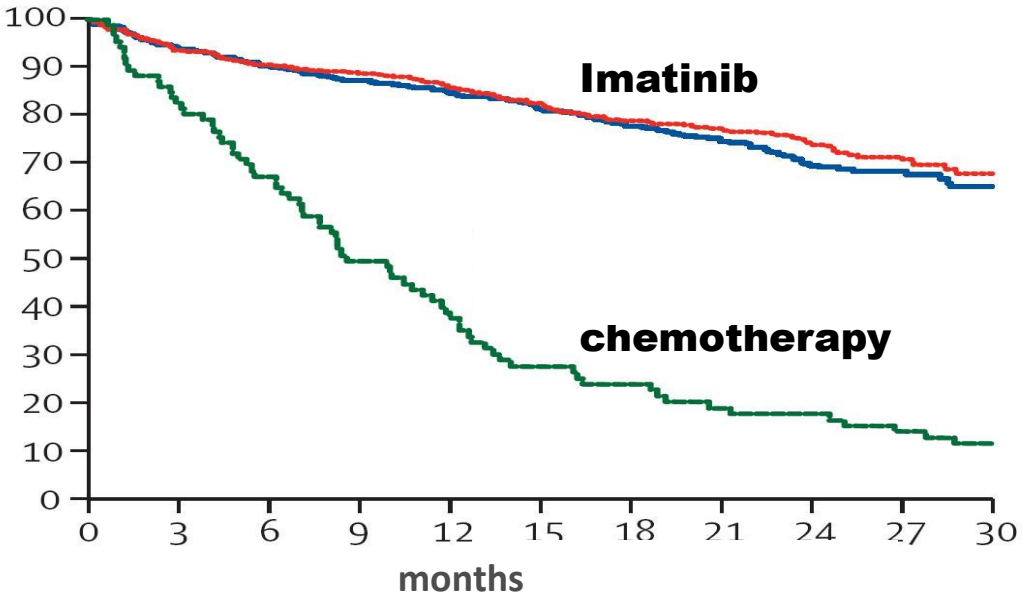

BIZARRE SMOOTH MUSCLE TUMORS OF THE STOMACH

ARTHUR PURDY STOUT, M.D.

WHEN the fascicle on Tumors of the Stomach of the *Atlas of Tumor Pathology*[1] was prepared by the writer, the subject of smooth muscle tumors seemed to necessitate only a description of the common benign and malignant varieties and an attempt to correct the relatively frequent error of calling smooth muscle tumors neurogenous simply because leiomyoblasts so frequently tend to palisade their nuclei. I was aware that smooth muscle tumors can sometimes assume very bizarre aspects but I hesitated to deal with this in detail because I thought it would necessitate an extensive and perhaps confusing discussion. This was a mistake that I have regretted because I have been consulted repeatedly by pathologists and surgeons who have been puzzled by growths in the stomach that they did not understand. The recent excellent paper by Martin et al.[8] dealing with 6 cases of bizarre intramural myoid tumors of the stomach finally persuaded me that it is time to present these tumors to the English speaking public and to try to determine whether they are benign or malignant tumors. In 1 of Martin et al.'s[8] cases the tumor was definitely malignant and metastasized, so that some of them must be malignant. But, because of this 1 case, is it proper to consider all of them malignant tumors, and are there any features that will permit one to recognize the biologically malignant ones from the others? This is an important aspect of the subject but it is also important to try to rescue these tumors from the extraordinarily varied ideas about them that have been expressed by pathologists who have seen sections of the tumors reported herewith. In Table 1 will be found a list of these diagnoses. It is quite obvious from this that in only 30 of the 108 diagnoses suggested was it realized that these were smooth muscle tumors and among the 30 there was a sharp division of opinion as to whether they were benign or malignant.

REVIEW OF THE LITERATURE

Martin et al.[8] observed that case 13, called questionable leiomyosarcoma of the stomach

From the Laboratory of Surgical Pathology, Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York 32, N.Y.

The following physicians contributed the cases and made every effort to furnish follow-up information. The author is greatly indebted to them for their co-operation.

Dr. H. W. Louria, Brooklyn, N.Y., case 1; Col. F. M. Townsend, Armed Forces Institute of Pathology, Washington, D.C., case 2; Dr. V. G. Brekke, Highland Park, Mich., case 3; Dr. S. M. Rabson, Fort Wayne, Ind., case 4; Dr. N. Block, Glen Cove, N.Y., case 5; Dr. E. W. Gray, W. Brentwood, N.Y., case 6; Dr. I. V. Ackerman and Dr. W. J. Holaday, St. Louis, Mo., cases 7 and 17; Dr. G. S. Mahon, Knoxville, Tenn., case 8; Dr. D. Magner, Ottawa, Ontario, Canada, and Dr. H. A. Bird, St. John, New Brunswick, Canada, case 9; Dr. W. N. Campbell, Chester, Pa., case 10; Dr. E. R. Marino, Brooklyn, N.Y., case 11; Dr. H. Subin and Dr. H. Ackerman, Atlantic City, N.J., case 12; Dr. H. Fischer, Clarksburg, W. Va., cases 13 and 31; Dr. G. Fine and Dr. J. P. O'Connell, Portsmouth, Va., case 14; Dr. J. D. Bauer, St. Louis, Mo., case 15; Dr. G. Fine, Portsmouth, Va., case 16; Dr. F. C. Coleman, Des Moines, Iowa, case 18; Dr. P. Kimmelstiel, Milwaukee, Wis., case 19; Dr. M. C. Bracken, Pittsburgh, Pa., case 20; Dr. P. Flynn, Redding, Calif., case 21; Dr. G. L. Wiltse, Wahpeton, N. Dak., case 22; Dr. E. F. Koster, Cleveland, Ohio, case 23; Dr. S. H. Polayes, Brooklyn, N.Y., case 24; Dr. S. Hanson, Edmonton, Alberta, Canada, case 25; Dr. C. Solomon, New York, N.Y., case 26; Dr. A. S. Ralston, New Orleans, La., case 27; Dr. J. A. Schaefer, Syracuse, N.Y., cases 28 and 57; Dr. F. H. Langley, St. Petersburg, Fla., case 29; Dr. S. Wood, Jr., Baltimore, Md., case 30; Dr. O. Leary, Jr., Boston, Mass., case 32; Dr. J. B. Tully, Long Beach, Calif., case 33; Dr. L. Rappaport, Brooklyn, N.Y., case 34; Dr. R. W. Huntington, Jr., Bakersfield, Calif., cases 35 and 65; Dr. D. R. Meranze, Philadelphia, Pa., case 36; Dr. M. M. Rice, Santa Ana, Calif., case 37; Dr. R. L. Cabrini, Buenos Aires, Argentina, case 38; Dr. S. Robbins, Boston, Mass., case 39; Dr. W. F. Eisenstaedt, Chicago, Ill., case 40; Dr. P. Jernstrom and Dr. P. A. Herbut, Philadelphia, Pa., case 41; Dr. R. S. Totten, Pittsburgh, Pa., case 42; Dr. A. Santamaria, Bogota, Colombia, case 43; Dr. J. R. Gillis, Youngstown, Ohio, case 44; Dr. M. E. Cox, Waterbury, Conn., case 45; Dr. W. Lochte, Montgomery, Ala., case 46; Dr. R. P. Saunders, Grand Junction, Colo., and Dr. R. E. Benitez, St. Louis, Mo., case 47; Dr. J. L. Heard, San Diego, Calif., case 48; Dr. R. R. Williams, Middletown, Ohio, case 49; Dr. P. M. Marcuse, Houston, Texas, case 50; Dr. E. Lichtenberger, Bogota, Colombia, case 51; Dr. A. Valdes-Dapena, Philadelphia, Pa., case 52; Dr. B. K. Black, Vincennes, Ind., case 53; Dr. V. Scortecci, Milan, Italy, case 54; Dr. J. A. Forestiere, Denville, N.J., case 55; Dr. K. E. Fry, Philadelphia, Pa., case 56; Dr. M. E. Rubnitz, Hines, Ill., case 58; Dr. R. F. Dillon, Colorado Springs, Colo., case 59; Dr. A. Laufer, Jerusalem, Israel, case 60; Dr. J. Valaitis and Dr. J. J. Raoul, Chicago, Ill., case 61; Dr. R. C. Ross, Toronto, Ontario, Canada, case 62; Dr. J. C. Ehrlich and Dr. I. M. Ratner, New York, N.Y., case 63; Dr. P. I. Lewis, Philadelphia, Pa., case 64; Dr. C. Siderides, Stamford, Conn., case 66; Dr. J. J. Moran, Philadelphia, Pa., case 67; Dr. W. F. Enos, Arlington, Va., and Dr. C. F. Geschickter, Washington, D.C., case 68; Dr. M. Kannerstein, Newark, N.J., case 69.

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Arthur Purdy Stout

Tumeurs myoïdes intra-murales de l'estomac

Considérations microscopiques à propos de 6 cas

PAR MM.

J. F. MARTIN, P. BAZIN, J. FÉROLDI et F. CABANNE

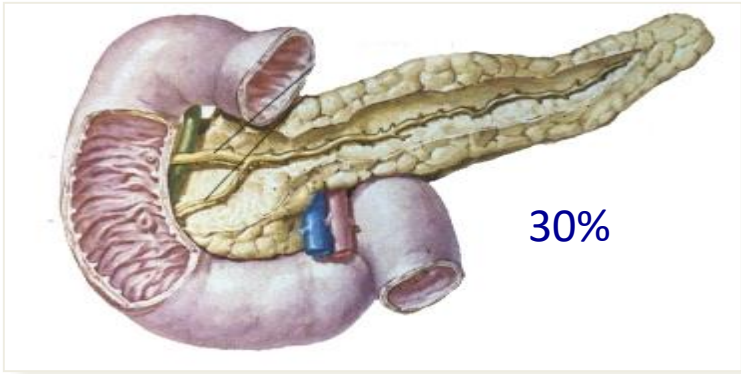
(Lyon-Dijon)

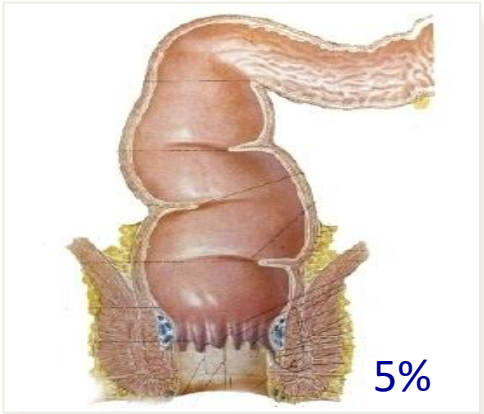
Depuis plusieurs années nous sommes intrigués par de curieuses tumeurs gastriques dont la description exacte n'a pas encore été donnée à notre connaissance, dans les nombreuses publications consacrées aux néoplasmes épithéliaux, mésenchymateux ou nerveux de l'estomac que nous avons pu consulter. Nous en possédons six cas, suffisamment comparables sous l'angle microscopique, pour qu'il nous paraisse justifié d'en indiquer les traits histo-pathologiques les plus marquants, en une revue d'ensemble.

Une telle revue sera naturellement précédée d'un bref aperçu clinique puis macroscopique de notre matériel d'études. Quelques commentaires pathogéniques et histogénétiques lui feront suite.

Martin JF et al. Ann Anat Path. 1960 5:484

GIST: anatomic sites





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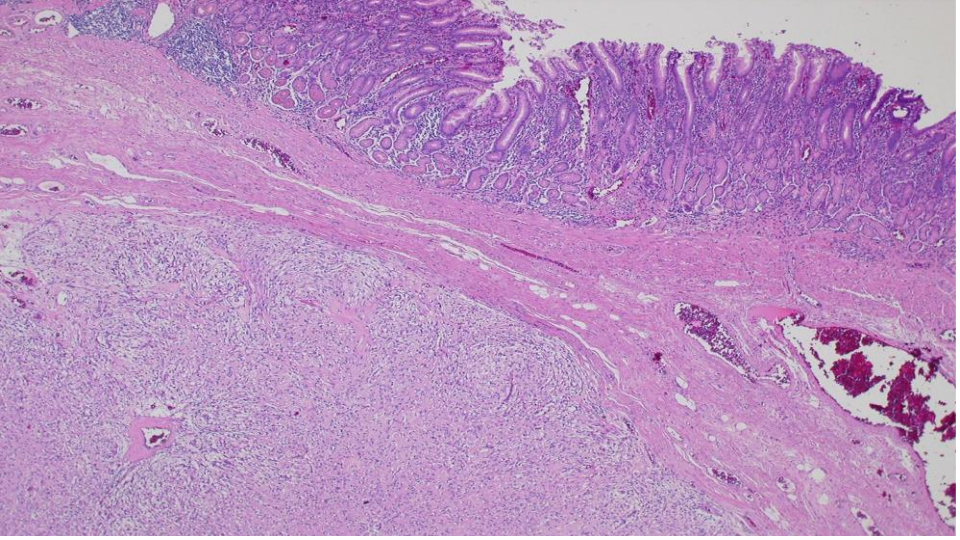
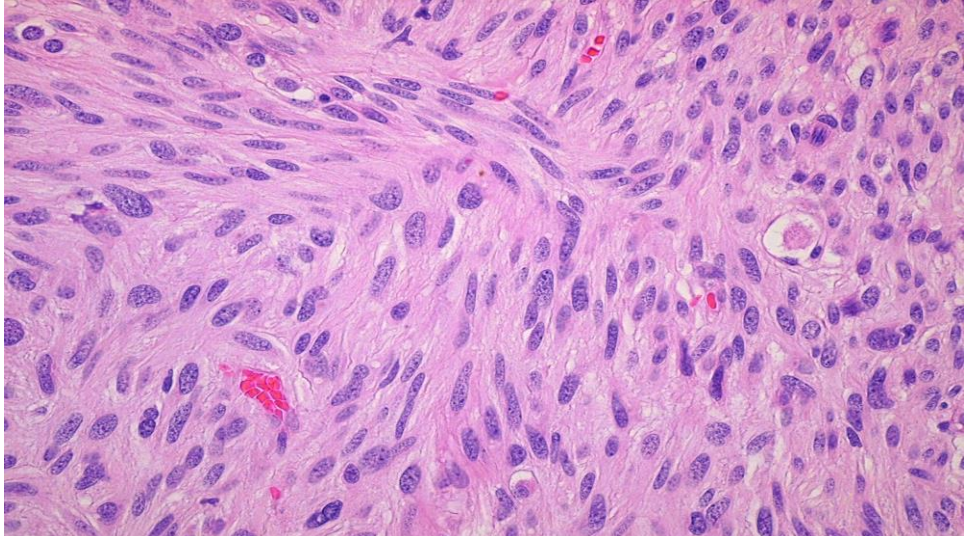
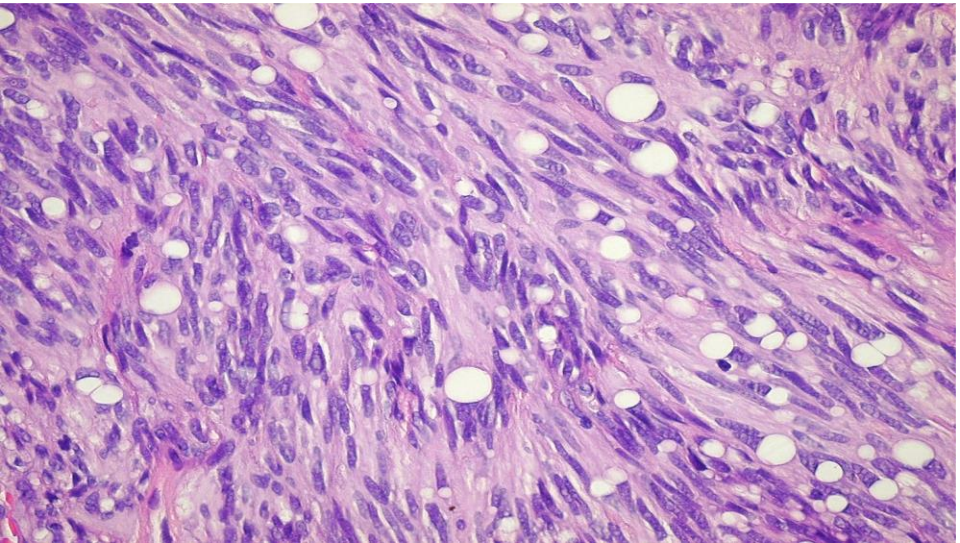
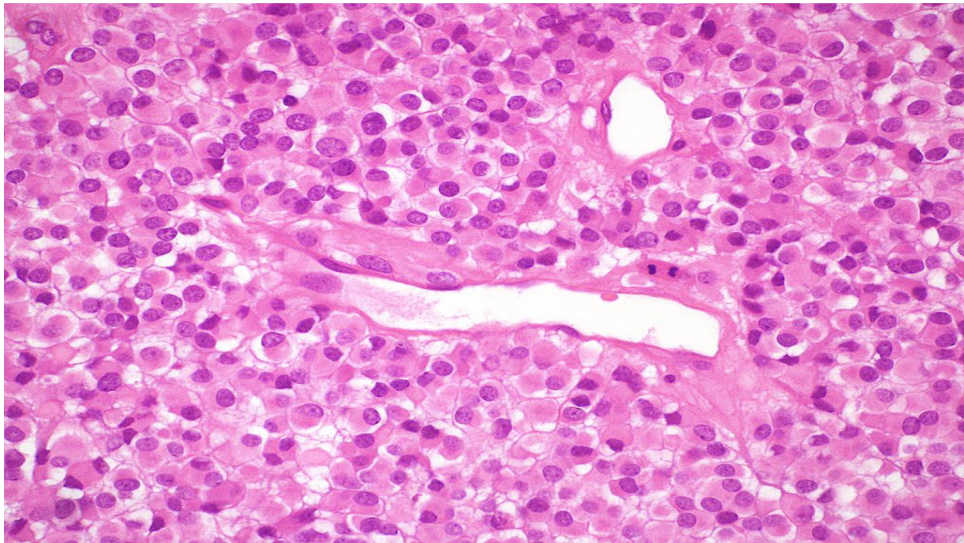
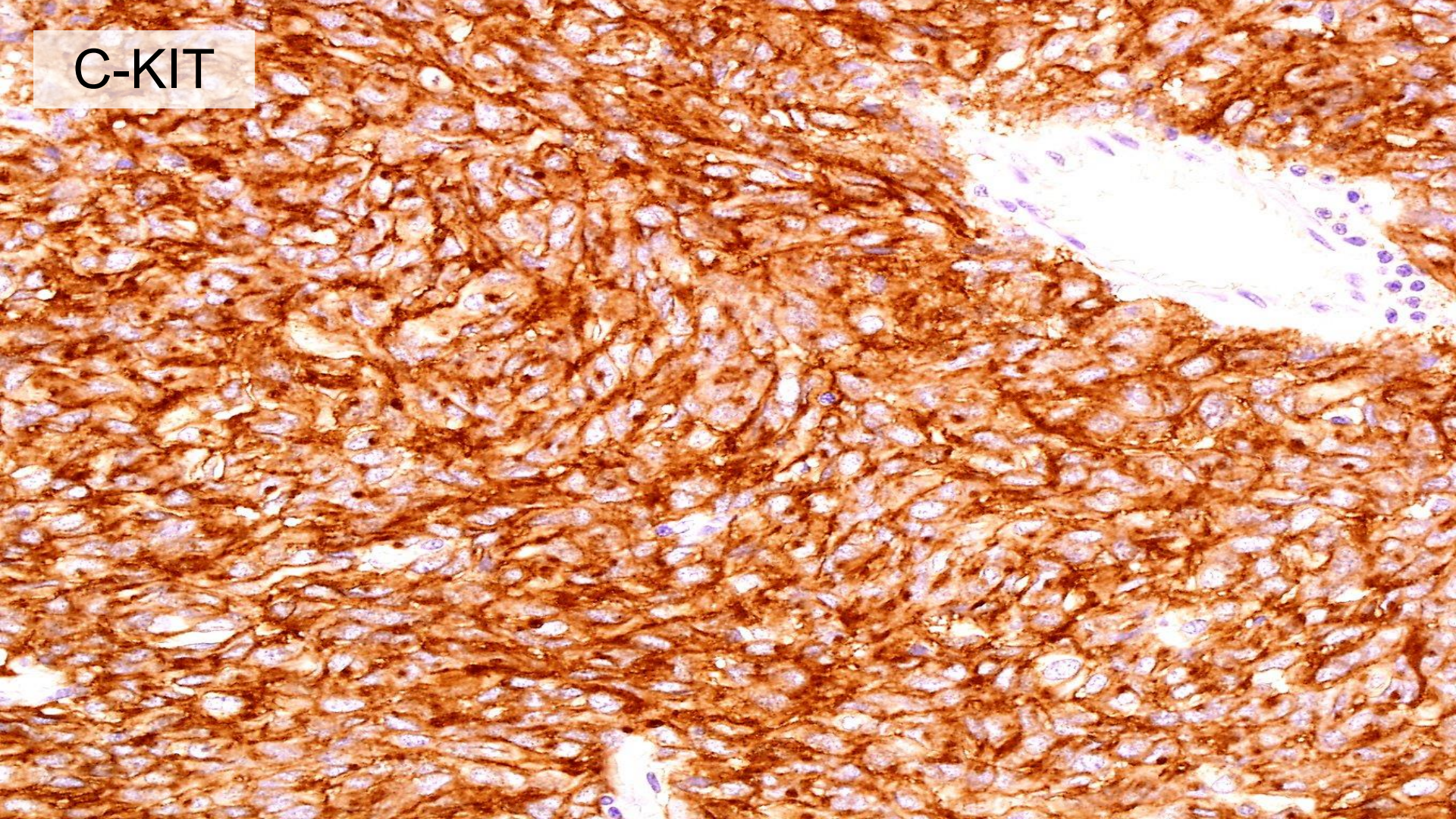






C-KIT

American Journal of Pathology, Vol. 165, No. 1, July 2004

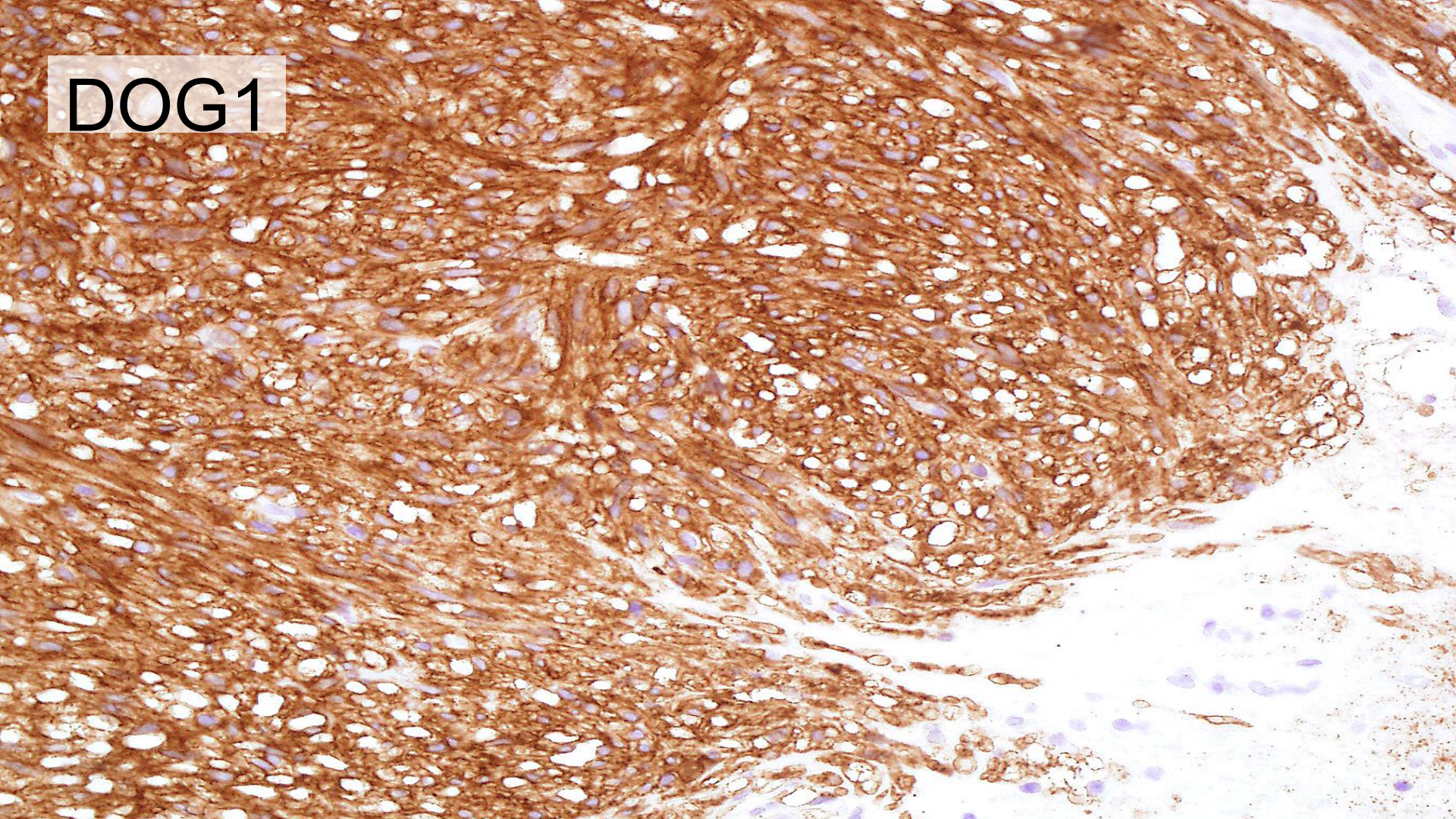
The Novel Marker, *DOG1*, Is Expressed Ubiquitously in Gastrointestinal Stromal Tumors Irrespective of *KIT* or *PDGFRA* Mutation Status

Robert B. West,* Christopher L. Corless,† Xin Chen,‡ Brian P. Rubin,§ Subbaya Subramanian,* Kelli Montgomery,* Shirley Zhu,* Catherine A. Ball,¶ Torsten O. Nielsen,‖ Rajiv Patel,** John R. Goldblum,** Patrick O. Brown,‡§§ Michael C. Heinrich,†† and Matt van de Rijn*

Histopathology 2010, **57**, 259–270. DOI: 10.1111/j.1365-2559.2010.03624.x

DOG1 and CD117 are the antibodies of choice in the diagnosis of gastrointestinal stromal tumours

Marco Novelli,[1]* Sabrina Rossi,[2]* Manuel Rodriguez-Justo,[1] Philippe Taniere,[3] Beatrice Seddon,[4] Luisa Toffolatti,[2] Chiara Sartor,[2] Pancras C W Hogendoorn,[5] Raf Sciot,[6] Martine Van Glabbeke,[7] Jaap Verweij,[8] Jean Yves Blay,[9] Peter Hohenberger,[10] Adrienne Flanagan[1] & Angelo P Dei Tos[2]

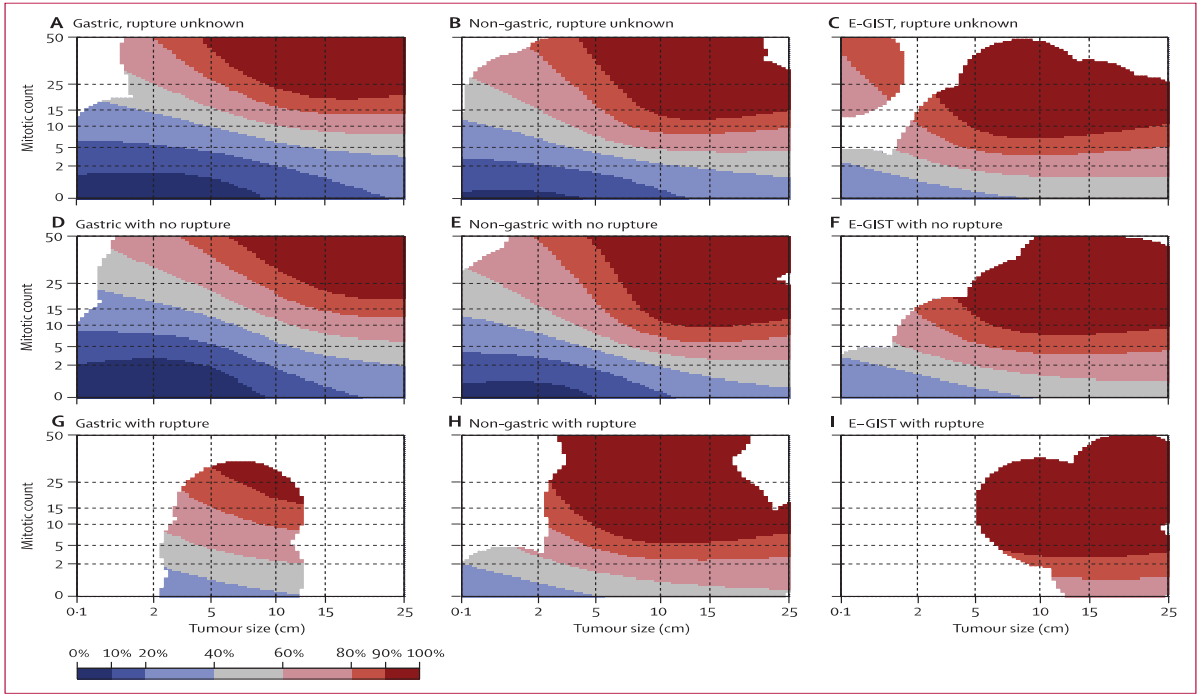

DOG1

How to Predict Behavior

- Combination of grading and staging
- Grading refers to the morphology of the tumor
- Staging refers to the extent of the disease
- Miotic activity, size, anatomic site, intrabdominal rupture
- Molecular status

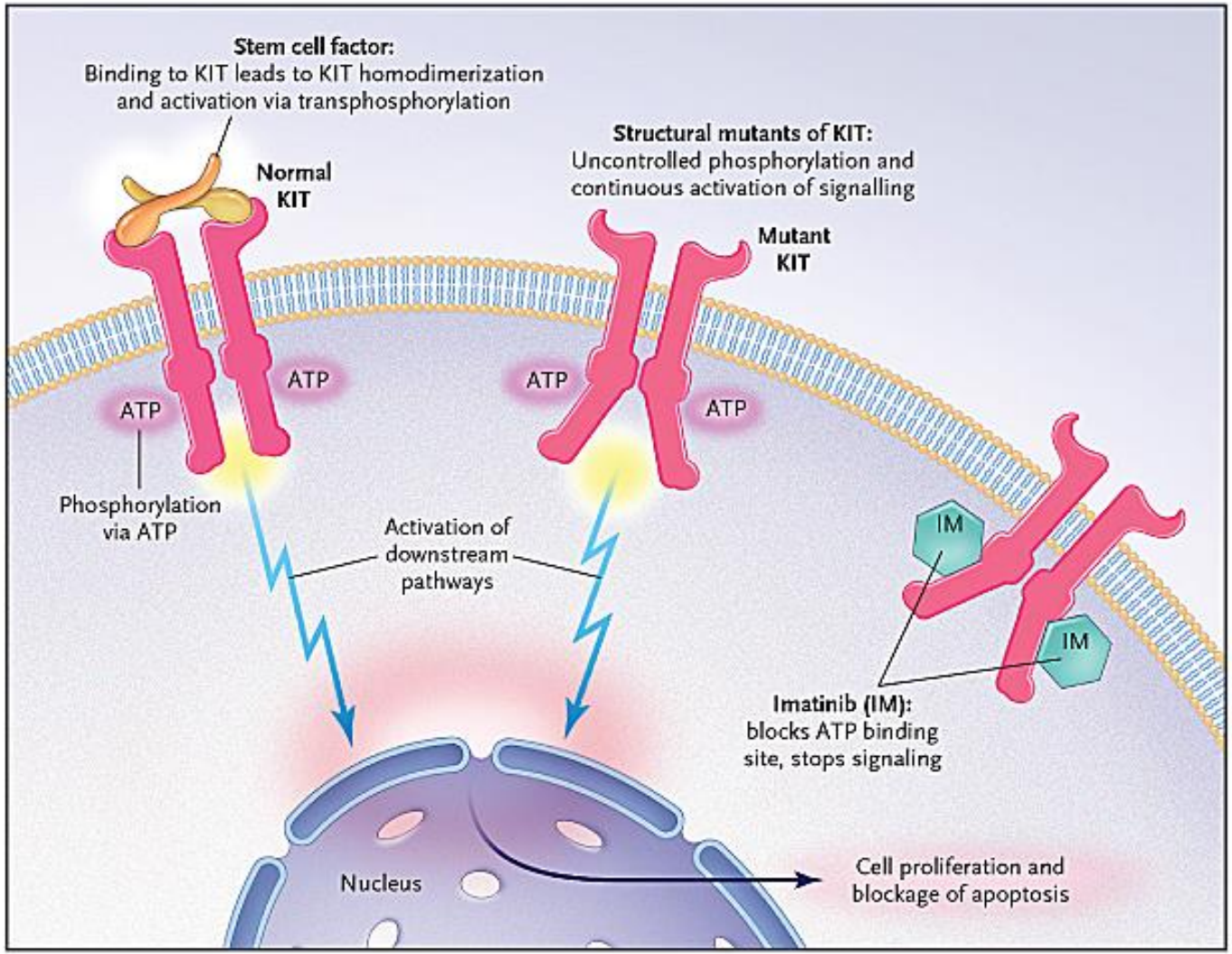
Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts

Heikki Joensuu, Aki Vehtari, Jaakko Riihimäki, Toshirou Nishida, Sonja E Steigen, Peter Brabec, Lukas Plank, Bengt Nilsson, Claudia Cirilli, Chiara Braconi, Andrea Bordoni, Magnus K Magnusson, Zdenek Linke, Jozef Sufliarsky, Massimo Federico, Jon G Jonasson, Angelo Paolo Dei Tos, Piotr Rutkowski

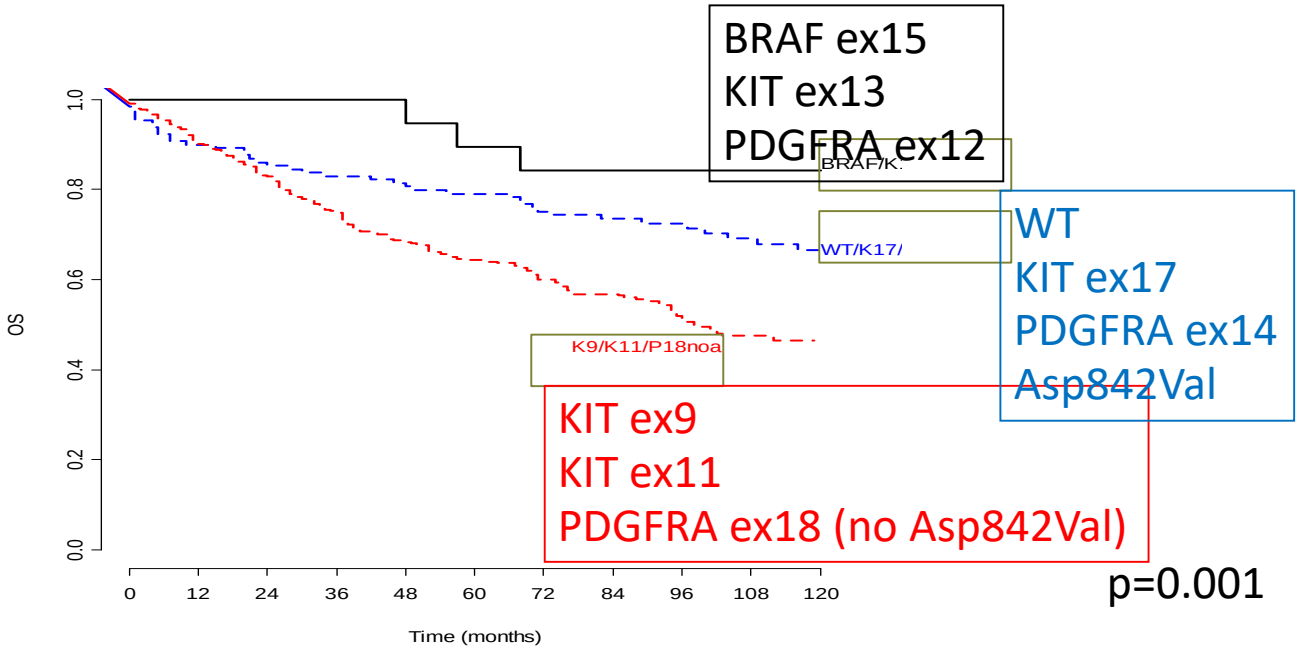


GIST is a heterogeneous disease

- KIT
- PDGFRA
- RAF
- NF1
- SDH
- NTRK3


Stem cell factor:
Binding to KIT leads to KIT homodimerization and activation via transphosphorylation
Normal KIT
Structural mutants of KIT:
Uncontrolled phosphorylation and continuous activation of signalling
Mutant KIT
ATP
ATP
ATP
ATP
Phosphorylation via ATP
Activation of downstream pathways
IM
IM
Imatinib (IM):
blocks ATP binding site, stops signaling
Nucleus
Cell proliferation and blockage of apoptosis

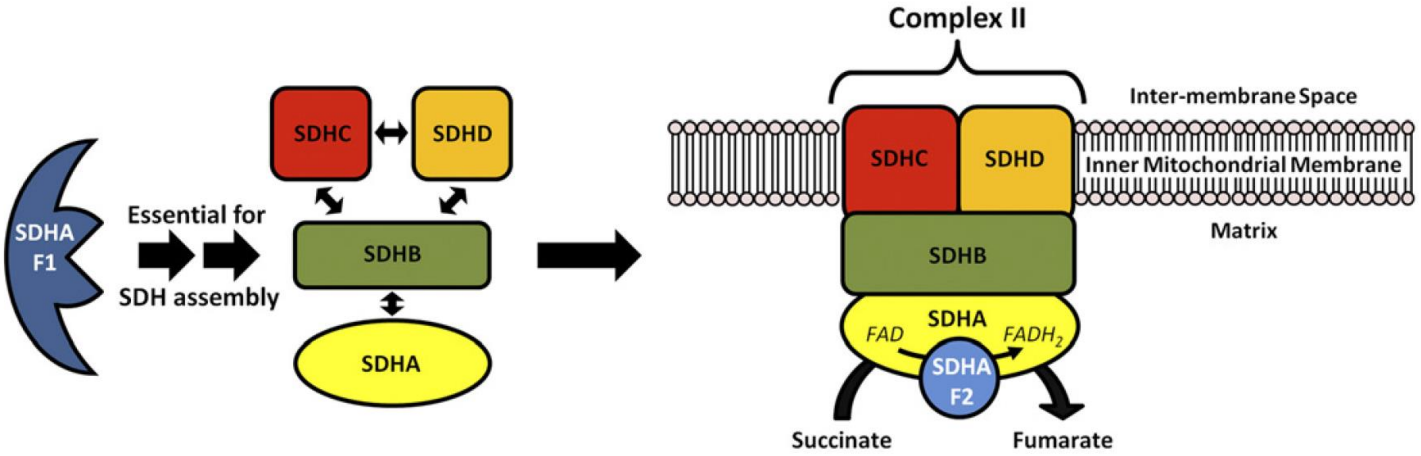
The molecular variable defines 3 prognostic subgroups



GISTs with Distinctive Architecture (Multinodular/Plexiform)

- Pediatric GISTs
  - Female predominance (peak 2nd decade)
  - Indolent, but late metastases common
  - Small subset with *SDH* mutations
  - Molecular genetic basis for most cases unknown
- Carney Triad
  - Gastric GIST, pulmonary chondroma, paraganglioma
  - Molecular genetic basis unknown
- Carney-Stratakis Syndrome
  - Gastric GIST and paraganglioma
  - Germline mutations in succinate dehydrogenase subunit genes

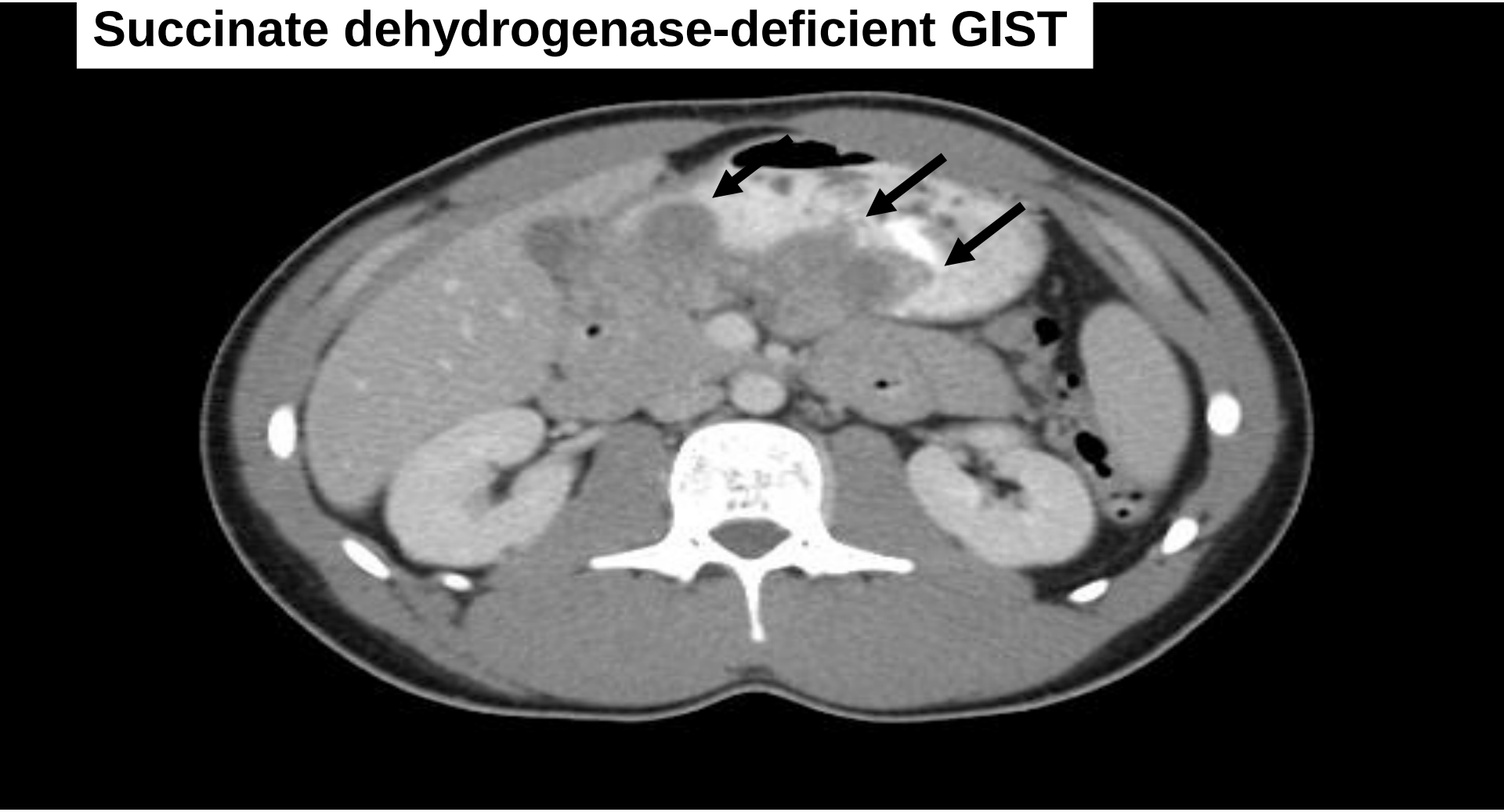
Succinate Dehydrogenase Complex

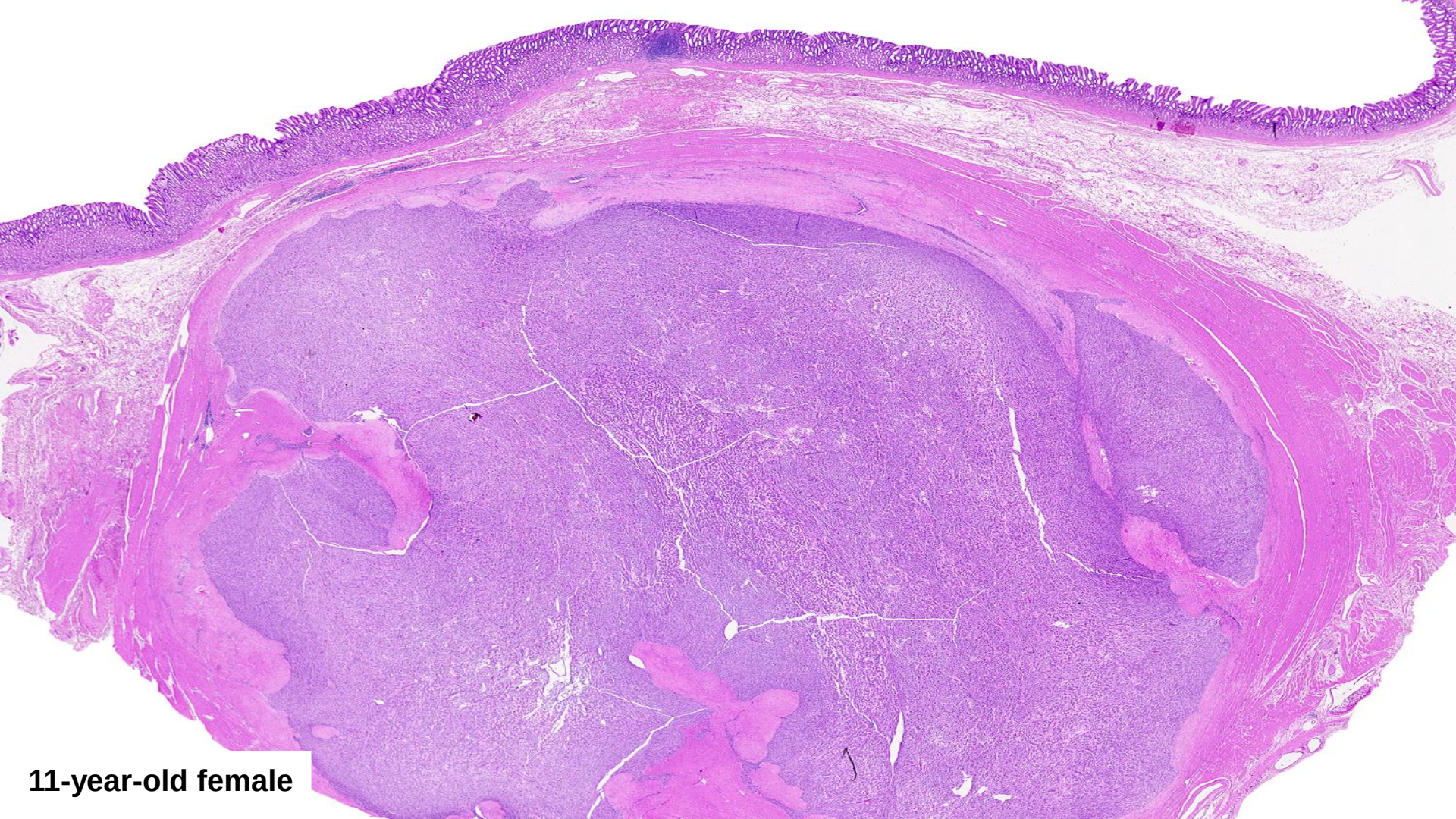


Succinate Dehydrogenase in GISTs

- IHC for SDHB: loss of normal cytoplasmic (mitochondrial) staining in Carney-Stratakis syndrome-associated GISTs
- Similar findings observed in pediatric, Carney triad-associated, and adult multinodular “wild-type” gastric GISTs
- IHC for SDHB is a good screening tool for identifying this clinically distinctive class of gastric GISTs: SDH-deficient GISTs

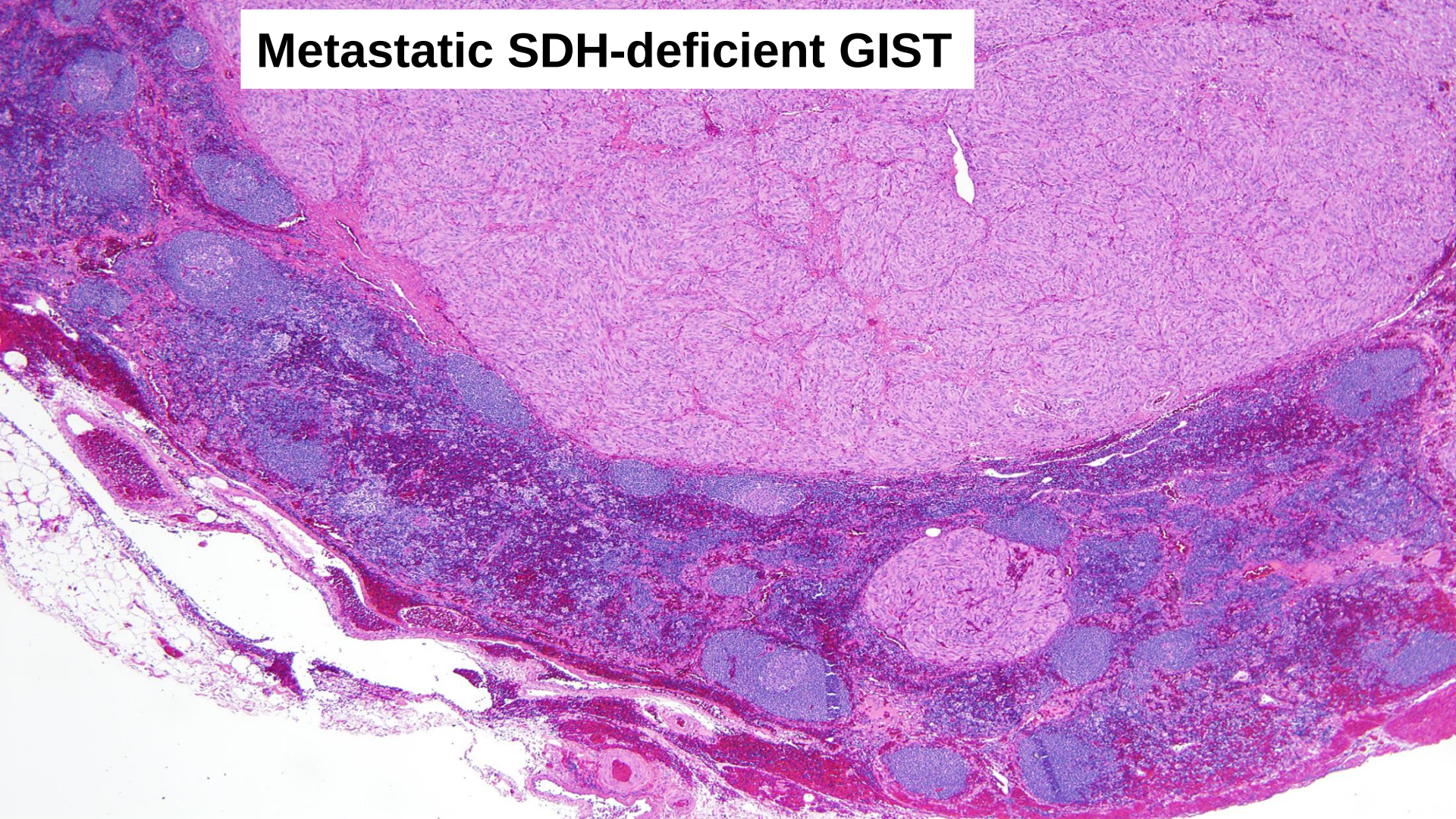
Succinate dehydrogenase-deficient GIST





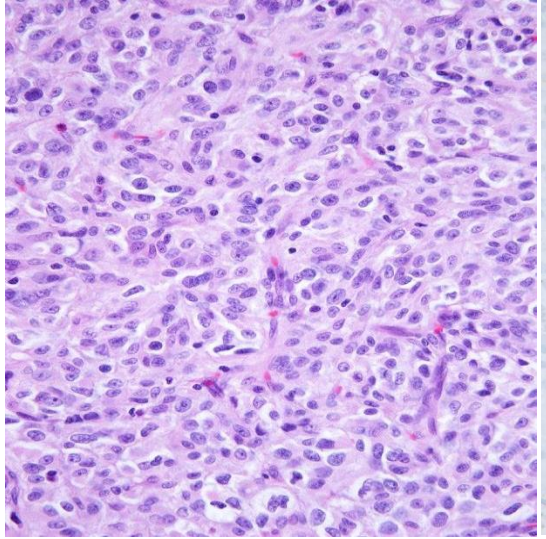
11-year-old female

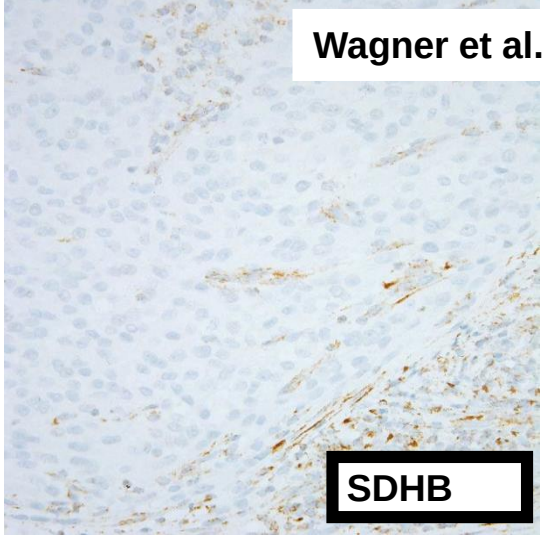
Metastatic SDH-deficient GIST



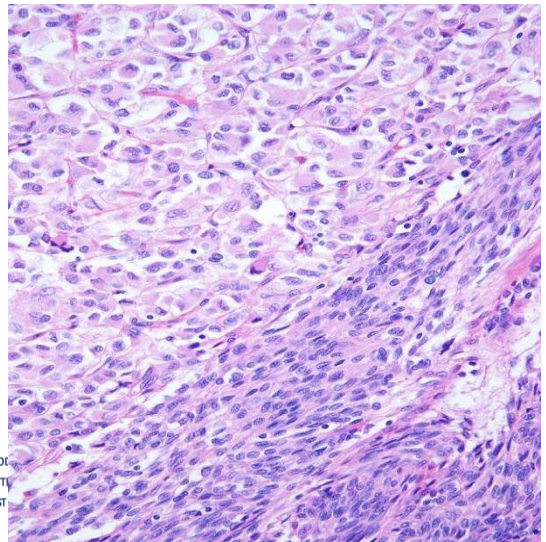
Wagner et al. Mod Pathol. 2013

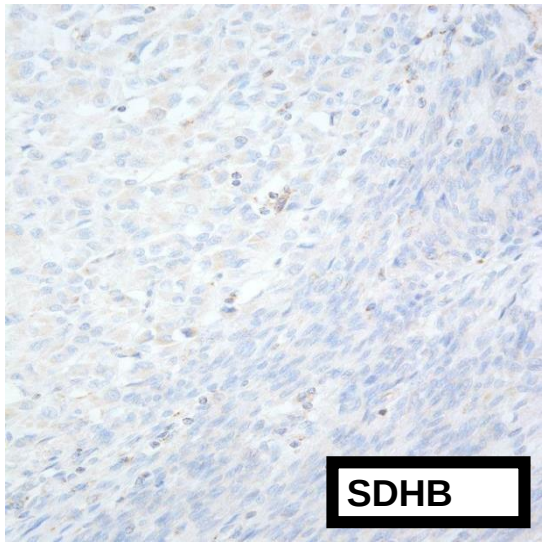
***SDHA*-mutant GIST**

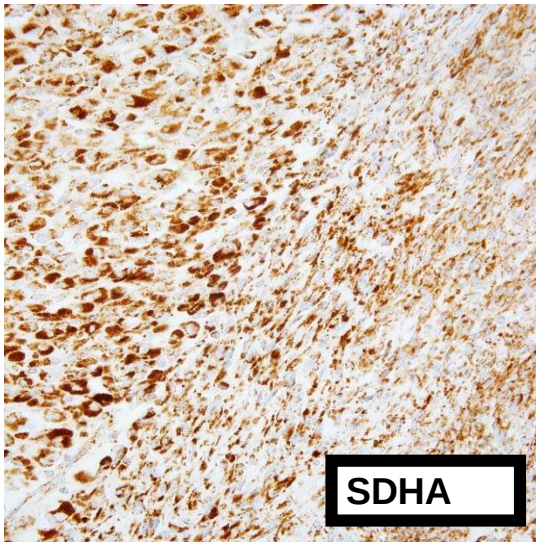




***SDHB*-mutant GIST**







Feature	SDH-deficient GISTs	GISTs with intact SDH
Age predilection	Children and young adults	Older adults
Gender distribution	F >> M	F = M
Anatomic site	Stomach	Entire GI tract
Multifocality	Common	Rare
Multinodular architecture	Always	Rare
Cytomorphology	Epithelioid or mixed	Spindle cell >> epithelioid
Prognosis predicted by site, size, and mitotic rate	No	Yes
Lymph node metastasis	Common	Exceptional
Clinical course of metastases	Indolent	Aggressive
Sensitive to Imatinib	No	Most cases
KIT/PDGFRA mutations	None	~95%
SDHx mutations (germline)	~50%	None
Syndromic associations	Carney-Stratakis syndrome Carney Triad	Neurofibromatosis 1 Familial GIST (germline *KIT* or *PDGFRA* mutations)

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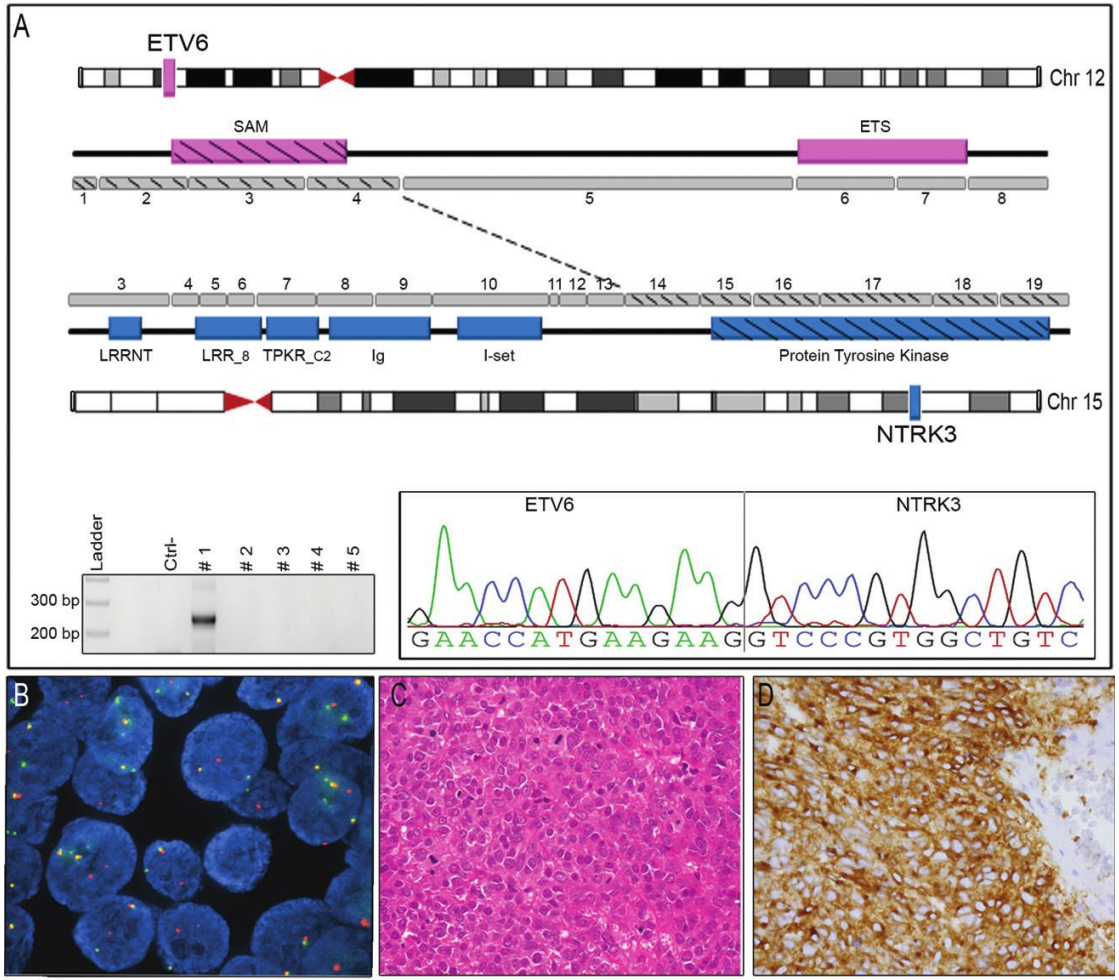
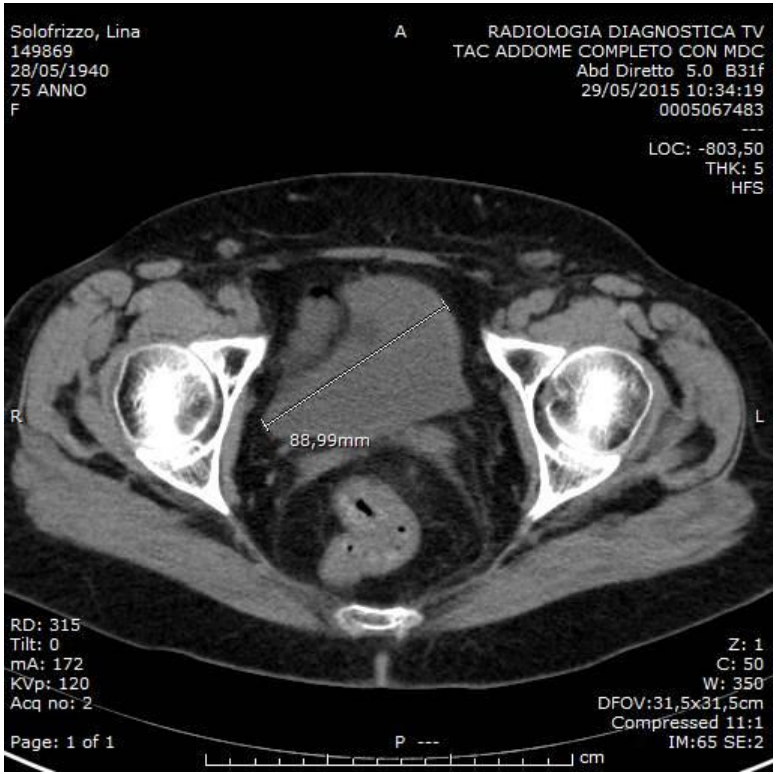
ORIGINAL PAPER

Transcriptome sequencing identifies *ETV6–NTRK3* as a gene fusion involved in GIST

Monica Brenca,[1*] Sabrina Rossi,[2*] Maurizio Polano,[1] Daniela Gasparotto,[1] Lucia Zanatta,[2] Dominga Racanelli,[1] Laura Valori,[2] Stefano Lamon,[3] Angelo Paolo Dei Tos[2**] and Roberta Maestro[1**]

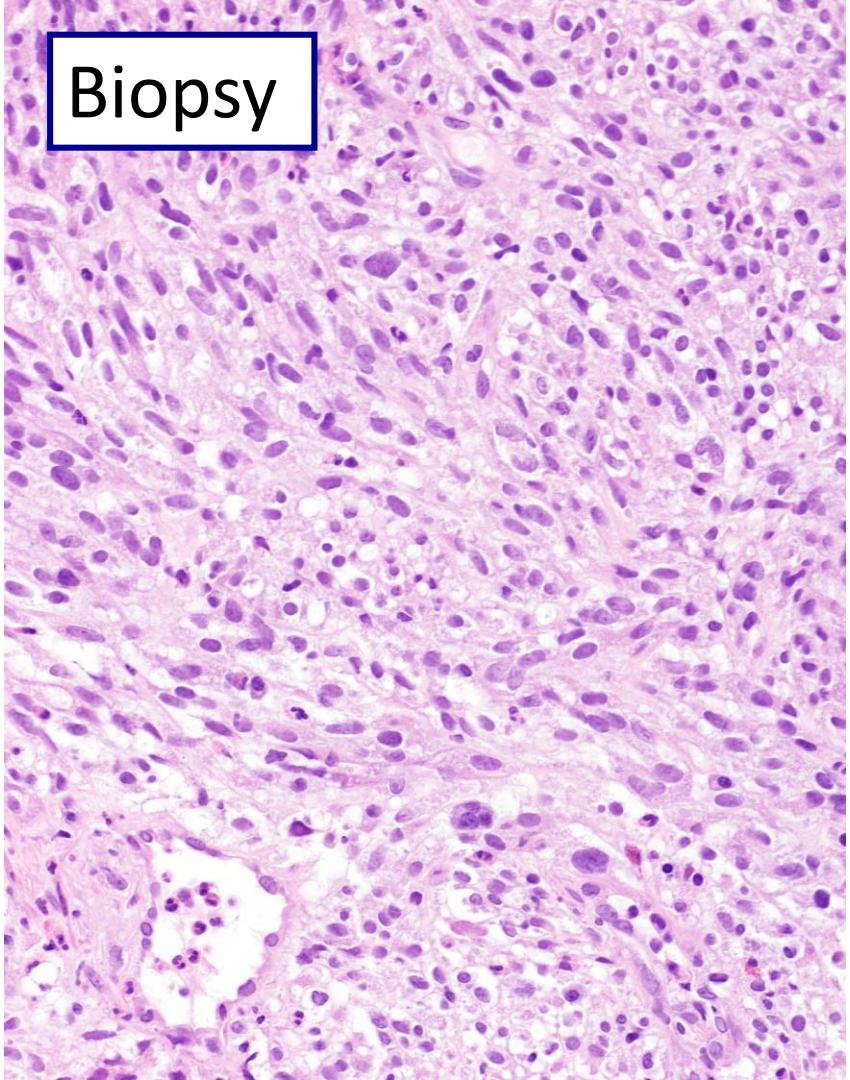


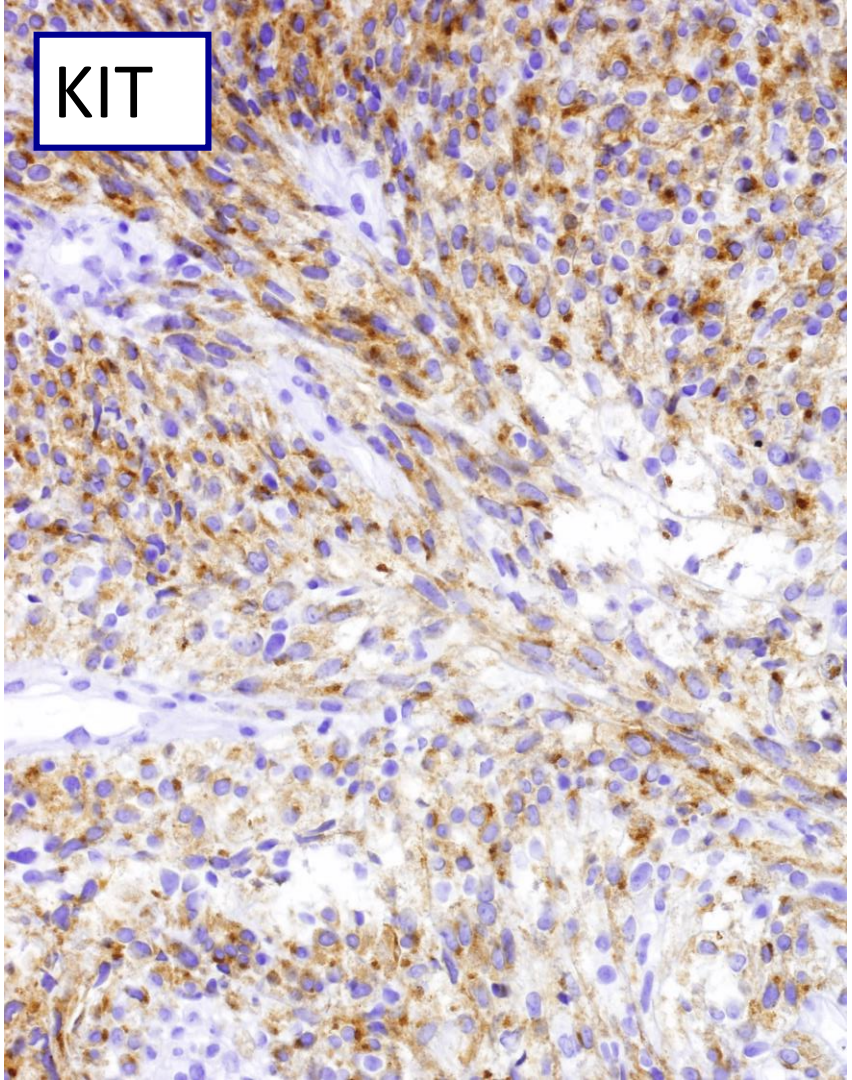
- Female of 75
- Rectal GIST
- KIT exon 11
- Dimensional response
- Surgical resection

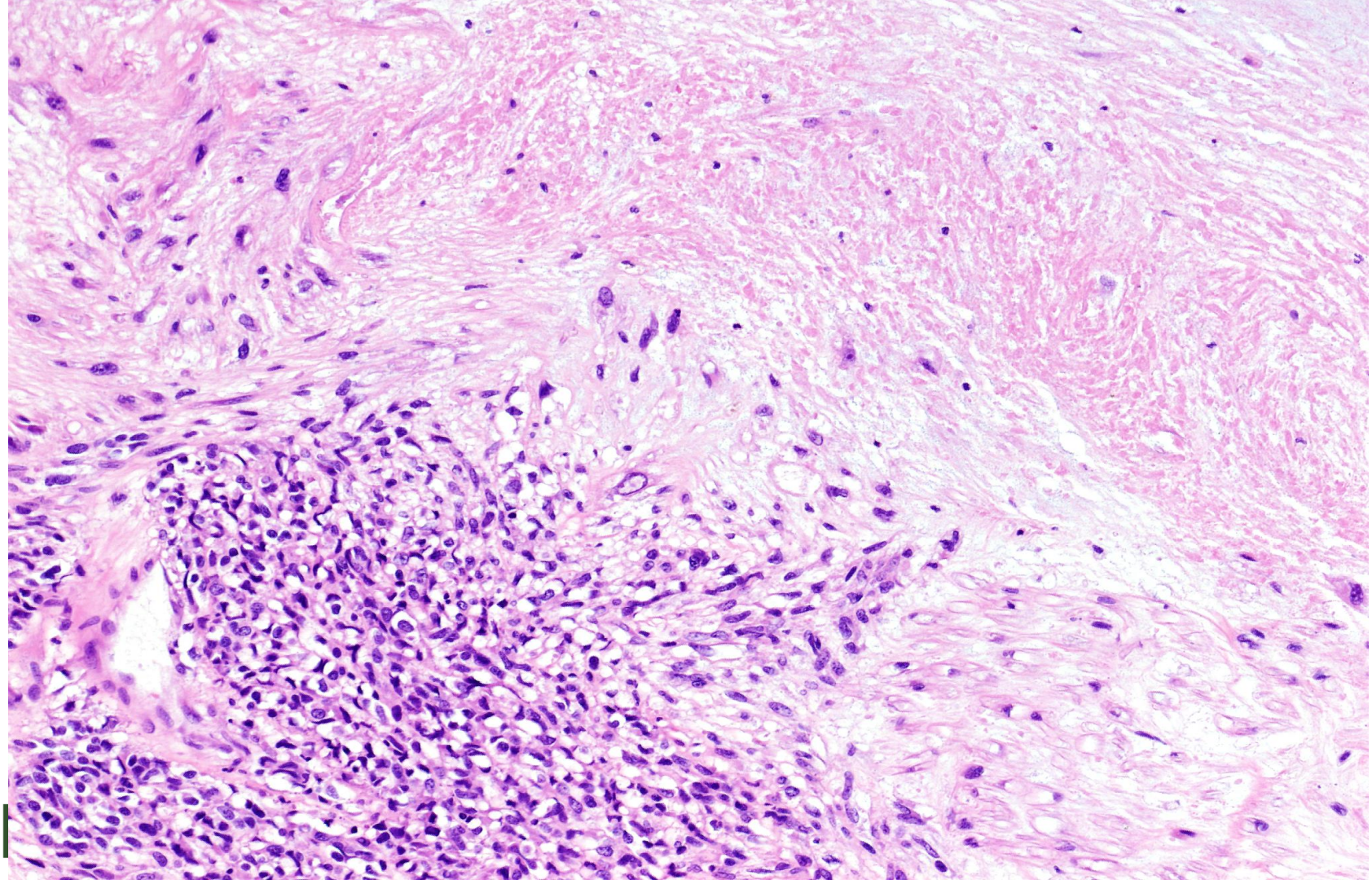


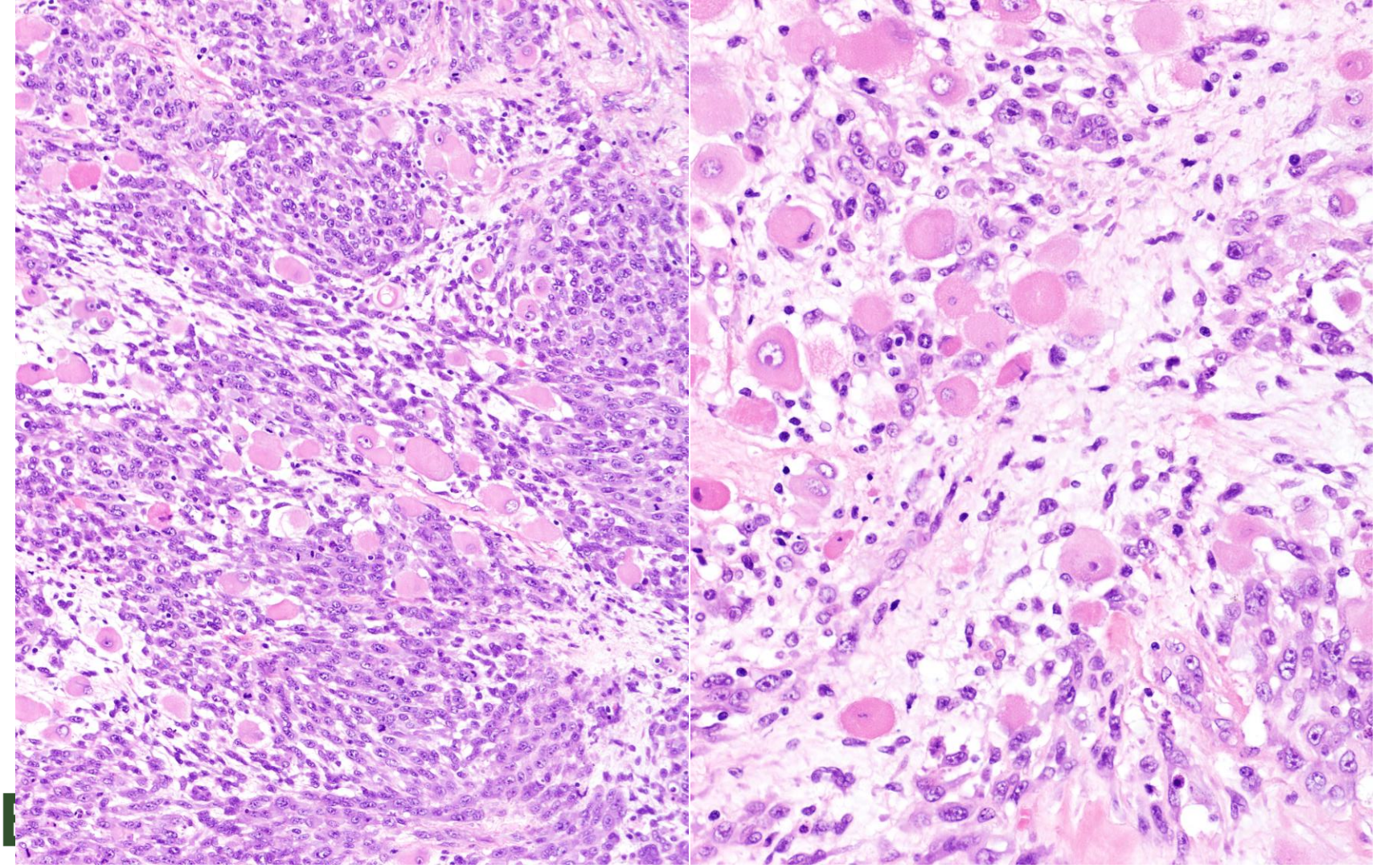
What would you expect as pathologic response?

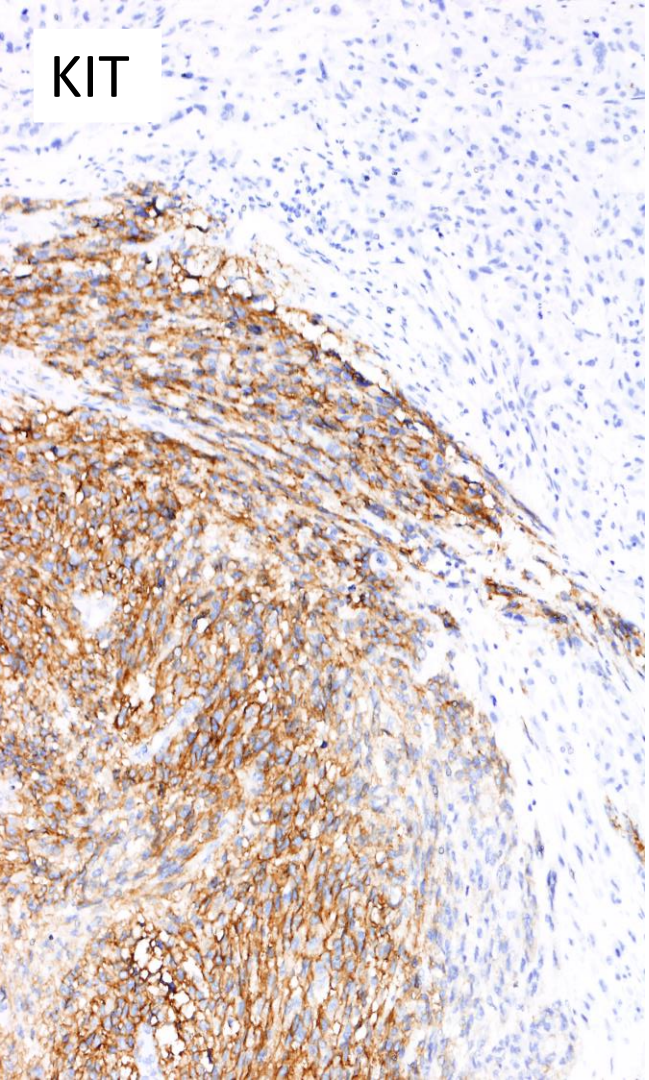
- Complete response
- No response
- Partial response
- Morphologic progression

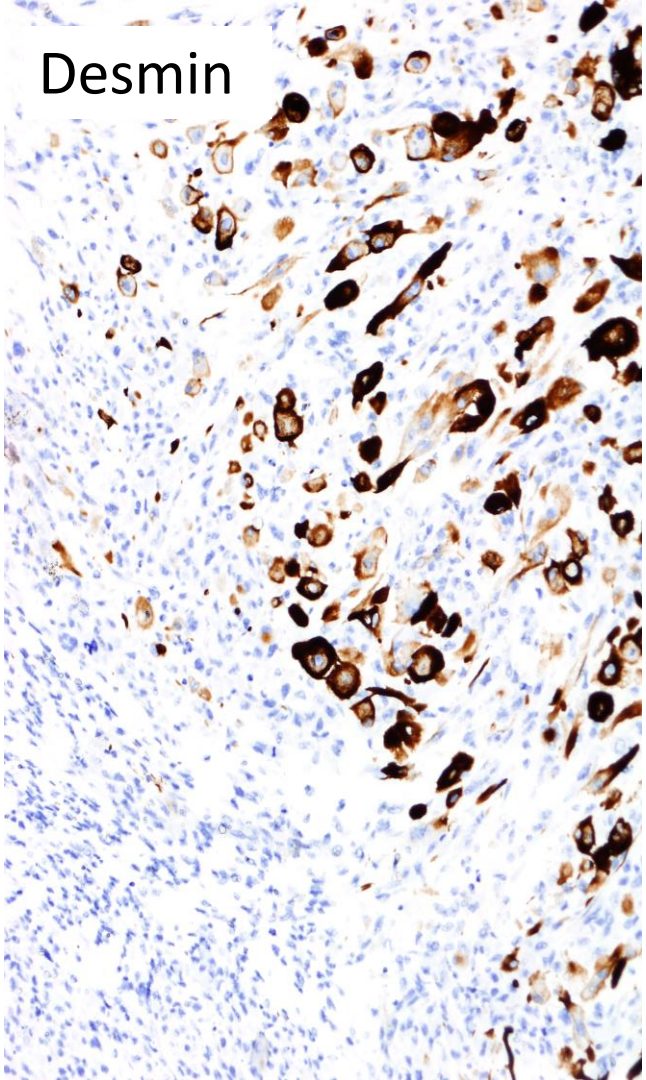

Biopsy


KIT






KIT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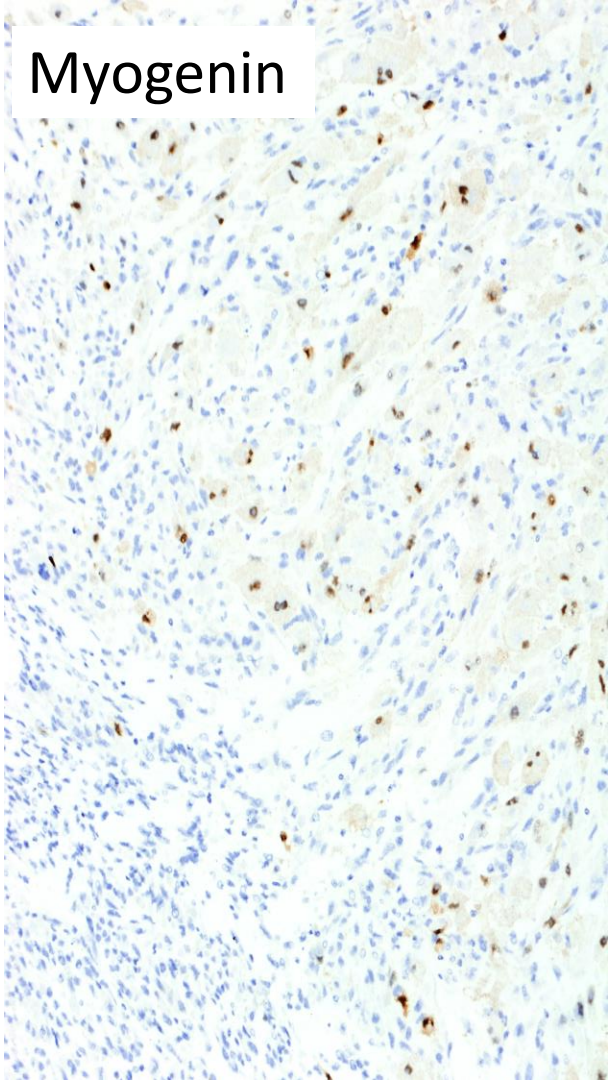
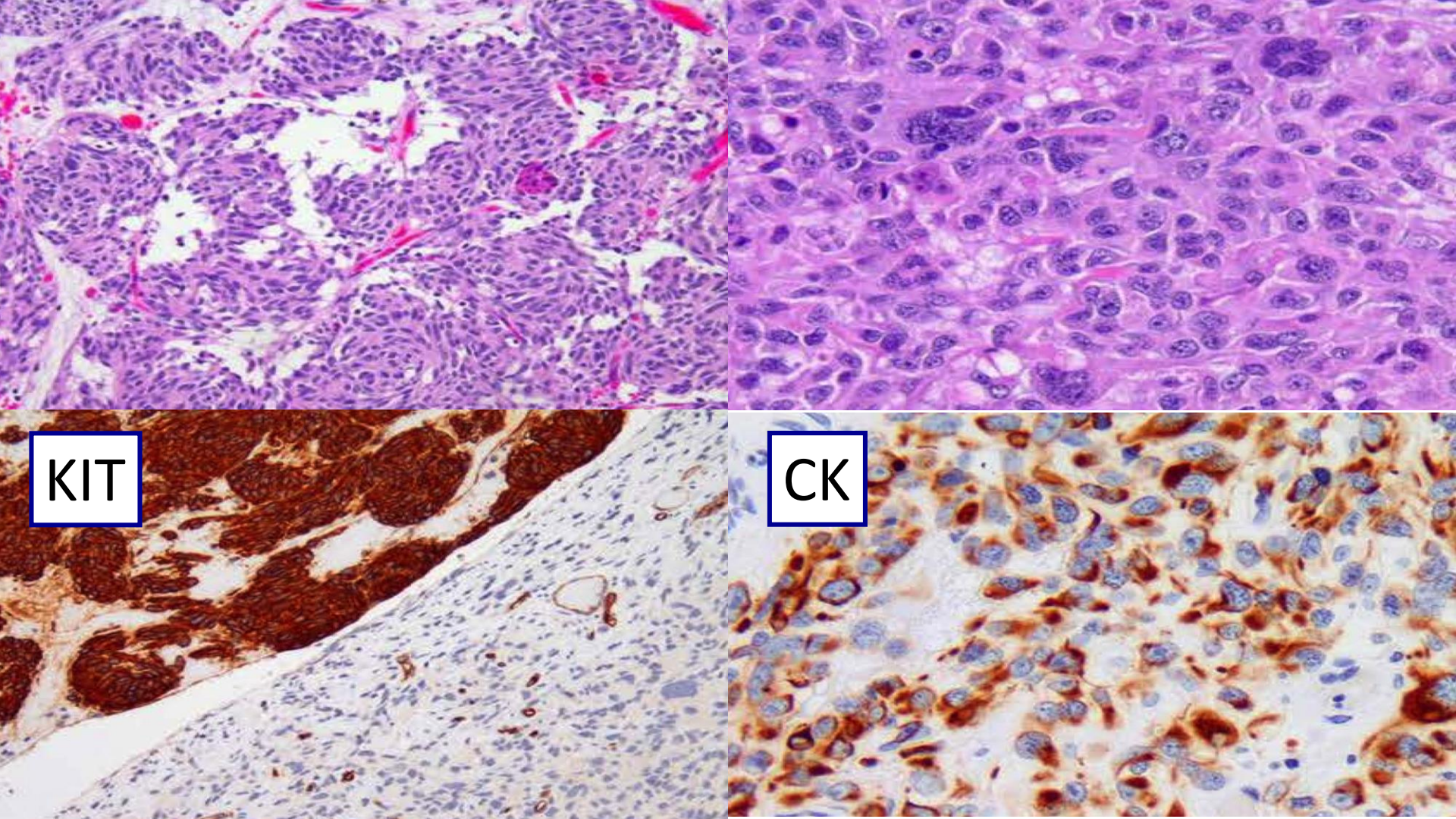

Myogenin

Dedifferentiation in Gastrointestinal Stromal Tumor to an Anaplastic KIT-negative Phenotype: A Diagnostic Pitfall

Morphologic and Molecular Characterization of 8 Cases Occurring Either De Novo or After Imatinib Therapy

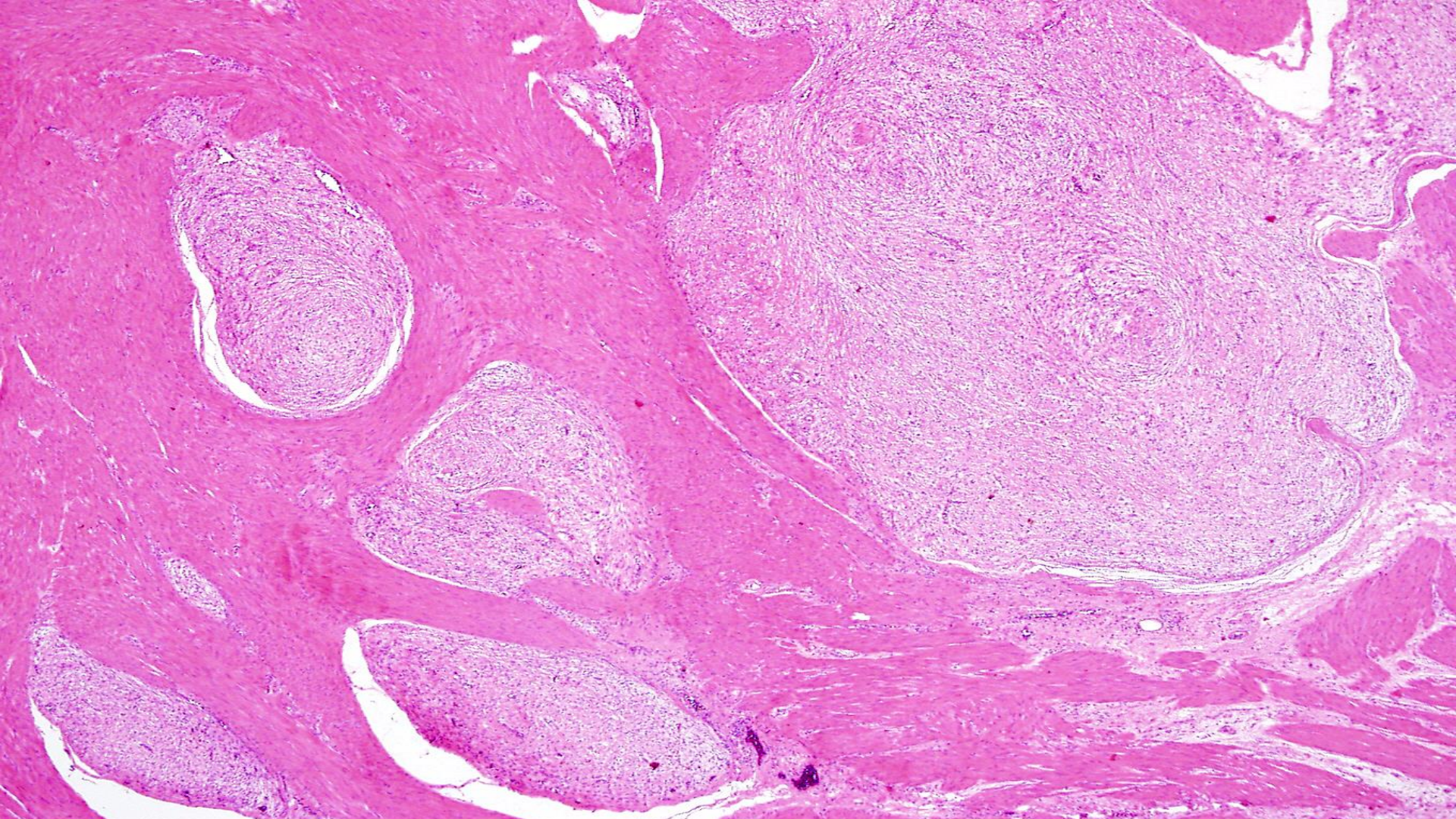
Cristina R. Antonescu, MD, Salvatore Romeo, MD,† Lei Zhang, MD,* Khedoudja Nafa, PhD,* Jason L. Hornick, MD, PhD,‡ Gunnlaugur Petur Nielsen, MD,§ Mari Mino-Kenudson, MD,§ Hsuan-Ying Huang, MD,‖ Juan-Miguel Mosquera, MD,¶ Paolo A. Dei Tos, MD,† and Christopher D.M. Fletcher, MD‡*

In summary, dedifferentiation in GIST may occur either de novo or after chronic imatinib exposure and can represent a diagnostic pitfall. This phenomenon is not related to additional *KIT* mutations, but might be secondary to genetic instability, either represented by loss of heterozygosity or low level of *KIT* amplification.


KIT
CK

Differential Diagnosis

Not all GI tract sarcomas are GIST



ORIGINAL ARTICLE

Plexiform Angiomyxoid Myofibroblastic Tumor of the Stomach

Yoshihisa Takahashi, MD, Seiichiro Shimizu, MD,† Tsuyoshi Ishida, MD,‡ Kiyoshi Aita, BS,* Suzuko Toida, PhD,* Toshio Fukusato, MD,* and Shigeo Mori, MD**

ORIGINAL ARTICLE

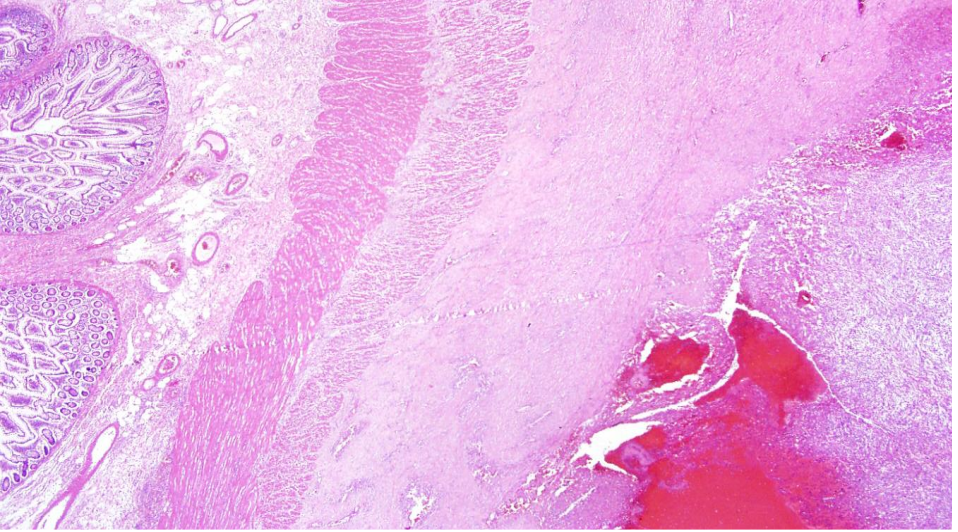
Plexiform Fibromyxoma

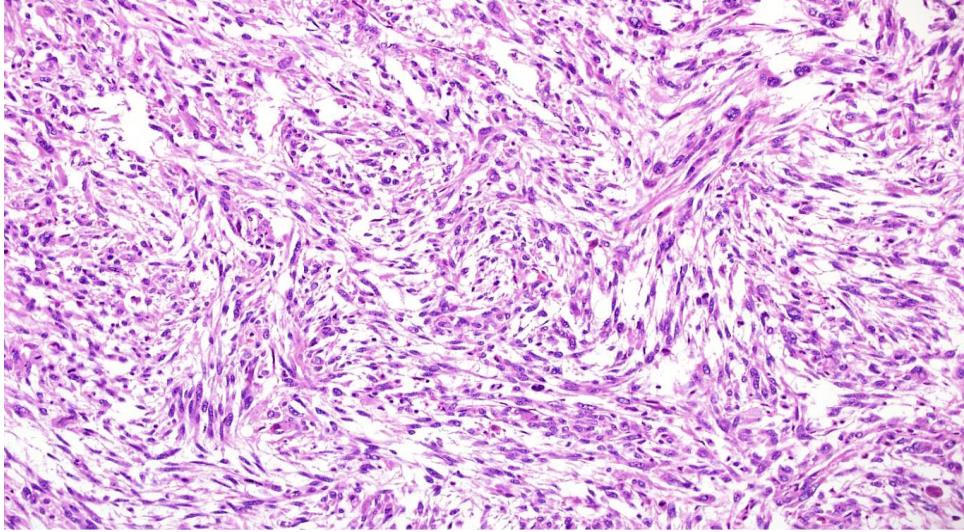
A Distinctive Benign Gastric Antral Neoplasm Not to be Confused With a Myxoid GIST

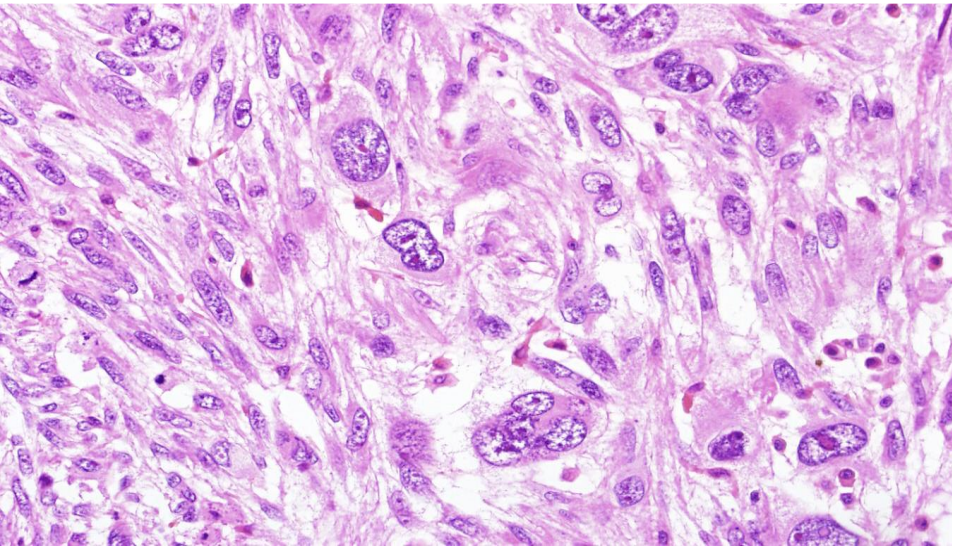
Markku Miettinen, MD, Hala R. Makhlouf, MD,† Leslie H. Sobin, MD,† and Jerzy Lasota, MD**

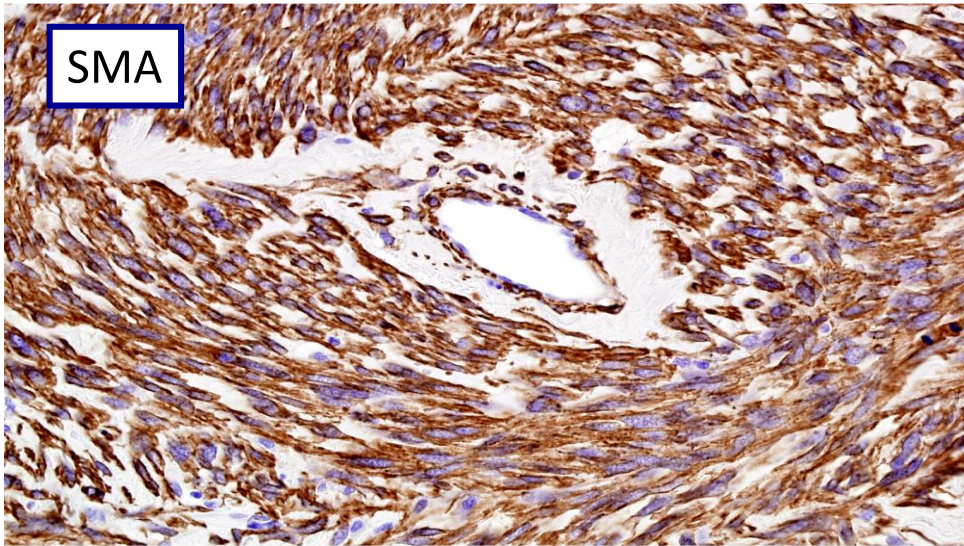
Differential Diagnosis

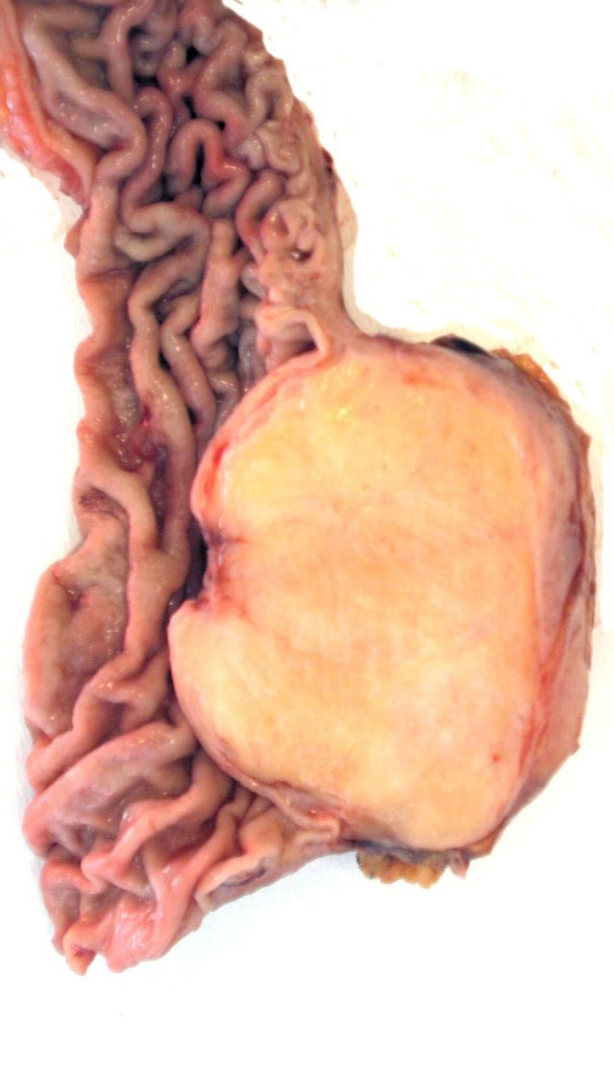
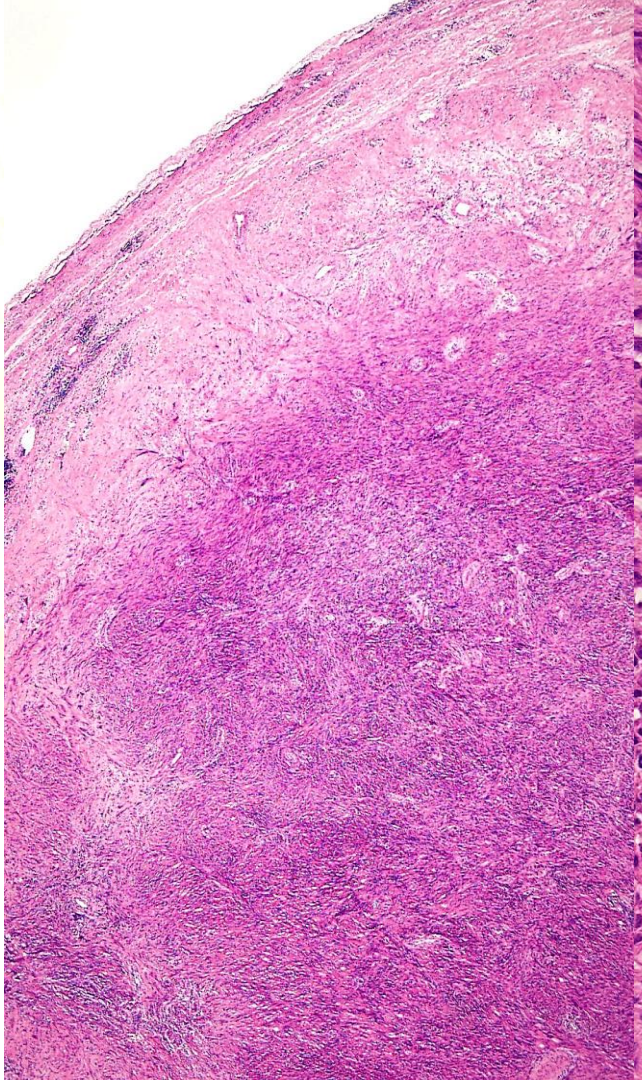
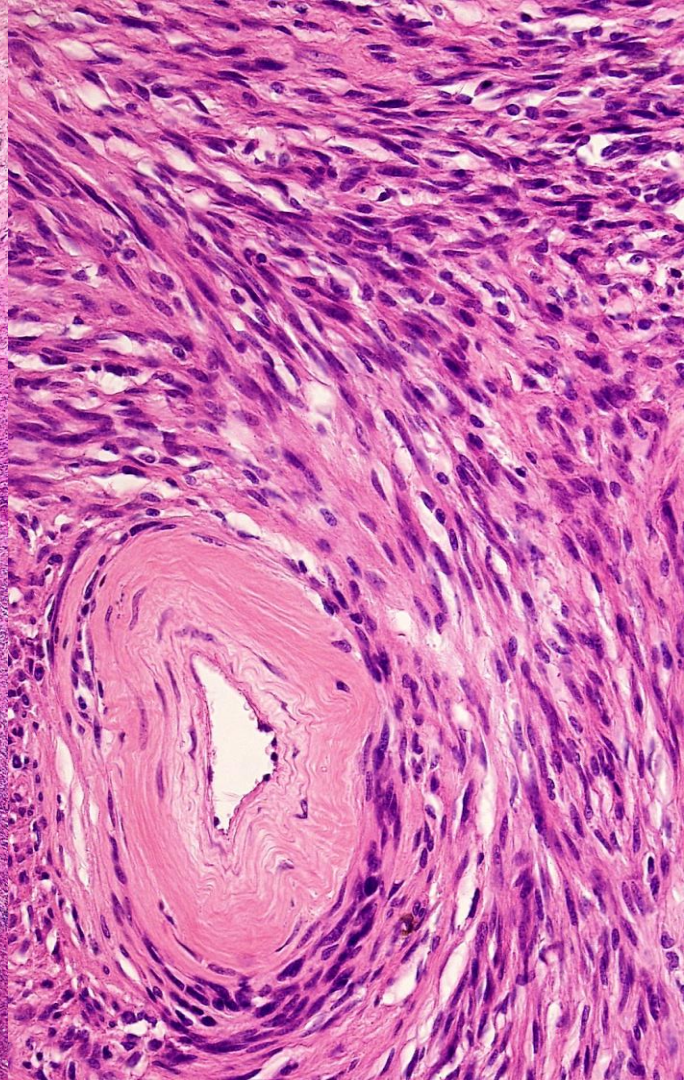
- Smooth muscle tumors
  - Desmin/h-Caldesmon +
- Neural tumors
  - S-100 +; podoplanin/SOX10+
- Intraabdominal fibromatosis
  - Beta catenin +
- Inflammatory myofibroblastic tumor
  - Alk-1 +
- Sarcomatoid carcinoma
  - CK/EMA+ (SMA+)
- FDC sarcoma
  - CD21/CD35+; Clusterin+
- PEComa
  - HMB45/MiTF1+; myogenic markers
- Glomus tumors
  - SMA +
- Synovial sarcoma
  - CK/EMA+; CD99+

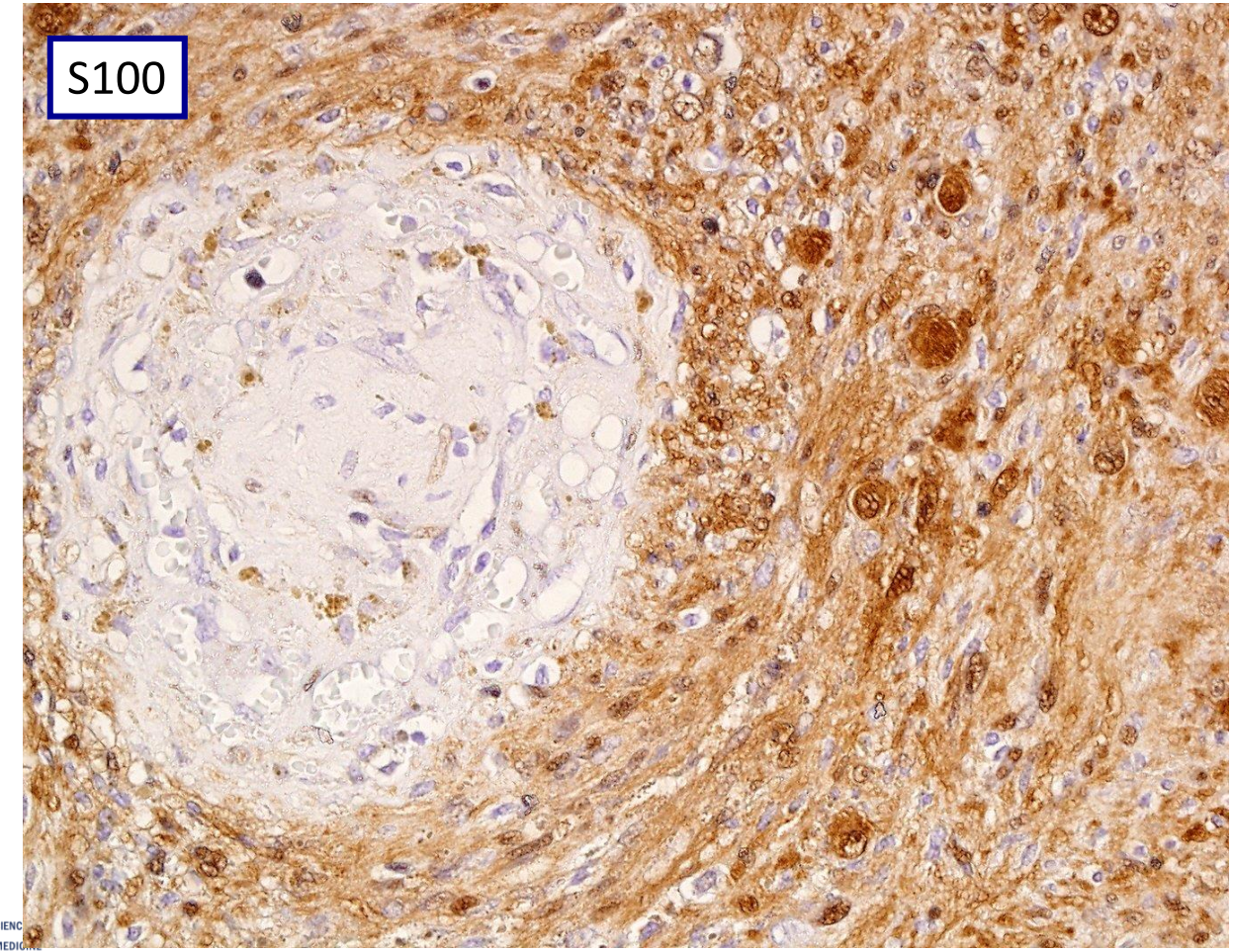


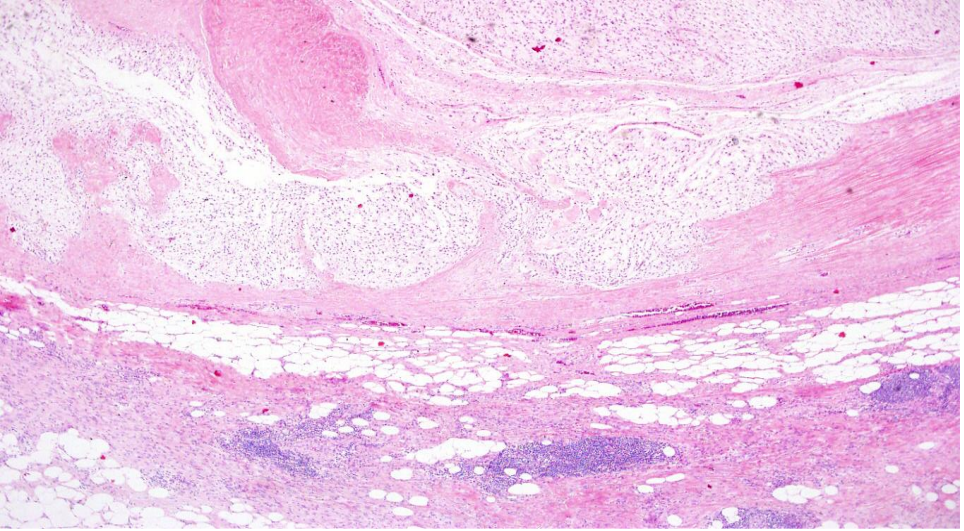


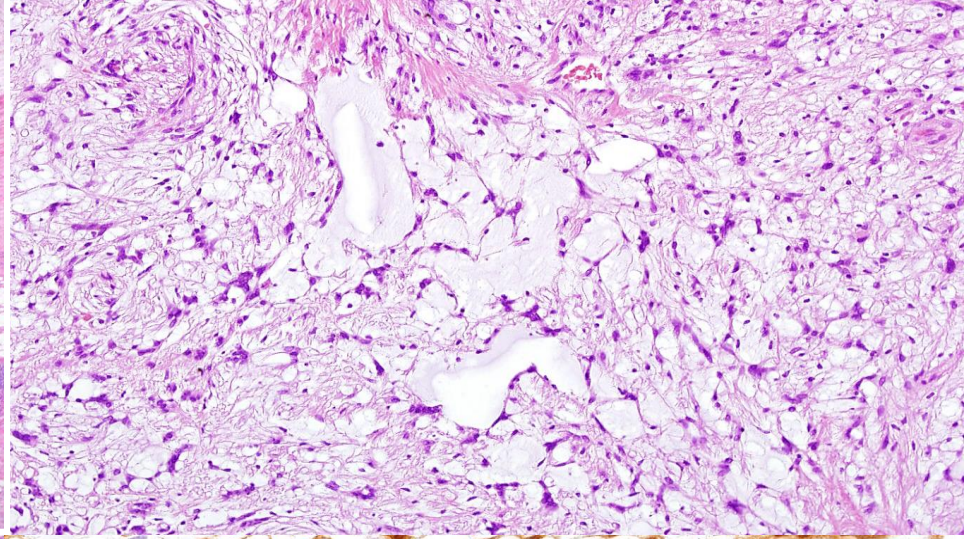


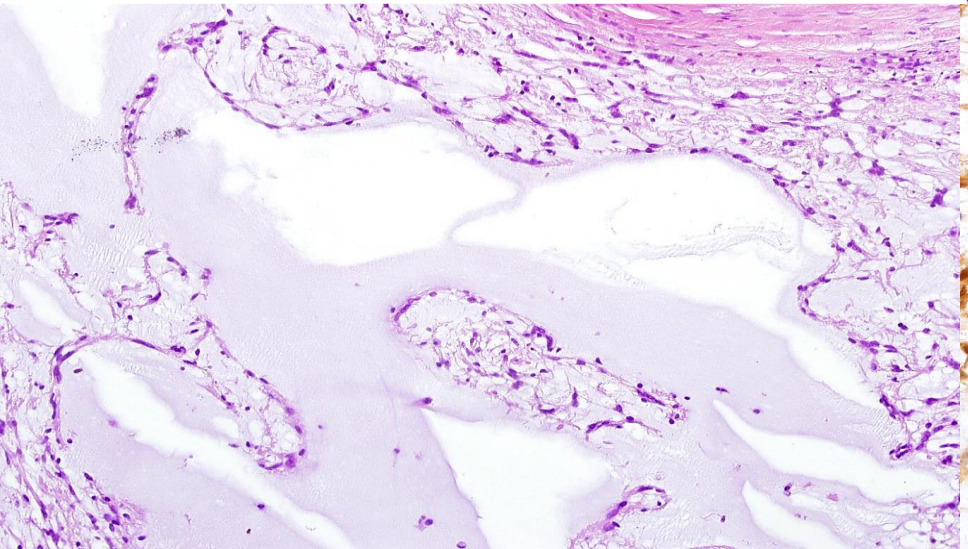

SMA

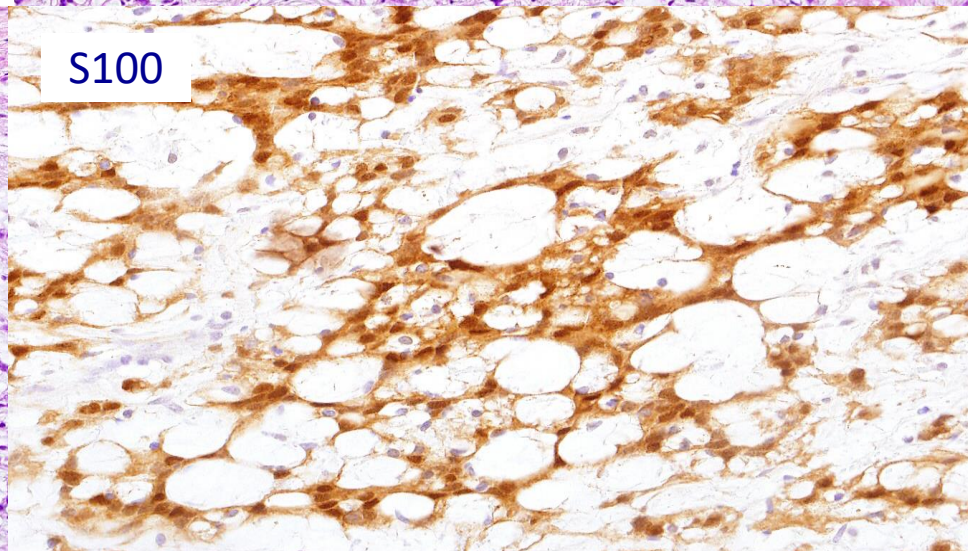












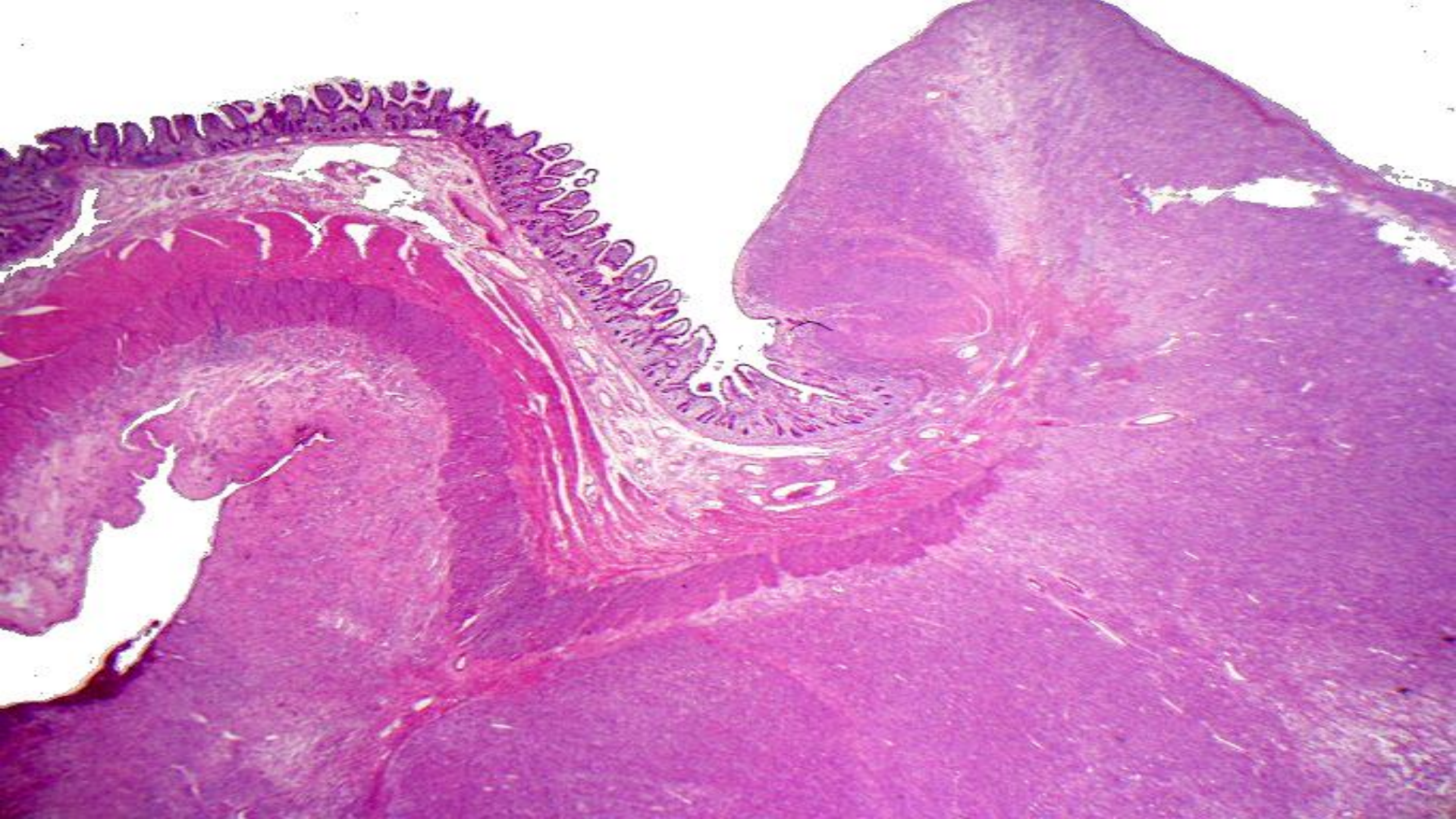

S100

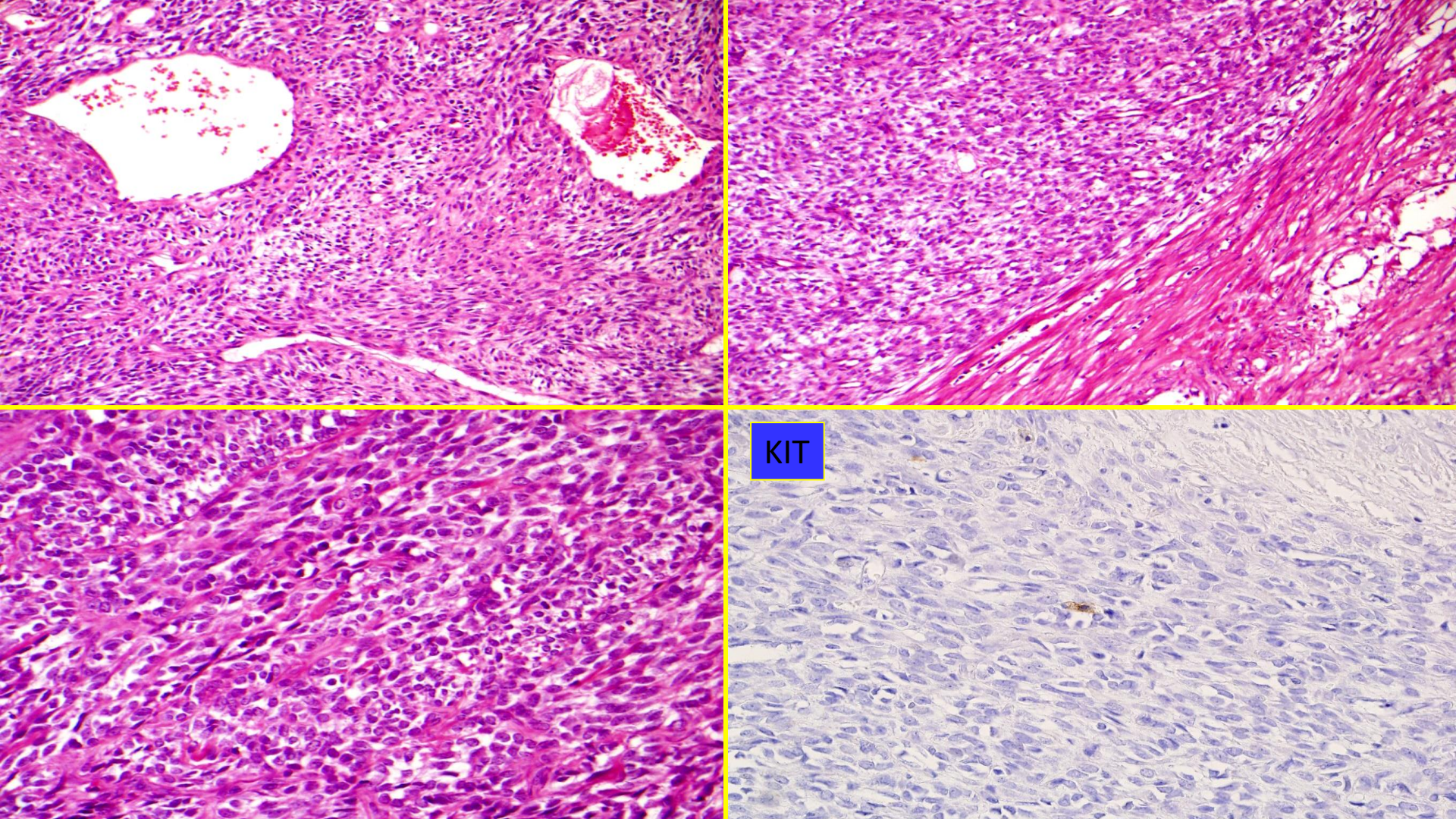
ORIGINAL ARTICLE

Microcystic/Reticular Schwannoma: A Distinct Variant With Predilection for Visceral Locations

Bernadette Liegl, MD,† Michael W. Bennett, MB, BCh, BAO, MRCPI,* and Christopher D.M. Fletcher, MD, FRCPath**

(*Am J Surg Pathol* 2008;32:1080–1087)

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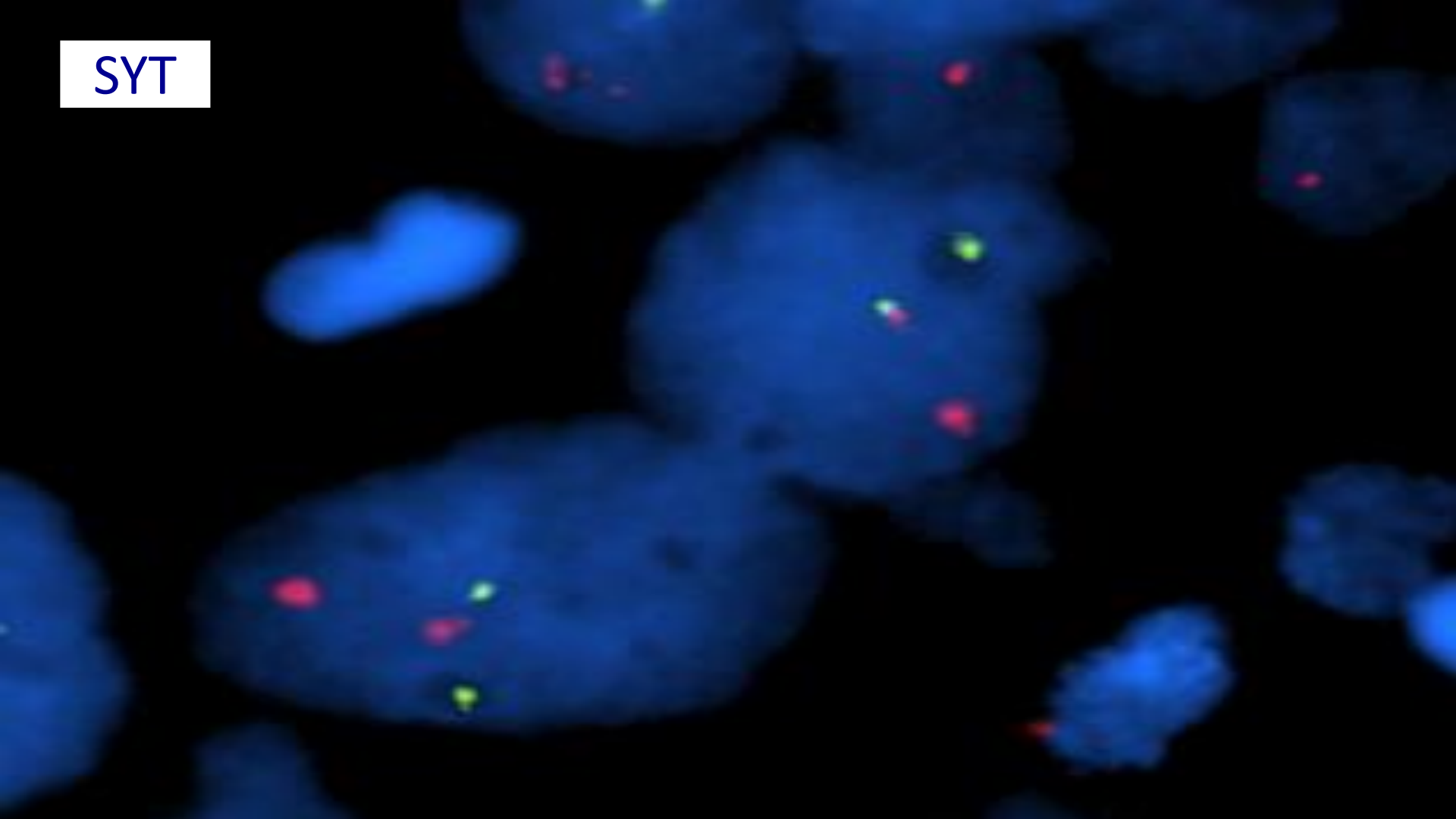

SYT

Romeo *et al. Clinical Sarcoma Research* (2015) 5:7
DOI 10.1186/s13569-015-0021-3

CLINICAL SARCOMA RESEARCH

RESEARCH Open Access

Primary Synovial Sarcoma (SS) of the digestive system: a molecular and clinicopathological study of fifteen cases

Salvatore Romeo[1], Sabrina Rossi[1], Marthelena Acosta Marín[2], Fabio Canal[1], Marta Sbaraglia[1], Licia Laurino[1], Guido Mazzoleni[3], Maria Cristina Montesco[4], Laura Valori[1], Marta Campo Dell'Orto[1], Andrea Gianatti[5], Alexander Joseph Lazar[2] and Angelo Paolo Dei Tos[1*]

What to Expect from Pathologic Report?

- Anatomic location
- Size
- Mitotic count/5mm^2
- Diagnosis
- Risk class (?)
  - Clinician can guess themselves
  - Not applicable to WT GIST
- Molecular Status
- If Wild Type (KIT, PDGRA, BRAF, NTRK, NF1) SDHB status (IHC)

When Clinicians should Doubt?

- GIST diagnosed at uncommon anatomic locations
  - Esophagus and extra GI sites
  - Most mesenteric "GIST" are mesenteric desmoids
- KIT/DOG1 negative GIST
  - DOG1 alone is seen in LMS
- GIST featuring pleomorphism and/or high mitotic count
- WT or D842V GISTs behaving aggressively
- KIT exon 11 GIST not responding to TKI
- KIT/PDGFRA mutation in multinodular/pediatric GISTs

Molecular Testing

- Diagnosis
  - KIT/DOG1 negative GIST
  - Pleomorphic GIST
- Prognosis
- Prediction
  - D842V
  - Exon 9 kit mutations

Mutational Analysis

- VEQ
  - Bordeaux, Lyon, Treviso
- High concordance among referral centers (96%)
- Not so much within non referral centers

J Gastroenterol
DOI 10.1007/s00535-011-0375-0

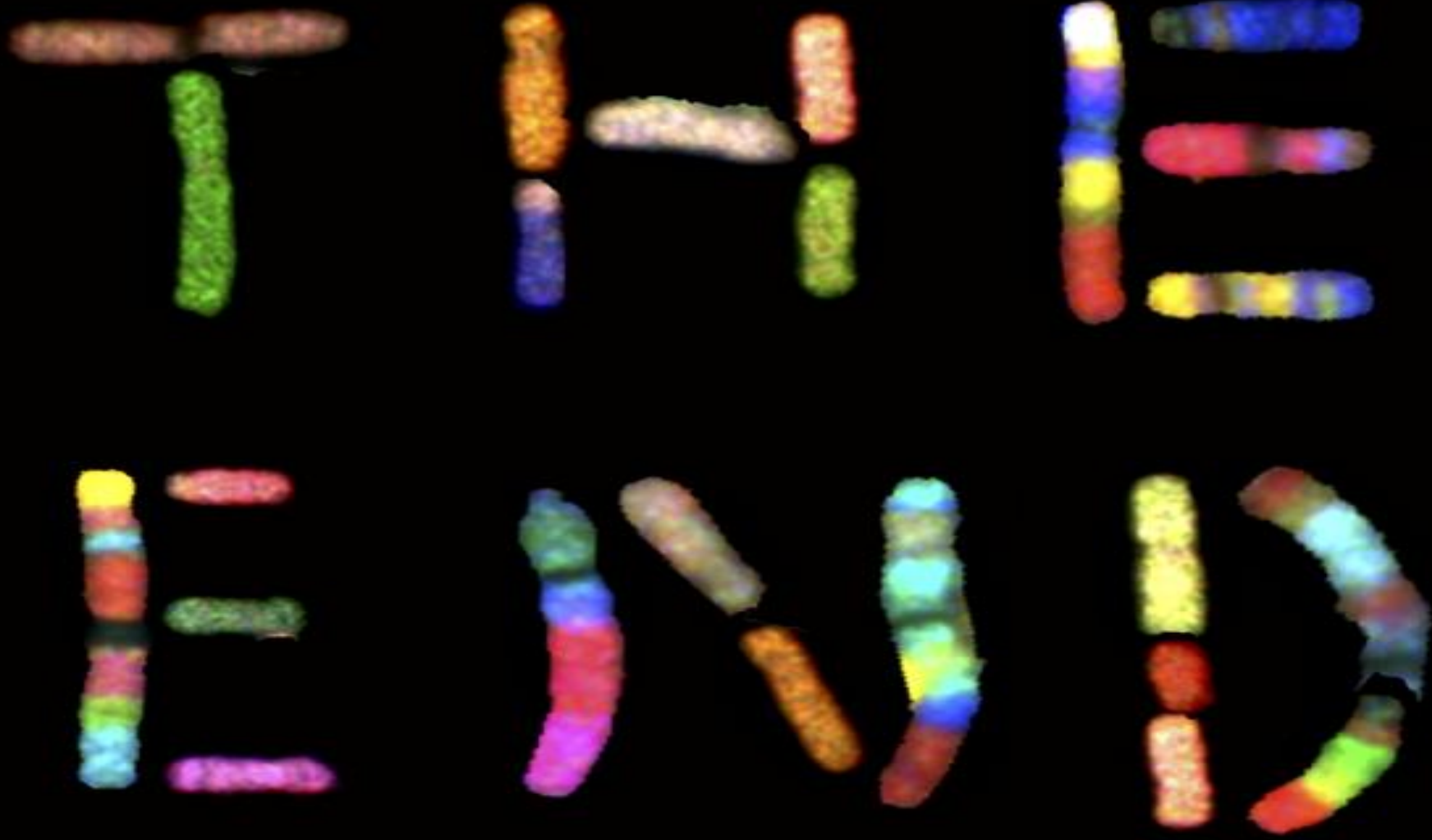
ORIGINAL ARTICLE—ALIMENTARY TRACT

A quality control program for mutation detection in *KIT* and *PDGFRA* in gastrointestinal stromal tumours

Isabelle Hostein · Maria Debiec-Rychter · Sylvianne Olschwang · Pierre-Paul Bringuier · Louisa Toffolati · David Gonzalez · Sébastien Forget · Fabienne Escande · Lucyna Morzuch · Elena Tamborini · Nicolas Faur · Silvana Pilotti · Paolo Dei Tos · Jean-François Emile · Jean-Michel Coindre

Conclusions

- GIST diagnosis is challenging
- Differential diagnosis rather broad
- Combination of morphology, immunohistochemistry and molecular genetics
- Strict connection with treatment


THE END