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The role of Pathology in GIST
Morphology – Diagnostic pitfalls- Mutational analysis

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Erwin-Schrödinger Stipendium September 2006

HARVARD MEDICAL SCHOOL Sep 2006-Aug 2008

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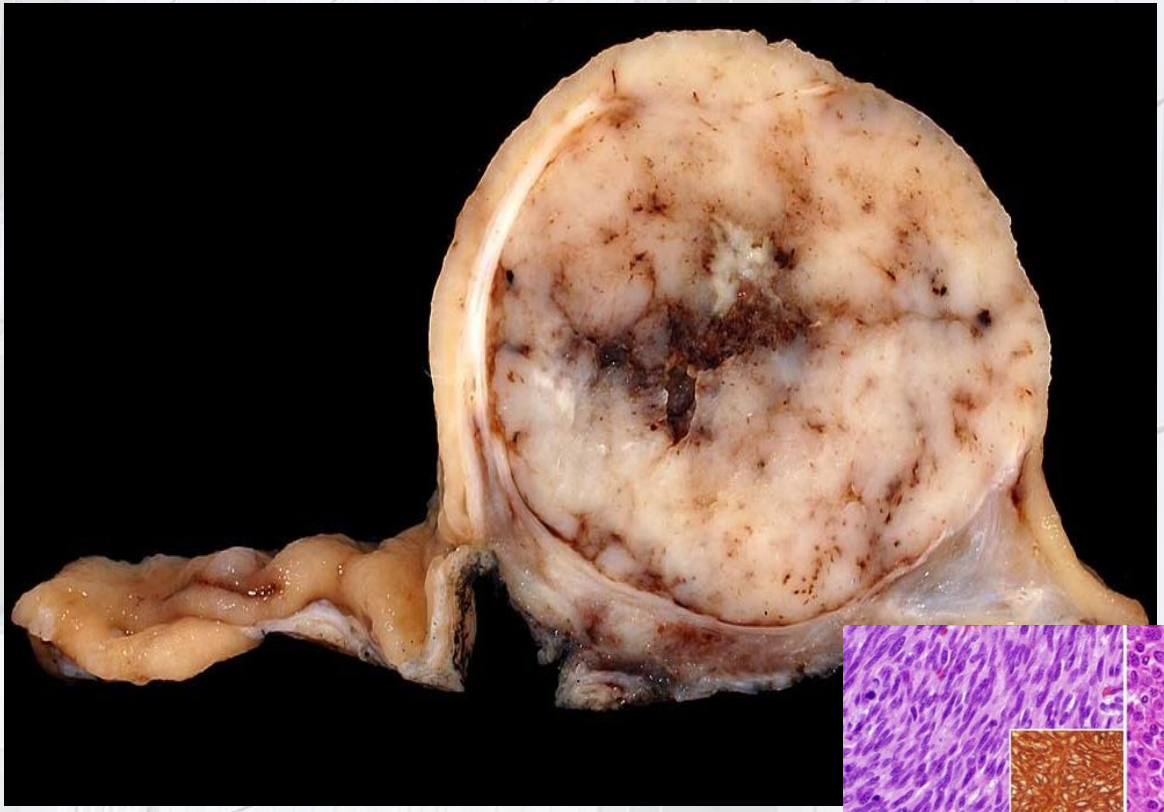
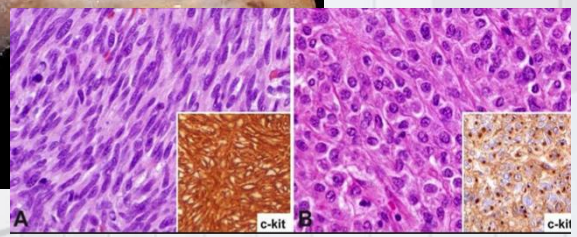


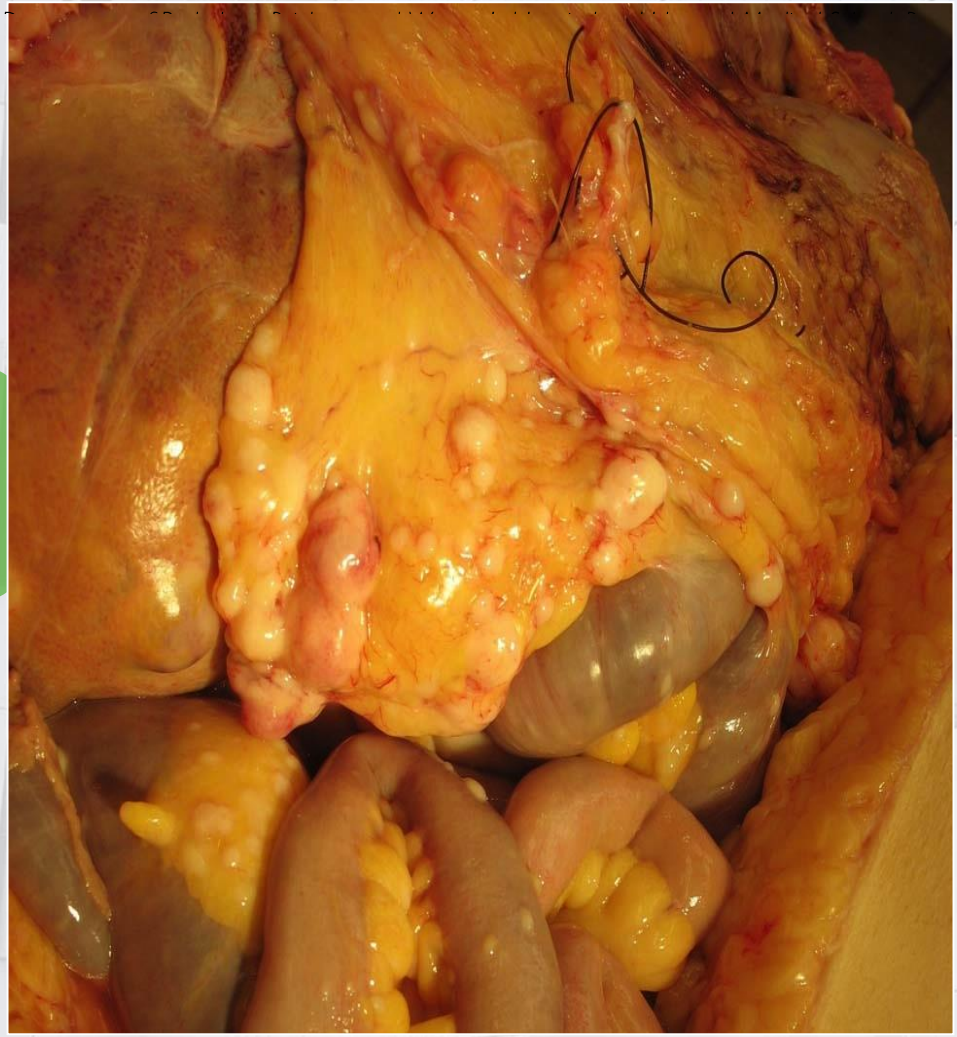


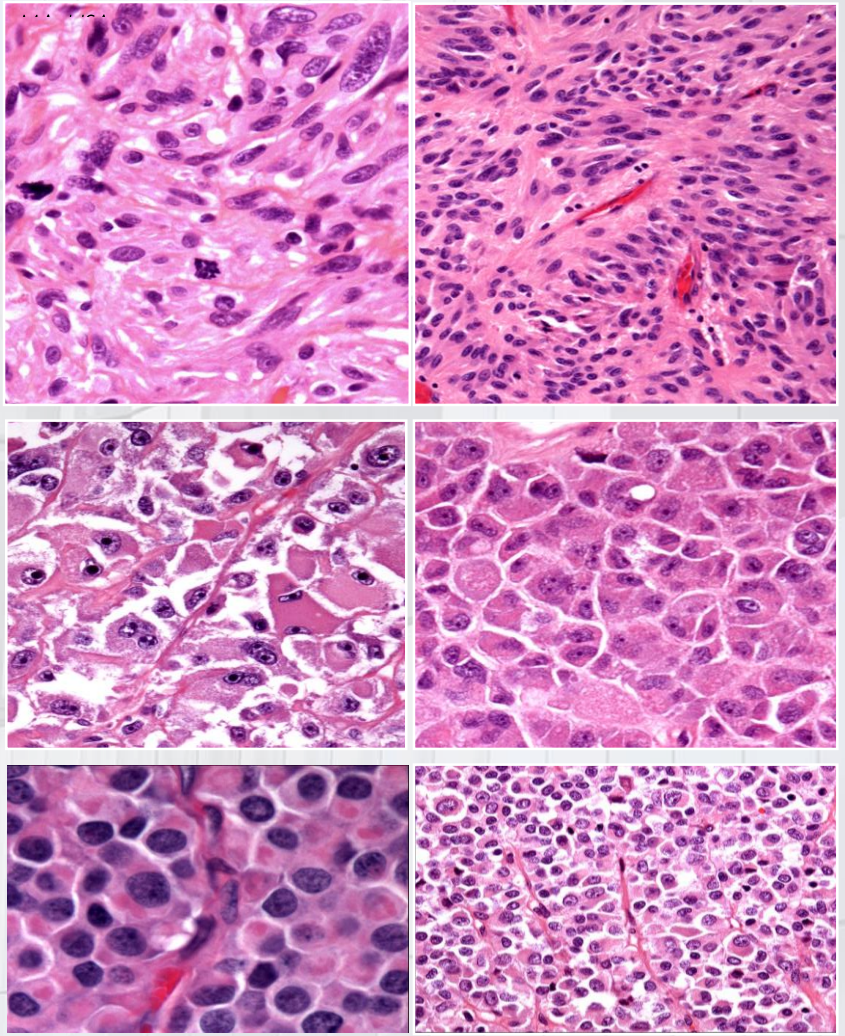
Erwin-Schrödinger-Stipendium

Original Paper

Heterogeneity of kinase inhibitor resistance mechanisms in GIST

B Liegl,[1,2] I Kepten,[3] C Le,[3] M Zhu,[1] GD Demetri,[4] MC Heinrich,[5,6] CDM Fletcher,[1] CL Corless[3] and JA Fletcher[1]*





ORIGINAL ARTICLE

Am J Surg Pathol • Volume 33, Number 2, February 2009

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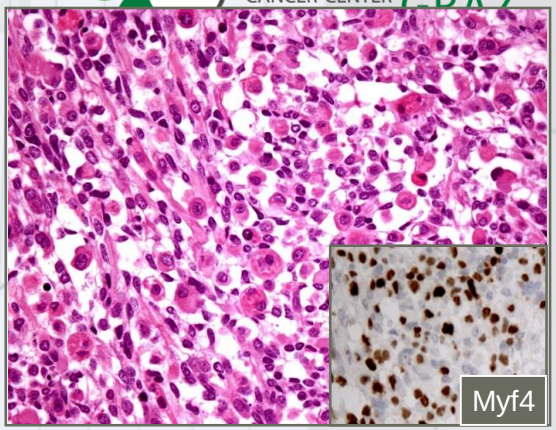
Rhabdomyosarcomatous Differentiation in Gastrointestinal Stromal Tumors After Tyrosine Kinase Inhibitor Therapy

A Novel Form of Tumor Progression

Bernadette Liegl, MD,† Jason L. Hornick, MD, PhD,* Cristina R. Antonescu, MD,‡ Christopher L. Corless, MD,§ and Christopher D. M. Fletcher, MD, FRCPath**



ORIGINAL ARTICLE

Am J Surg Pathol • Volume 33, Number 3, March 2009

Monoclonal Antibody DOG1.1 Shows Higher Sensitivity Than KIT in the Diagnosis of Gastrointestinal Stromal Tumors, Including Unusual Subtypes

Bernadette Liegl, MD,† Jason L. Hornick, MD, PhD,* Christopher L. Corless, MD,‡ and Christopher D. M. Fletcher, MD, FRCPath**

Virchows Arch (2010) 456:111–127
DOI 10.1007/s00428-010-0891-y

REVIEW AND PERSPECTIVE

Gastrointestinal stromal tumors

Bernadette Liegl-Atzwanger · Jonathan A. Fletcher · Christopher D. M. Fletcher

Review
Contemporary Gist Pathology
B.Liegl, JL.Hornick, AJ. Lazar
Hematol Oncol Clin North Am. 2009 Feb;23(1):49-68

Research Article

Pediatric *KIT*–Wild-Type and Platelet-Derived Growth Factor Receptor α–Wild-Type Gastrointestinal Stromal Tumors Share KIT Activation but not Mechanisms of Genetic Progression with Adult Gastrointestinal Stromal Tumors

Katherine A. Janeway,[1,3,4] Bernadette Liegl,[4,5] Amy Harlow,[6] Claudia Le,[6] Antonio Perez-Atayde,[2] Harry Kozakewich,[2] Christopher L. Corless,[6,7,8] Michael C. Heinrich,[6,7,8] and Jonathan A. Fletcher[1,3,4]

Departments of [1]Medicine and [2]Pathology, Children's Hospital Boston, [3]Pediatric Oncology, Dana-Farber Cancer Institute; [4]Department of Pathology, Bringham and Women's, Hospital, Boston, Massachusetts; [5]Department of Pathology, Medical University, Graz, Austria; and Departments of [6]Medicine, and [7]Cell and Developmental Biology, Oregon Health and Science University and [8]Portland VA Medical Center, Portland, Oregon

Cancer Res 2007; 67: (19). October 1, 2007

BMC Medical Genetics

Research article

Mutation analysis of SDHB and SDHC: novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma

Jean-Pierre Bayley[1], Ivonne van Minderhout[1], Marjan M Weiss[1], Jeroen C Jansen[3], Peter HN Oomen[4], Fred H Menko[5], Barbara Pasini[6], Barbara Ferrando[6], Nora Wong[7,9], Lesley C Alpert[8,9], Rosie Williams[10], Edward Blair[11], Peter Devilee[1,2] and Peter EM Taschner*[1]

BMC Medical Genetics

Research article

Open Access

Mutation analysis of SDHB and SDHC: novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma

Jean-Pierre Bayley, Ivonne van Minderhout, Marjan M Weiss, Jeroen C Jansen, Peter HN Oomen, Fred H Menko, Barbara Pasini, Barbara Ferrando, Nora Wong, Lesley C Alpert, Rosie Williams, Edward Blair, Peter Devilee and Peter EM Taschner*

Genetics of Carney Triad: Recurrent Losses at Chromosome 1 but Lack of Germline Mutations in Genes Associated with Paragangliomas and Gastrointestinal Stromal Tumors

Ludmila Matyakhina, Thalia A. Bei, Sarah R. McWhinney, Barbara Pasini, Silke Cameron, Bastian Gunawan, Sotirios G. Stergiopoulos, Sosipatros Boikos, Michael Muchow, Amalia Dutra, Evgenia Pak, Elias Campo, Maria C. Cid, Fulgencio Gomez, Rolf C. Gaillard, Guillaume Assie, Laszlo Füzesi, Bora E. Baysal, Charis Eng, J. Aidan Carney, and Constantine A. Stratakis

ARTICLE

Clinical and molecular genetics of patients with the Carney–Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD

Barbara Pasini[1,16], Sarah R McWhinney[2,16], Thalia Bei[3], Ludmila Matyakhina[3], Sotirios Stergiopoulos[3], Michael Muchow[3], Sosipatros A Boikos[3], Barbara Ferrando[1], Karel Pacak[4], Guillaume Assie[5,14], Eric Baudin[6], Agnes Chompret[7], Jay W Ellison[8], Jean-Jacques Briere[9,10], Pierre Rustin[9,10], Anne-Paule Gimenez-Roqueplo[11,12,13,16], Charis Eng[2,14,16], J Aidan Carney[15,16] and Constantine A Stratakis*[3,16]

Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking *KIT* and *PDGFRA* mutations

Katherine A. Janeway[a,1,2], Su Young Kim[b,1], Maya Lodish[c], Vânia Nosé[d], Pierre Rustin[e], José Gaal[f], Patricia L. M. Dahia[g], Bernadette Liegl[h], Evan R. Ball[c], Margarita Raygada[i], Angela H. Lai[a], Lorna Kelly[j], Jason L. Hornick[k], NIH Pediatric and Wild-Type GIST Clinic[l,m,n,o,p,3], Maureen O'Sullivan[j,q], Ronald R. de Krijger[f], Winand N. M. Dinjens[f], George D. Demetri[r], Cristina R. Antonescu[s], Jonathan A. Fletcher[k], Lee Helman[b], and Constantine A. Stratakis[c]

314–318 | PNAS | January 4, 2011 | vol. 108 | no. 1

Am J Surg Pathol • Volume 32, Number 4, April 2008

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„DEPART TO SERVE BETTER THY COUNTRY AND THY KIND"

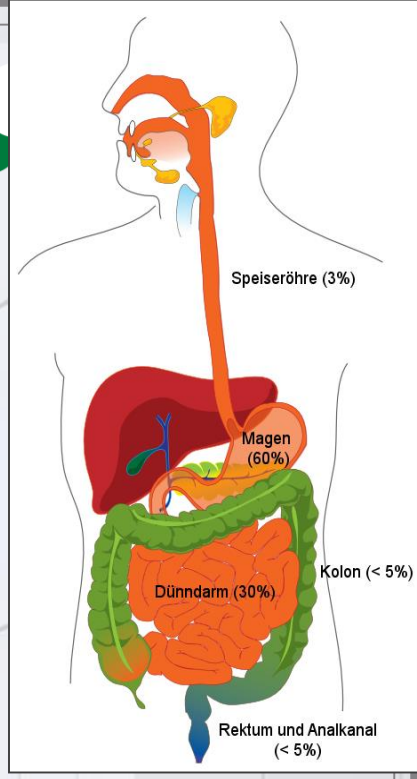
Aims

Role of pathology in the diagnosis of Gist

- Morphology
- Immunohistochemistry
- Rare and challanging Gist cases
- Differential Diagnosis
- Molecular Pathology in Gist - Mutational Analysis

Peculiar Morphology/growth pattern of WT-Gists

Introduction GIST



- Most common mesenchymal tumor of the
- GI tract (0.2% of malignant GI tumors)
- ~8000 new cases/yr in Europe.
- Median age: 55-60a
- Can occur throughout the GI tract
- Most Gists in adults(sporadic) show activating mutations in the *KIT* or *PDGFRA* genes
- Most Gists express KIT and DOG1 by IHC
- Risk stratification according to Miettinen (size, location and mitotic count in $5mm^2$ =20-25 HPF)

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Clinical Information:
- Age
- Location
- Solitary or multiple lesion(s)
- Size
- Relevant clinical history

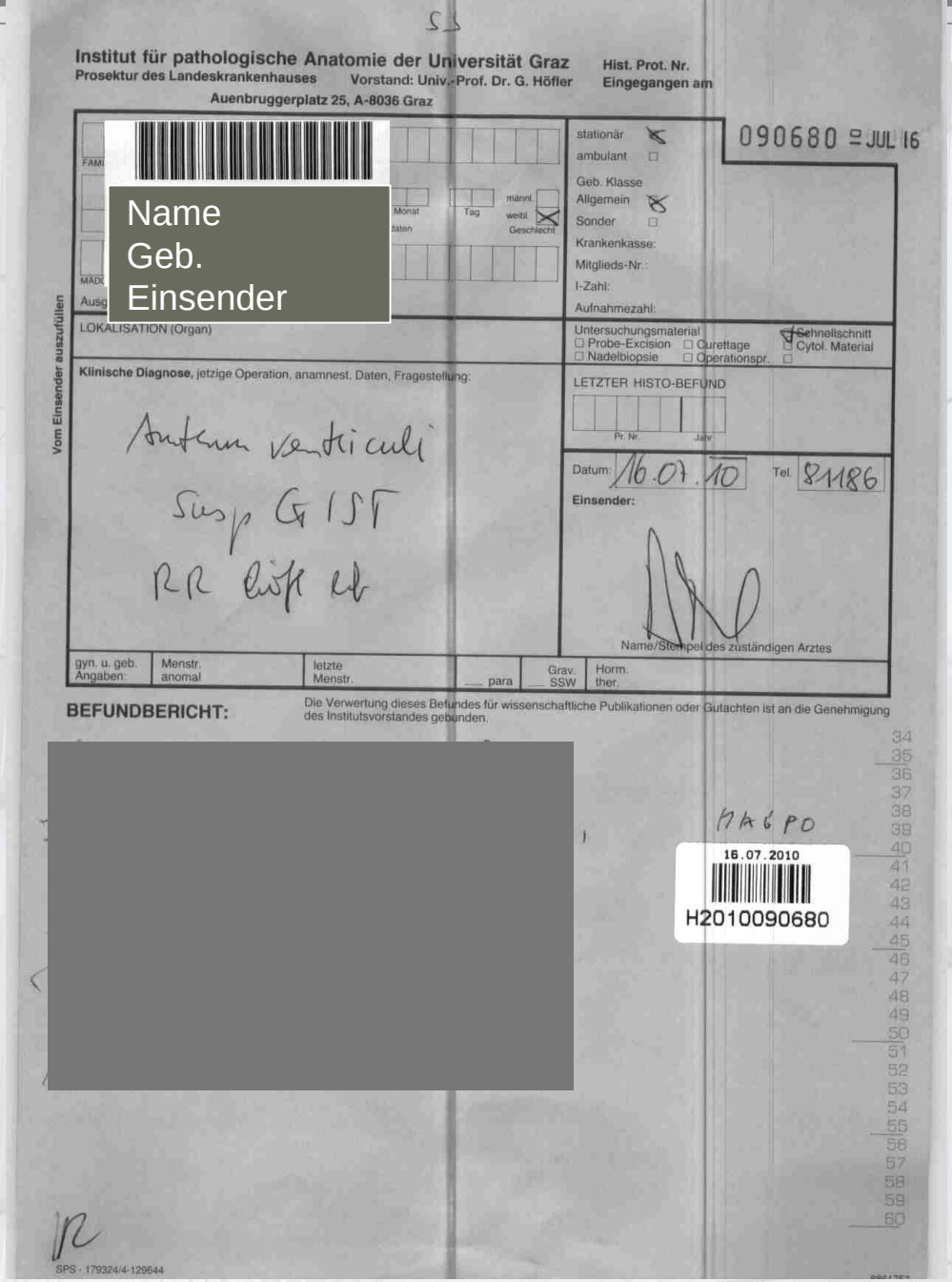
Diagnosis

Pathology
- Morphology
- IHC
- DDx
- Mitotic Activity 5mm^2
- Molekular Diagnostics

Predictive Pathology

Therapy

Prognosis



Institut für pathologische Anatomie der Universität Graz
Prosektur des Landeskrankenhauses Vorstand: Univ.-Prof. Dr. G. Höfler
Auenbruggerplatz 25, A-8036 Graz

Hist. Prot. Nr.
Eingegangen am

090680 JUL 16

Name
Geb.
Einsender

stationär ☒
ambulant ☐
Geb. Klasse
Allgemein ☒
Sonder ☐
Krankenkasse:
Mitglieds-Nr.:
I-Zahl:
Aufnahmezahl:

männl. ☐ weibl. ☒ Geschlecht

Vom Einsender auszufüllen

LOKALISATION (Organ)

Untersuchungsmaterial
☐ Probe-Excision ☐ Curettage ☑ Schnellschnitt
☐ Nadelbiopsie ☐ Operationspr. ☐ Cytol. Material

Klinische Diagnose, jetzige Operation, anamnest. Daten, Fragestellung:

Antrum ventriculi
Susp GIST
RR

LETZTER HISTO-BEFUND
Pr. Nr. Jahr

Datum: 16.07.10 Tel. 81186

Einsender:

Name/Stempel des zuständigen Arztes

gyn. u. geb. Angaben:	Menstr. anomal	letzte Menstr.	para	Grav. SSW	Horm. ther.

BEFUNDBERICHT: Die Verwertung dieses Befundes für wissenschaftliche Publikationen oder Gutachten ist an die Genehmigung des Institutsvorstandes gebunden.

[redacted]

MAGPO

16.07.2010
H2010090680

SPS - 179324/4-129644

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Gross Morphology

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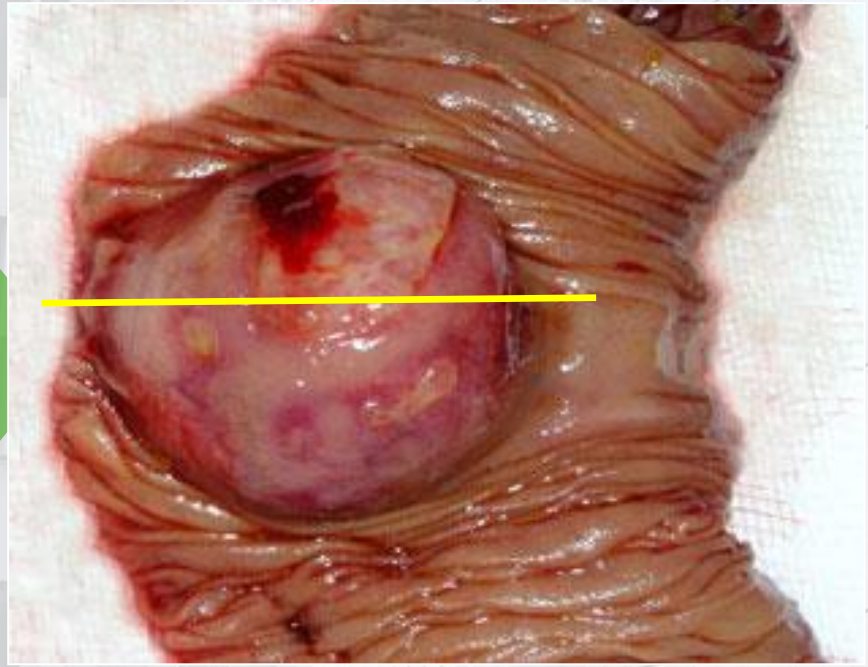
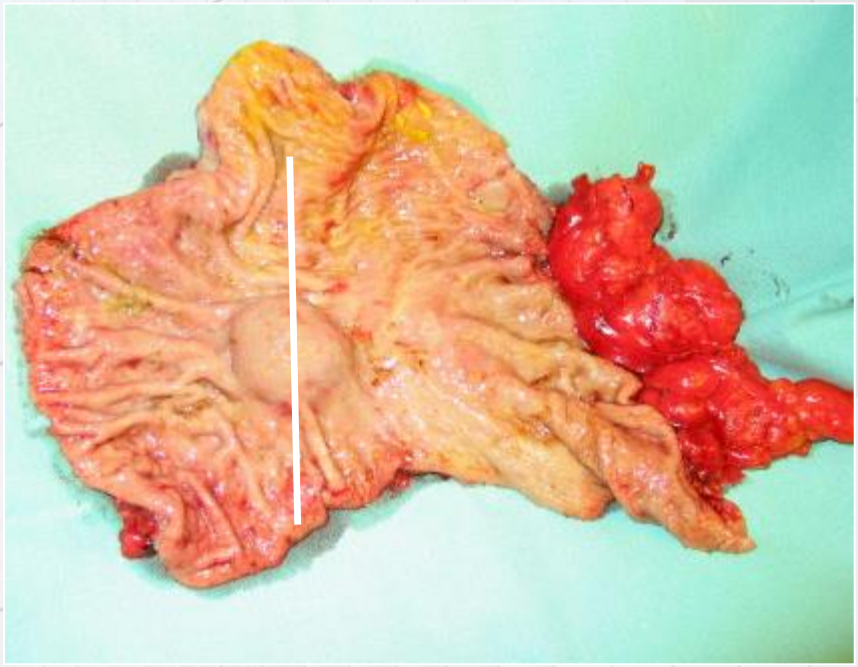
Gross Morphology



GIST Dünndarm



GIST Magen

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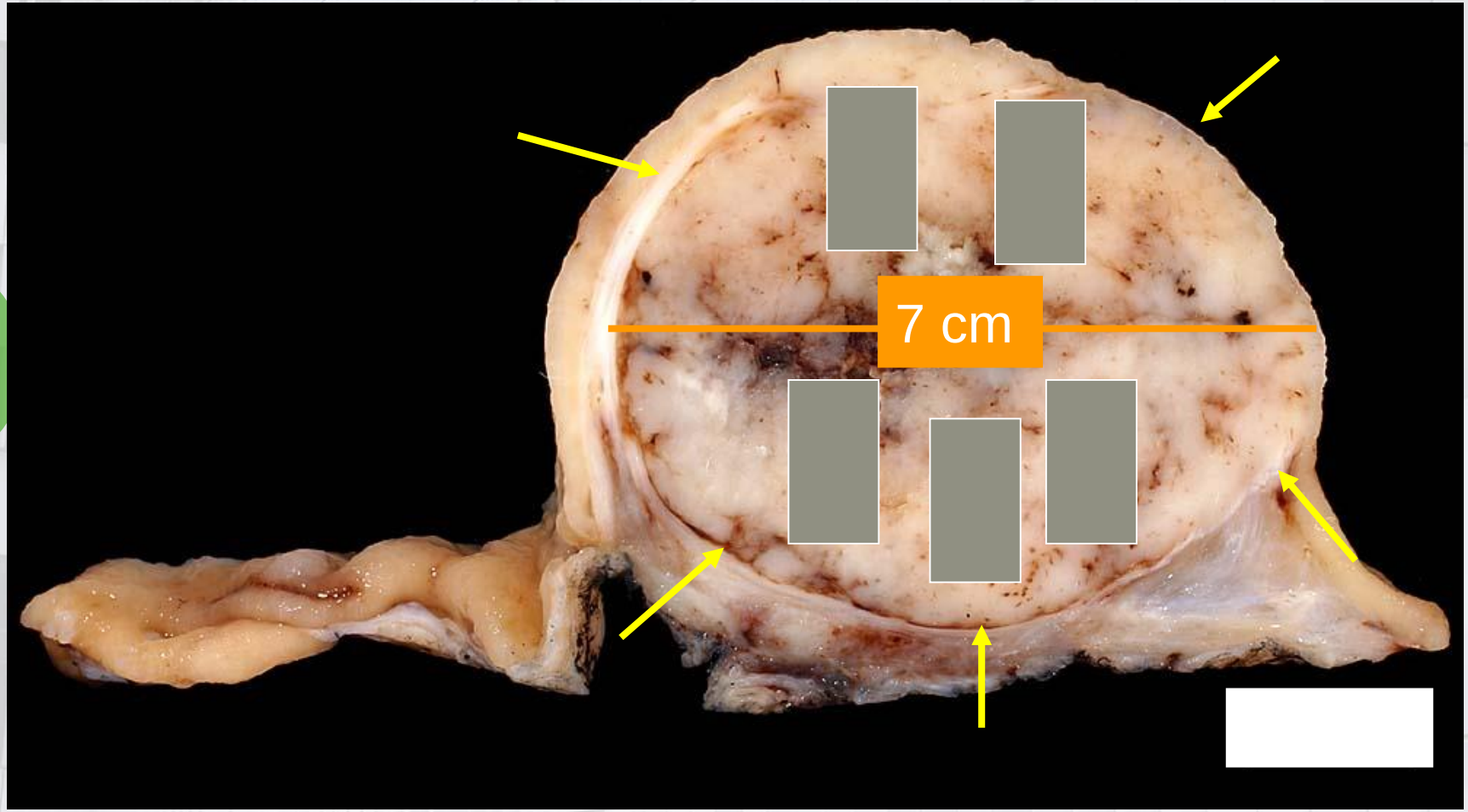
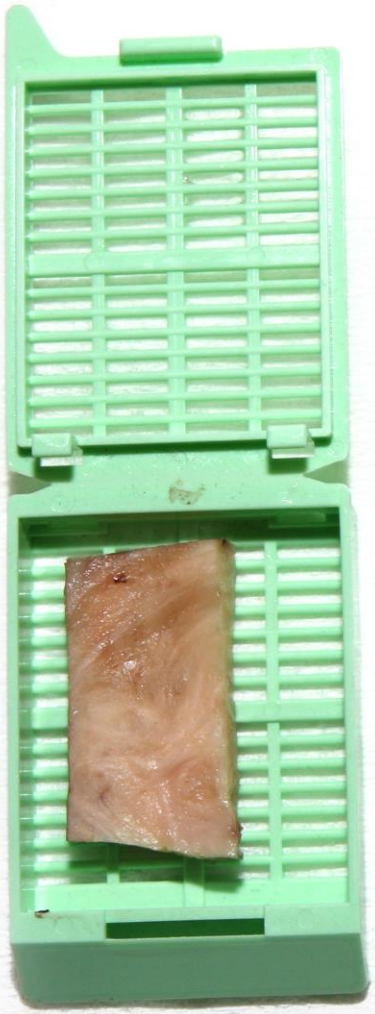
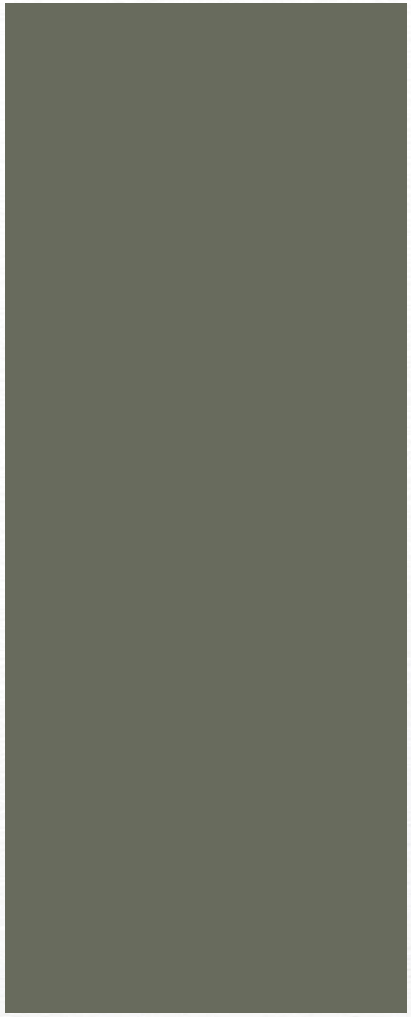
Gross morphology Gist stomach







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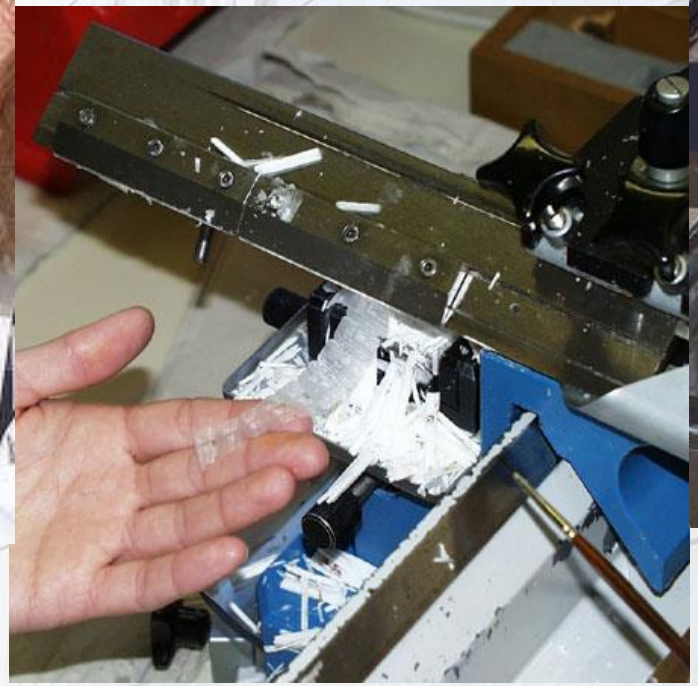

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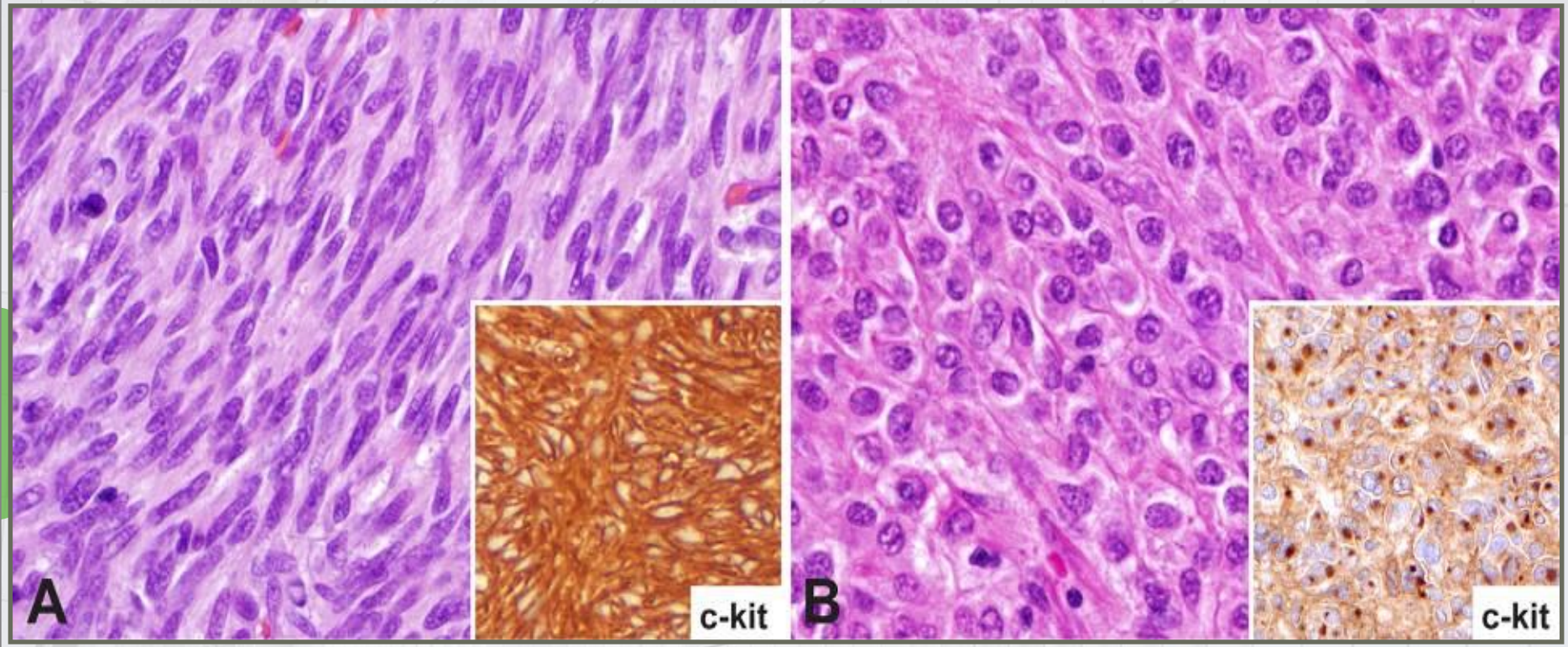
Morphology

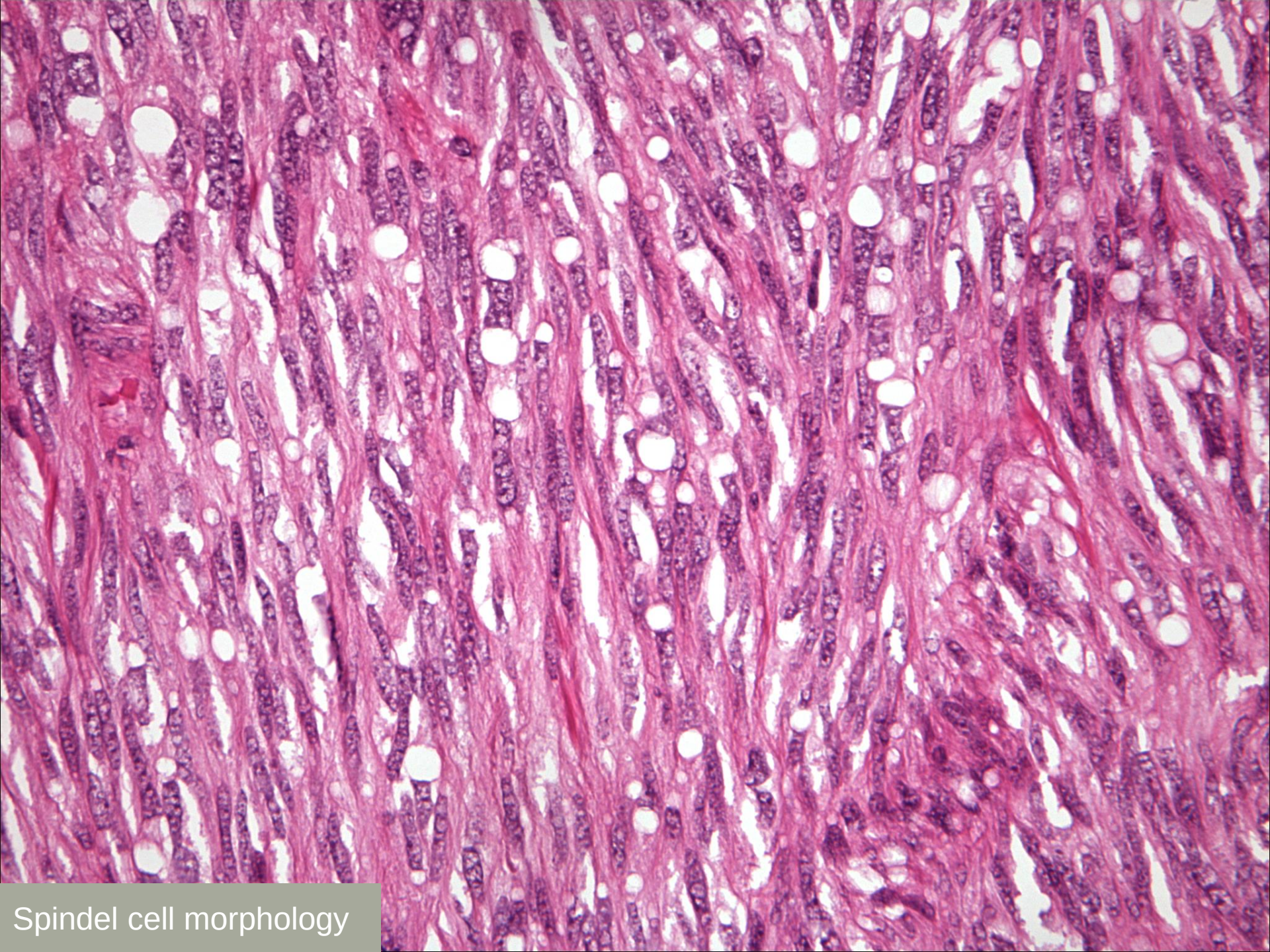


Spindel 70%

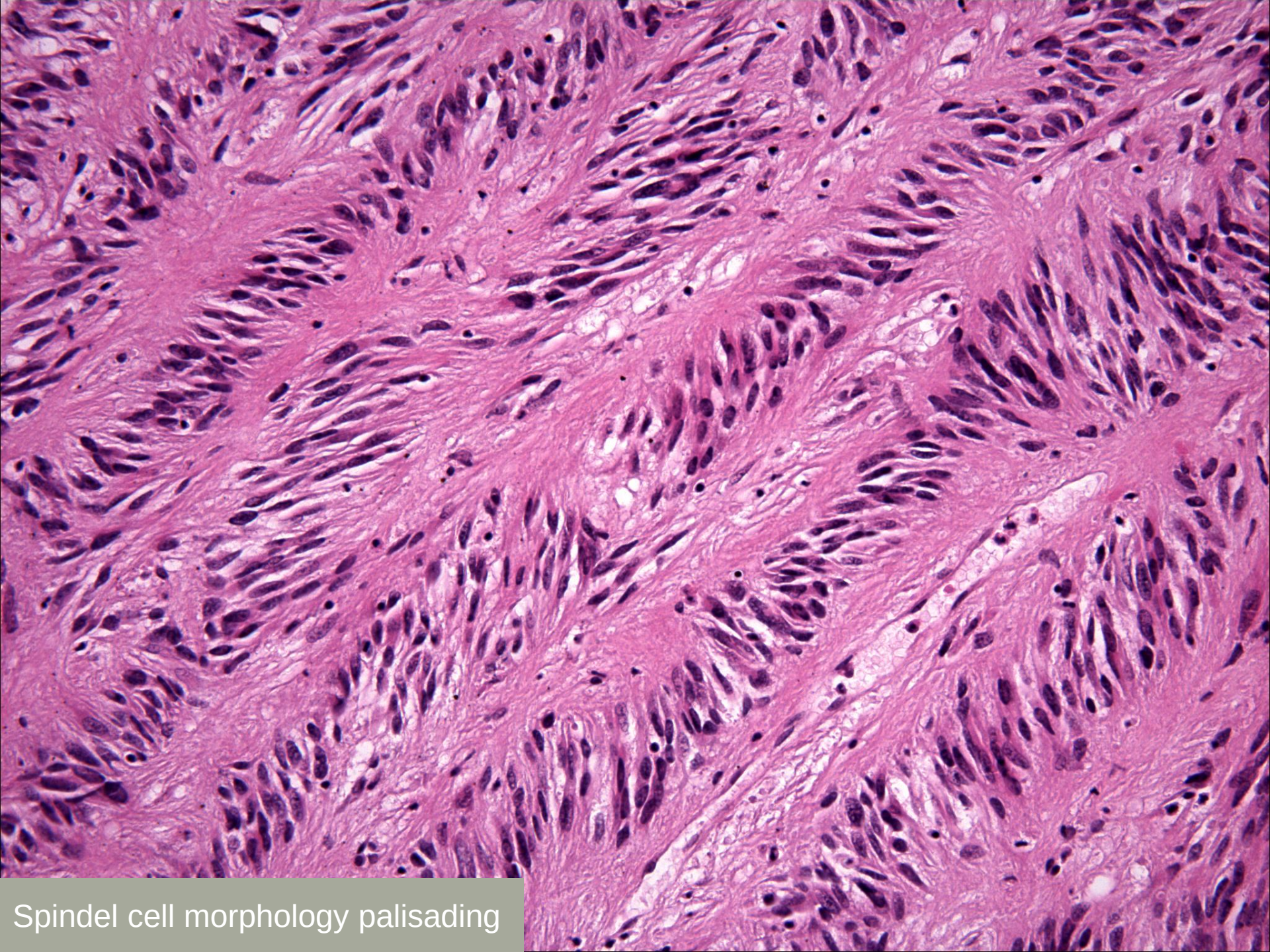
Epitheloid 10%

Mixed 10%

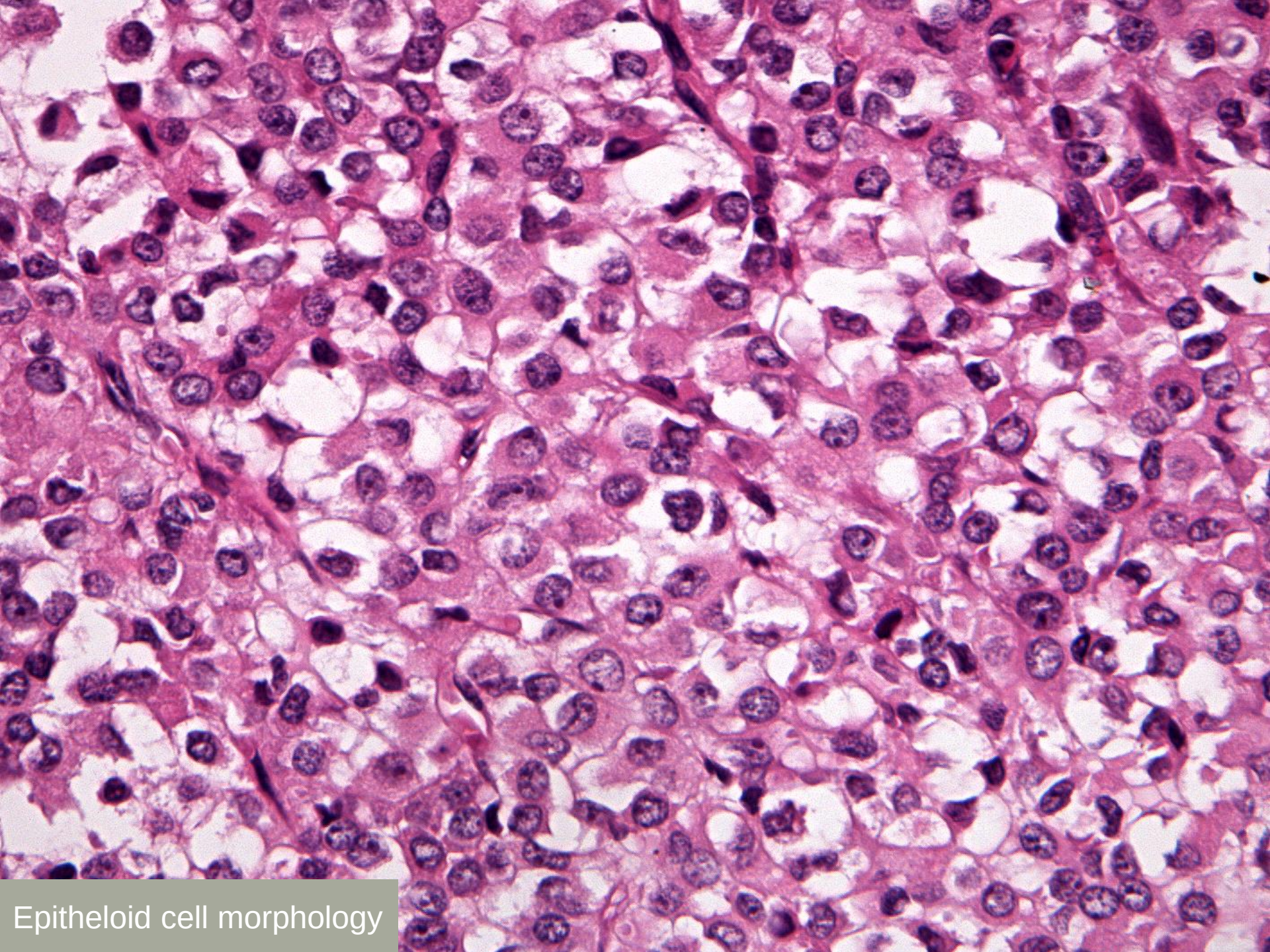
Liegl et al Hematol Oncol Clin North Am. 2009



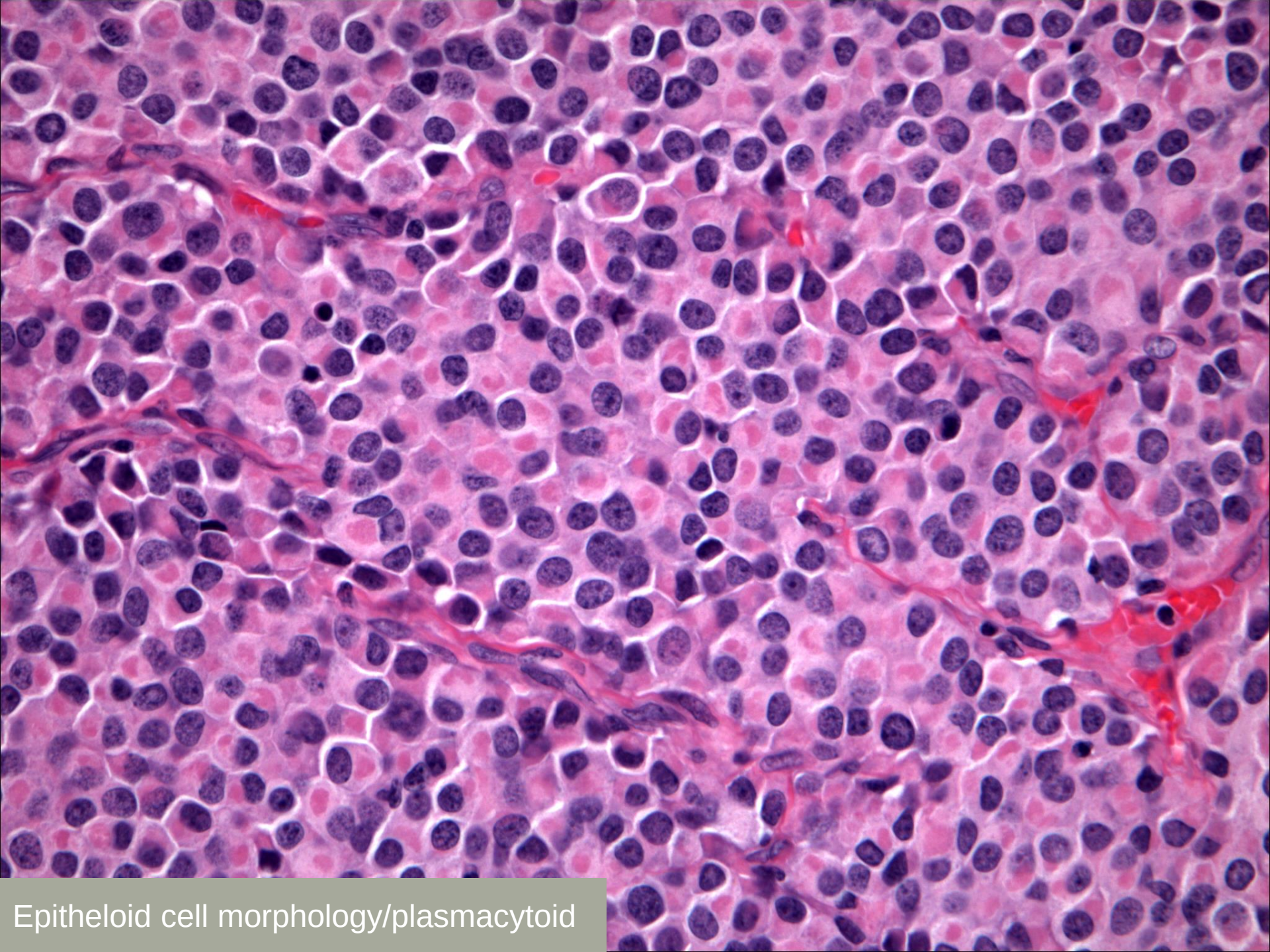
Spindel cell morphology



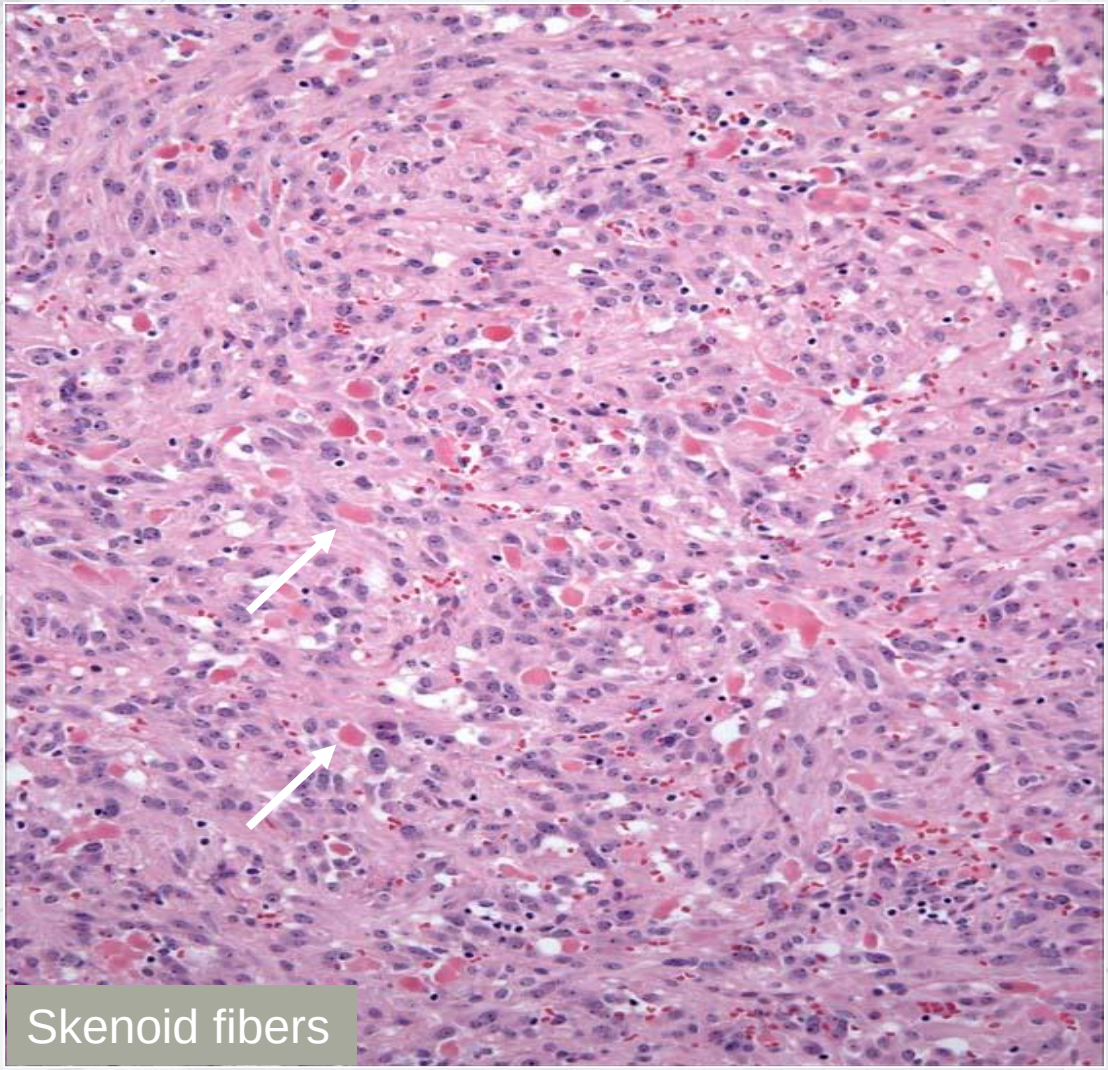
Spindel cell morphology palisading



Epitheloid cell morphology



Epitheloid cell morphology/plasmacytoid



Skenoid fibers

IMMUNOHISTOCHEMISTRY

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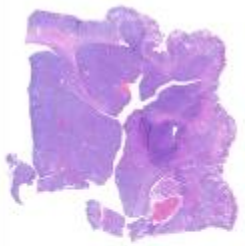
H&E	CD117 DOG 1	CD34	Smooth muscle actin	S100 protein	Desmin	Pan-keratin
	95%	70%	30%	5%	2%	<1%
						
+ +	+ +	+ +	+ +	+ +	+ +	+ +

Liegl et al Hematol Oncol Clin North Am. 2009

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DIFFERENTIALDIAGNOSIS IN GIST

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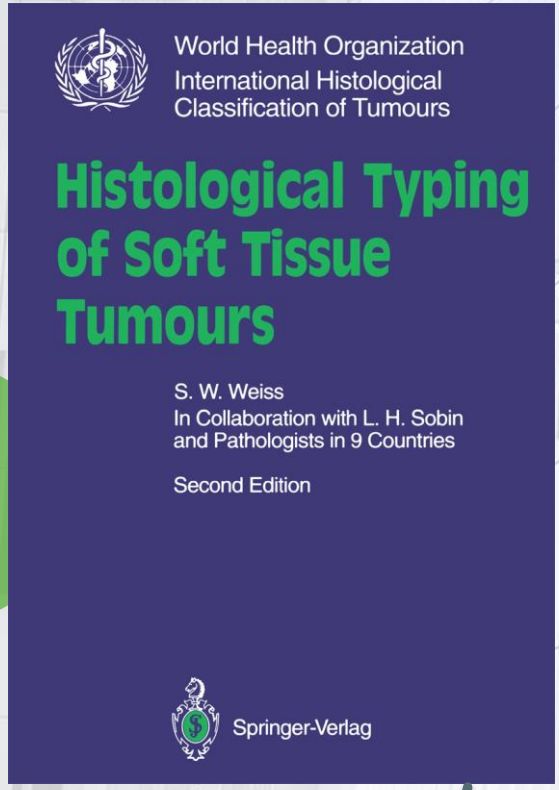
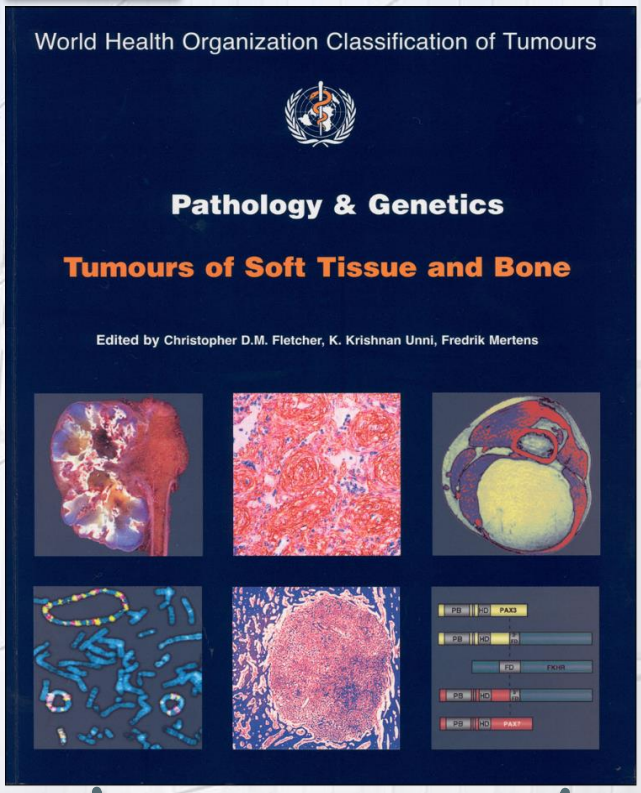
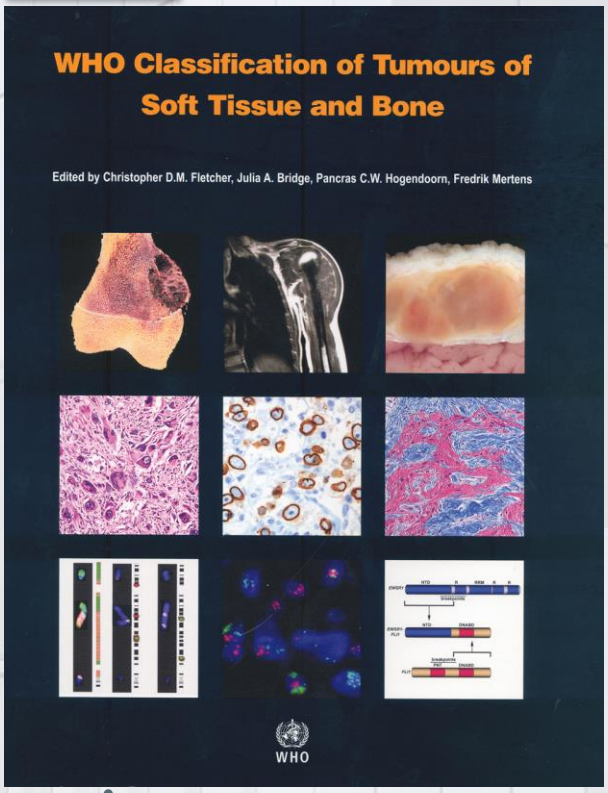
1997



2000



2013



Genetics

Genetics/molecular Classification New Entities

Classification of STT (line of differentiation)

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ain
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muscle
muscle

Personalised Therapy

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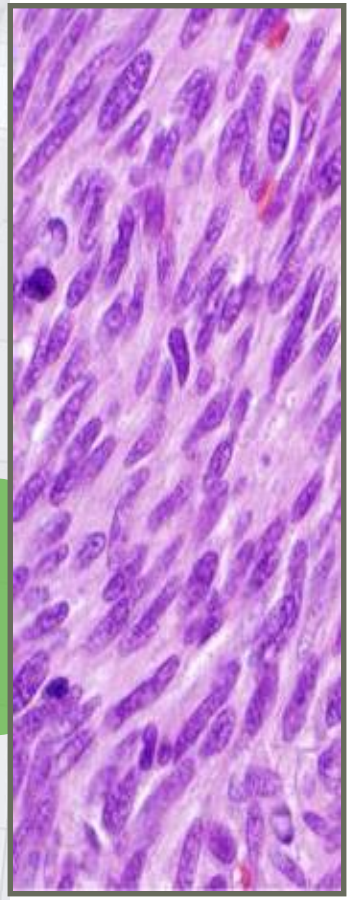
Differential Diagnosis:
Gist with spindle cell morphology



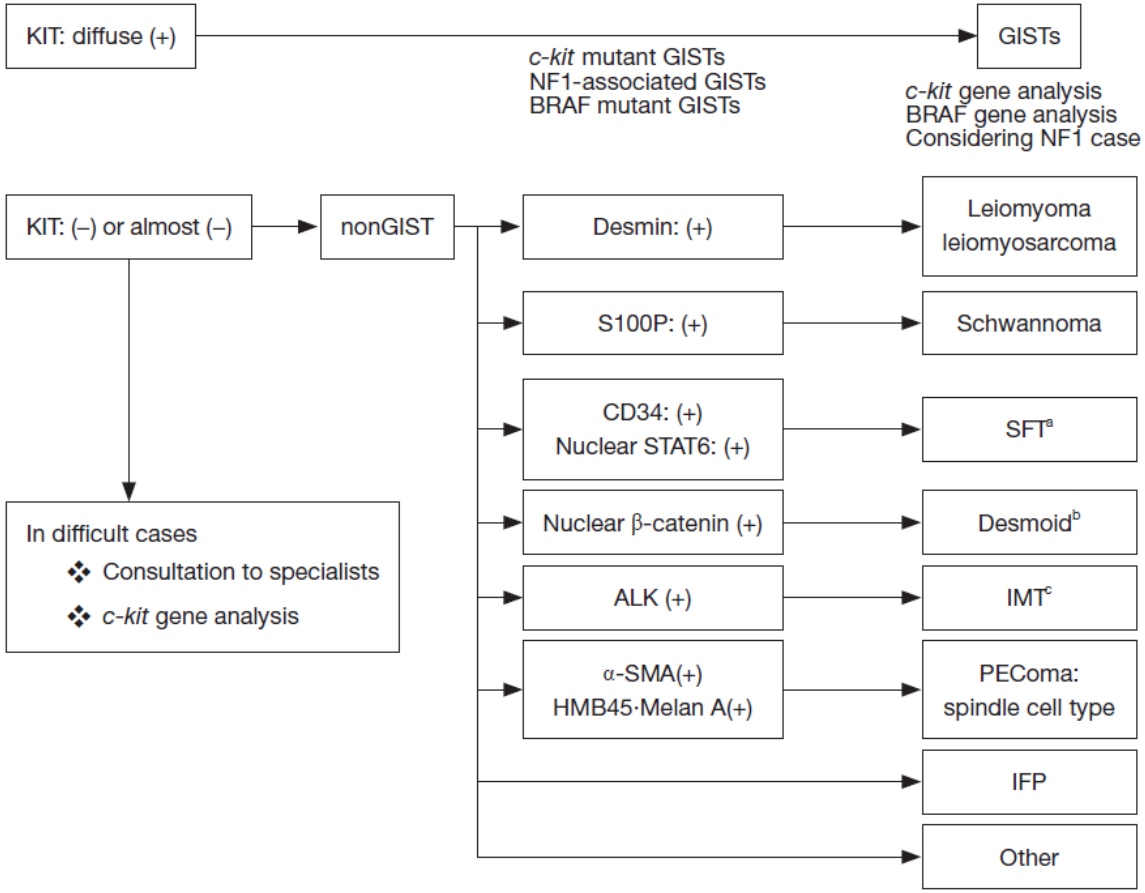


Figure 1 Flow chart of differential diagnoses of spindle cell mesenchymal tumors. [a], NAB2-STAT6 fusion gene analysis is useful; [b], β-catenin gene analysis is useful; [c], ALK FISH is useful. GIST, gastrointestinal stromal tumor; SFT, solitary fibrous tumor; IMT, inflammatory myofibroblastic tumor; IFP, inflammatory fibroid polyp; ALK, anaplastic lymphoma kinase; FISH, fluorescent in situ hybridization; STAT, signal transducer and activator of transcription; NAB2, NGFI-A binding protein-2; α-SMA, α-smooth muscle actin.

Transl Gastroenterol Hepatol 2018;3:27

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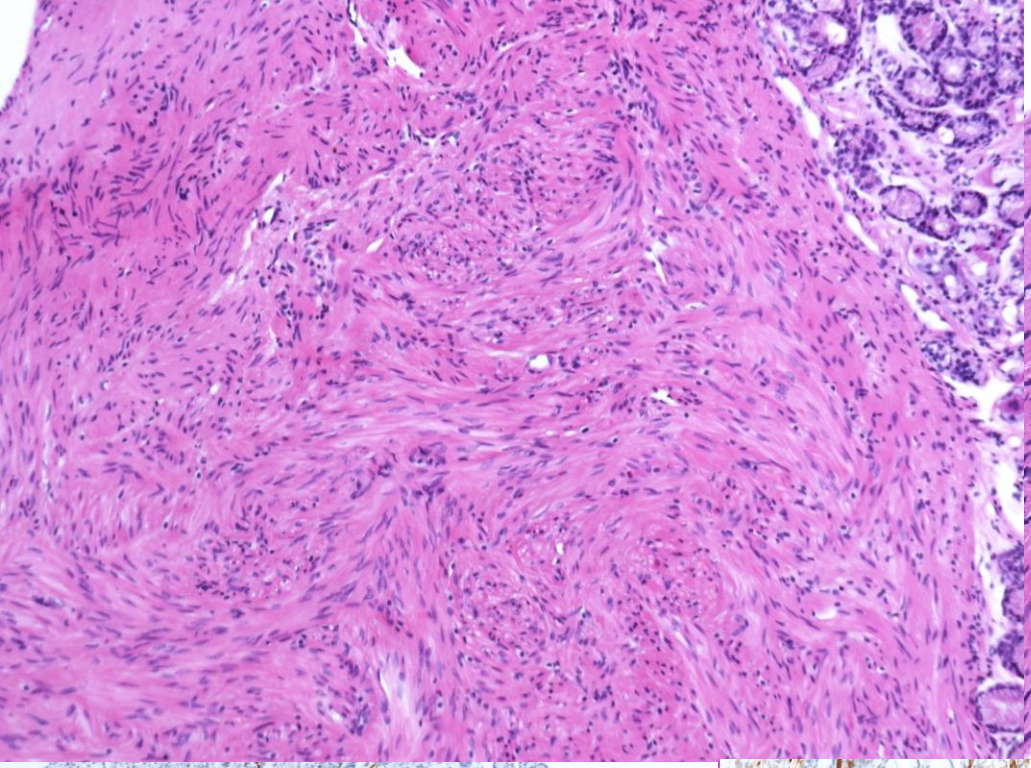
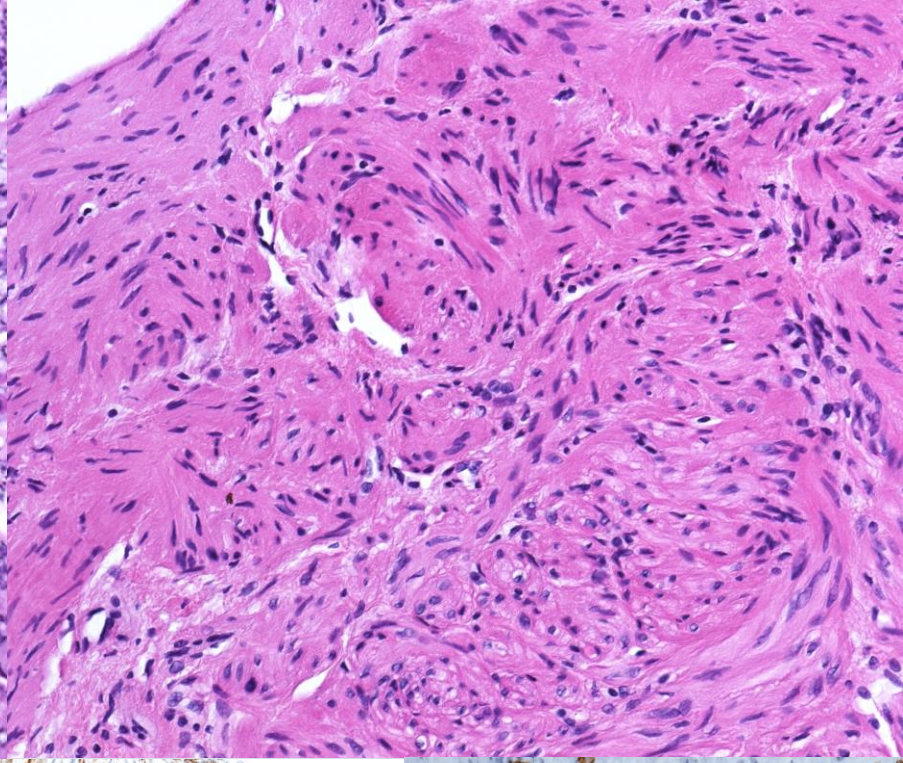
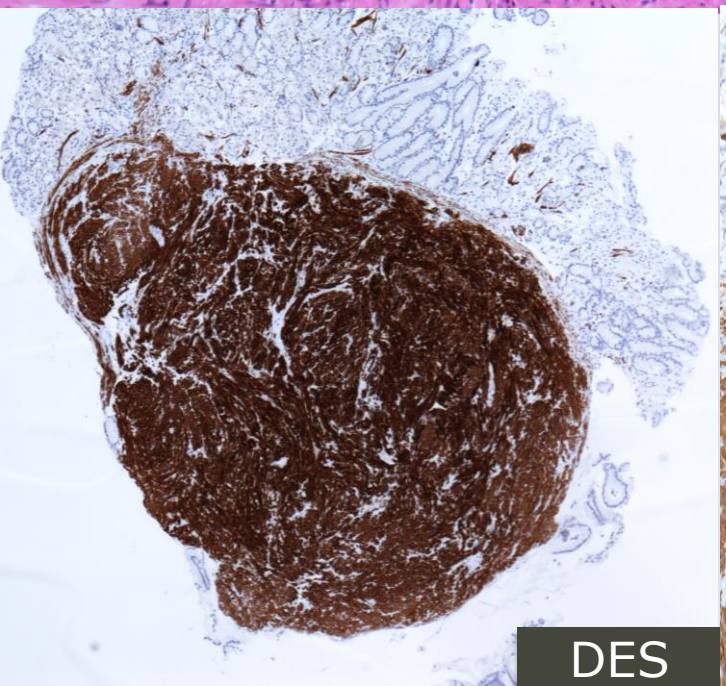
Smooth muscle tumors

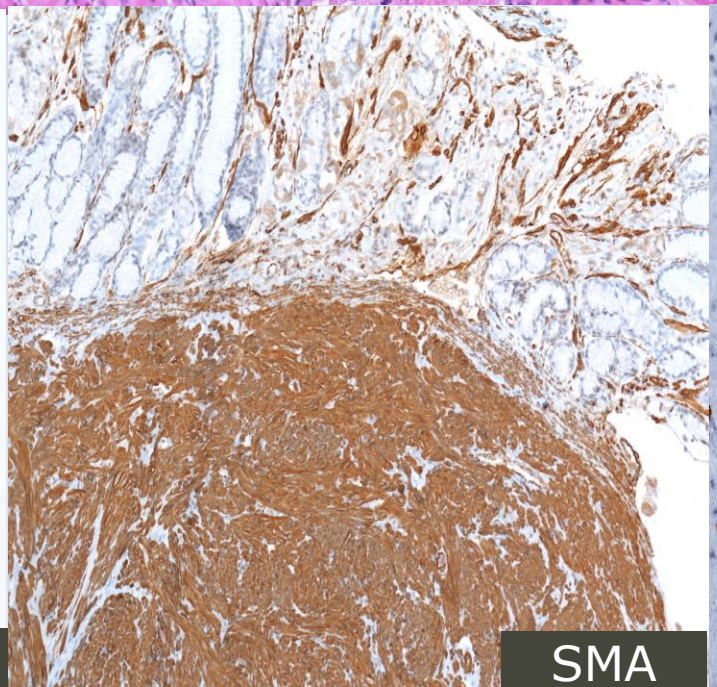
Leiomyoma



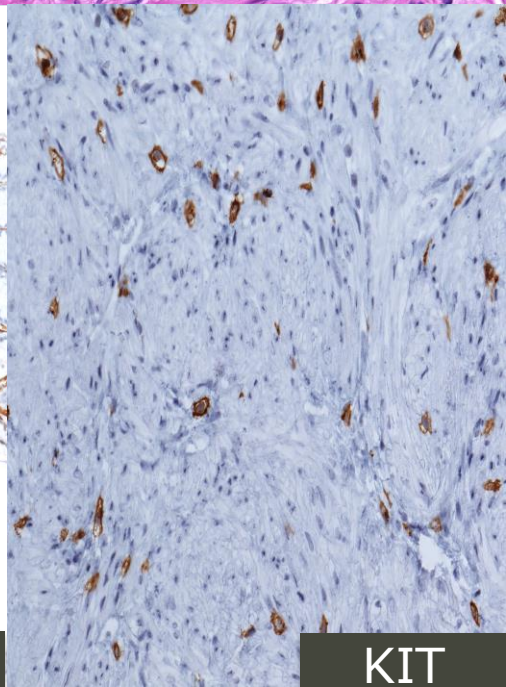




DES



SMA



KIT

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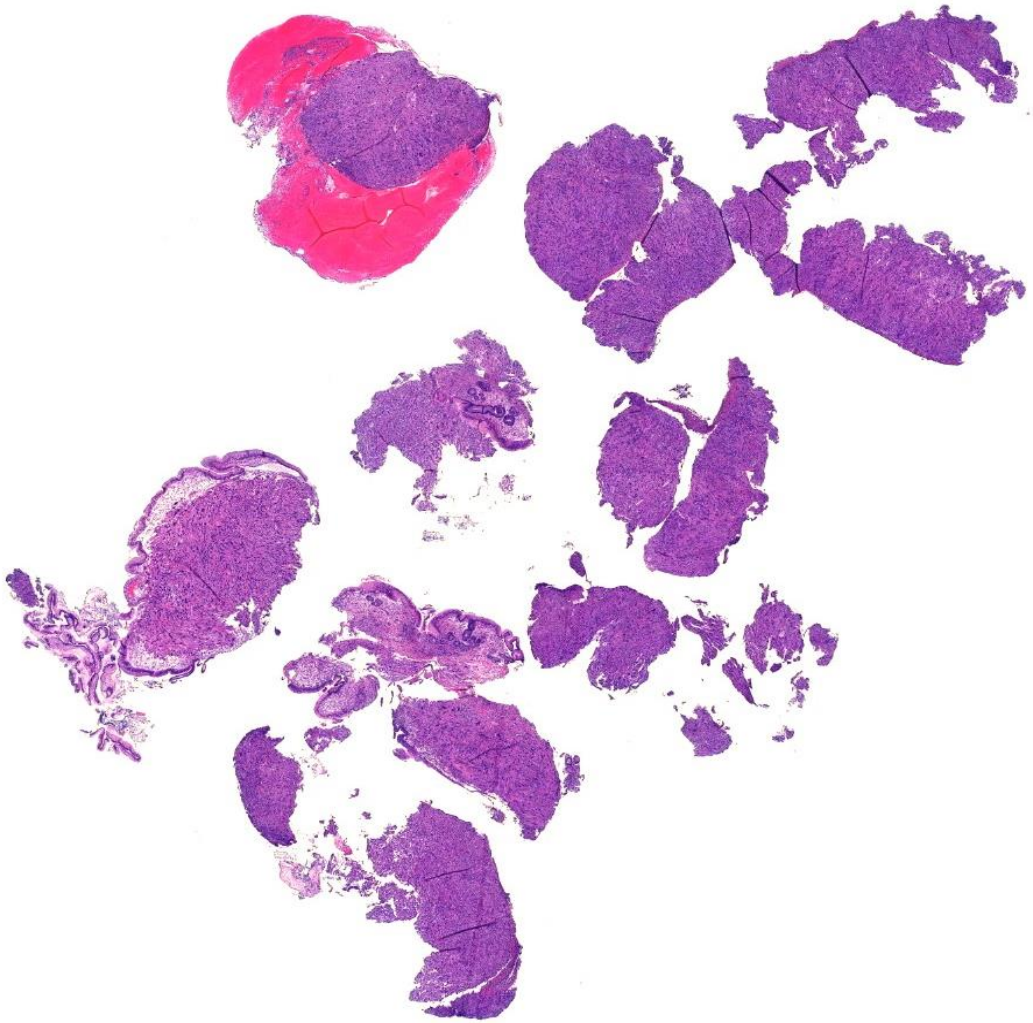
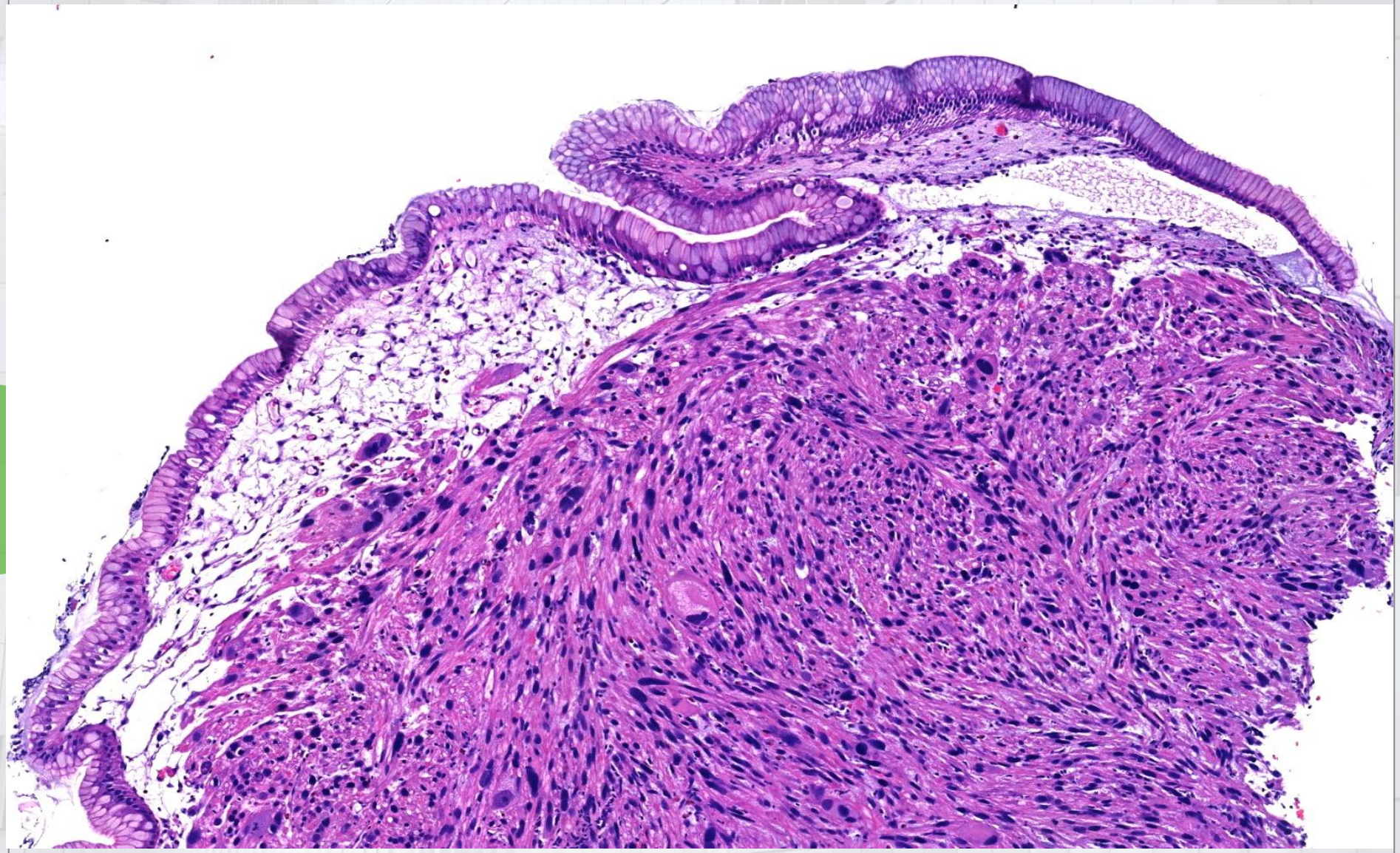
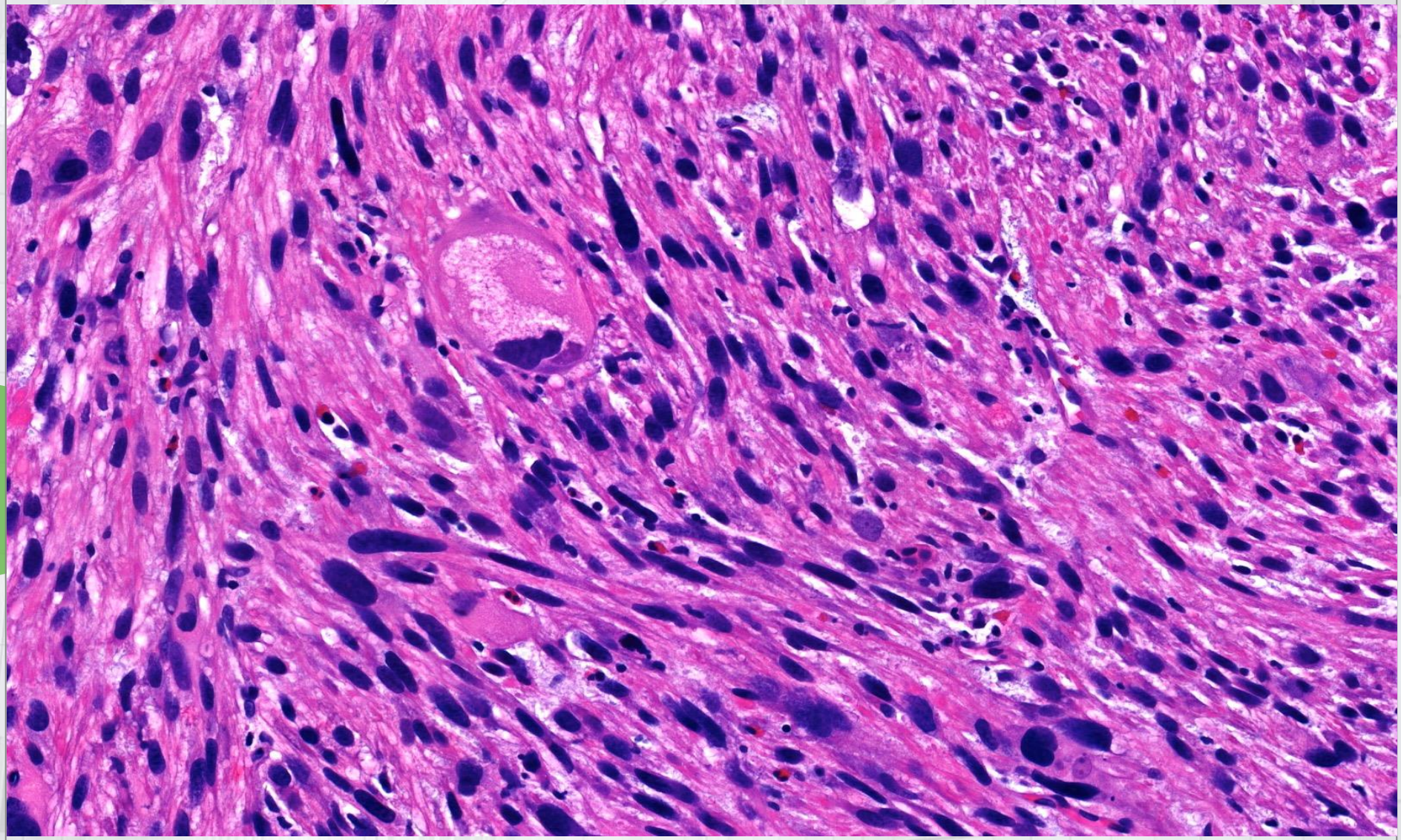
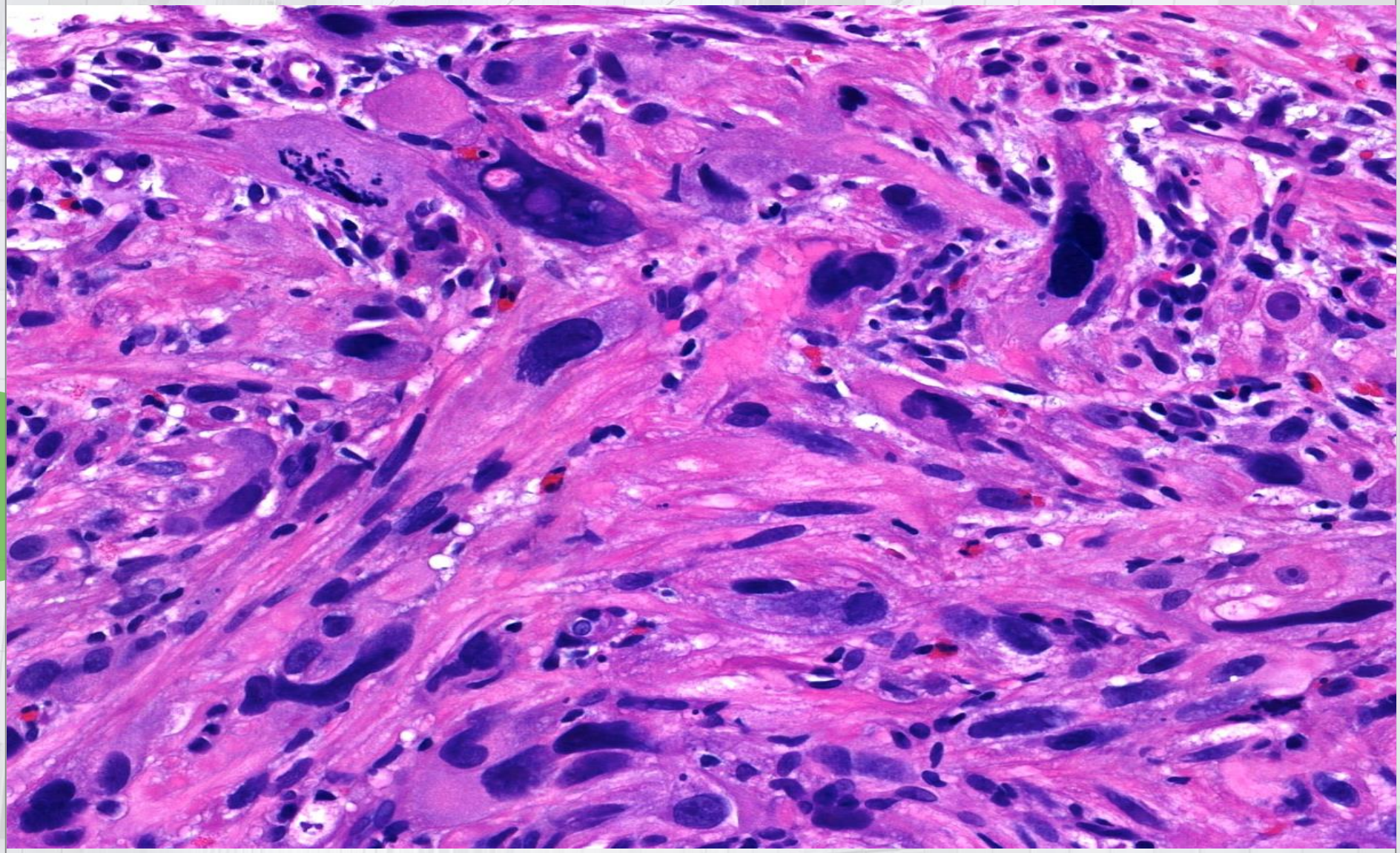
Smooth muscle tumors

Leiomyosarcoma



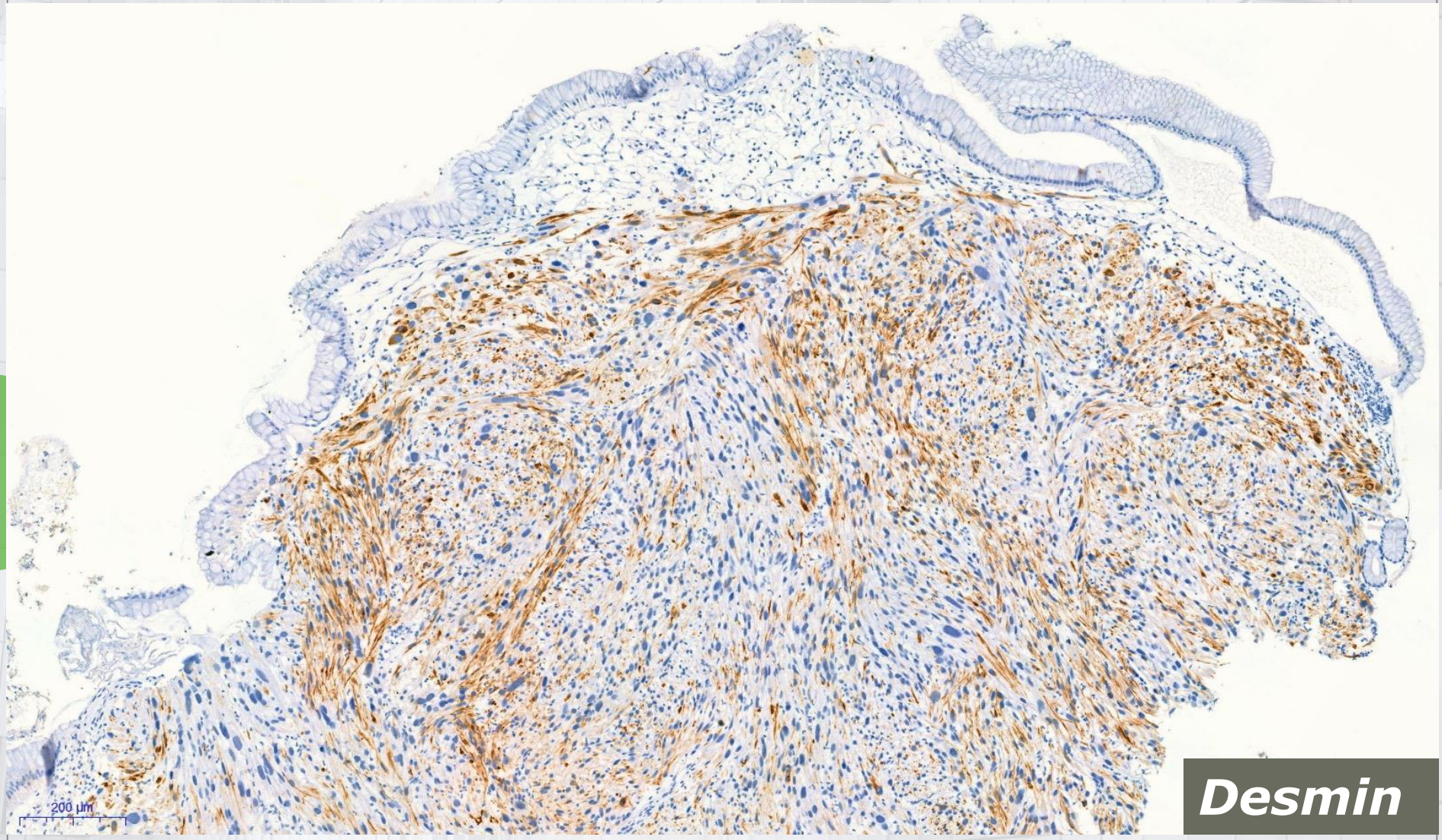






SMA

Caldesmom



Desmin

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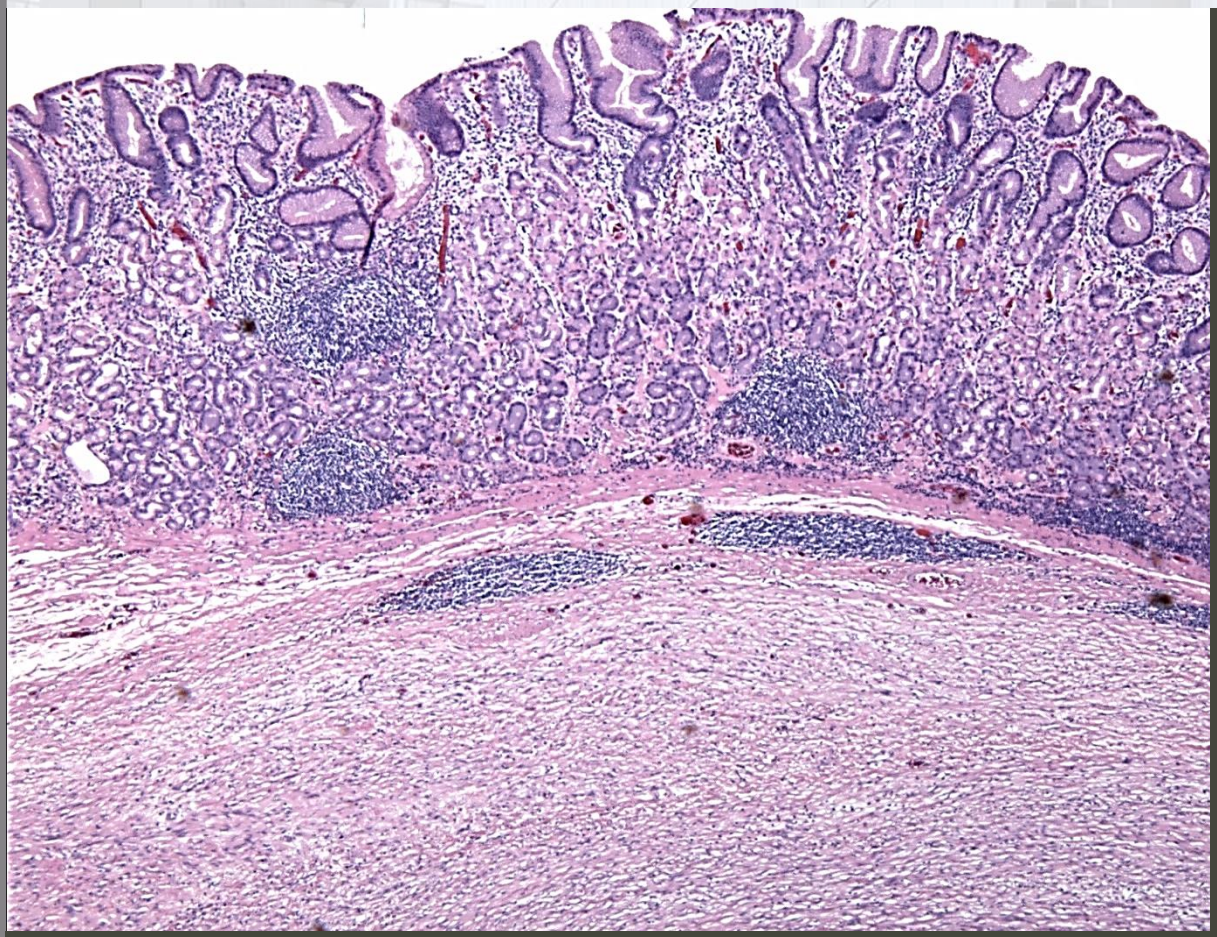
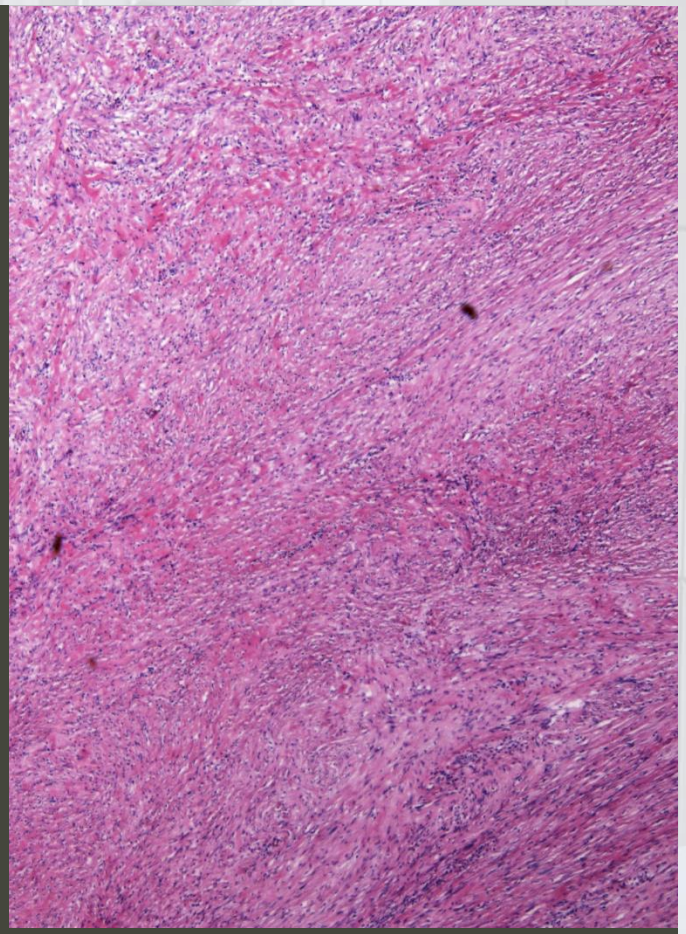
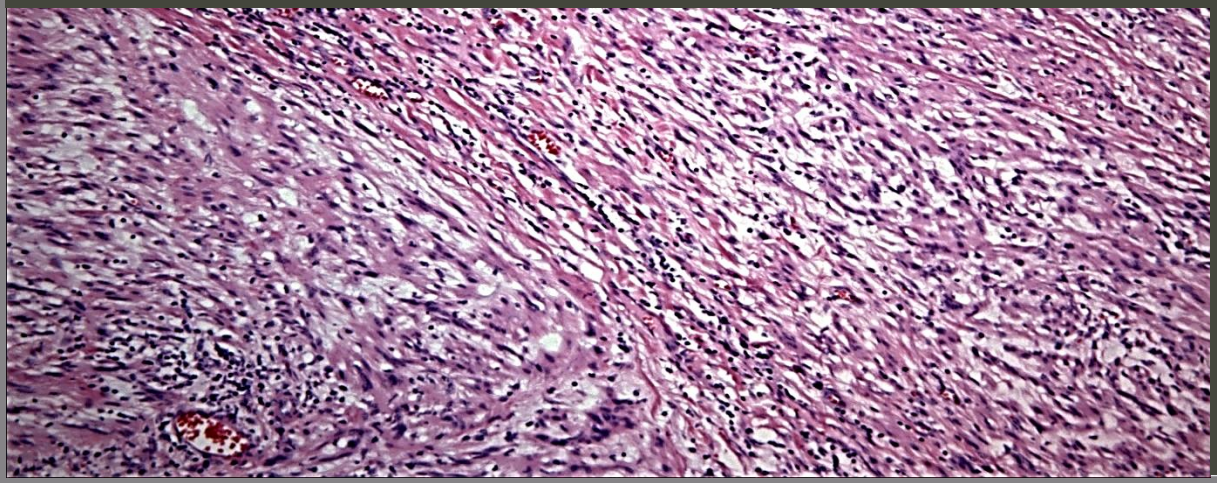
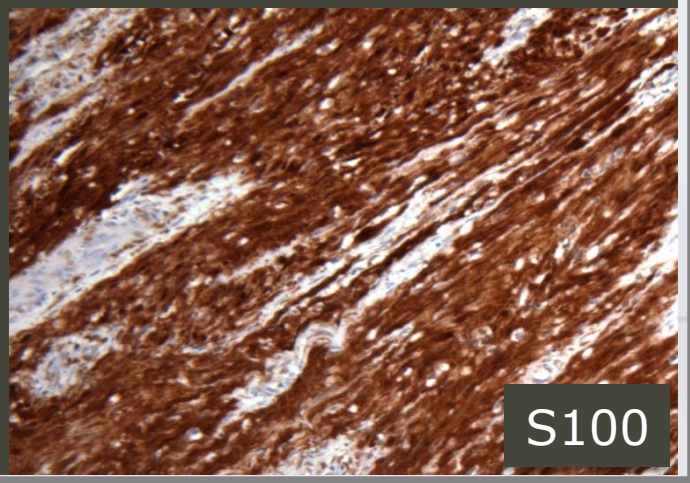
Neural tumors

Schwannoma








S100

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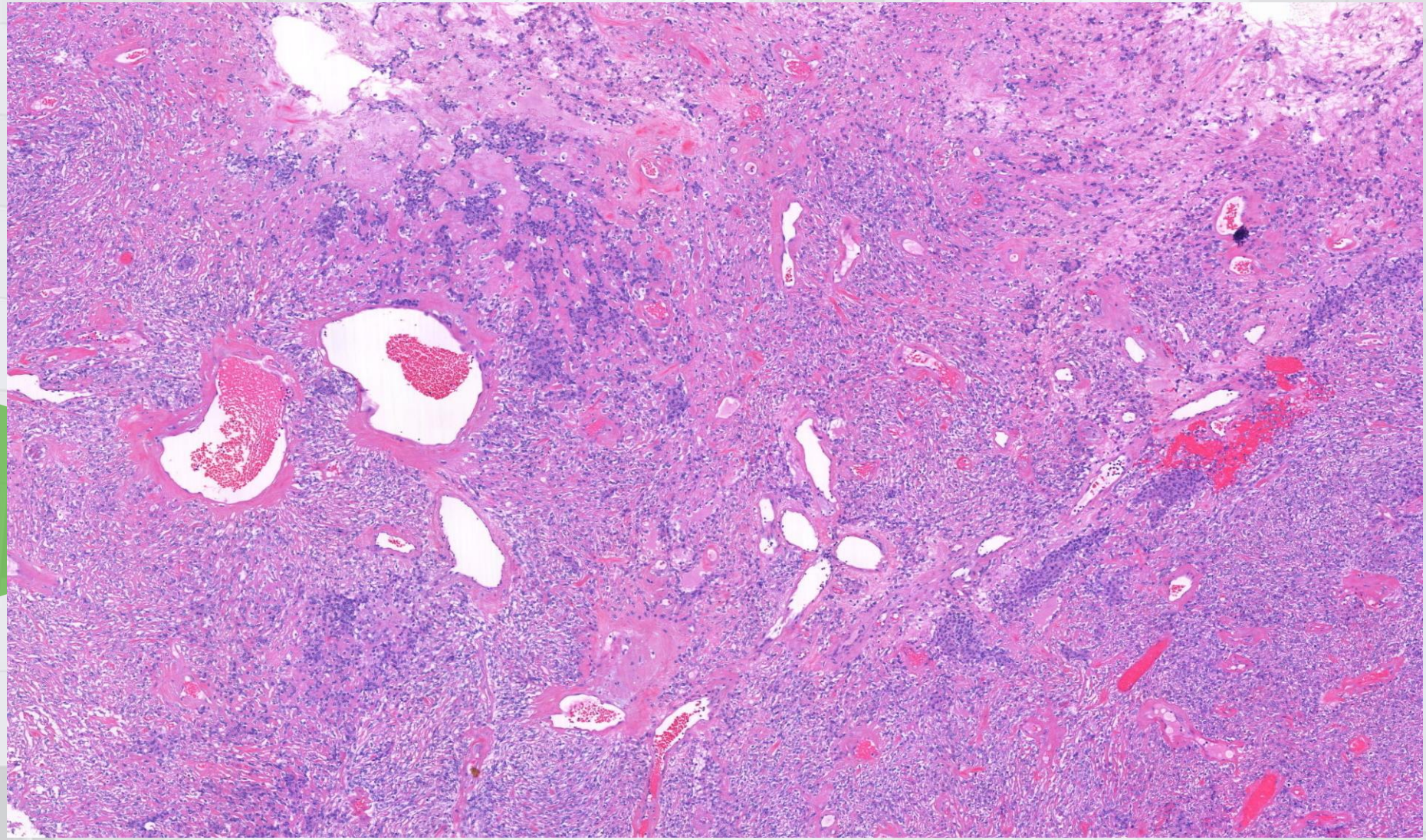
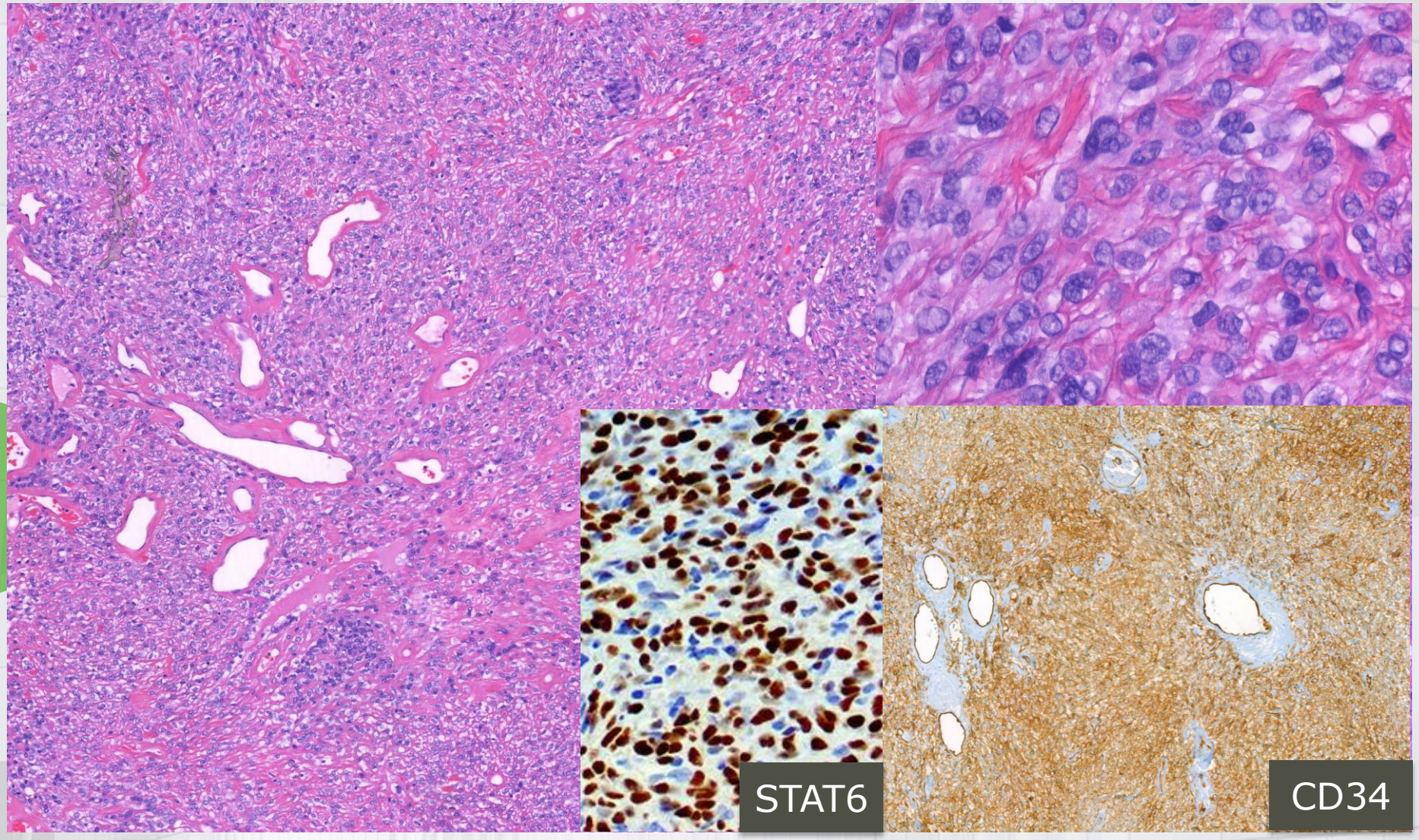
Fibroblastic and Myofibroblastic tumors

Solitary fibrous tumor




STAT6
CD34

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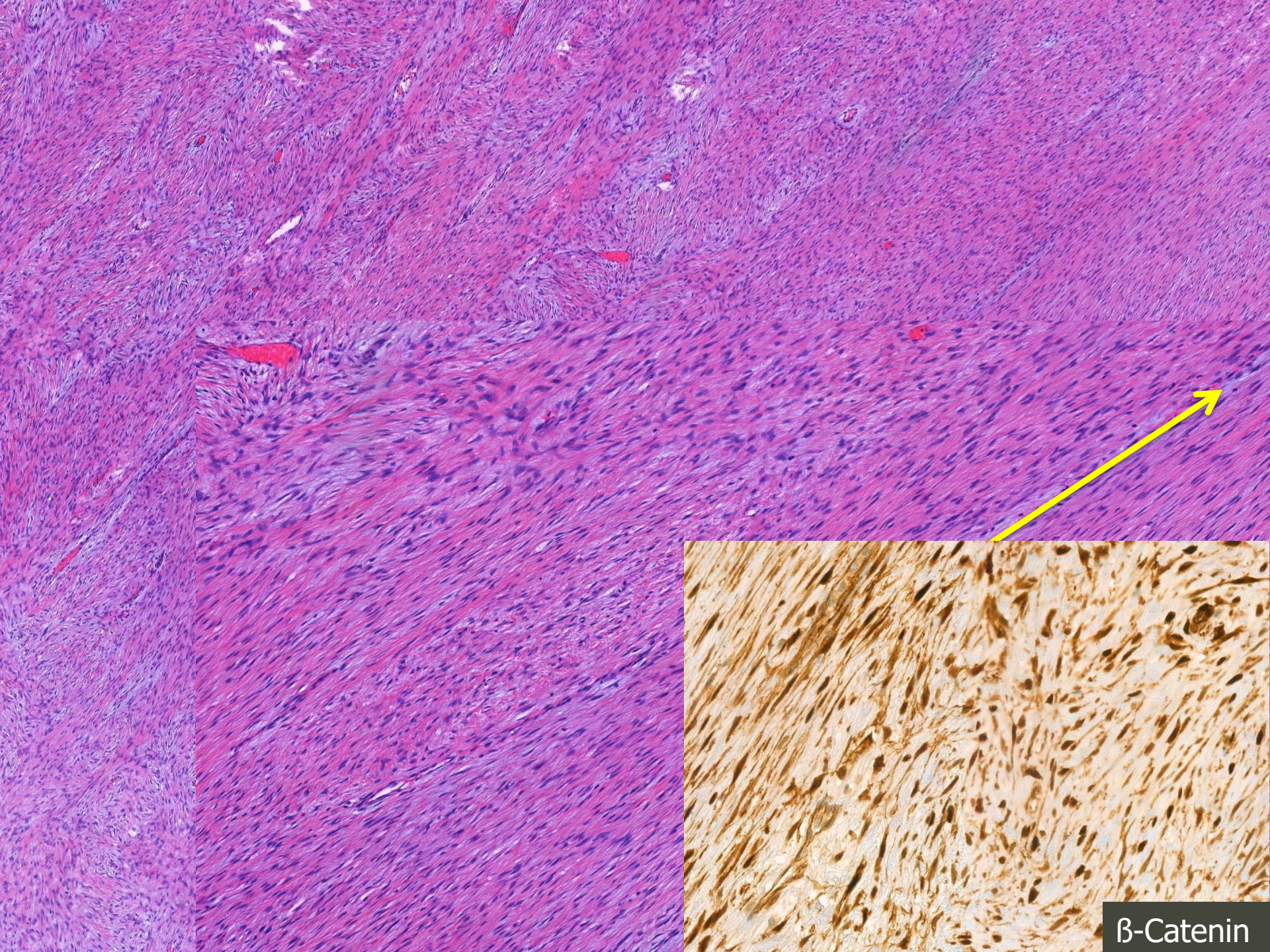
Fibroblastic and Myofibroblastic tumors

Fibromatosis - Desmoid


ß-Catenin

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Fibroblastic and Myofibroblastic tumors

Inflammatory myofibroblastic tumor

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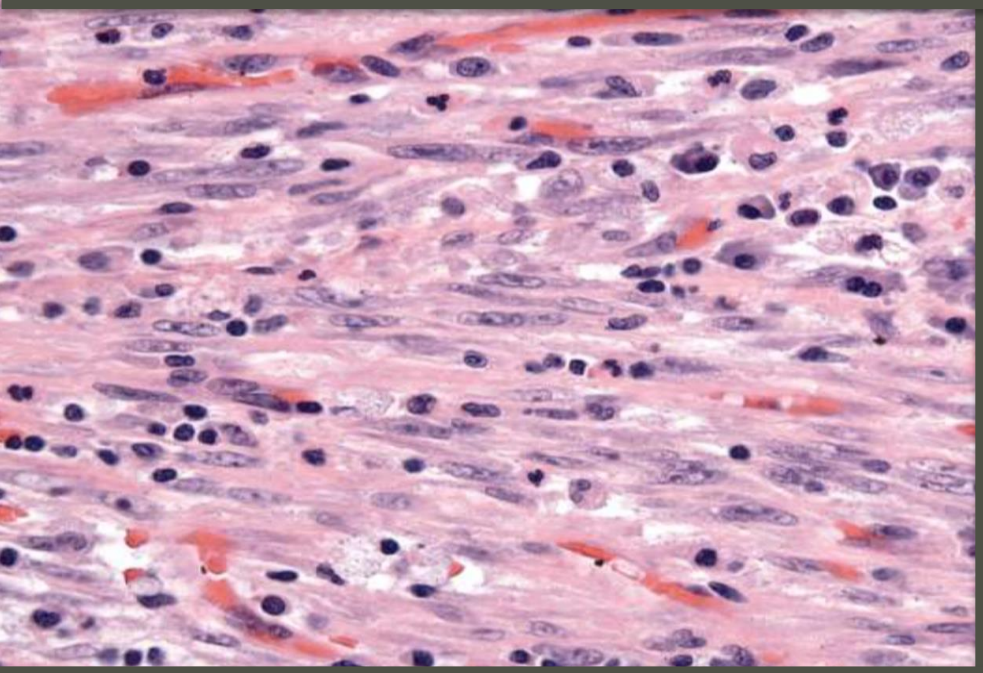
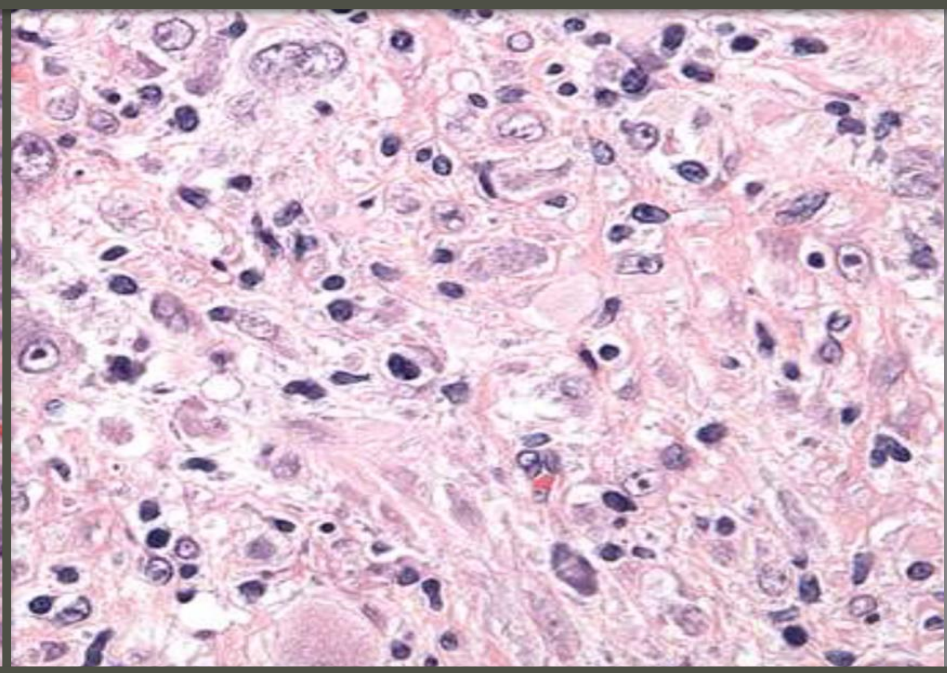
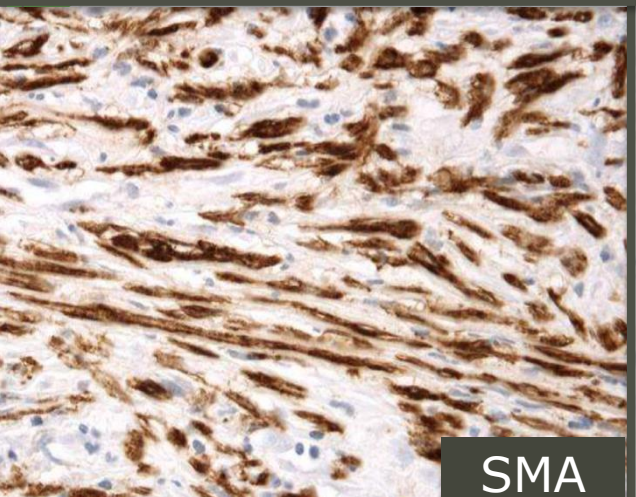
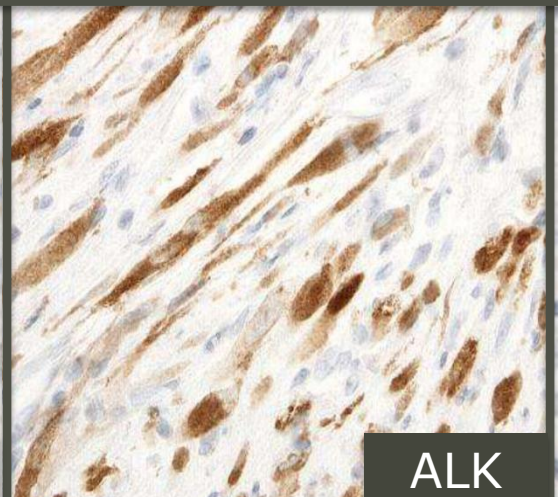
Inflammatory Myofibroblastic Tumor









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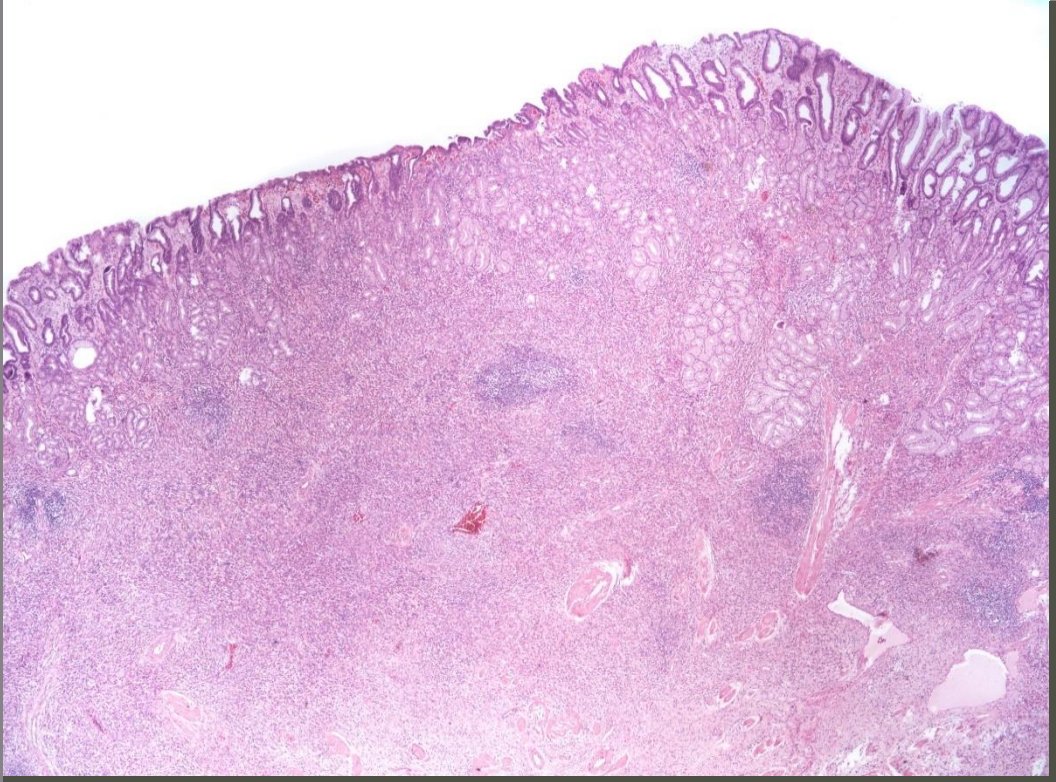
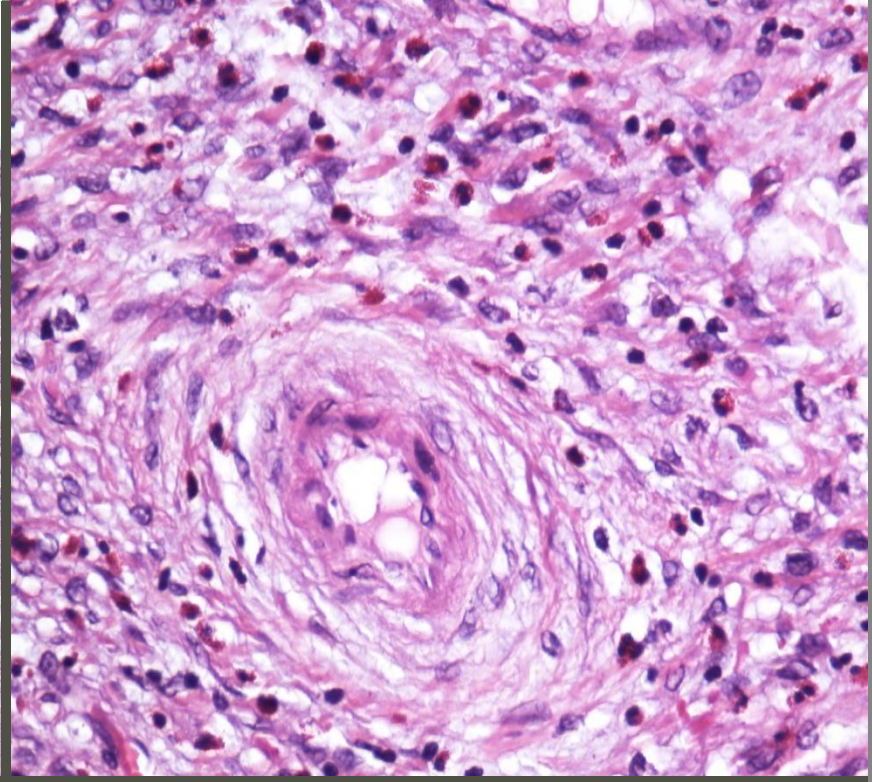
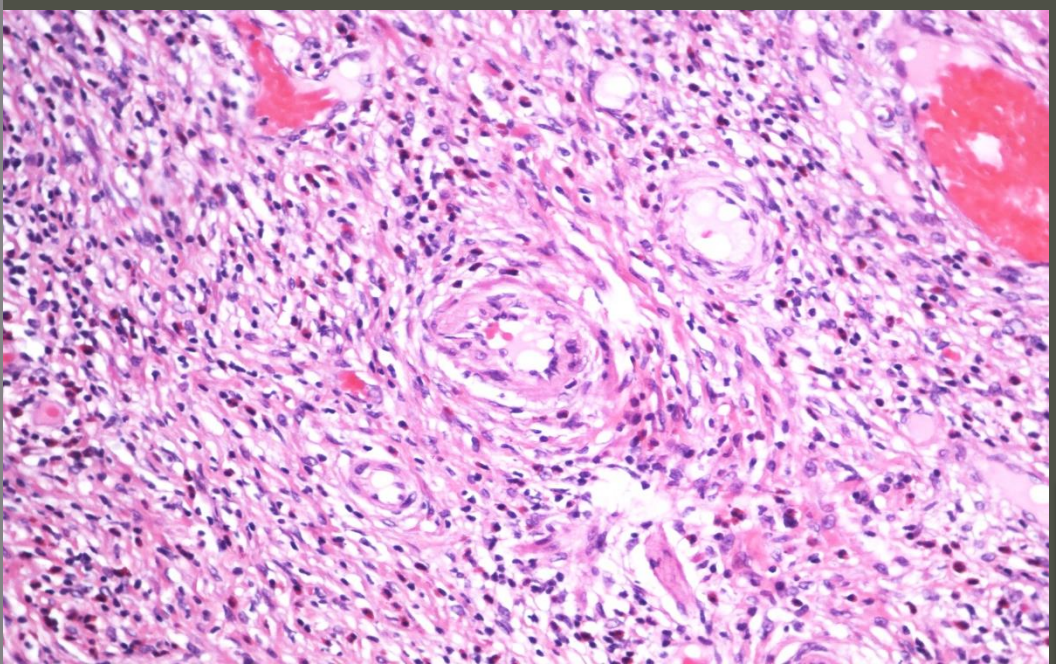
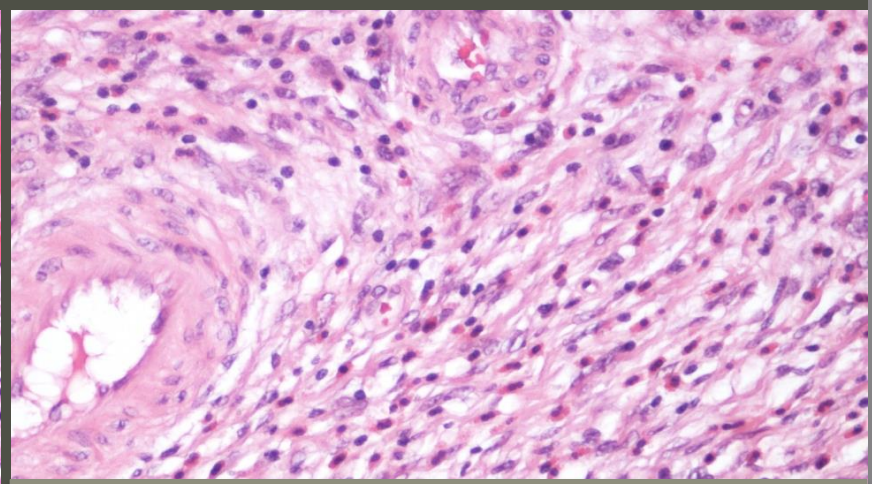
Fibroblastic and Myofibroblastic tumors

Inflammatory fibroid polyp









Mutations in PDGFRA
Stomach: exon 18 mutations
Small bowel: exon 12 mutations

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Fibroblastic and Myofibroblastic tumors

Plexiform fibromyxoid tumor

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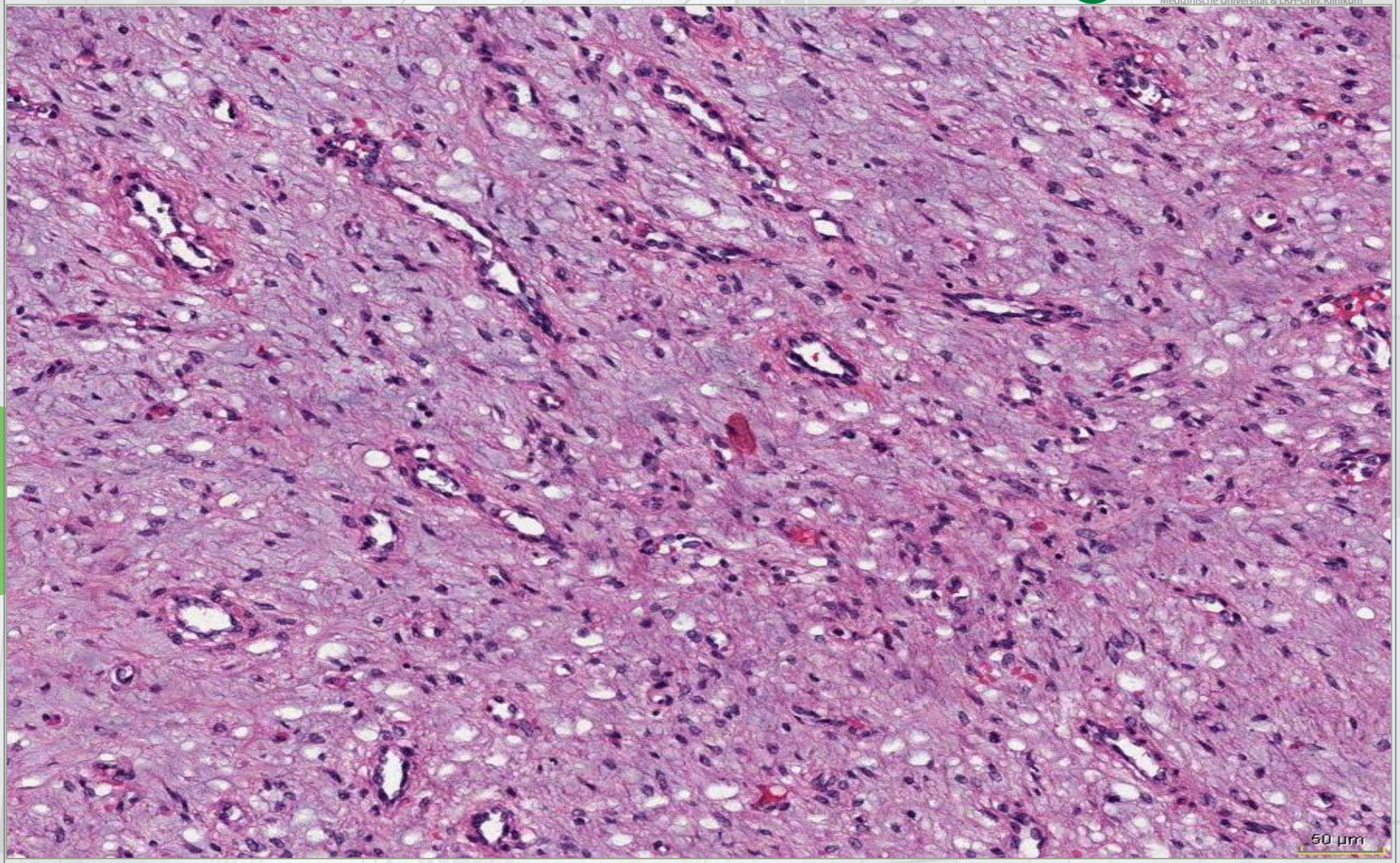
50 µm

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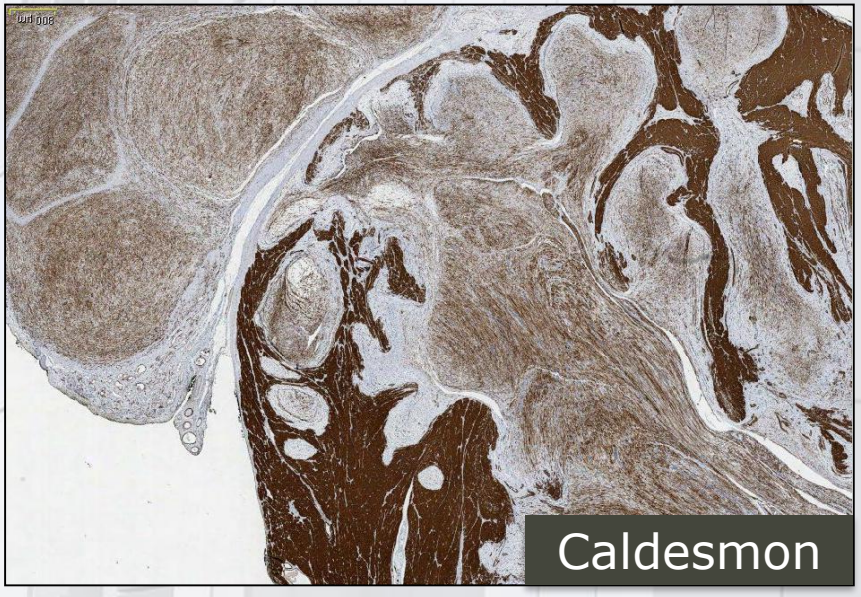
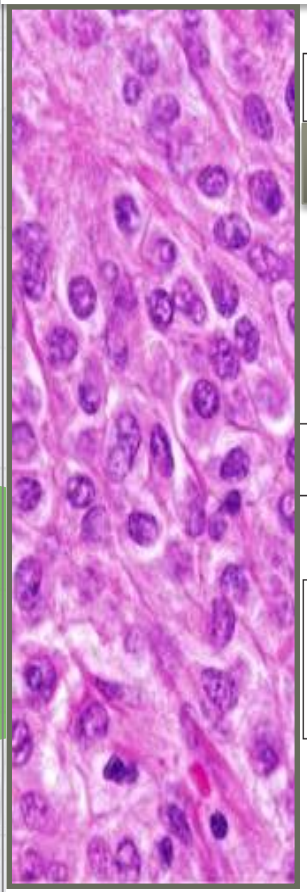


Differential Diagnosis:
Gist with epithelioid or mixed morphology



growth pattern

KIT: diffuse (+)

- SDHB: (–) → GIST
  - Stomach: GISTs in Carney Stratakis syndrome
    GISTs in Carney triad
    So-called juvenile GIST
- SDHB: (+) → GIST
  - Stomach: a part of *PDGFRA* gene mutant GISTs
    Stomach & small intestine: A part of *c-kit* mutant GISTs
    c-kit gene analysis
    PDGFRA gene anlysis

KIT: (–) or weakly (+)

- DOG1: (+) → GIST
  - Stomach: A part of *PDGFRA* gene mutant GISTs
    PDGFRA gene analysis
    (*c-kit* gene analysis)
- DOG1: (–) → Others
  - Epithelioid type PEComa
    α-SMA·HMB45·Melan A: (+)
  - Carcinoid (NET)
    chromogranin A·synaptophysin·CD56: (+)
  - Glomus tumor
    α-SMA: (+)

In difficult cases
- Consultation to specialists
- *PDGFRA* gene analysis

Figure 2 Flow chart of differential diagnosis of epithelioid cell mesenchymal tumors. SDHB, succinate dehydrogenase subunit B; GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; NET, neuroendocrine tumor; α-SMA, α-smooth muscle actin; PEComa, perivascular epithelioid cell tumor.

Transl Gastroenterol Hepatol 2018;3:27

IMMUNOHISTOCHEMISTRY

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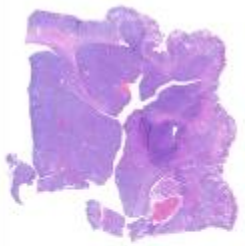
H&E	CD117 DOG 1	CD34	Smooth muscle actin	S100 protein	Desmin	Pan-keratin
	95%	70%	30%	5%	2%	<1%
						
+ +	+ +	+ +	+ +	+ +	+ +	+ +

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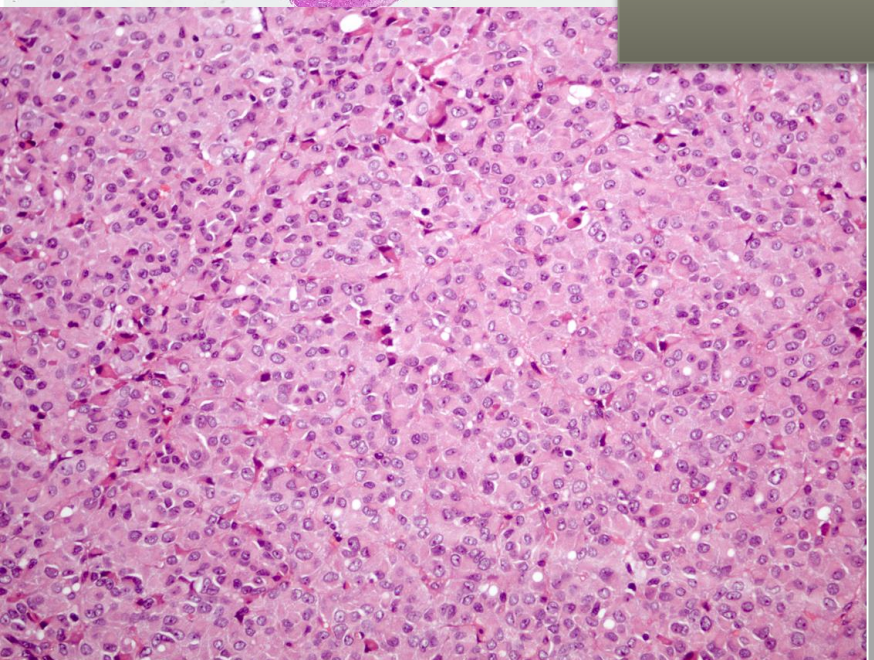
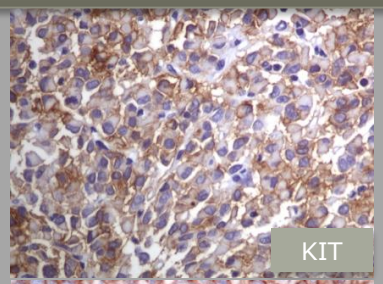
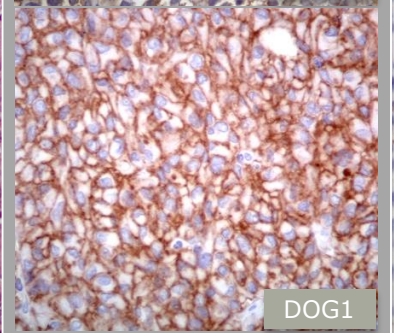
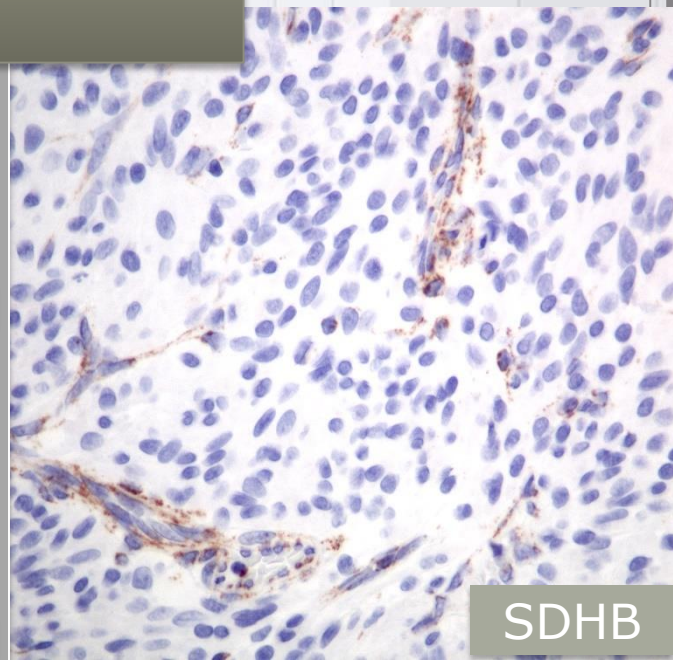
SDHB deficient GIST stomach

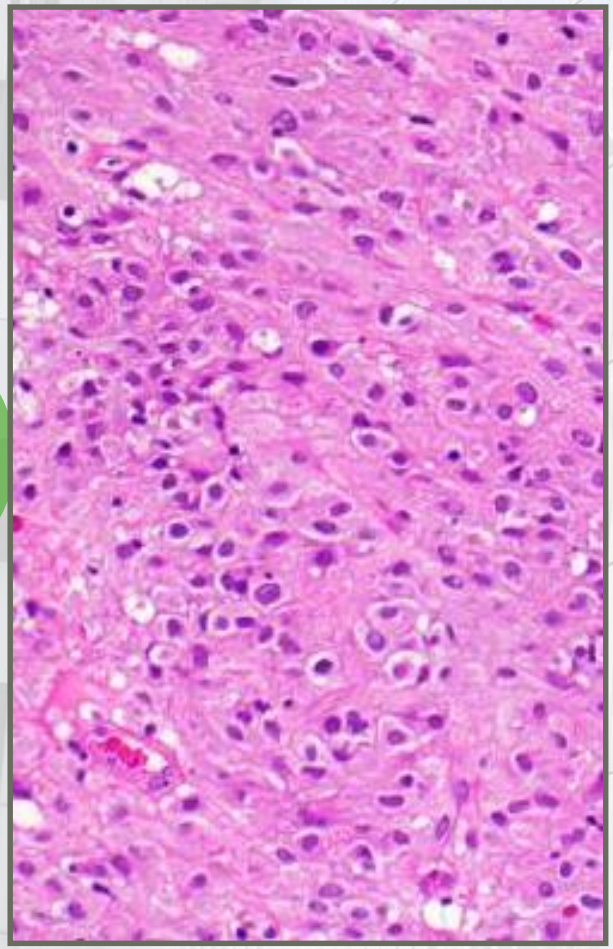


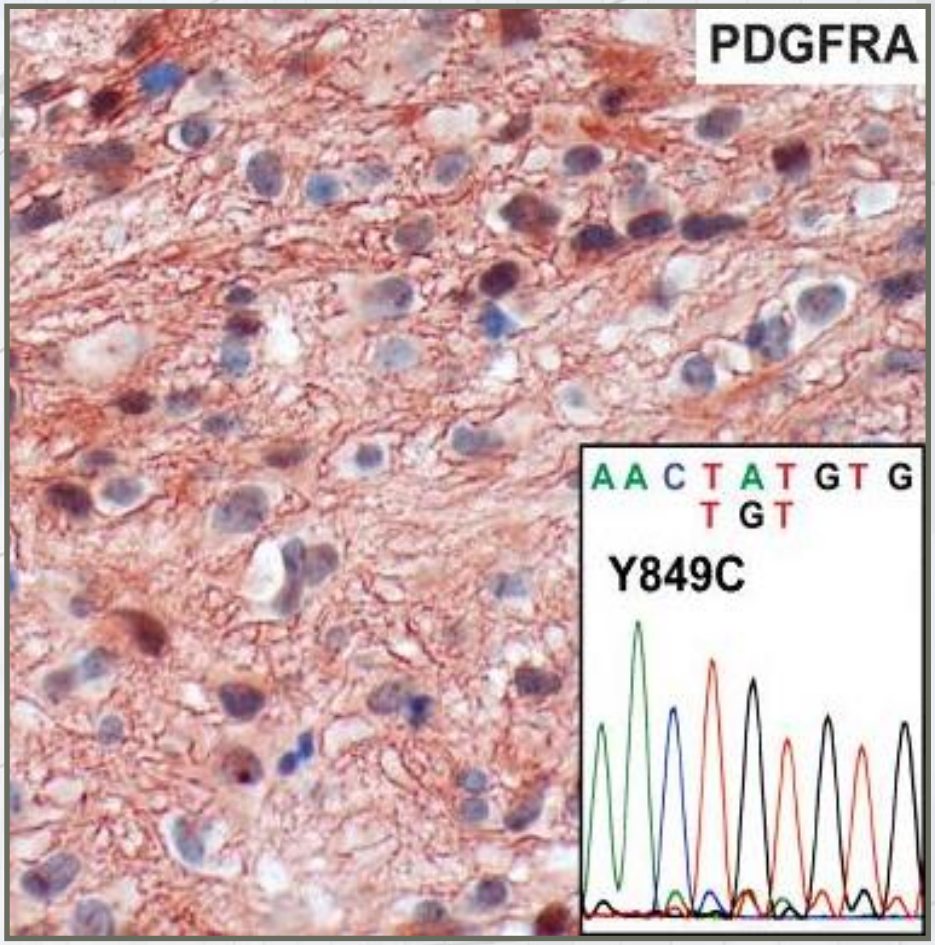




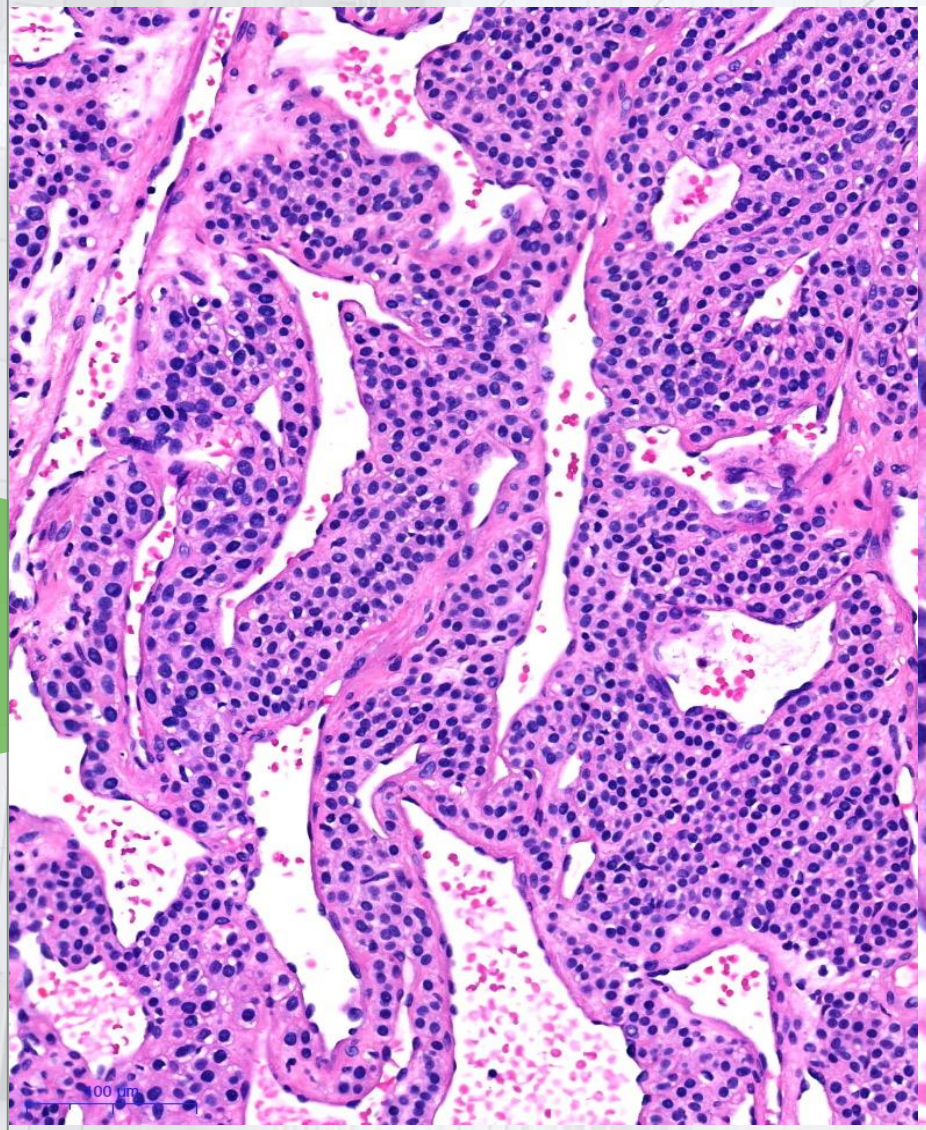


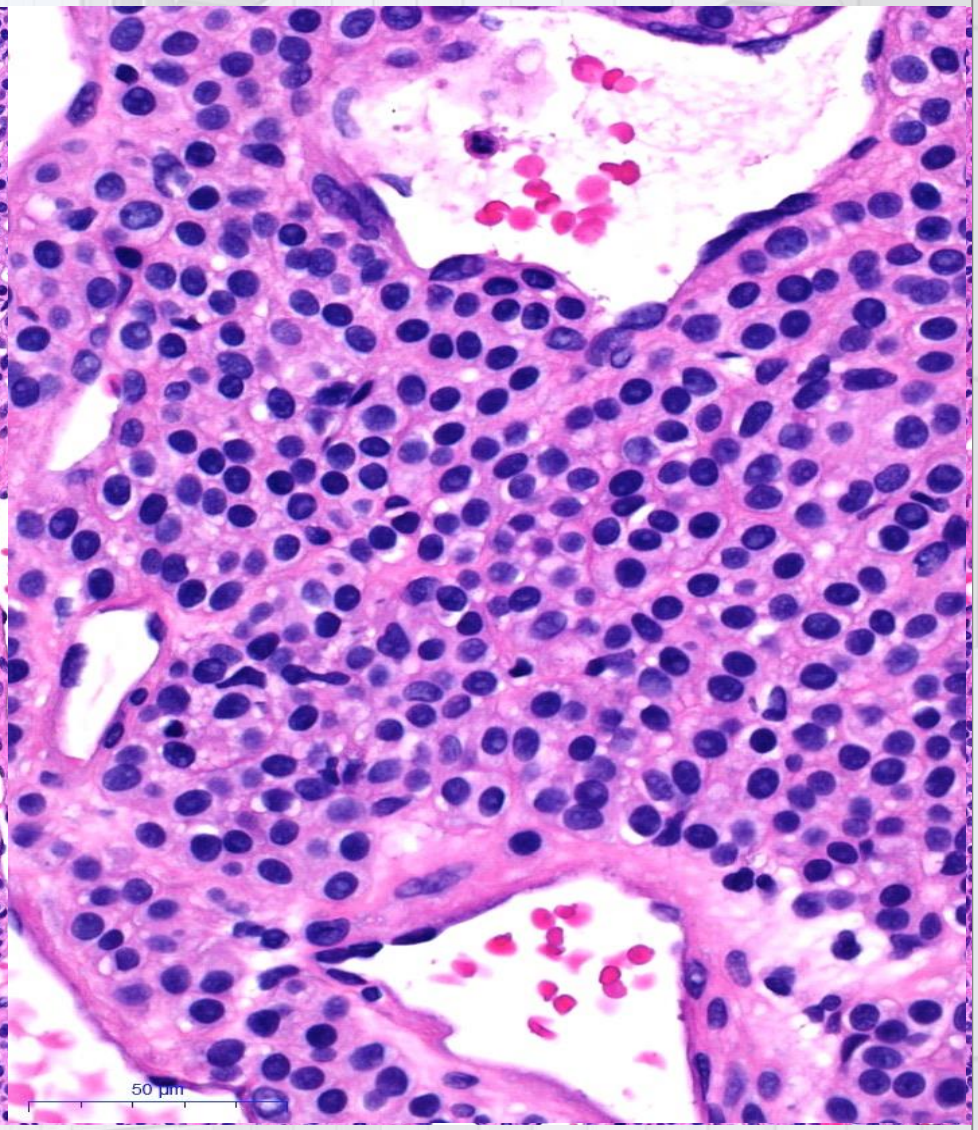
PDGFRA mutated GIST stomach





Glomustumor





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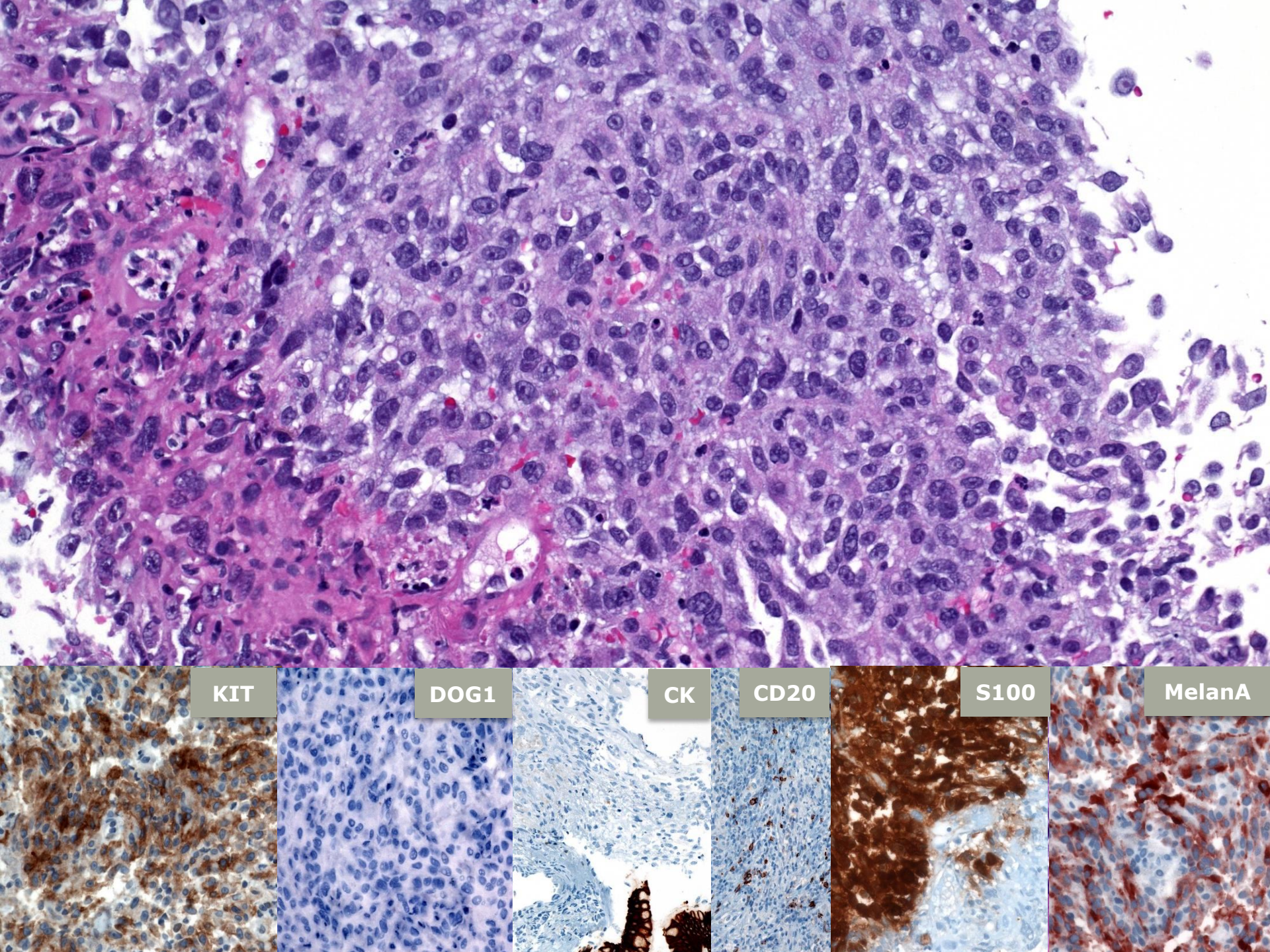
Other tumors
-Metastasis -


KIT
DOG1
CK
CD20
S100
MelanA

Differentialdiagnoses

- Malignant Melanom: S100, Melan A, HMB45 (50% KIT pos.)
- Angiosarcoma: CD31, ERG (can be KIT pos.)
- Sarcomatoid Carcinoma: CK
- Neuroendocrine Tumors: Synaptophysin and Chromogranin pos.
- Paraganglioma: Synaptophysin, S100
- PECOMA: HMB45, Melan A, SMA, Desmin
- Clear cell Sarcoma: S100 (+/-Melanommarker), Gen Fusion EWSR1–CREB1 oder –ATF1

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Diagnostic Challenge

- Pleomorphic GIST*
- Dedifferentiated GIST* („sarcomatous“)
- GIST heterologous differentation
- „Uncommon“ morphology („rhabdoid“)*
- KIT negative GIST*

*occur before and after treatment

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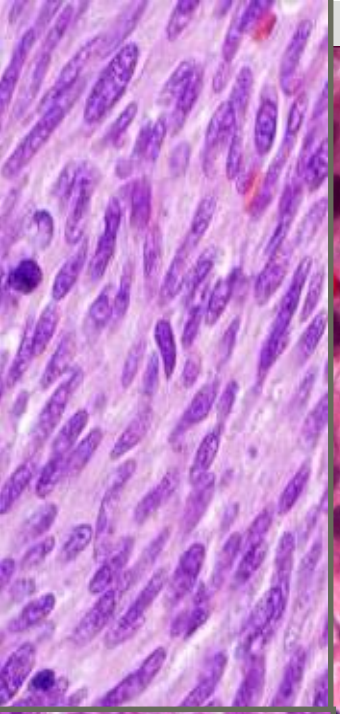
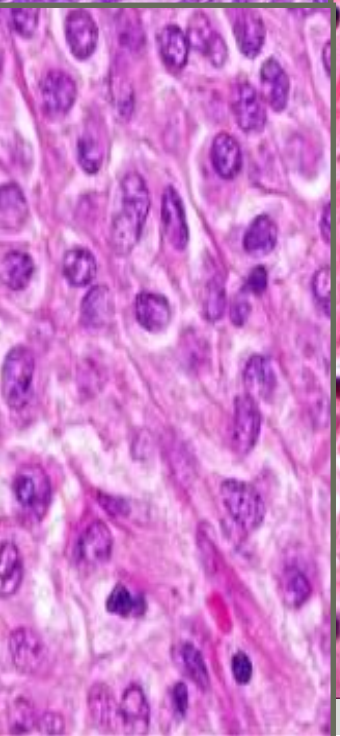
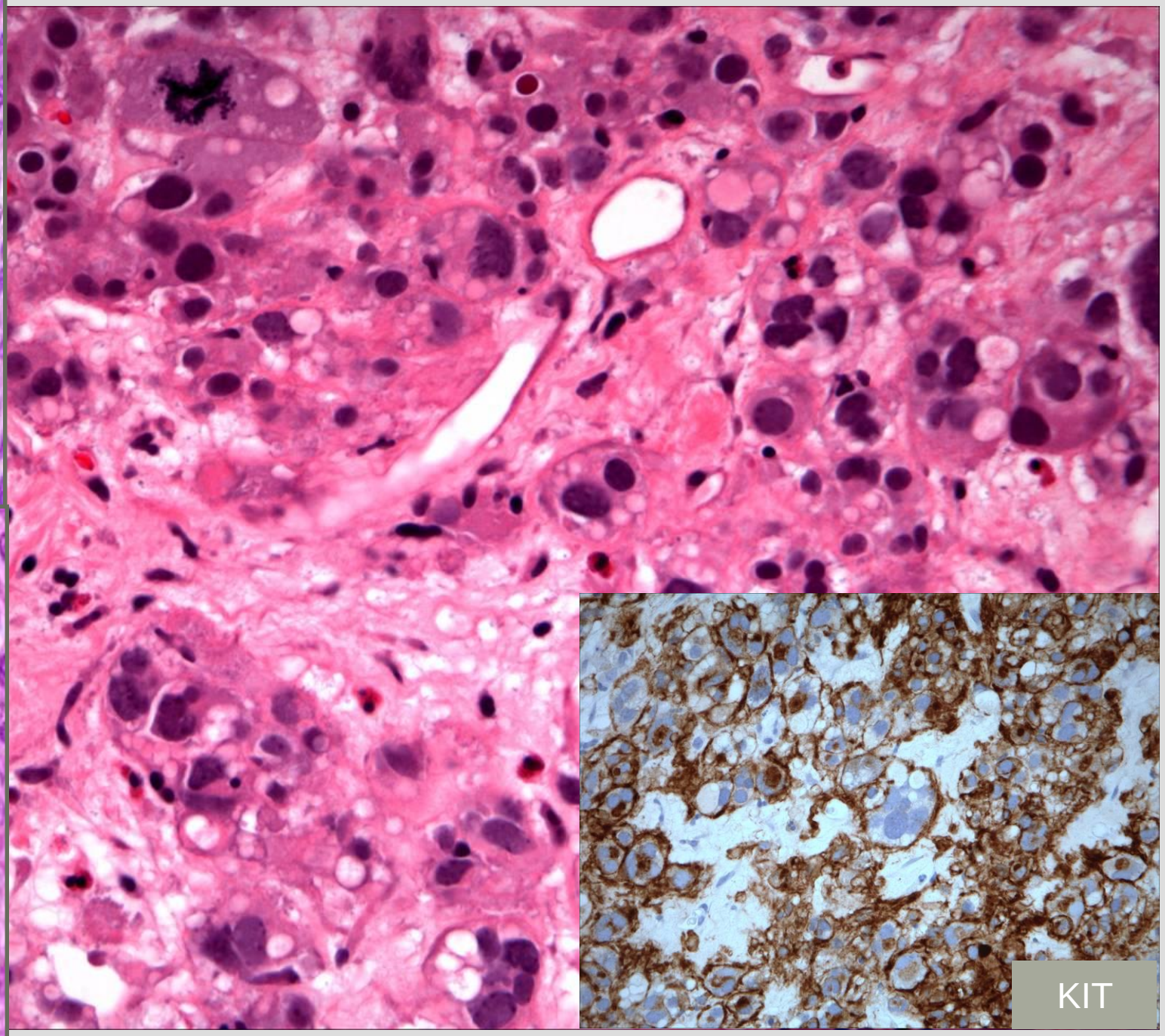
Pleomorphic Gist







KIT

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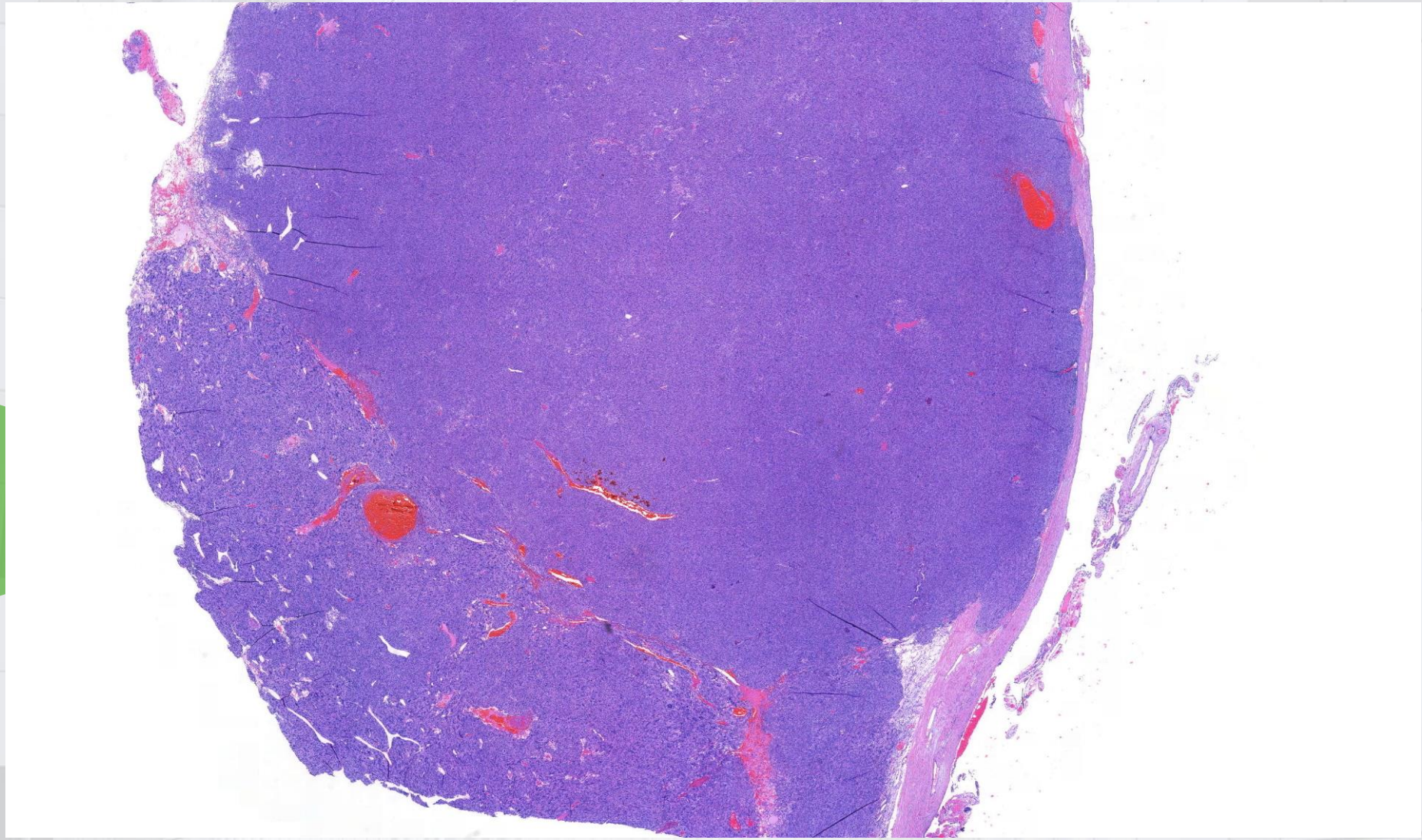
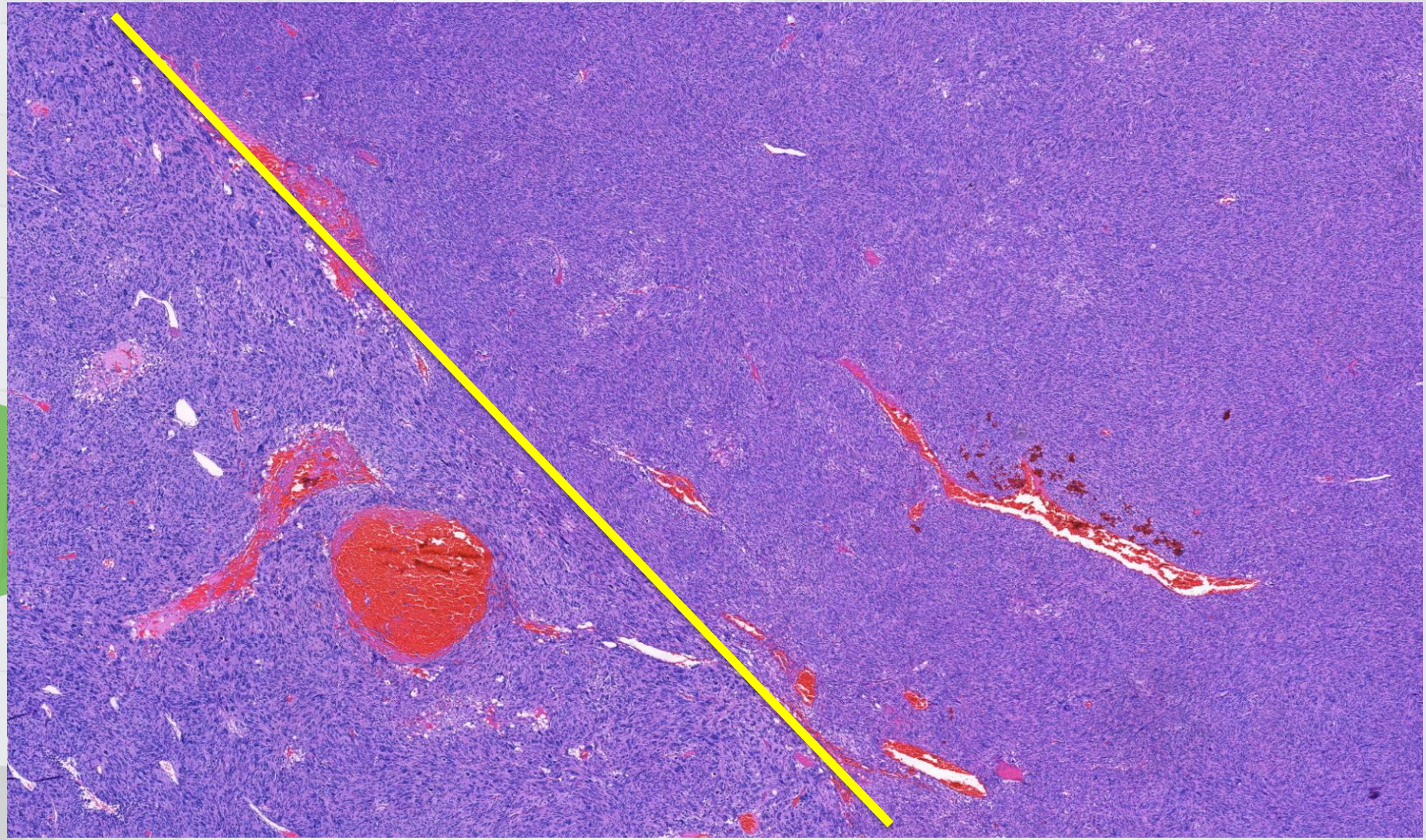
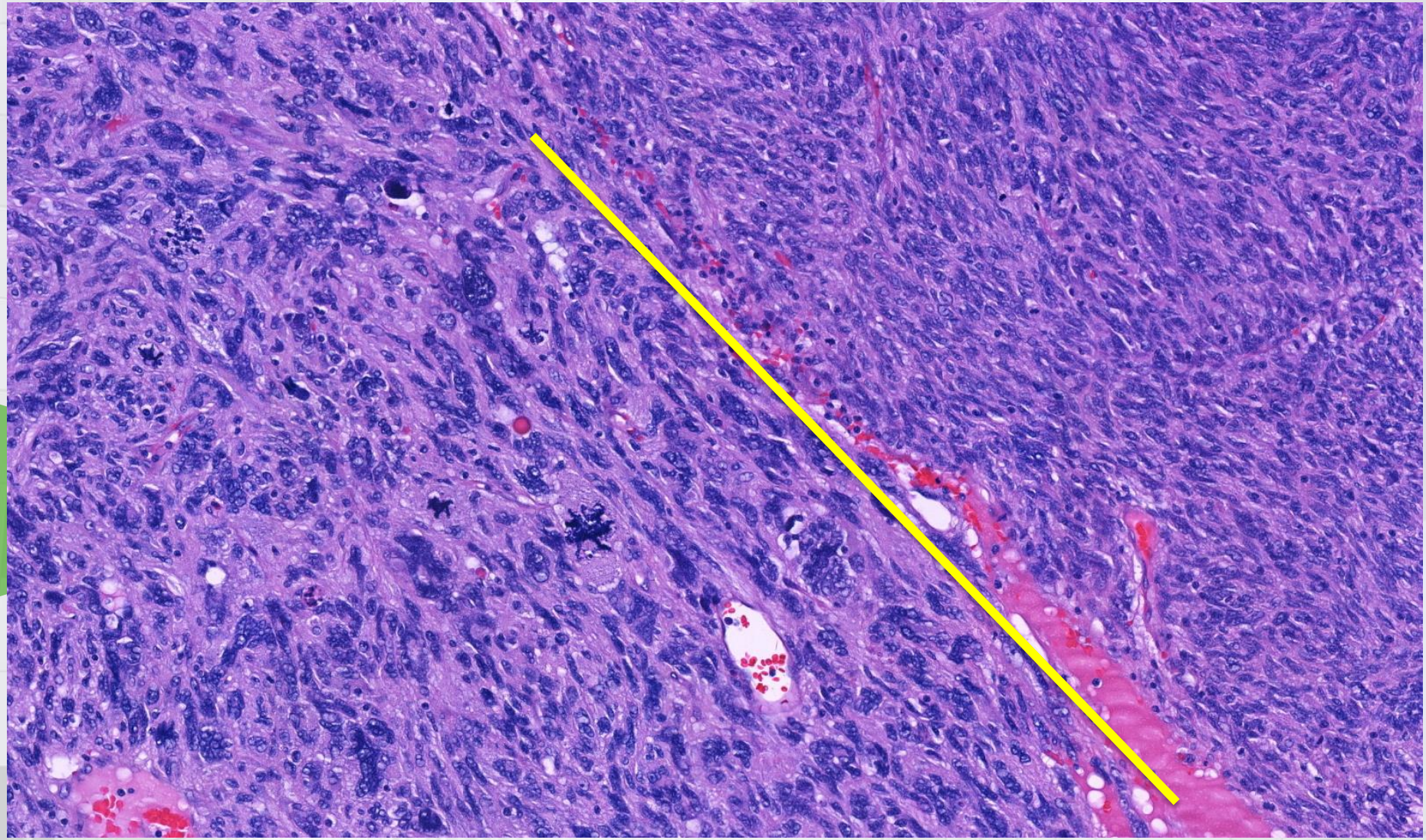
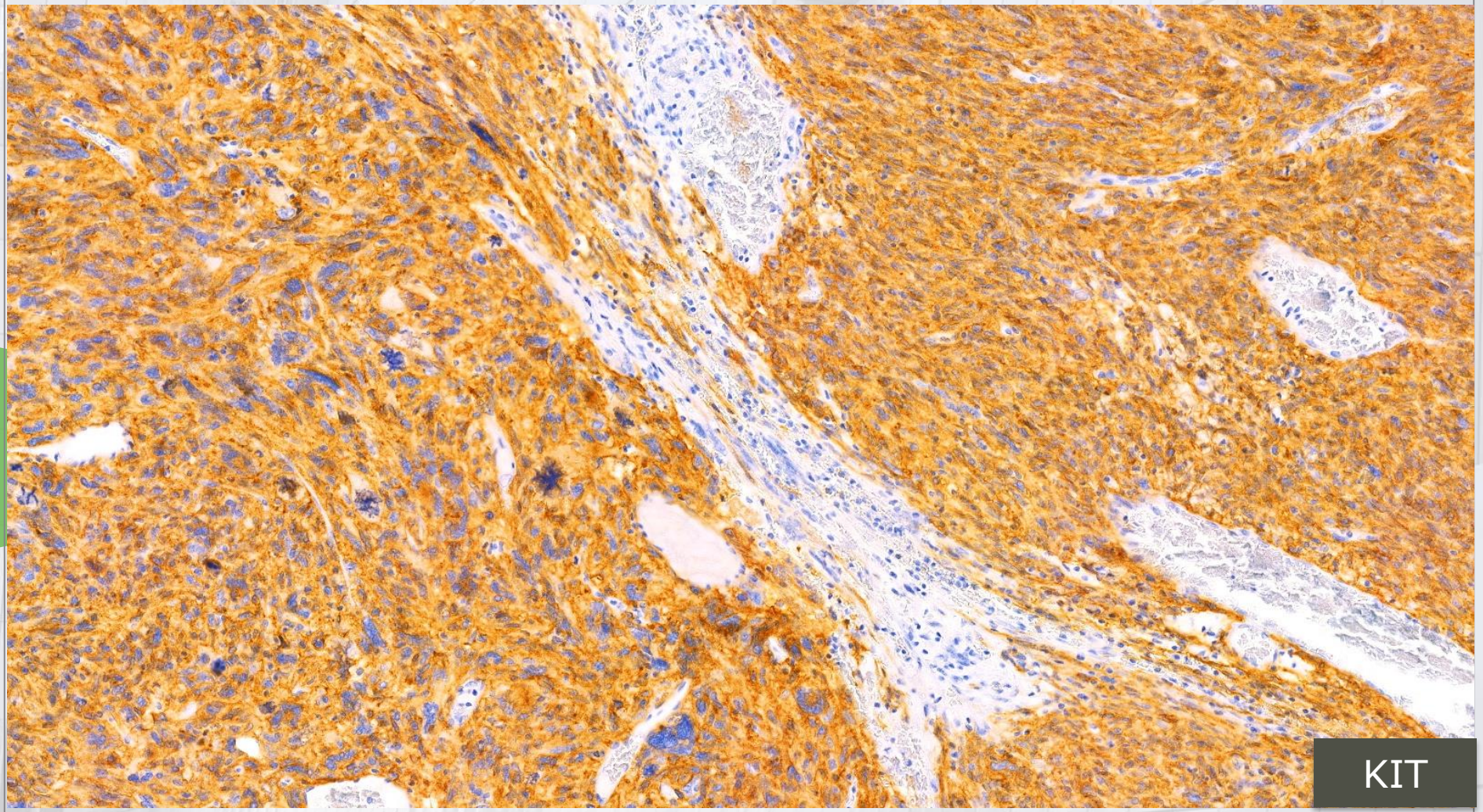
Dedifferentiated GIST („sarcomatous“)








KIT

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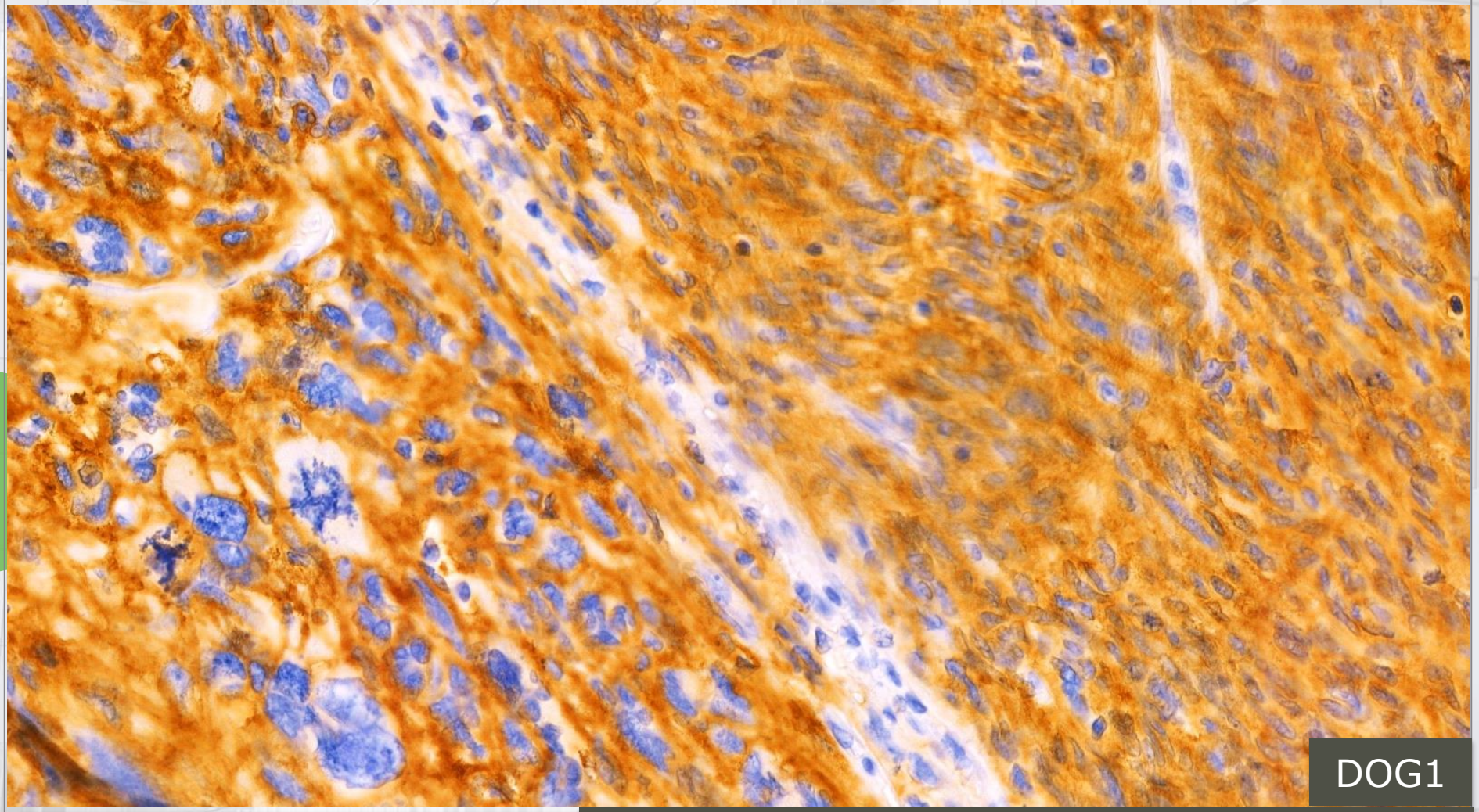

KIT Exon 11 mutation
P53 and *RB1* mutation

AJCP / Original Article

Inactivating Mutations of *RB1* and *TP53* Correlate With Sarcomatous Histomorphology and Metastasis/Recurrence in Gastrointestinal Stromal Tumors

Larissa Merten,[1] Abbas Agaimy, MD,[1] Evgeny A. Moskalev, PhD,[1] Johannes Giedl, MD,[1] Claudia Kayser, MD,[2] Helene Geddert, MD,[3] Inga-Marie Schaefer, MD,[4] Silke Cameron, MD,[5] Martin Werner, MD,[2] Philip Ströbel, MD,[6] Arndt Hartmann, MD,[1] and Florian Haller, MD[1]

From the [1]Institute of Pathology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [2]Institute of Pathology, Albert-Ludwigs University, Freiburg, Germany; [3]Institute of Pathology, St. Vincentius Hospital, Karlsruhe, Germany; [4]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and [5]Clinic for Gastroenterology and Gastrointestinal Oncology and [6]Institute of Pathology, Georg August University, Göttingen, Germany.

Key Words: GIST; Mutation; *RB1*; *TP53*; *CDKN2A*

Am J Clin Pathol December 2016;146:718-726

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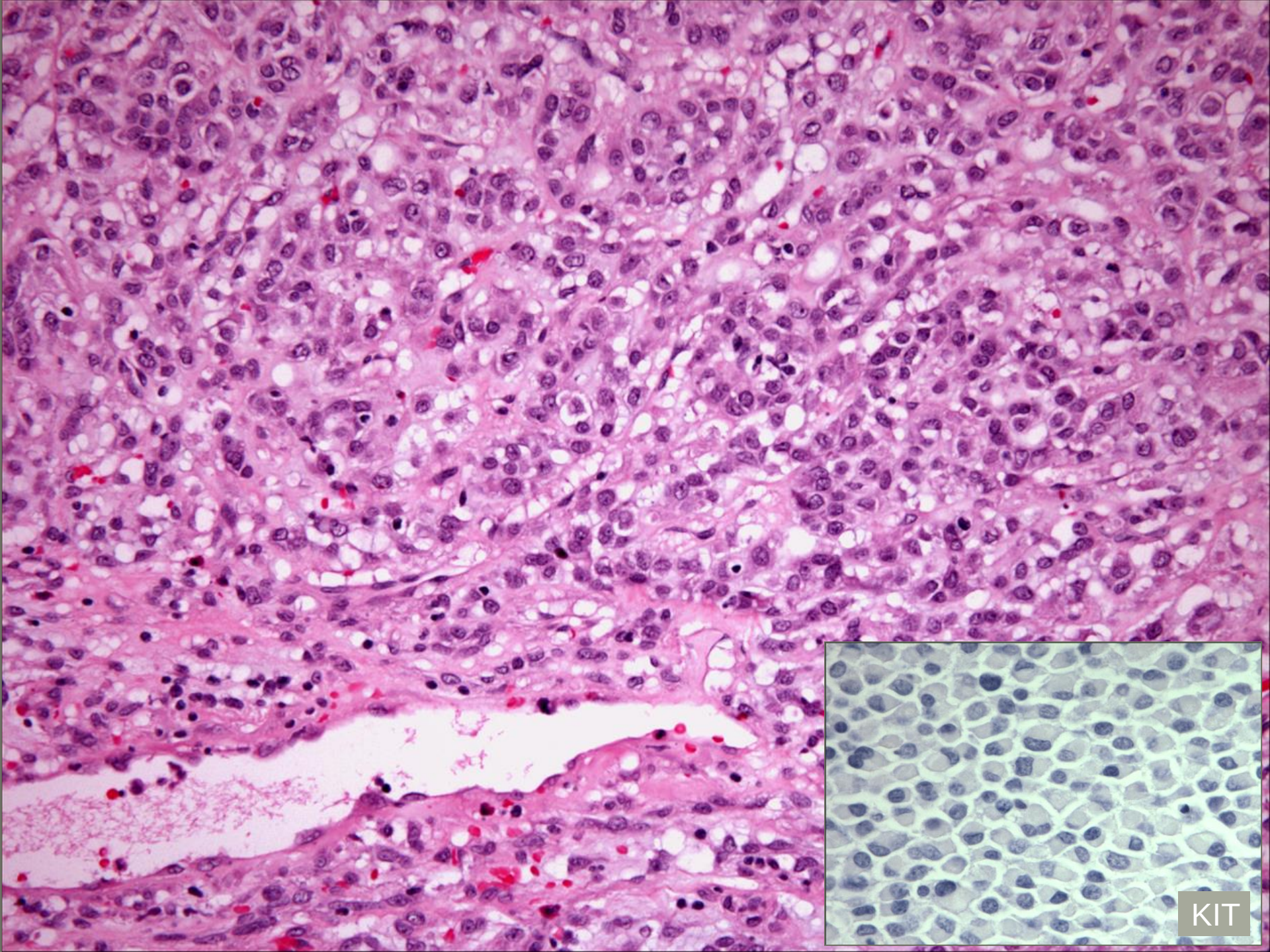
KIT negative GIST


KIT

Immunohistochemie

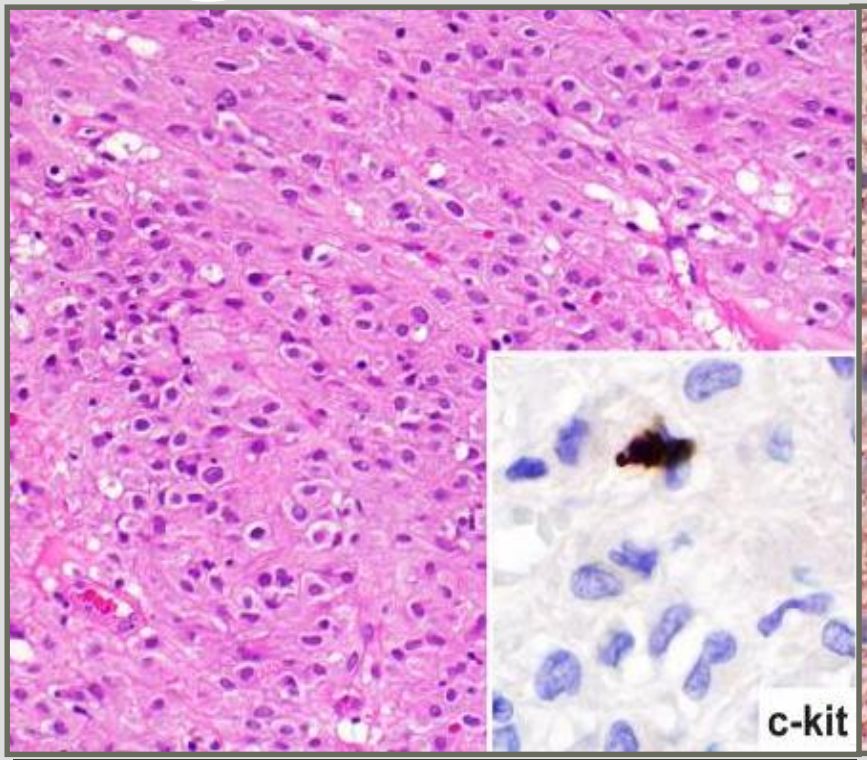
KIT positive GISTs
95%

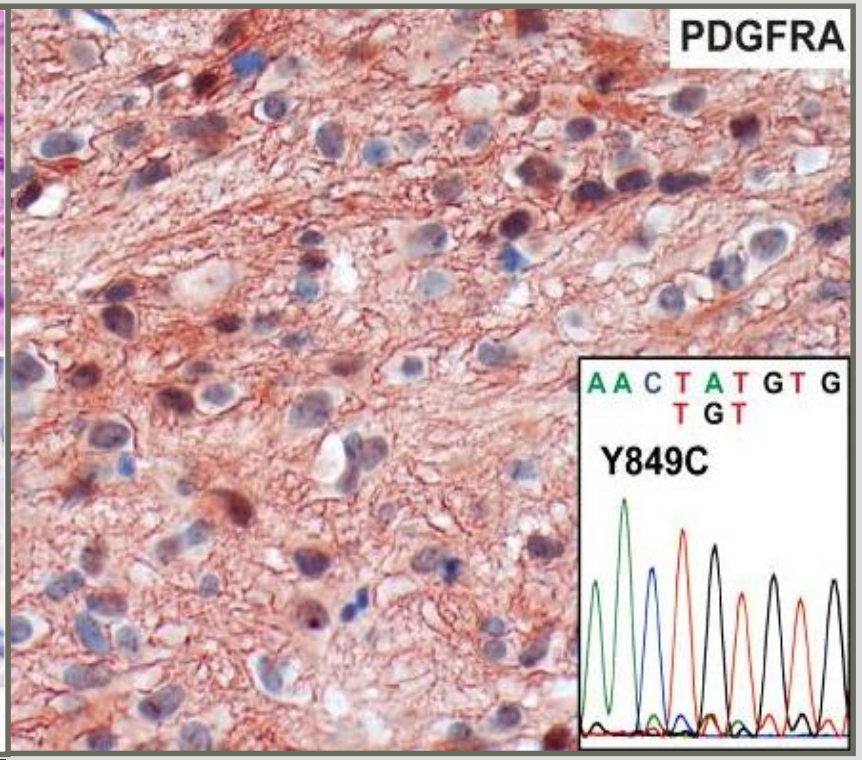
KIT negative GISTS
5%

all

Nestin,
PKC-theta

DOG1, CA II, PDGFRA





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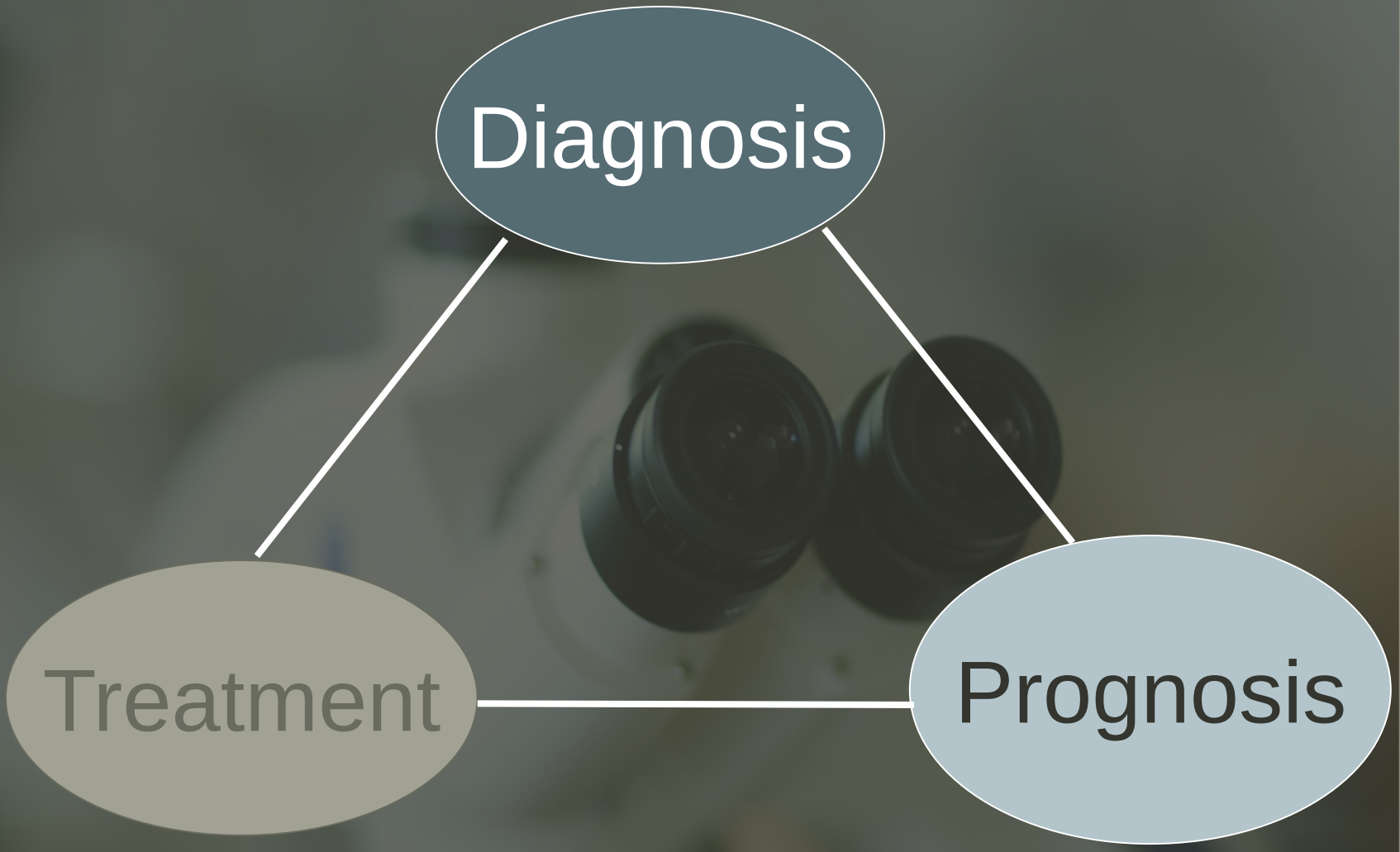
MORPHOLOGY and IMMUNOHISTOCHEMISTRY
Need a panel of AB to exclude other tumors in the DDX

-> Diagnosis GIST



Predictive Pathology

5mm²

H&E

20-25 HPF

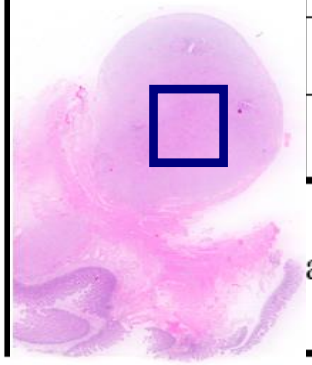


Table 1: Risk stratification of primary GIST

Mitotic index	Size	Risk of progressive disease [+] Gastric	Duodenum	Jejunum/Ileum	Rectum
	≤2cm	None	none	None	none
	>2≤5cm	very low (1.9%)	low (8.3%)	low (4.3%)	Low (8.5%)
	>5≤10cm	low (3.6%)	#	Moderate (24%)	#
	>10cm	moderate (10%)	high (34%)	high (52%)	high (57%)
	≤2cm	none*	#	high*	high (54%)
	>2≤5cm	moderate (16%)	high (50%)	high (73%)	high (52%)
	>5≤10cm	high (55%)	#	high (85%)	#
	>10cm	high (86%)	high (86%)	high (90%)	high (71%)

as metastasis

Tumour rupture is an additional adverse prognostic factor and should be recorded

Table based on Miettinen et al, Semin Diagn Pathol, 2006.
Data based on long-term follow-up of 1055 gastric,
629 small intestinal, 144 duodenal and 111 rectal GISTs. Modified NCCN guidelines.

~25 HPF

H&E

50 HPF

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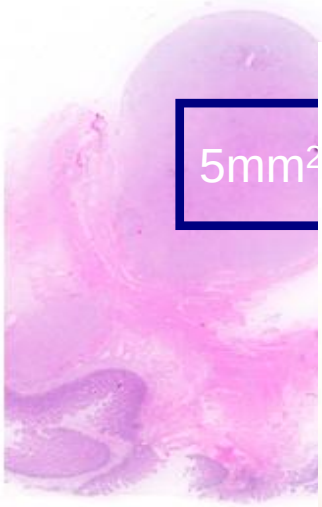
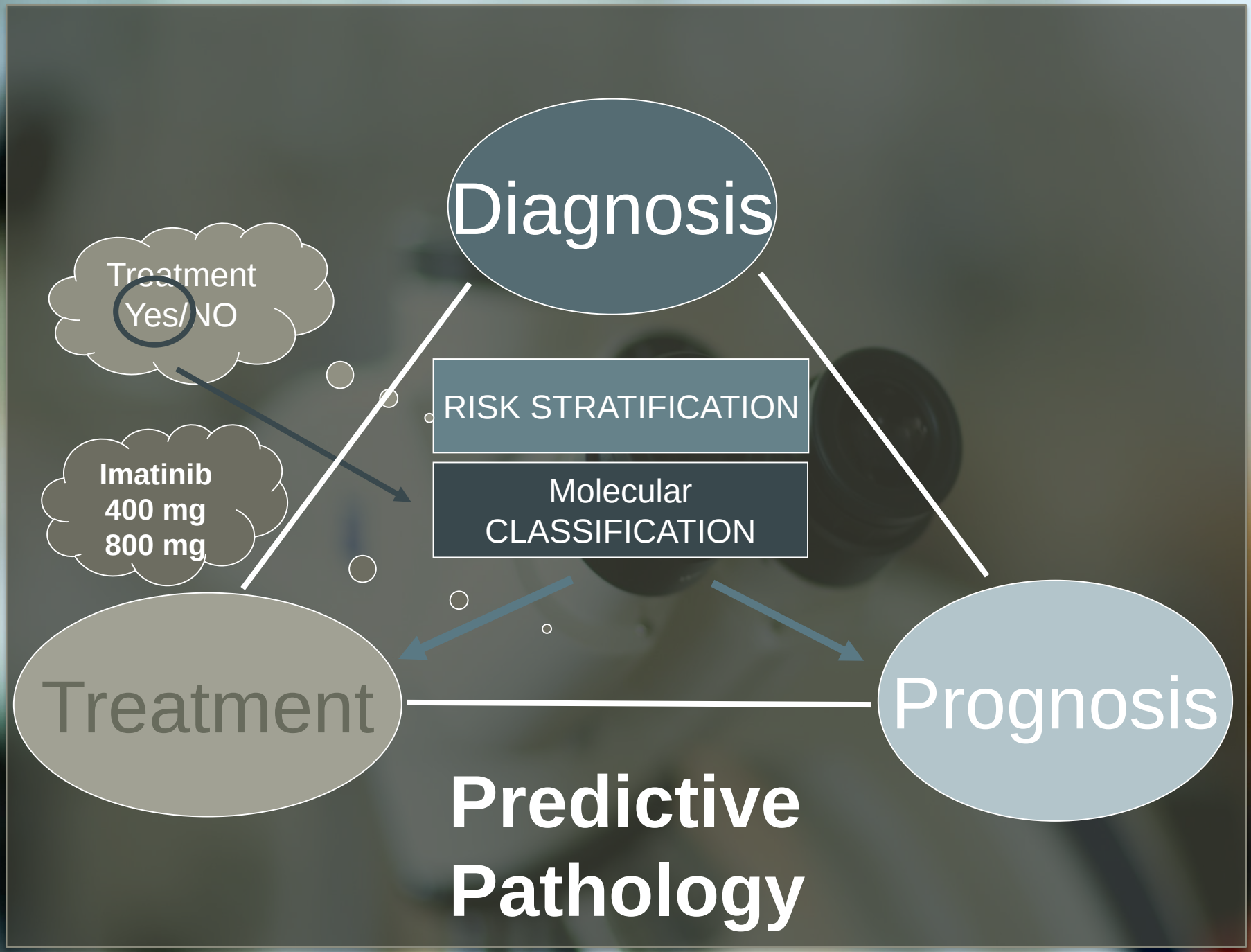


5mm²

WHO 2013 and ESMO 2018

Prognostic factors

The best documented prognostic factors are tumour size, mitotic activity, and anatomical site {1885}. It should be noted that mitotic counts have been defined with small-field microscope with a total area of 5 mm² per 50 HPFs. Therefore, one should generally count a smaller number of wide fields to reach a comparable total area (usually about 25 fields). In the TNM classification, grading is based on mitotic rate (5 mitoses per 50 HPFs is considered to


Diagnosis
Treatment
Yes/NO
Imatinib
400 mg
800 mg
RISK STRATIFICATION
Molecular
CLASSIFICATION
Treatment
Prognosis
Predictive
Pathology

- Metastatic GIST
- Before adjuvant treatment
  - Children and young adults
  - Diagnostic challenging cases

Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy and to prognostic value. Its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (with the possible exclusion of < 2 cm non-rectal GISTs, which are very unlikely ever to be candidates for medical treatment)

ESMO 2018

Annals of Oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL PRACTICE GUIDELINES

Gastrointestinal stromal tumo
Clinical Practice Guidelines fo
and follow-up†

Table 1. Personalised medicine synopsis table

Biomarker	Method	Use	LoE	GoR
Mitotic index	Pathology	Disease classification Prognostic relevance Used for medical treatment decisions	IV	A
KIT/PDGFRA/ BRAF	Sanger sequencing or NGS	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions Currently actionable/ targetable	I	A
SDH	IHC	Disease classification Prognostic relevance Predictive relevance Used for medical treatment decisions	III	A

Area of 5mm²

GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; NGS, next generation sequencing; PDGFRA, platelet-derived growth factor receptor alpha; SDH, succinate dehydrogenase.

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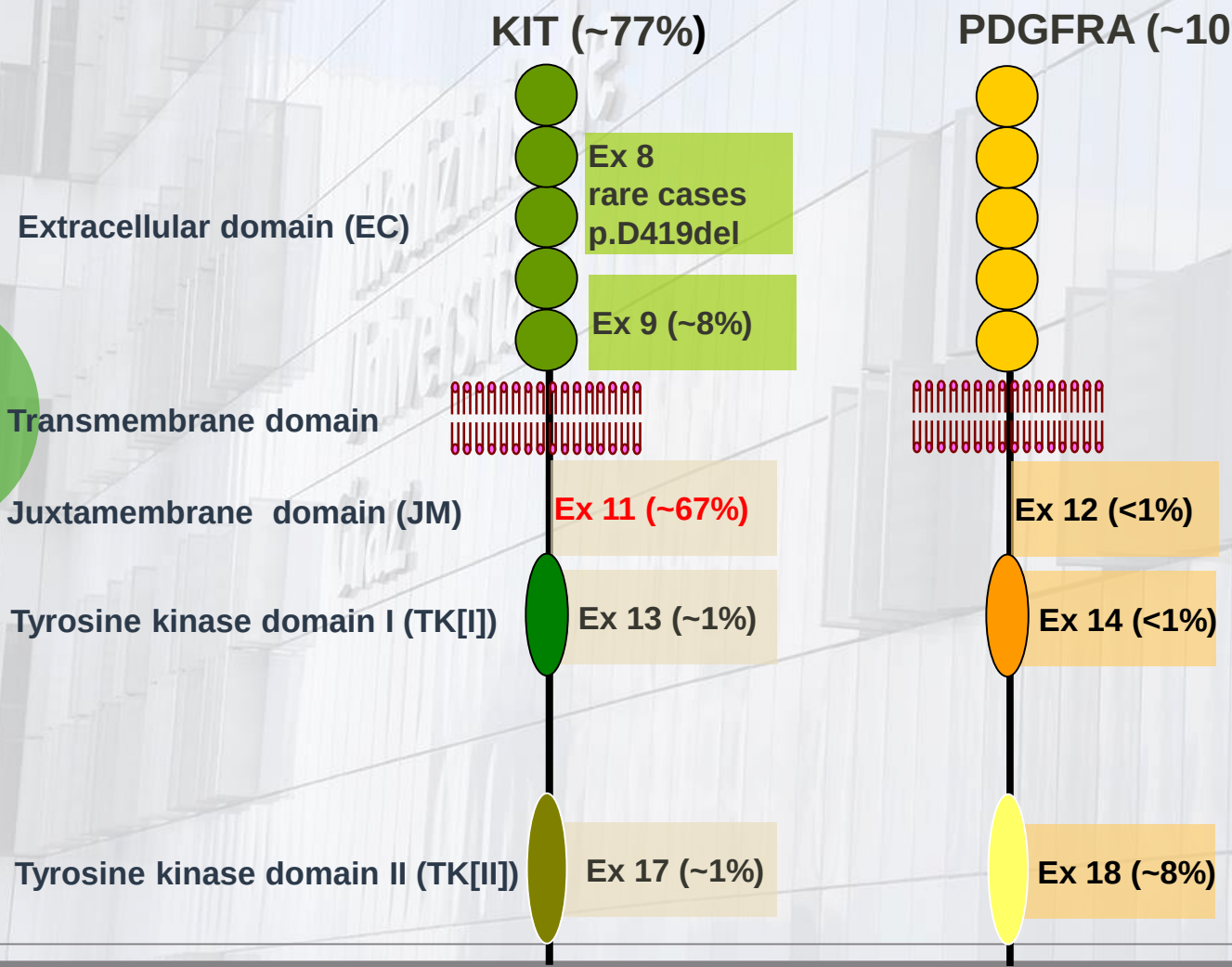
Mutations in GIST



KIT/
PDGFRA/
BRAF WT GIST
↓
SDHB IHC
↓
Quadruple-
negative
KIT
PDGFRA
BRAF
SDH
↓
Exclude
unrecogniced
NF1

Esmo 2018

Genotype	Sites and histology	Comments	Imatinib response
KIT-mutant			
Exon 11	All locations; usually spindle cell or mixed	Gastric tumours with exon 11 deletions more aggressive	Excellent
Exon 9	Small and large intestines; usually spindle cell or mixed		Respond better to higher dose
Exon 13	Usually small intestine; spindle cell	Uncommon	Some
Exon 17	Usually small intestine; spindle cell	Uncommon	Some
Exon 8 p.D419 del	Small intestine; mixed	Very rare	Limited data
PDGFRA-mutant		Less aggressive than *KIT*-mutant tumours overall	
Exon 18	Stomach and omentum; epithelioid	D842V most common by far	Poor
Exon 12	Stomach; epithelioid	Uncommon	Variable
Exon 14	Stomach; epithelioid	Rare	Variable

Doyle et al Histopathology, 2014

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KIT, PDGFRA, and BRAF Mutational Spectrum Impacts on the Natural History of Imatinib-naive Localized GIST

A Population-based Study

Sabrina Rossi, MD, PhD, Daniela Gasparotto, PhD,† Rosalba Miceli, PhD,‡ Luisa Toffolatti, PhD,* Giovanna Gallina, PhD,* Enrico Scaramel, MSc,* Alessandra Marzotto, MSc,† Elena Boscato, MSc,† Luca Messerini, MD,§ Italo Bearzi, MD,‖ Guido Mazzoleni, MD,¶ Carlo Capella, MD,# Gianluigi Arrigoni, MD,** Aurelio Sonzogni, MD,†† Angelo Sidoni, MD,‡‡ Luigi Mariani, MD, PhD,‡ Paola Amore, PhD,§§ Alessandro Gronchi, MD,‖‖ Paolo G. Casali, MD,¶¶ Roberta Maestro, PhD,† and Angelo P. Dei Tos, MD**

(*Am J Surg Pathol* 2015;39:922–930)

Impact of KIT/PDGFRA/BRAF on GIST Natural History

low-moderate risk

high risk

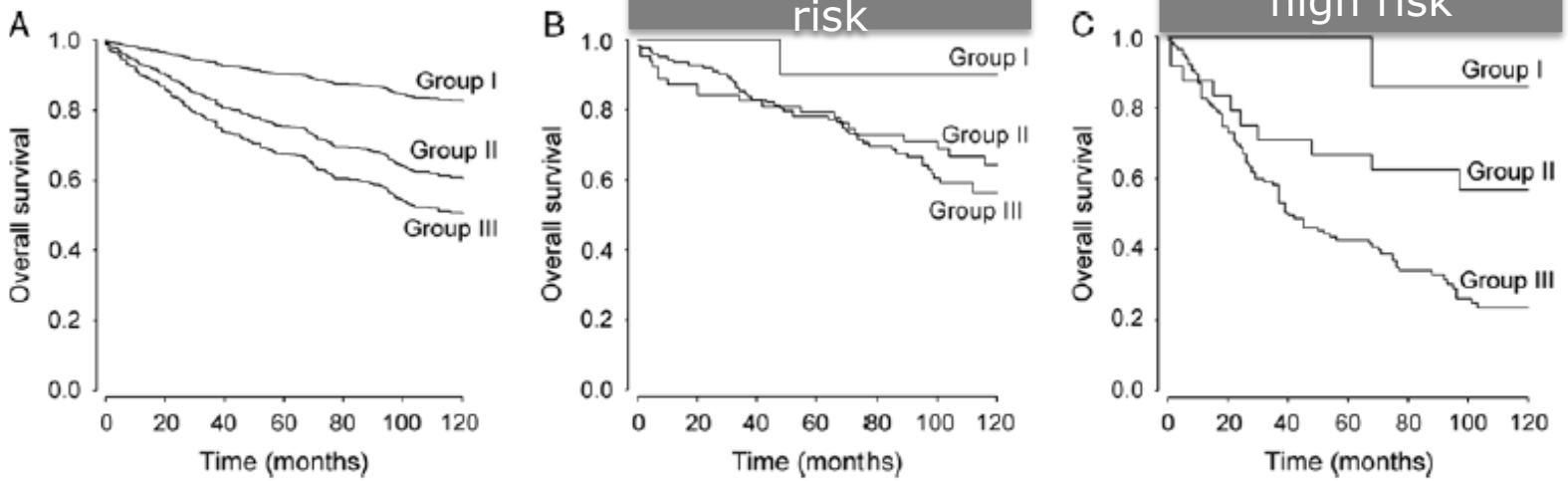

FIGURE 1. Patient stratification according to the molecular signature. A, Kaplan-Meier OS curves, estimated by multivariable Cox regression analyses, according to the 3 molecular prognostic groups: group I (*BRAF* exon 15, *KIT* exon 13, *PDGFRA* exon 12); group II (triple-negative, *KIT* exon 17, *PDGFRA* exon 14, *PDGFRA* exon 18 D842V); group III (*KIT* 9, *KIT* 11, *PDGFRA* 18-non842). B, OS according to the proposed molecular prognostic groups in the set of patients classified as low-moderate risk on the basis of the AFIP/Miettinen criteria. C, OS according to the proposed molecular prognostic groups in the set of patients classified as high risk on the basis of the AFIP/Miettinen criteria.

Gruppe 1: *BRAF* Exon 15, *KIT* Exon 13, *PDGFRA* Exon 12

Gruppe 2: *triple-negative*, *KIT* Exon 17, *PDGFRA* Exon 14, *PDGFRA Exon 18 D842V*

Gruppe 3: *KIT Exon 9*, *KIT* Exon 11, *PDGFRA* 18 –non 842

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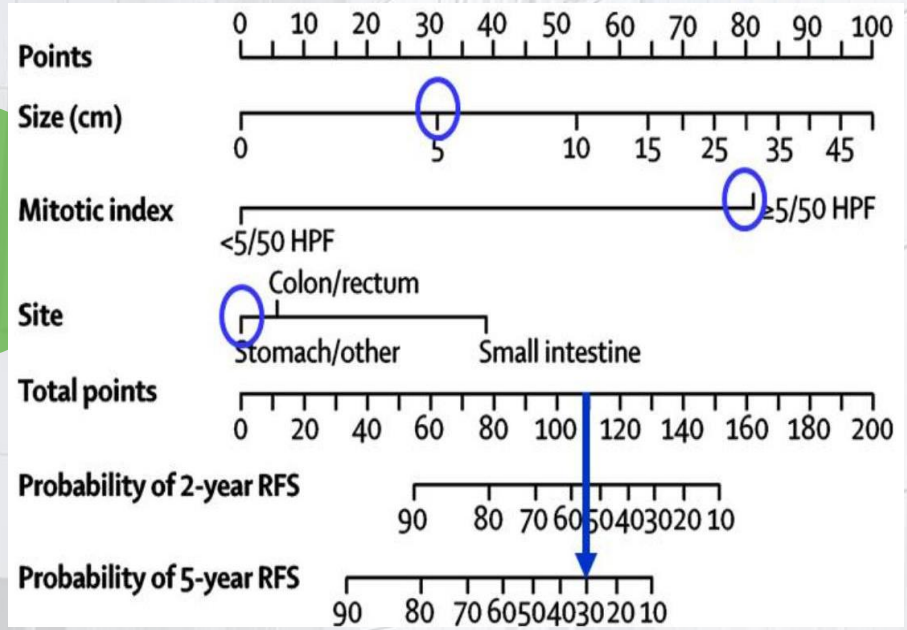
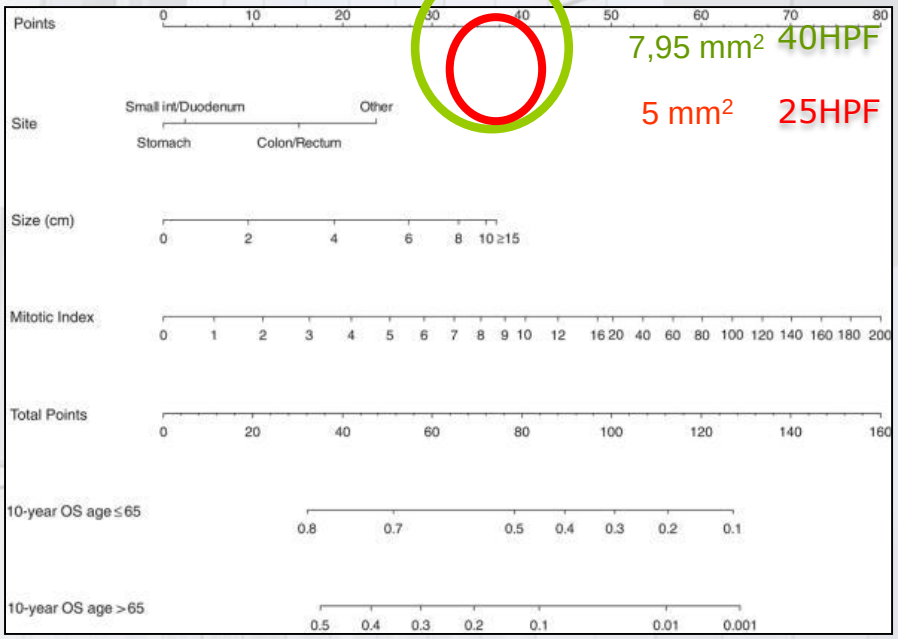
Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis



Gold et al. Lancet Oncol. 2009 Nov, 10(11):1025

Natural history of imatinib-naive GISTs: a retrospective analysis of 929 cases with long-term follow-up and development of a survival nomogram based on mitotic index and size as continuous variables.

Tumors > 2 cm
No history of other malignancy



Rossi et al AJSP Nov. 2011

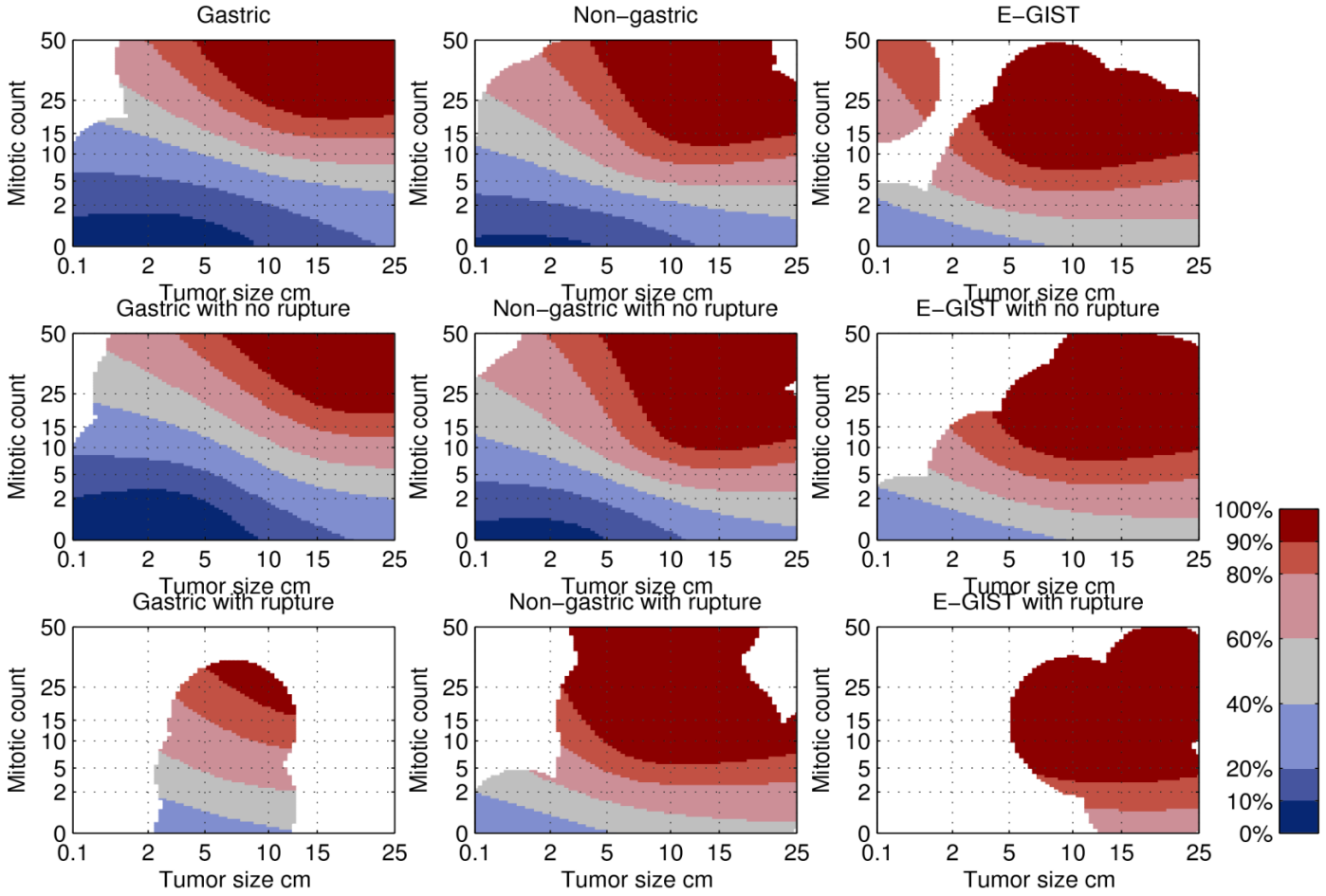
Adjuvant treatment after surgery?

Prognostic contour maps: 10-year RFS

Rupture ?

No rupture

Rupture present



Joensuu et al. Lancet Oncol 2012;13:265-274

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Resistance mechanisms in GIST

- 2/3 secondary aquired mutations
  - In 73-86% of pt. with *KIT* exon 11 primary mutations
  - In 19-33% of pt. with *KIT* exon 9 primary mutations
- 1/3 reactivation of KIT oncoprotein by other mechanisms

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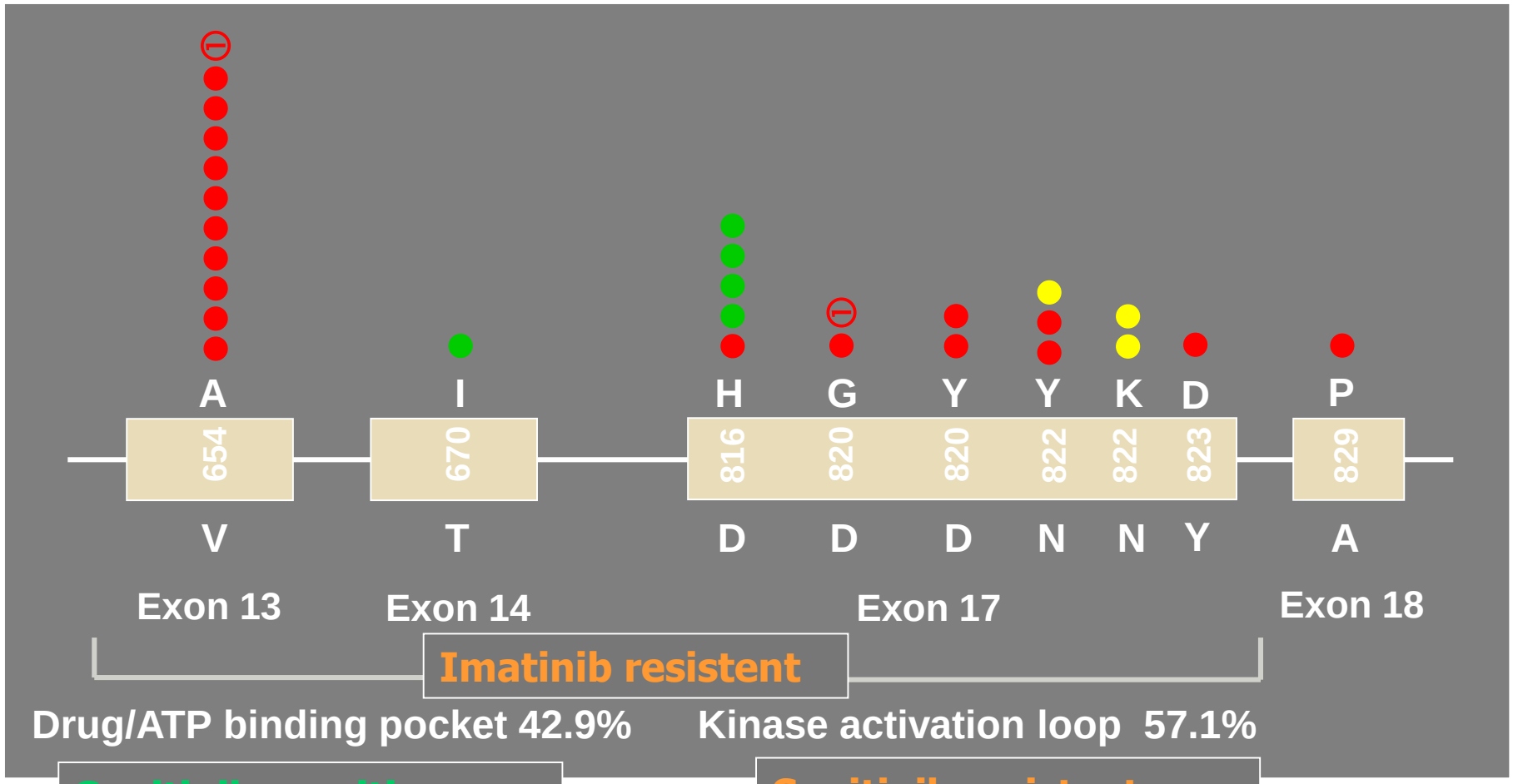
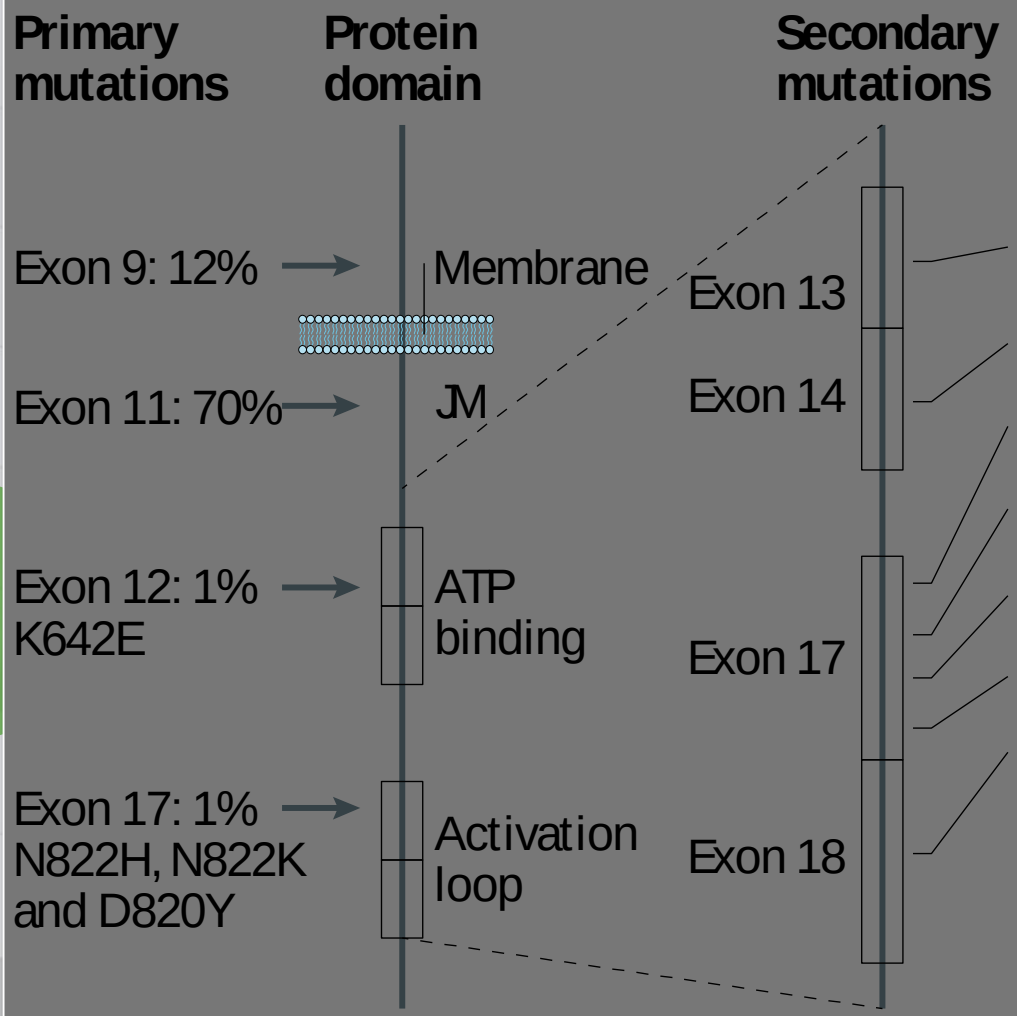
Secondary Mutations





Drug sensitivity

	IM	SU	SOR	NIL
V654A	R	S	S	I
T670I	R	S	S	R
D816A/G/H/V	R	R	R	R
D820A/E/G/Y	R	R	S	NR
N822H/K	I	R	S	R
Y823D	R	R	NR	NR
A829P	I	R	NR	NR

R Resistant S Sensitive I Intermediate NR Not reported

Corless, Nat. Rev. Cancer 2011

Mutational heterogeneity in a single metastasis and between metastases of a patient

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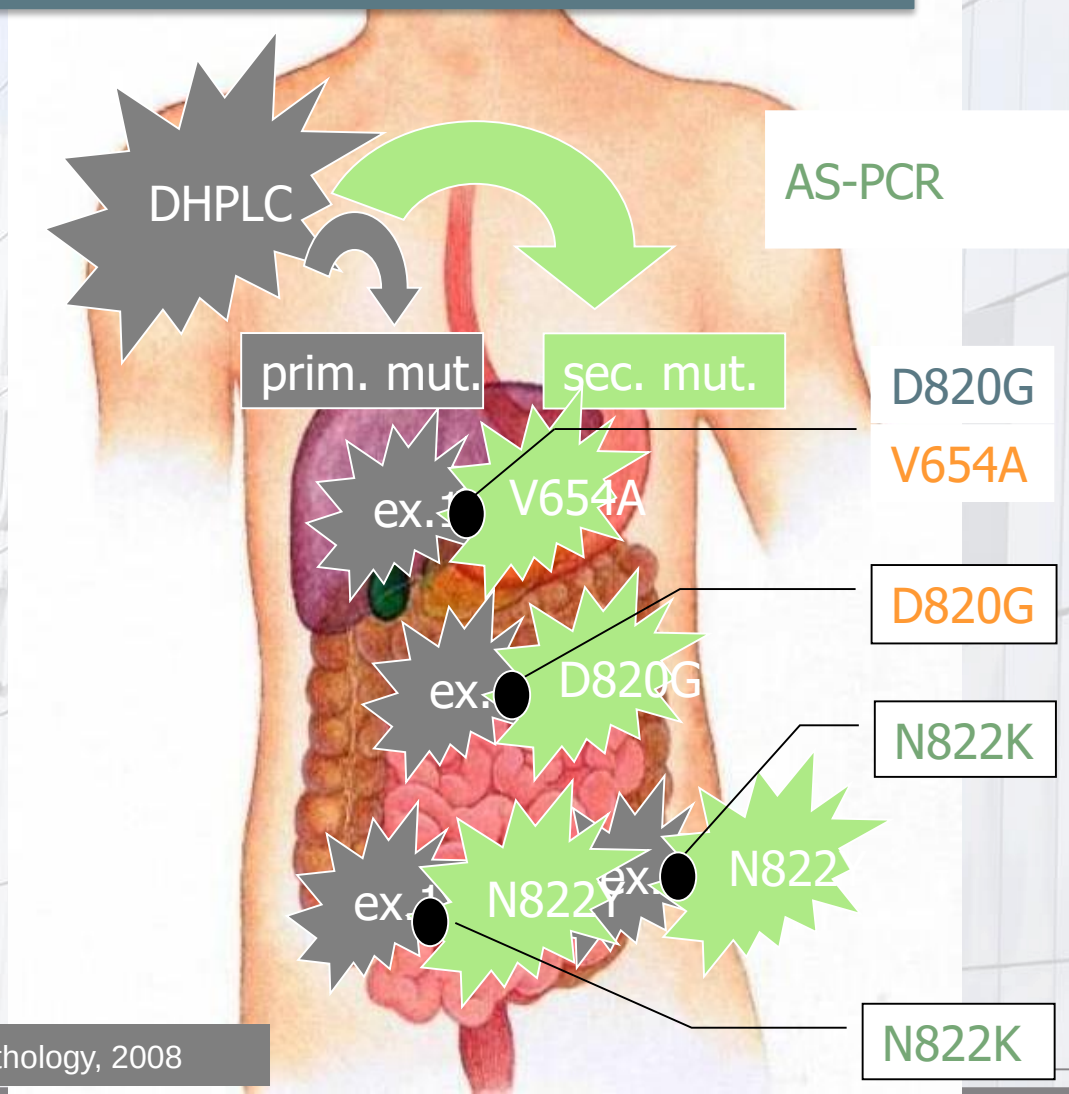

Liegl et al Journal of Pathology, 2008

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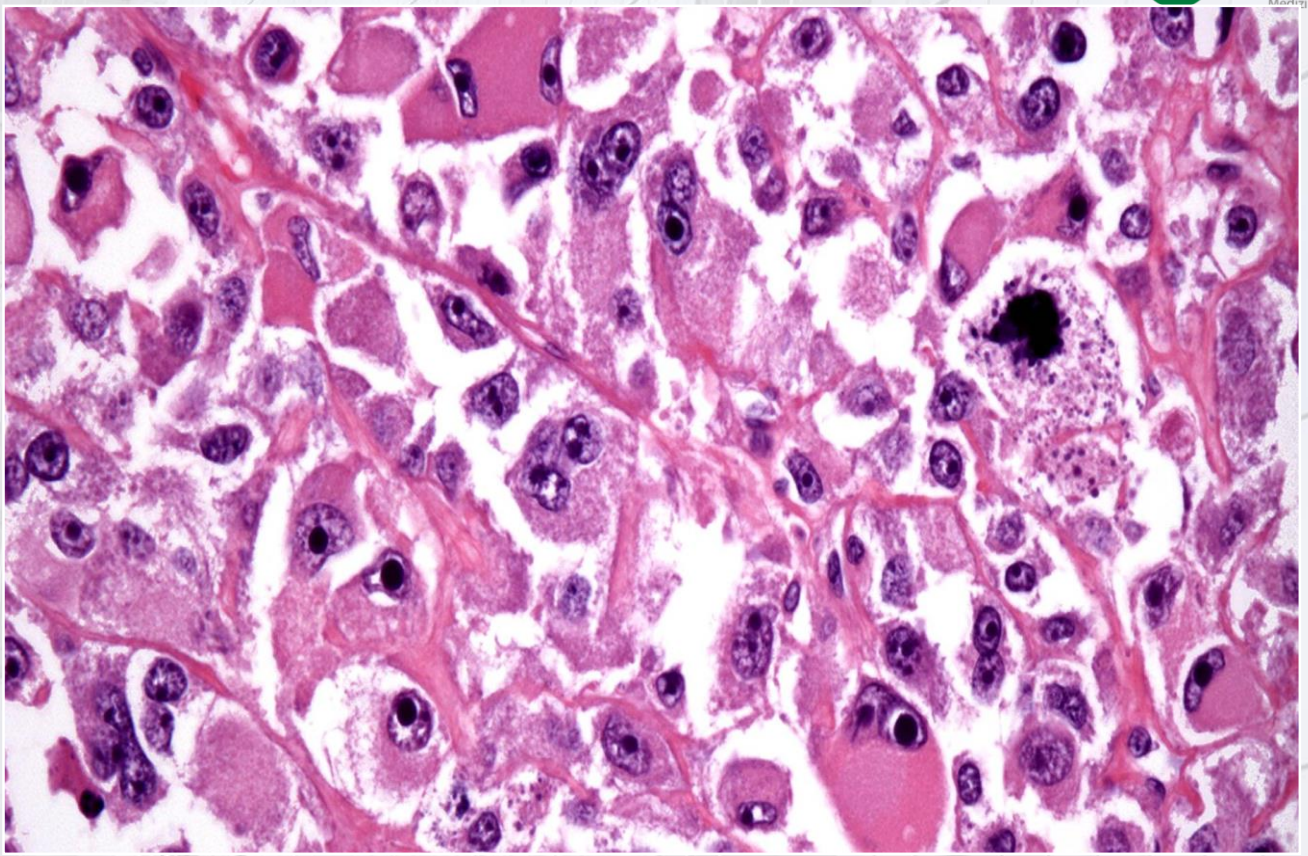


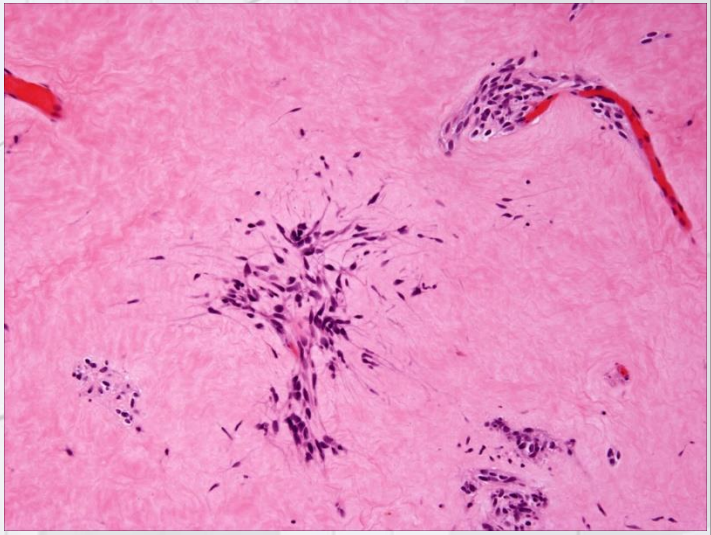
MORPHOLOGIC CHANGES UNDER TKI THERAPY

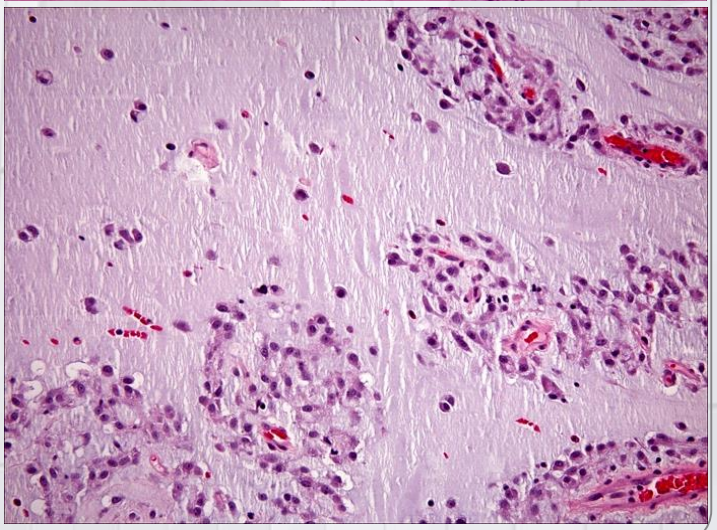
Common changes under TKI treatment

Hypocellularity

- Fibrosis
- Myxoid changes
- Necrosis

- *Report the percentage of viable tumor cells*





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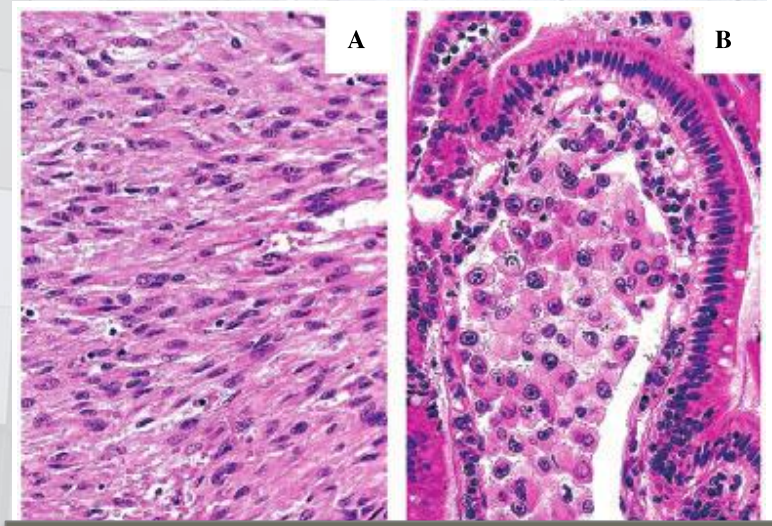
Morphologic changes

- Spindel cell -> epitheloid morphology
- Pleomorphic GIST
- Dedifferentiated GIST
- Rhabdomyosarcomatous differentiation in GIST

Metastases lost KIT expression but retained *KIT* exon 11 mutation



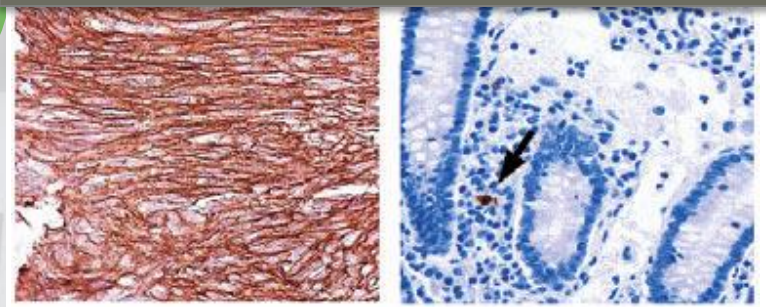
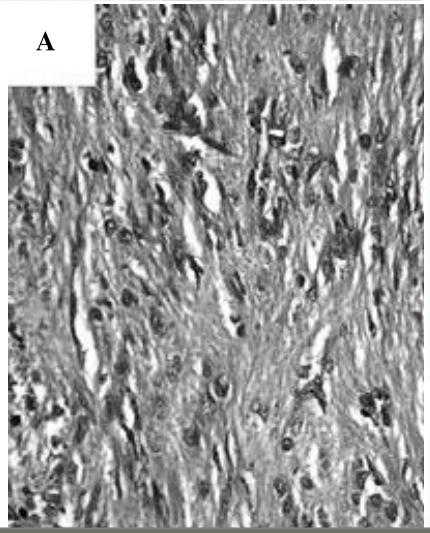


Figure 1. In the primary tumour of case 1, a dominantly spindle cell proliferation was seen (A). An endoscopic biopsy of the recurrence showed uniform, large round and epithelioid cells with copious



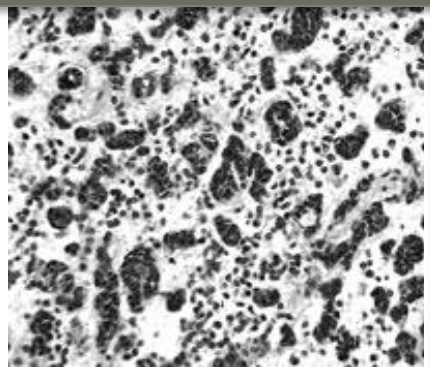


Figure 2. The primary tumour was c

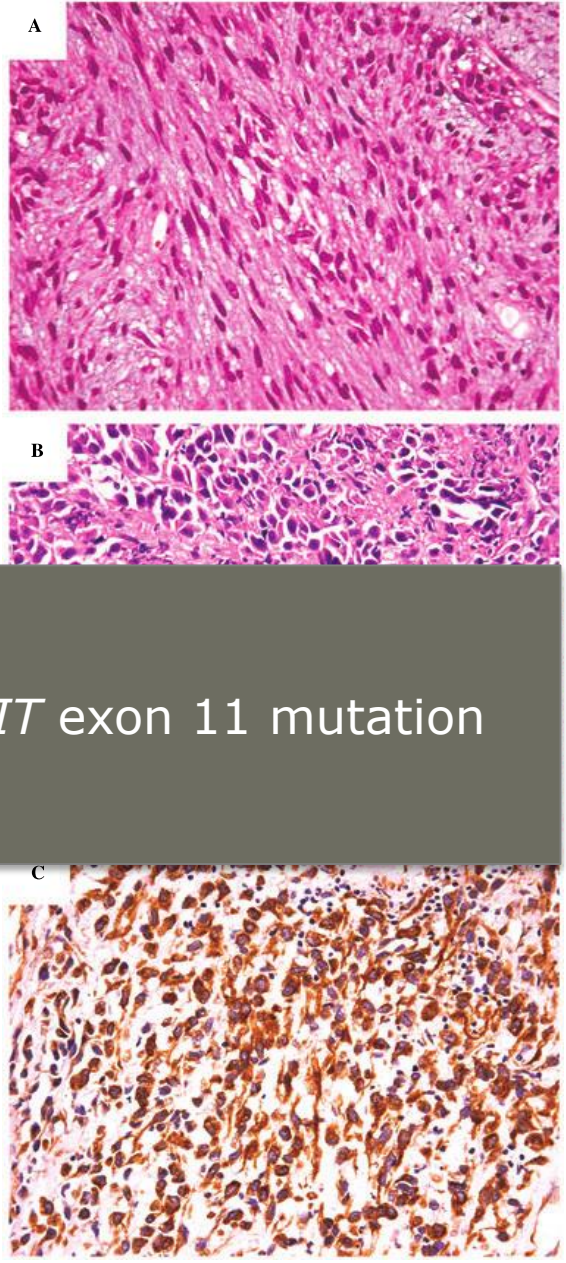
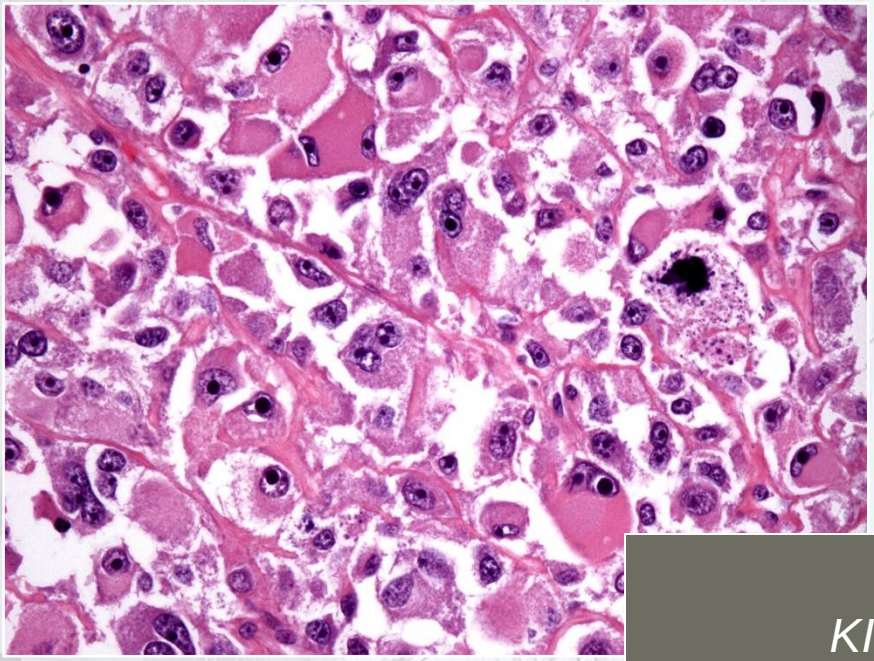
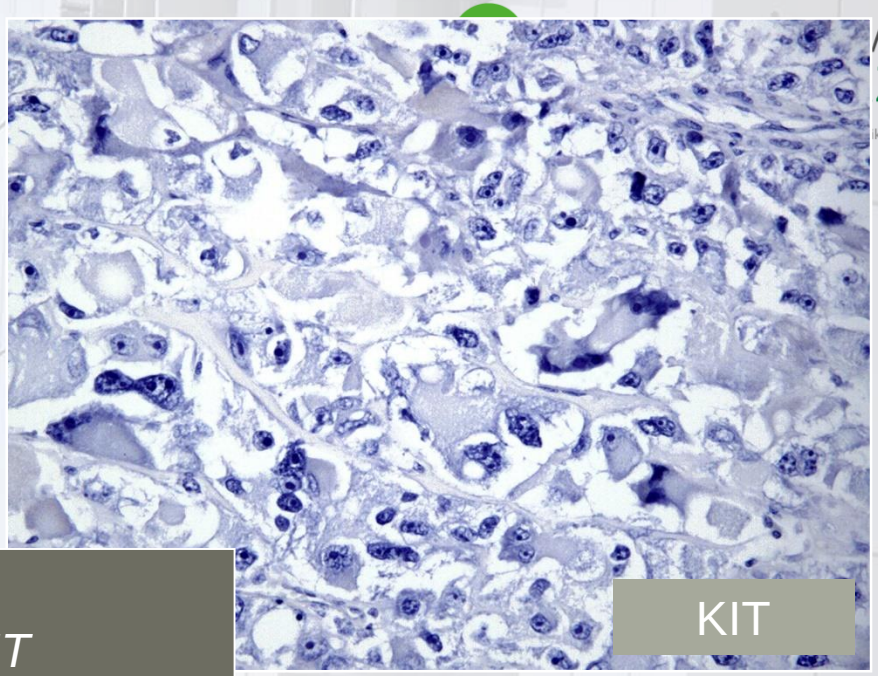


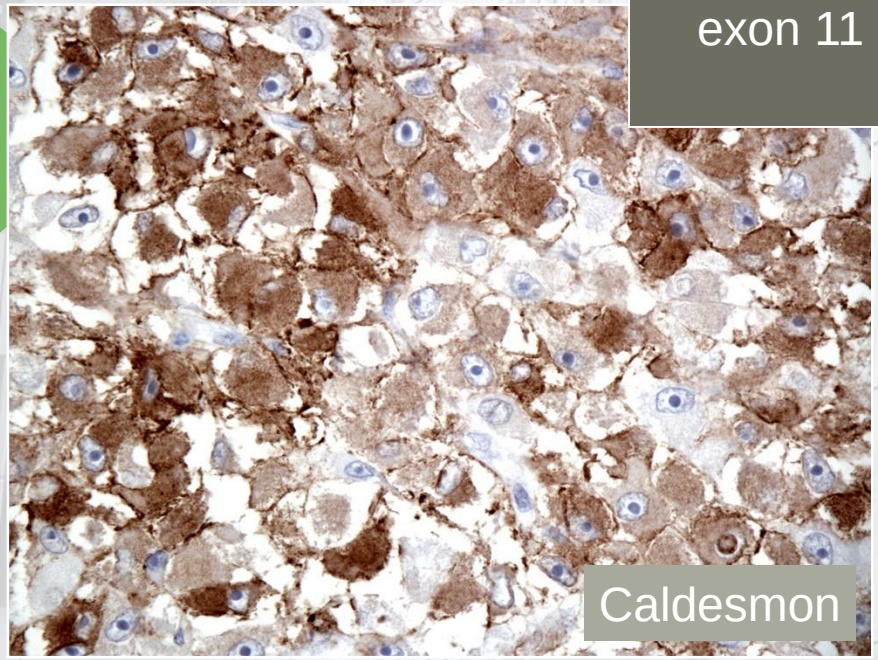
Figure 3. The primary tumour was composed of spindle-shaped cells

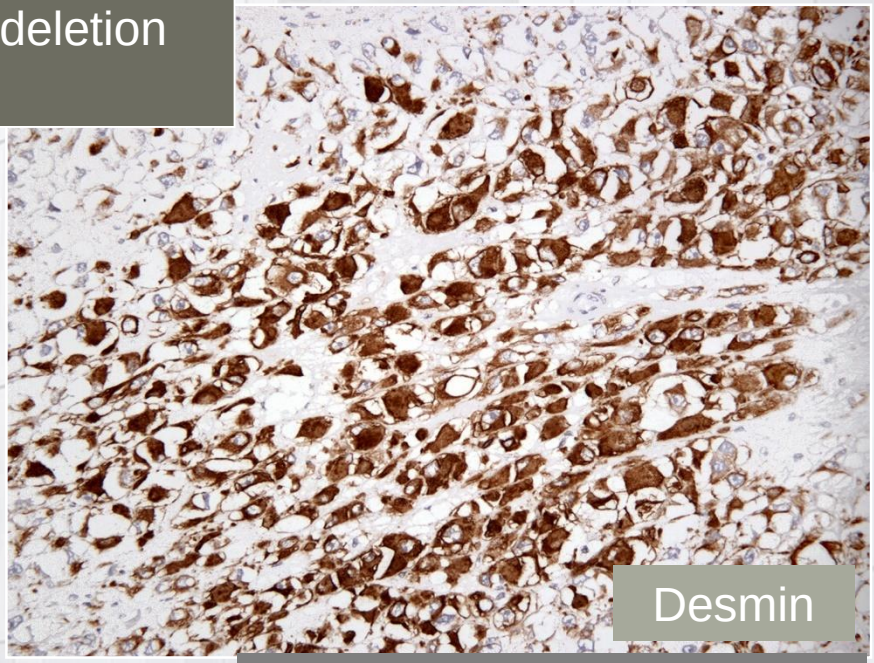
Changing phenotype of gastrointestinal stromal tumours under imatinib mesylate treatment: a potential diagnostic pitfall.
Pauwels P, Debiec-Rychter M, Stul M, De Wever I, Van Oosterom AT, Sciot R.
Histopathology. 2005 Jul;47(1):41-7



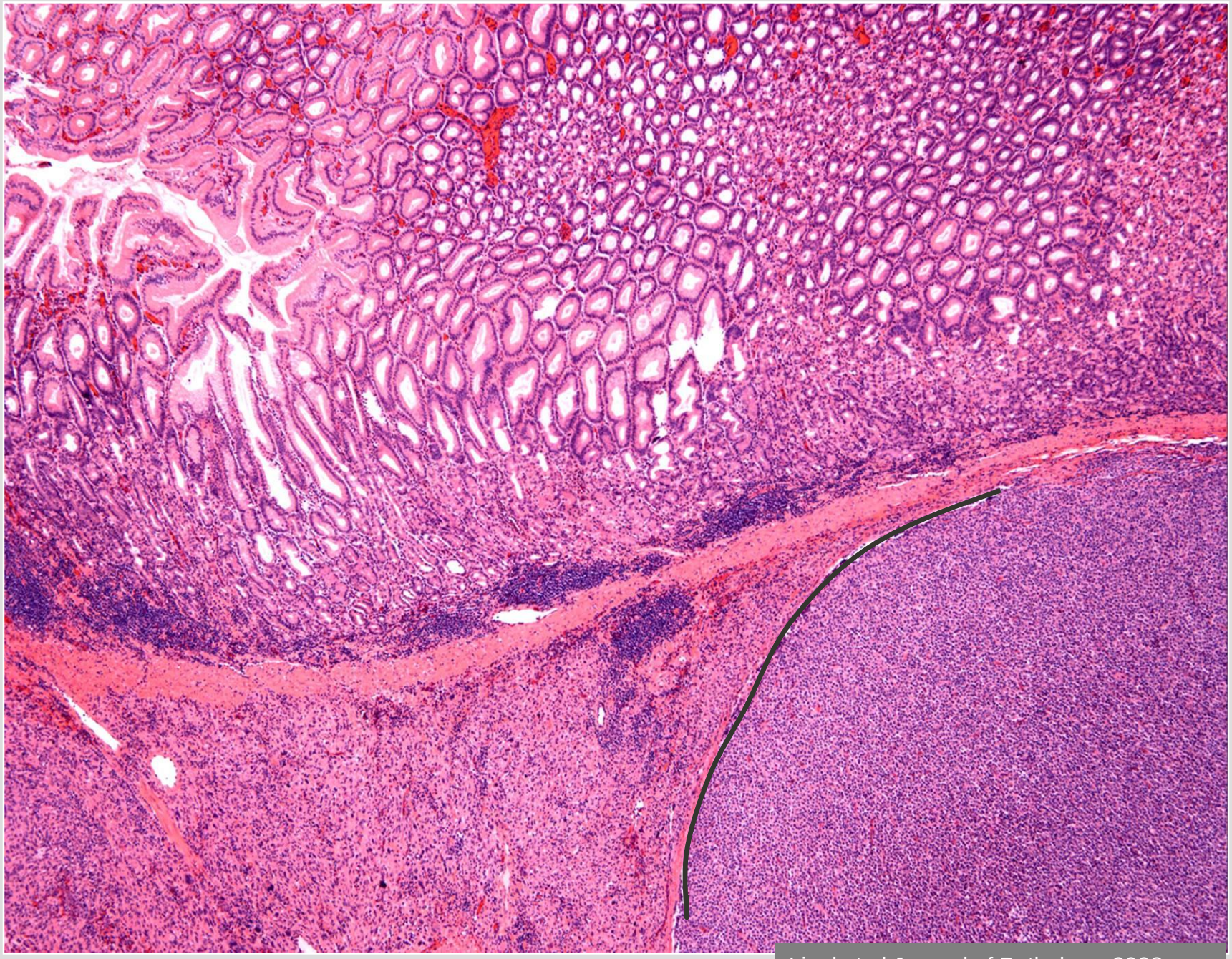


KIT
exon 11 deletion

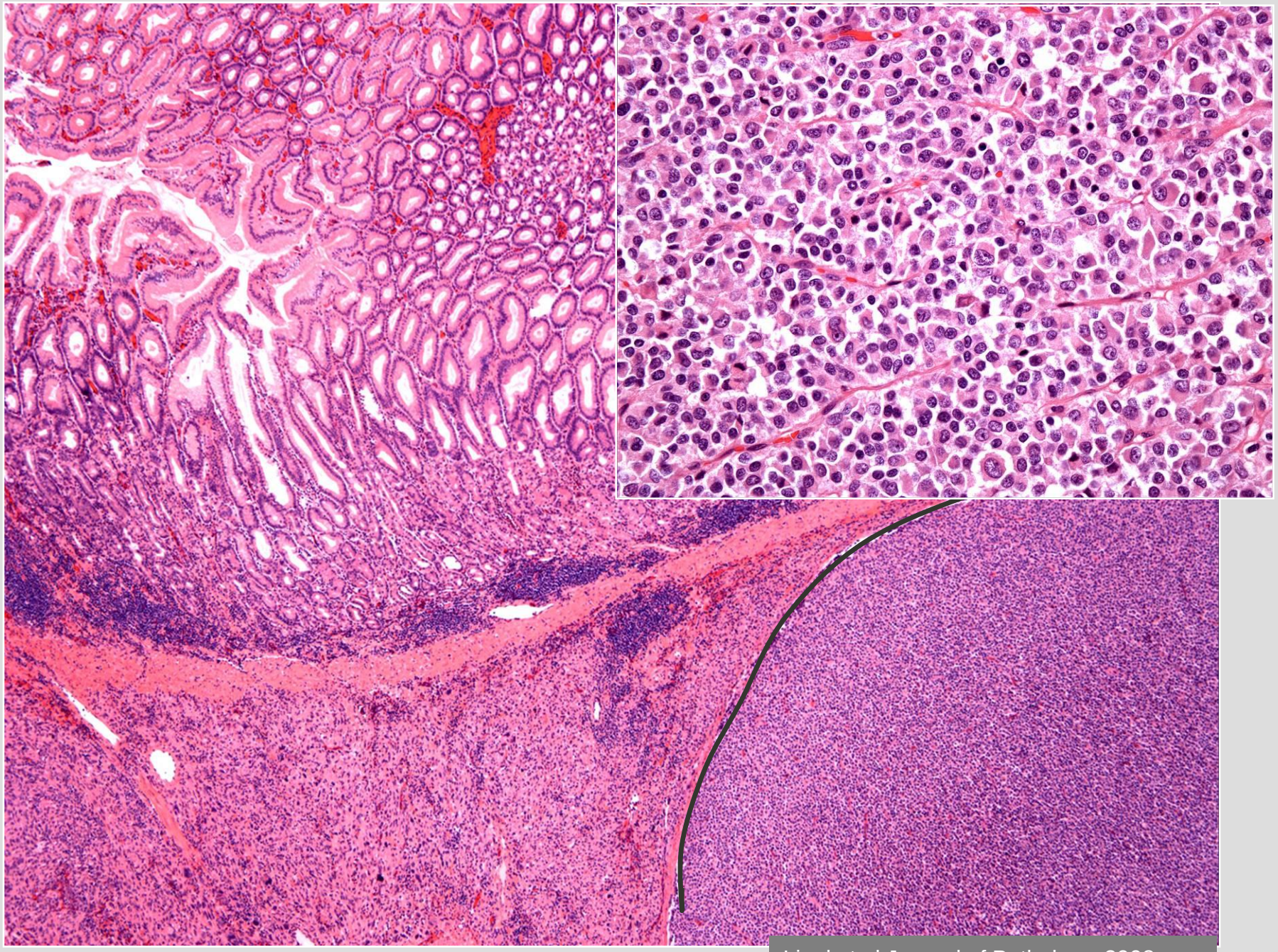




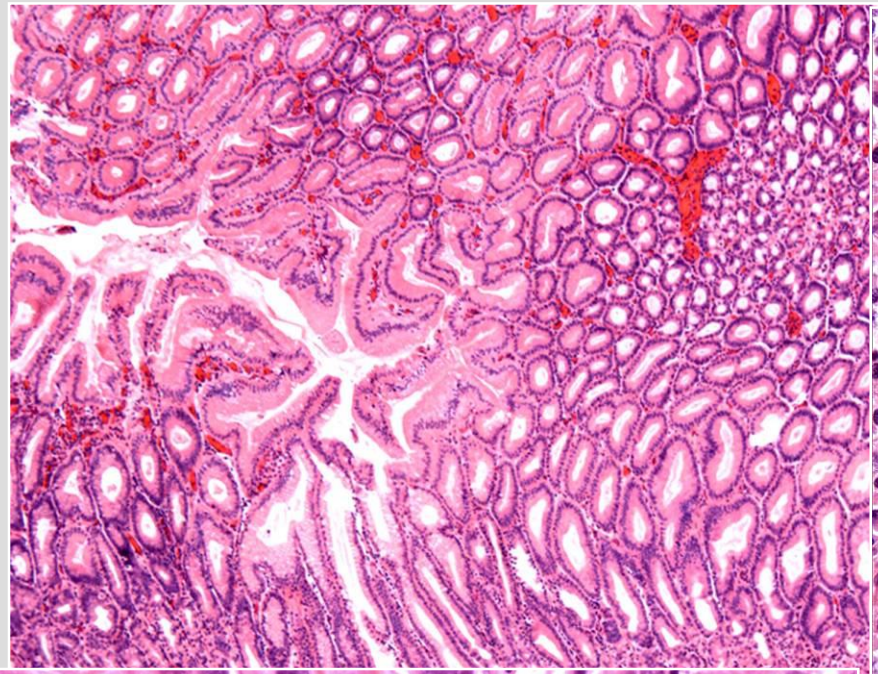
Liegl et al Journal of Pathology, 2008

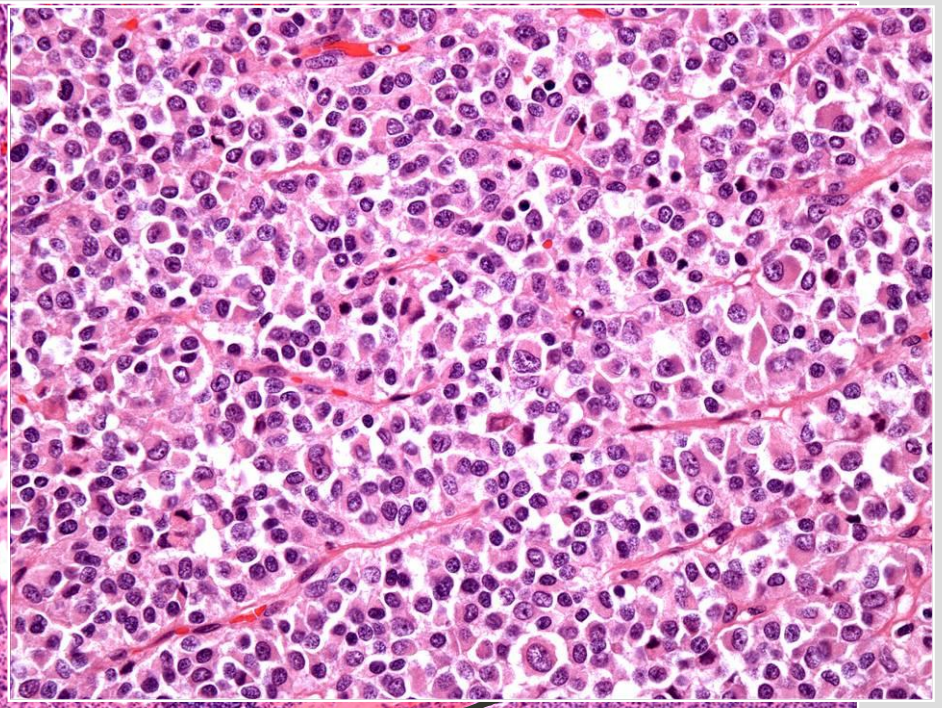


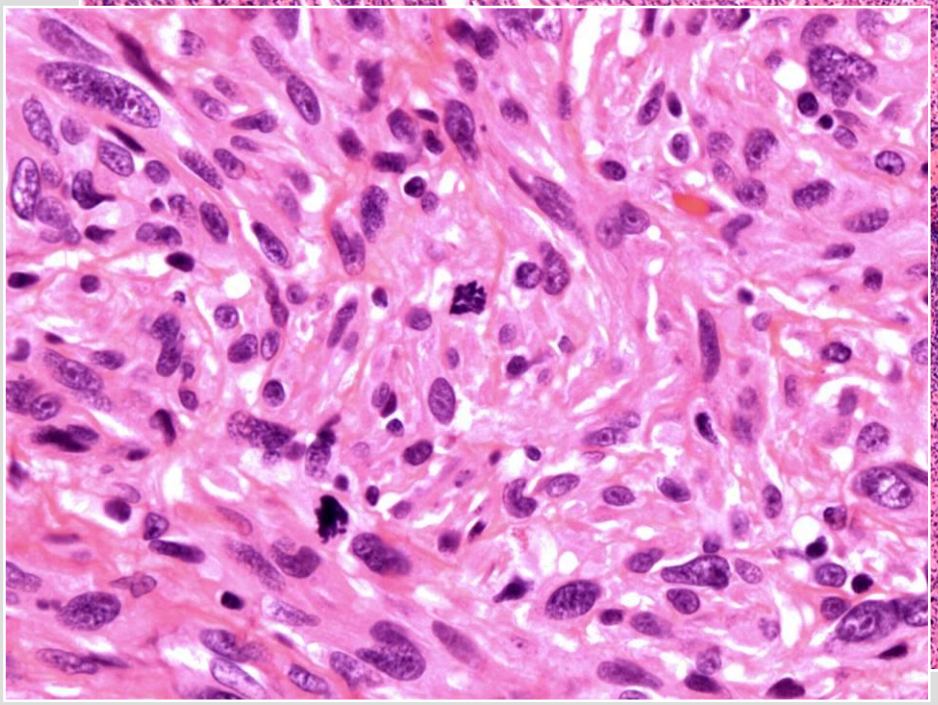
Liegl et al Journal of Pathology, 2008

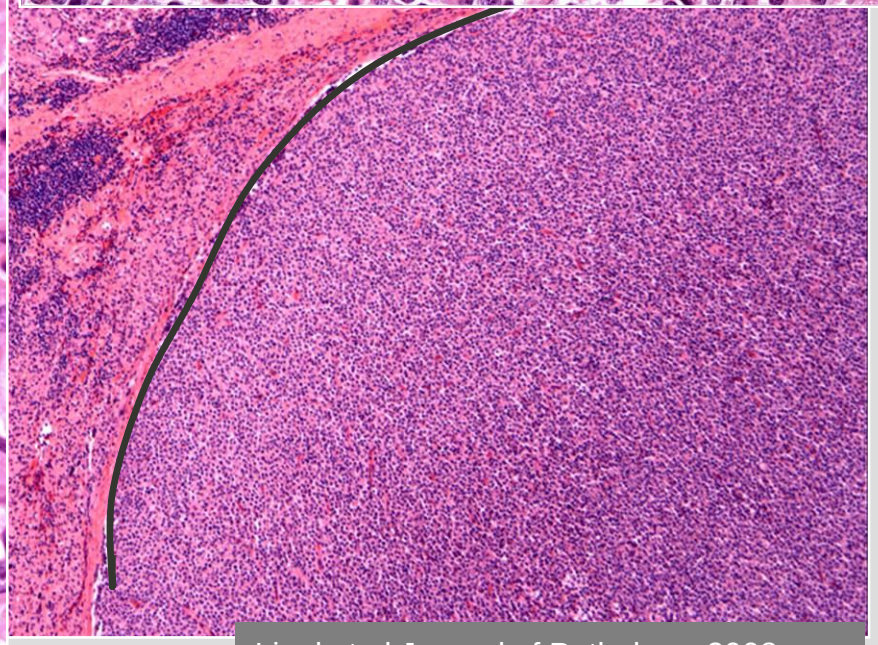


Liegl et al Journal of Pathology, 2008









Liegl et al Journal of Pathology, 2008

Liegl et al Journal of Pathology, 2008

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Am J Surg Pathol. 2013 March ; 37(3): 385–392. doi:10.1097/PAS.0b013e31826c1761.

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[1], **Salvatore Romeo**[2], **Lei Zhang**[1], **Khedoudja Nafa**[1], **Jason L. Hornick**[3], **G. Petur Nielsen**[4], **Mari Mino-Kenudson**[4], **Hsuan-Ying Huang**[5], **Juan-Miguel Mosquera**[6], **Paolo A Dei Tos**[2], and **Christopher D.M. Fletcher**[3]

Dedifferentiated GIST

- Reported 8 cases in imatinib treated (n=3) and untreated patients (n=5)
- Abrupt transition from a classic CD117 –positive spindle cell GIST to an anaplastic CD117 negative tumor
- IHC: expression of CK (n=4) and Desmin (n=1)
- Molecular findings:

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

Antonescu et al: Am J Surg Pathol. 2013 March ; 37(3): 385–392

Patient demographics, tumor characteristics and history of imatinib therapy

	Age/ Sex	Location	Size (cm)	Stage at Presentation	Metastases	Pre-op imatinib therapy
1	23/M	Stomach	NA*	Liver mets	Liver, Peritoneal	Yes
2	40/F	Stomach	8	Peritoneal mets	Peritoneal	No
3	55/M	Stomach	18	Primary	No	No
4	48/M	Stomach	5.5	Peritoneal mets	Liver, Peritoneal	No
5	58/M	Rectum	6	Primary	No	No
6	53/M	Stomach	7	Locoregional LN	Peritoneal	No
7	60/M	Small bowel	7.5	Primary	Liver, Peritoneal	Yes
8	65/M	Colon	25	Primary	Peritoneal	Yes

M, male; F, female; NA*, not available, primary not resected, size unknown; LN, lymph nodes.

Common abnormality in the CD117-negative dediff. GIST:
Genetic instability, represented either by

- loss of heterozygosity of KIT
- low level amplification of KIT

	KIT/PDGFRA genotype	FISH	P53 mutation
1A	WT	Normal	ND
1B	WT	Loss of one KIT copy	ND
2A	WT	Normal	WT
2B	WT	low level KIT amplification	WT
3A	KIT exon 11 557-8WKdel	Normal	WT
3B	KIT exon 11 557-8WKdel	Normal	WT
4A	WT	Normal	Ex 8 del
4B	WT	low level KIT amplification	Ex 8 del
5A	KIT exon 11 557-8WKdel	Normal	WT
5B	KIT exon 11 557-8WKdel	Normal	WT
6A	WT	ND	ND
6B	WT	ND	ND
7A	KIT exon 11 V559G KIT exon13 V654A	Normal	ND
7B	KIT exon 11 V559G / KIT exon13 V654A	Loss of one KIT copy	ND

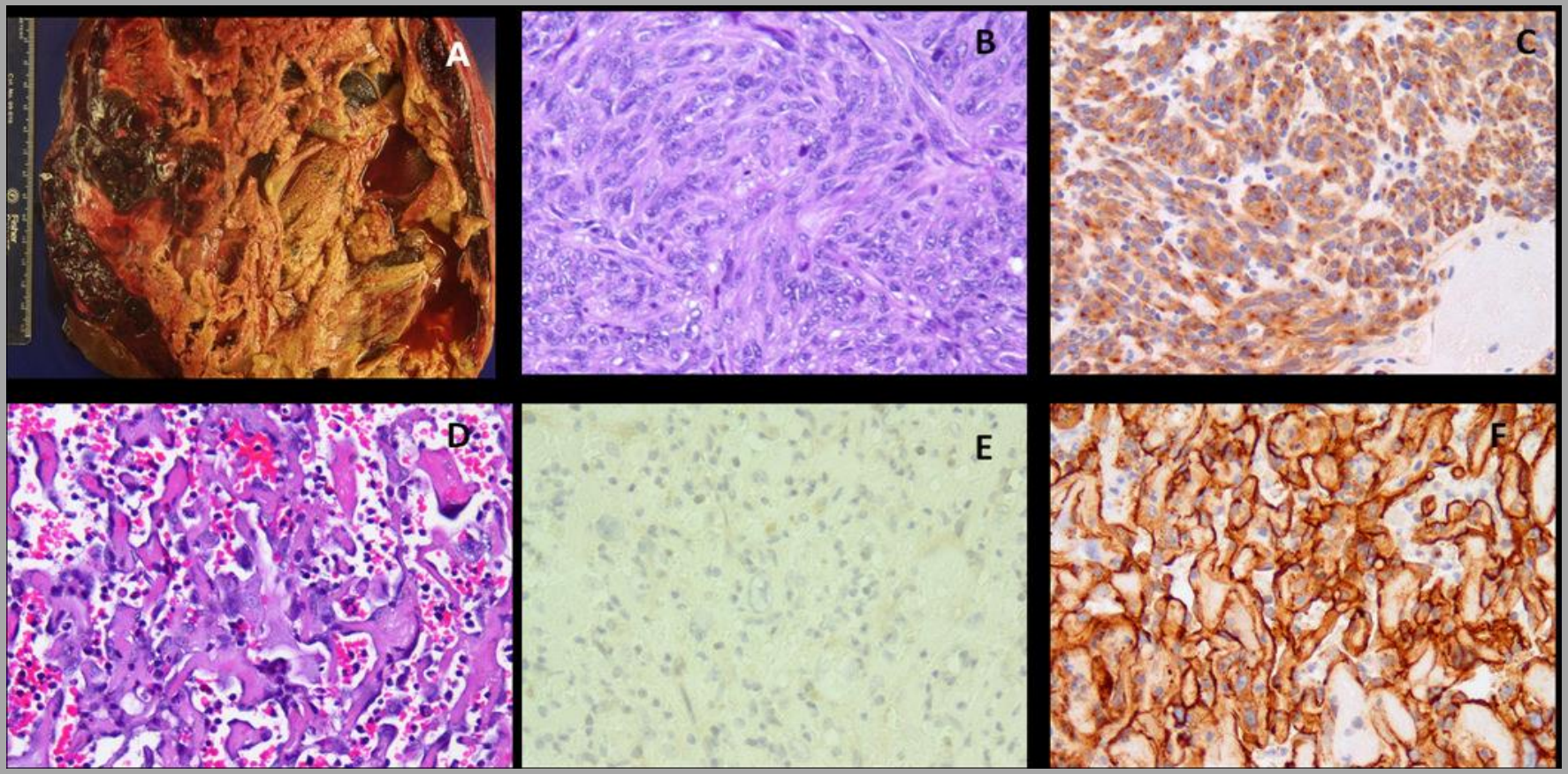

Figure 3.
In one of debulking procedure for imatinib-resistant disease (A), in addition to the classic spindle cell GIST component (B, 100×) which was strongly positive for CD117 (C, 100×), there were areas composed of complex, anastomotic vascular spaces, lined by highly atypical cells (D, 200×), which lost CD117 expression (E, 200×) and instead were strongly positive for CD31, in keeping with an angiosarcoma component (case#7).

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Rhabdomyosarcomatous differentiation in GIST

ORIGINAL ARTICLE

Rhabdomyosarcomatous Differentiation in Gastrointestinal Stromal Tumors After Tyrosine Kinase Inhibitor Therapy

A Novel Form of Tumor Progression

Bernadette Liegl, MD,† Jason L. Hornick, MD, PhD,* Cristina R. Antonescu, MD,‡ Christopher L. Corless, MD,§ and Christopher D. M. Fletcher, MD, FRCPath**

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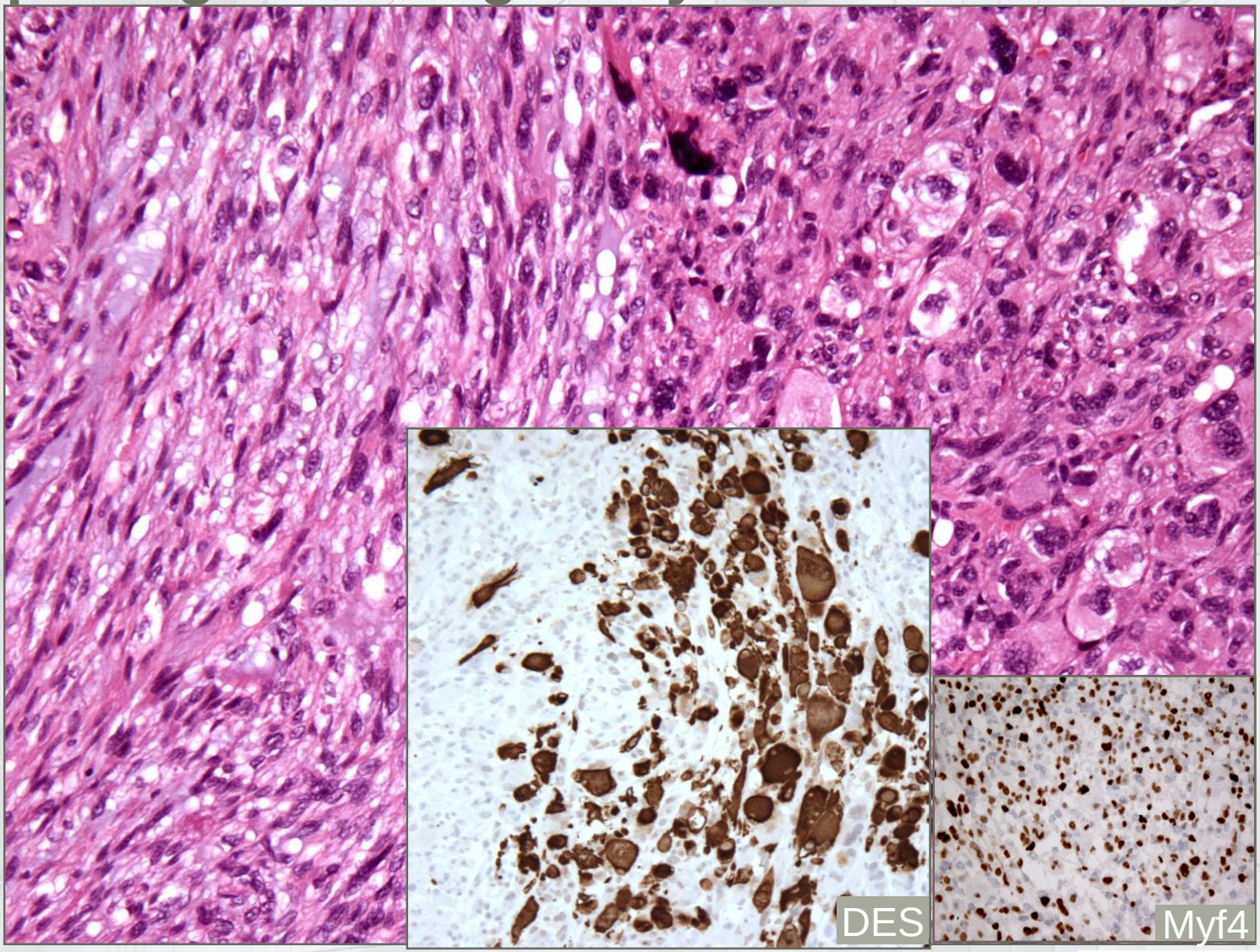
Morphologic heterogeneity after treatment with TKI



Liegl et al AJSP, 2009

TABLE 3. Summary of Mutational Analysis

Case	Anatomic Location	Morphology	Mutational Analysis	
			Primary Mutation	Secondary Mutation
1	Omentum (A)	Spindle cell	*KIT* exon 11 point mutation V559D (heterozygous)	ND
	Omentum (B)	Rhabdomyoblastic differentiation	*KIT* exon 11 point mutation V559D (heterozygous)	ND
	Liver	Epithelioid	*KIT* exon 11 point mutation V559D (heterozygous)	*KIT* exon 13 V654A
2	Omentum	Rhabdomyoblastic differentiation	*KIT* exon 11 deletion 556-574 (homozygous)	ND
	Liver	Spindle cell	*KIT* exon 11 deletion 556-574 (homozygous)	ND
3	Abdomen/colonic mesentery	Pleomorphic with rhabdomyoblastic differentiation	*KIT* exon 11 point mutation V559D (heterozygous)	ND
	Mesenteric deposit	Pleomorphic with rhabdomyoblastic differentiation	*KIT* exon 11 point mutation V559D (heterozygous)	ND
4	Left upper quadrant mass (gastrosplenic ligament)	Rhabdomyoblastic differentiation	*KIT* exon 11 deletion 556-574 (heterozygous)	ND
	Left upper quadrant mass (gastrosplenic ligament)	Spindle cell	*KIT* exon 11 deletion 556-574 (heterozygous)	ND
5	Stomach	Epithelioid	*PDGFRA* exon 18 deletion, *KIT* wild-type	ND
	Peritoneum	Rhabdomyoblastic differentiation	*PDGFRA* exon 18 deletion, *KIT* wild-type	ND

ND indicates not detected; PDGFA, platelet-derived growth factor receptor α.

BRAF exon 15 V600E

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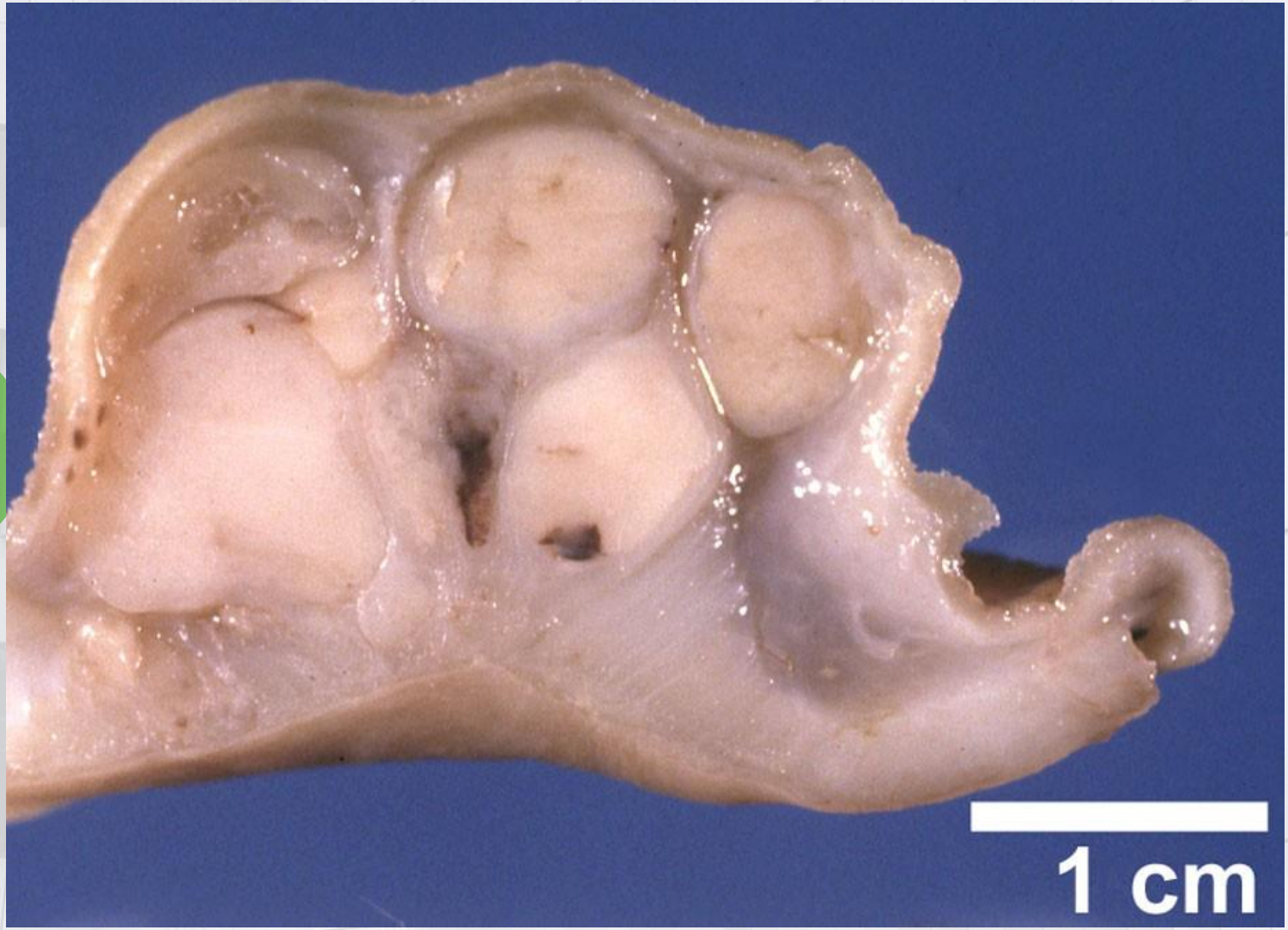
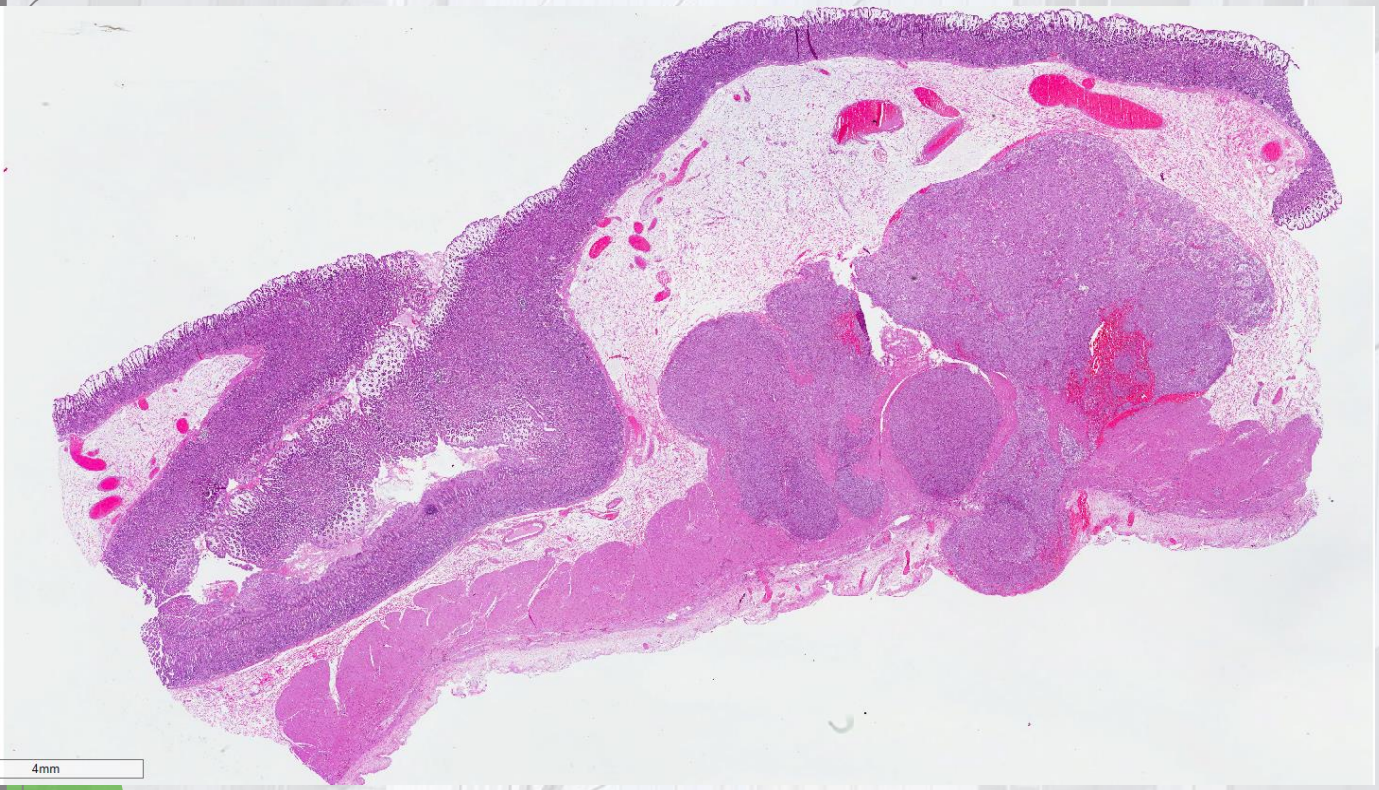
Morphology of SDHB deficient Gist

Plexiform/multinodular growth pattern


1 cm



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Gist with a distinctive plexiform or multinodular growth pattern located in the stomach!

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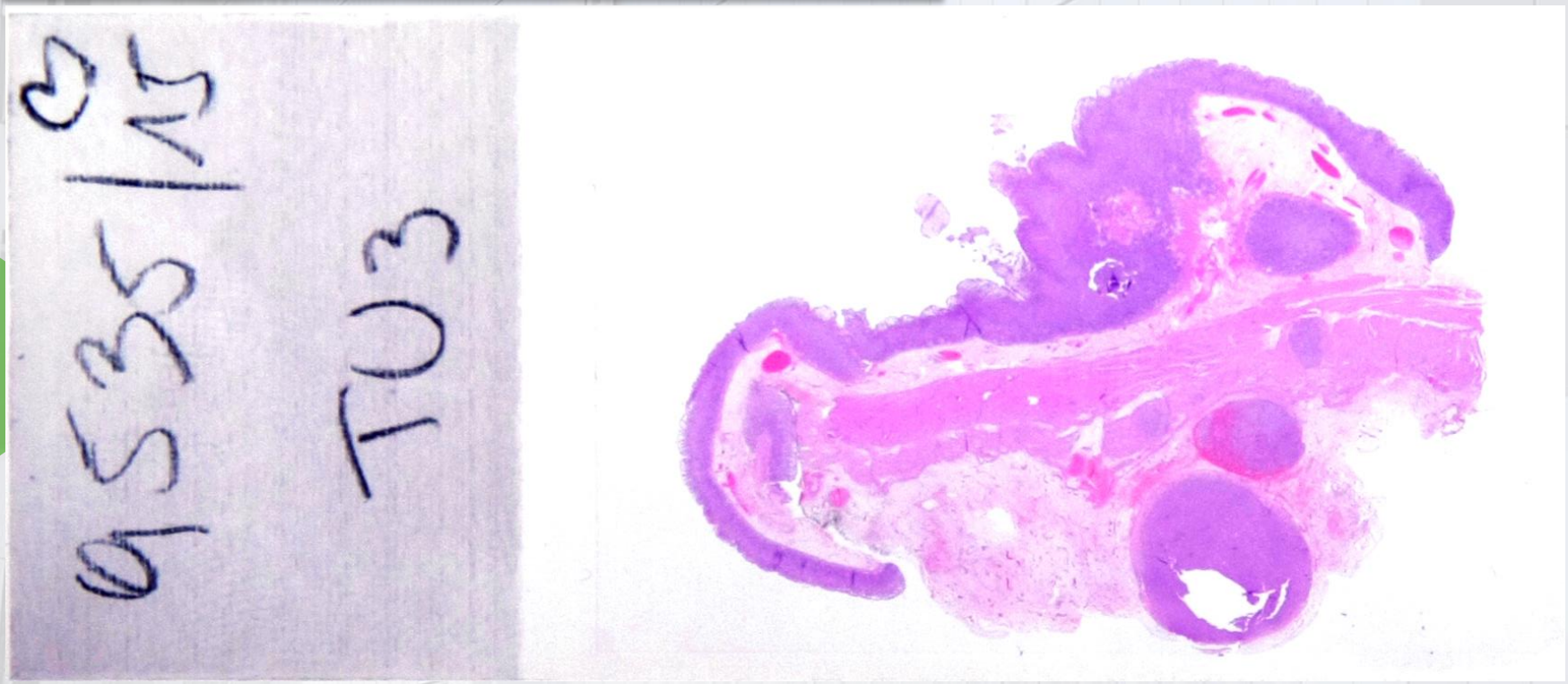
OP-Präparat vom 04.02.2015
9535-37/2015



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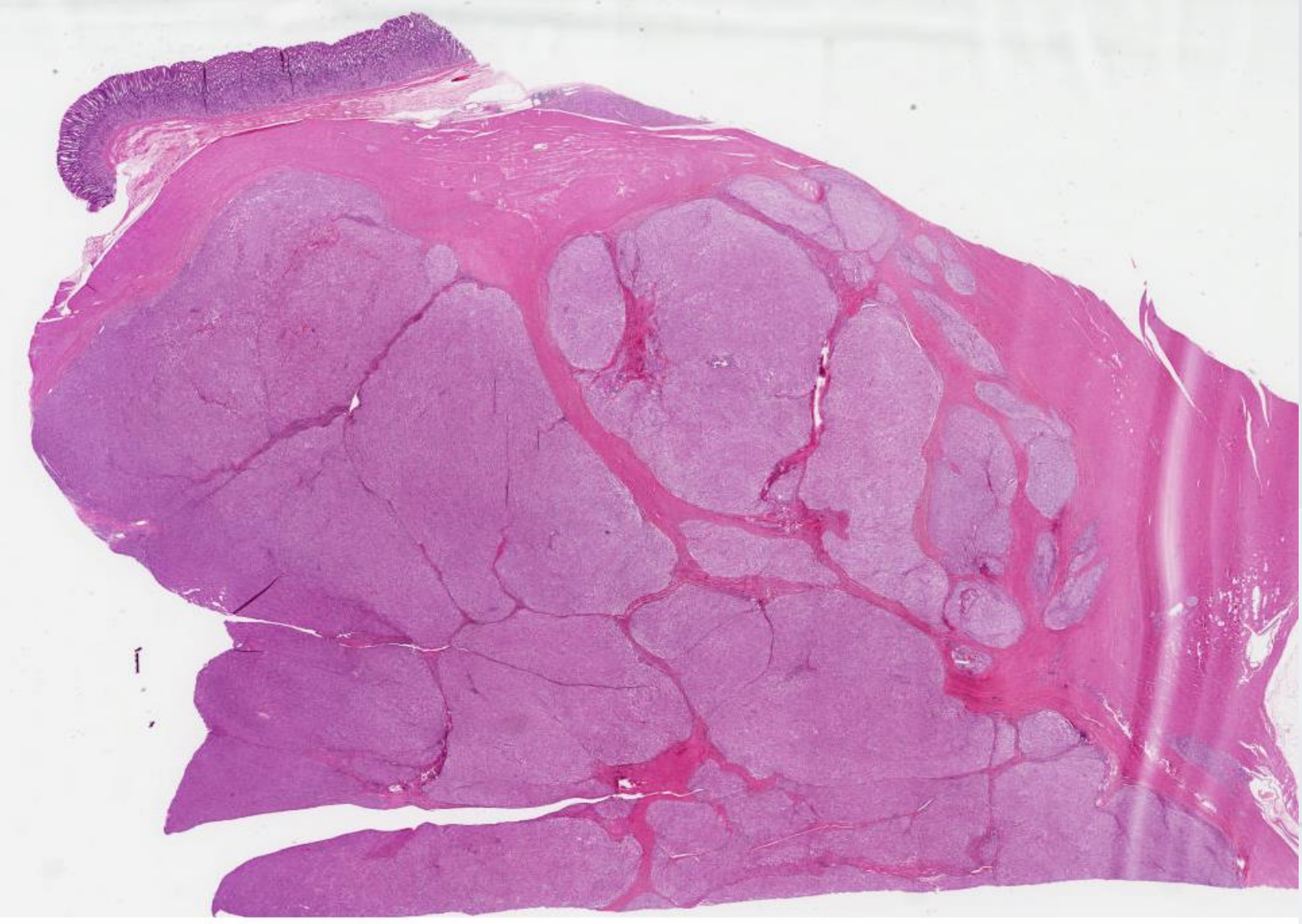
SDHB deficient 34a female



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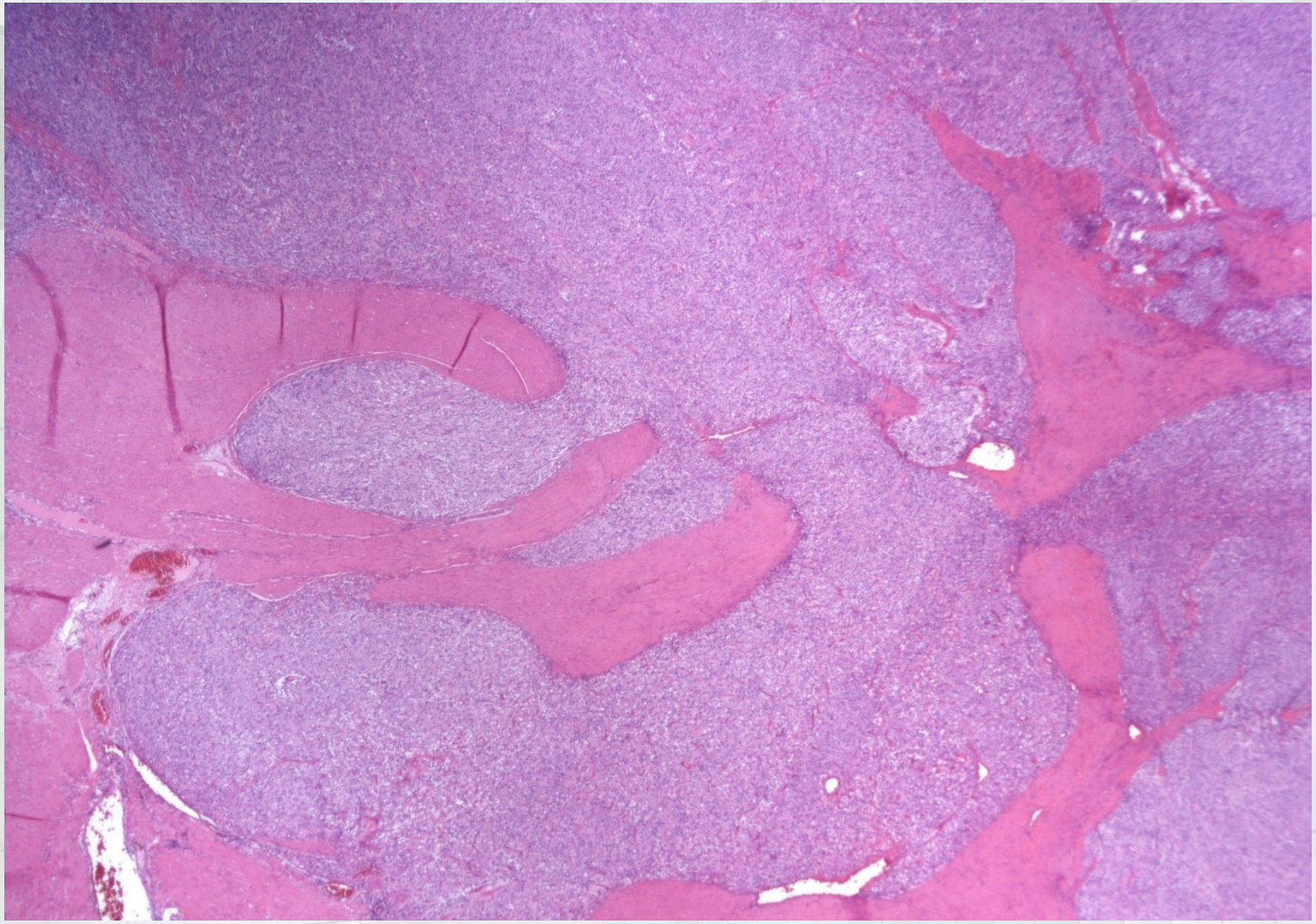
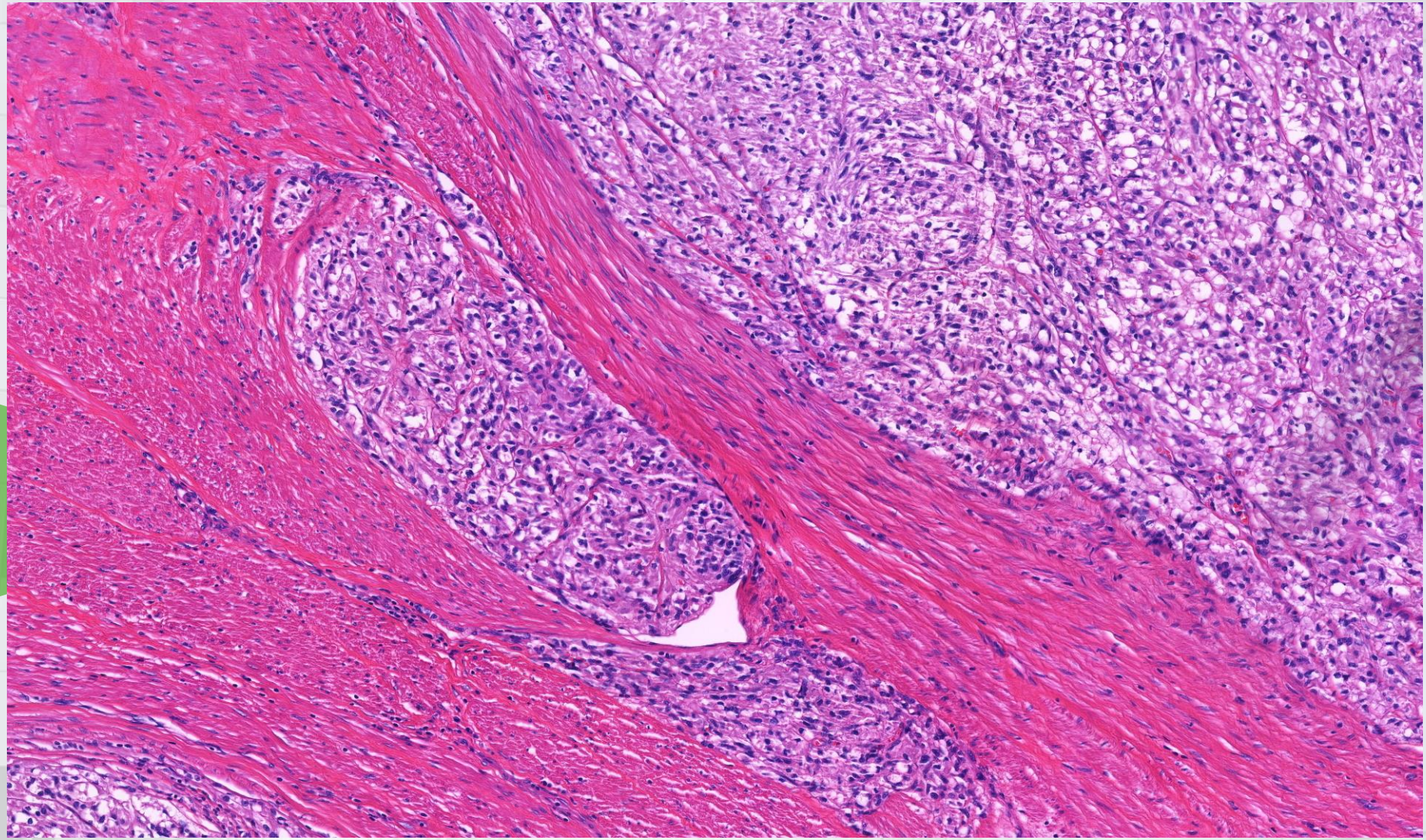
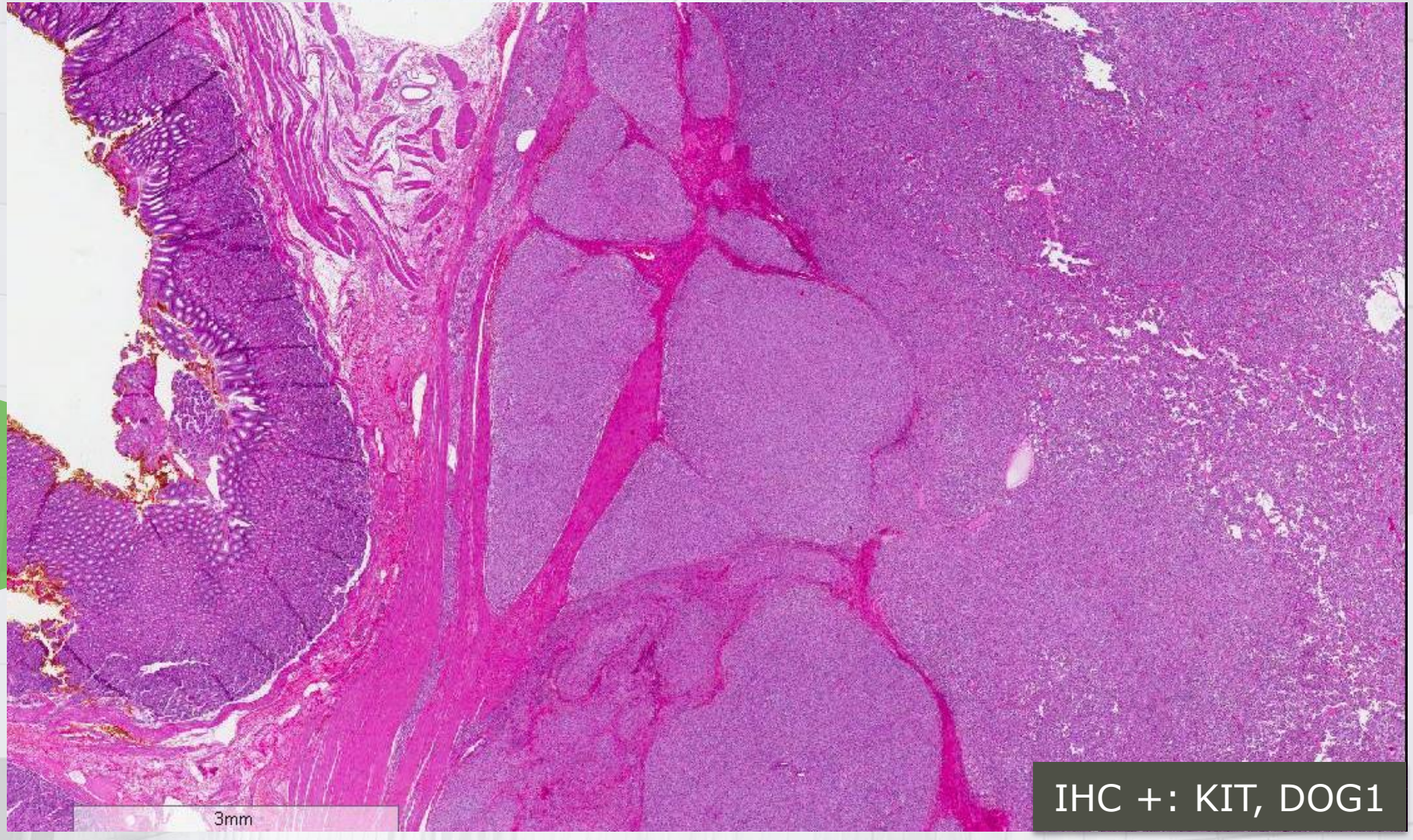
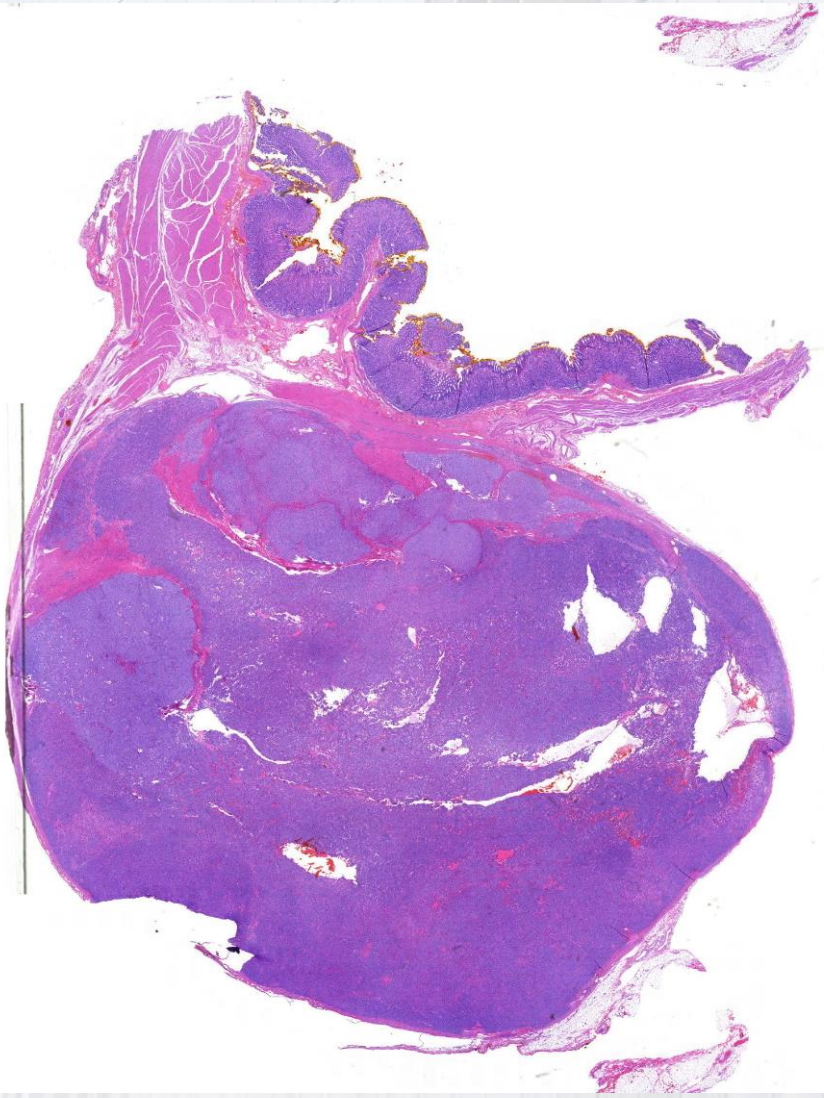
SDHB deficient 54 a female

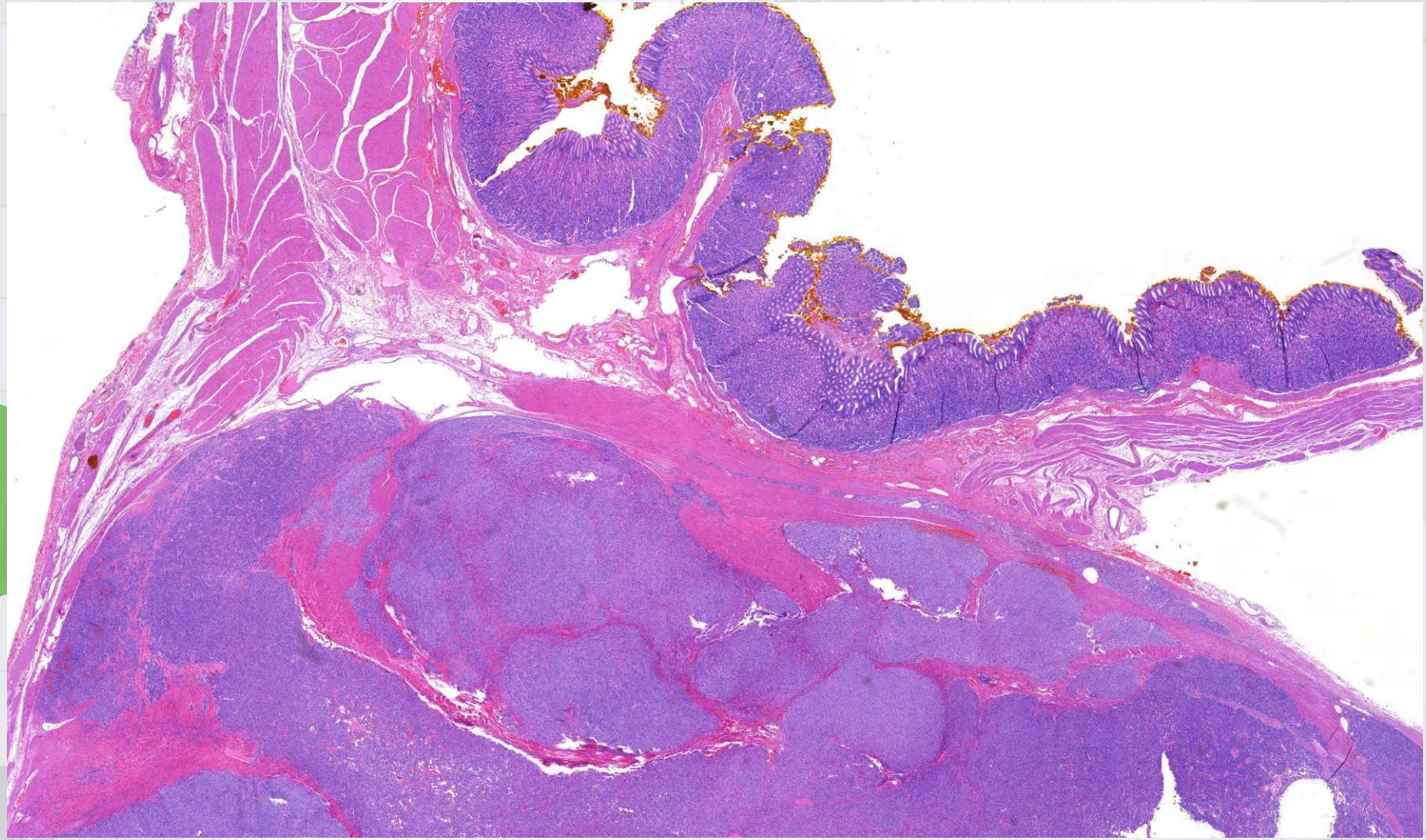


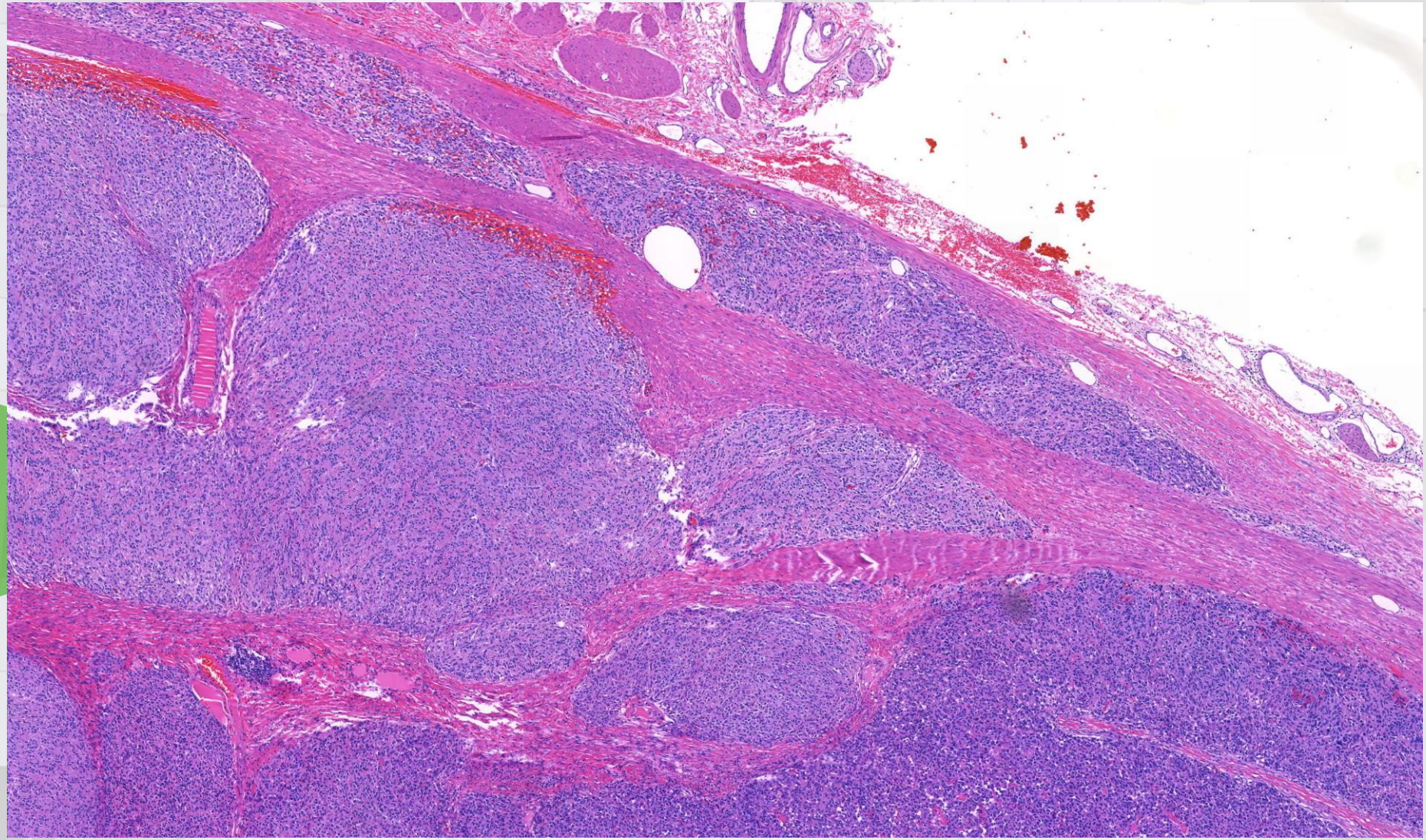


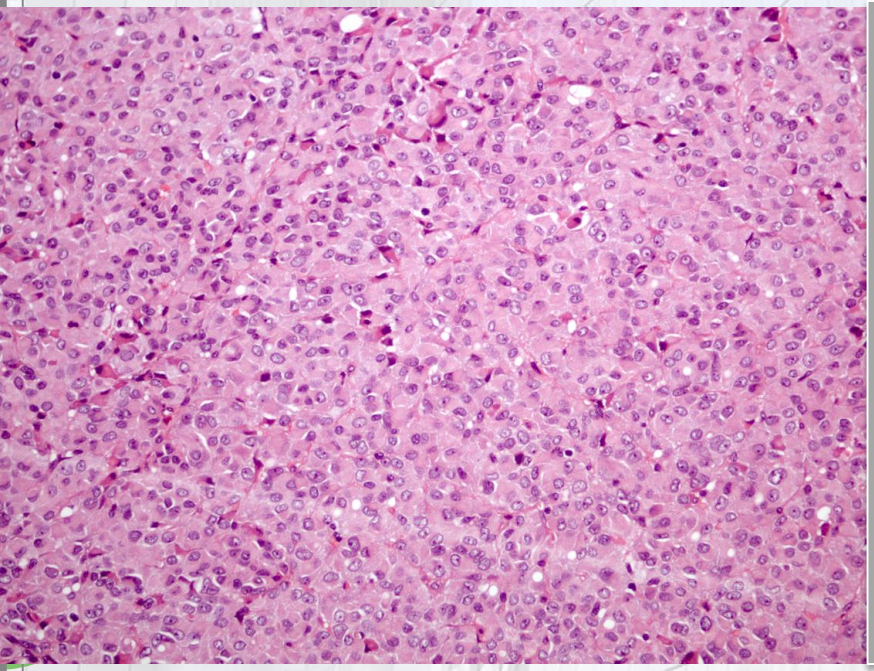


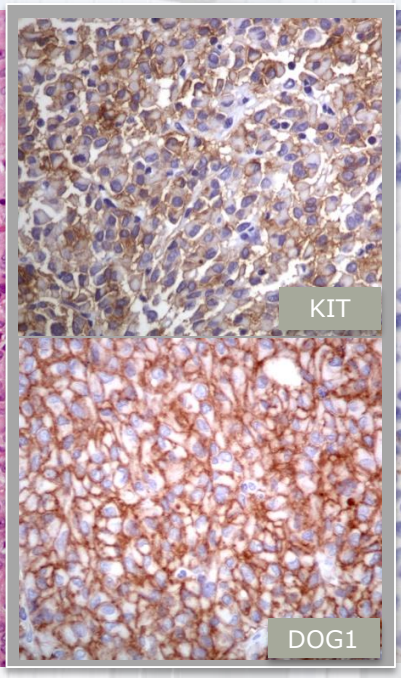
IHC +: KIT, DOG1

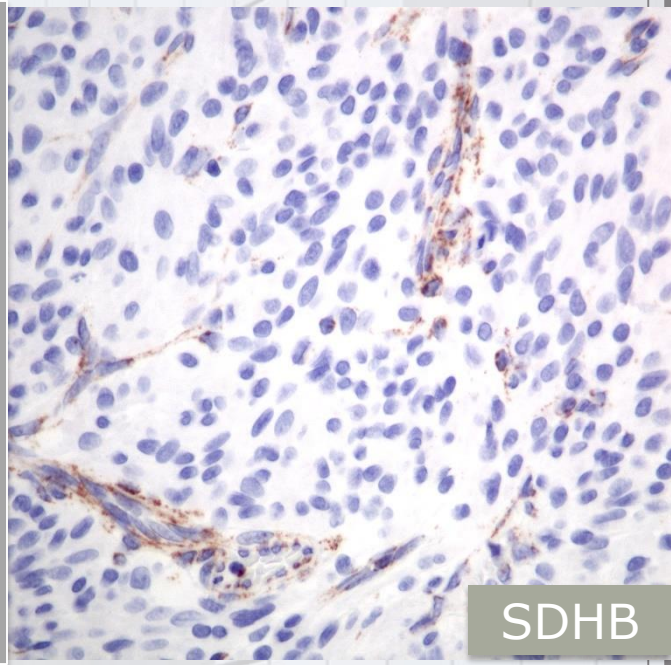






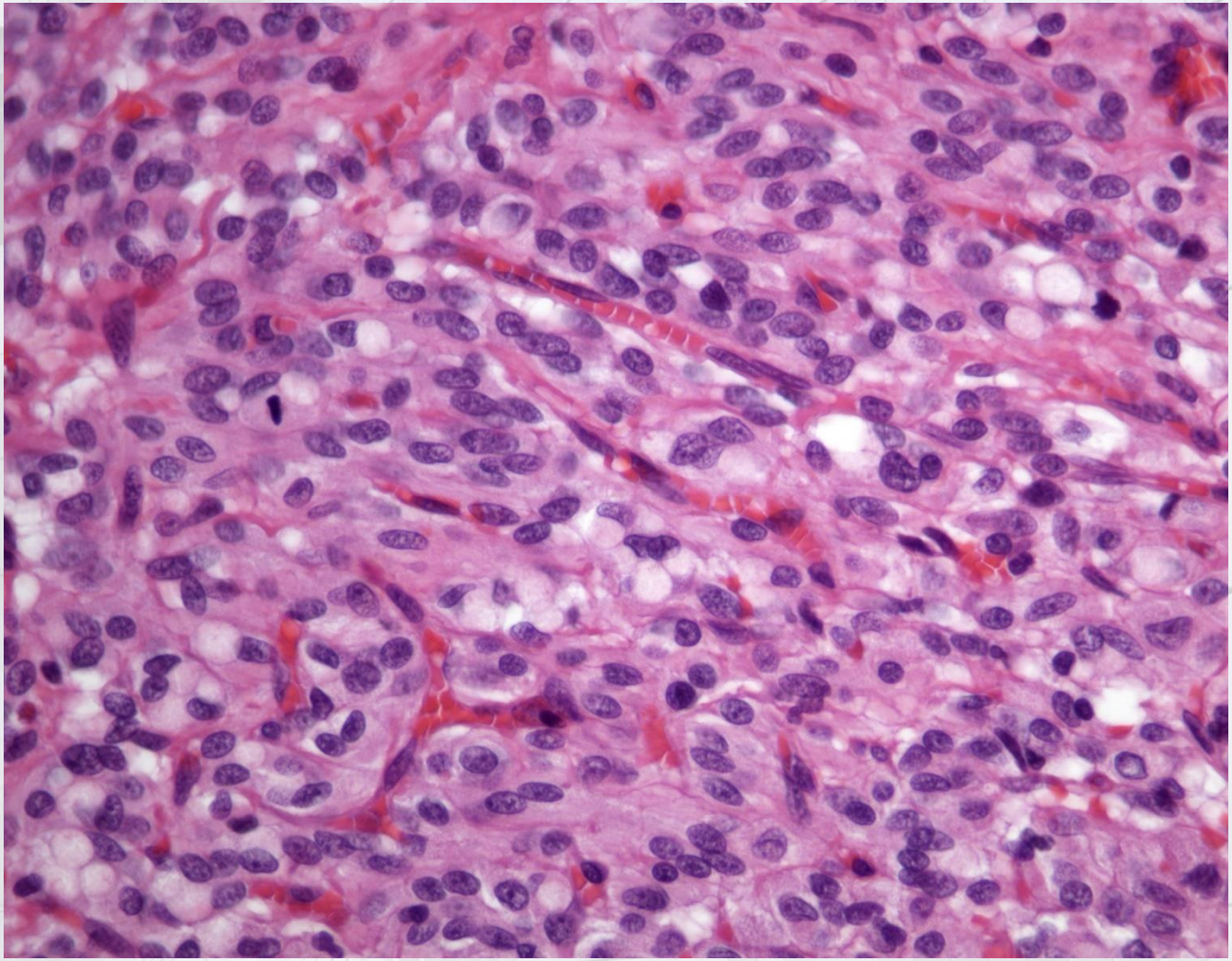






Commonly epitheloid morphology

SDHB deficient 54 a female



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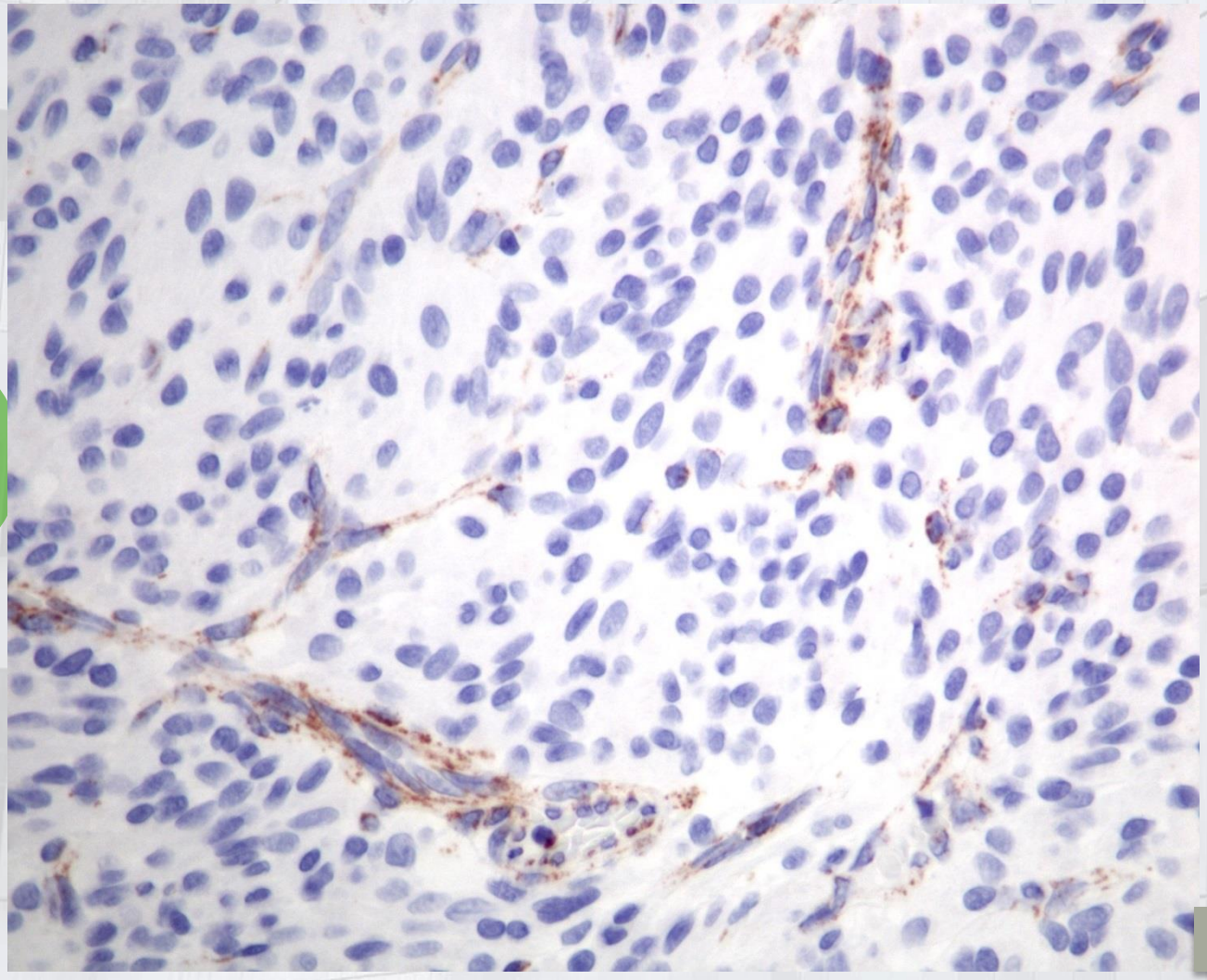
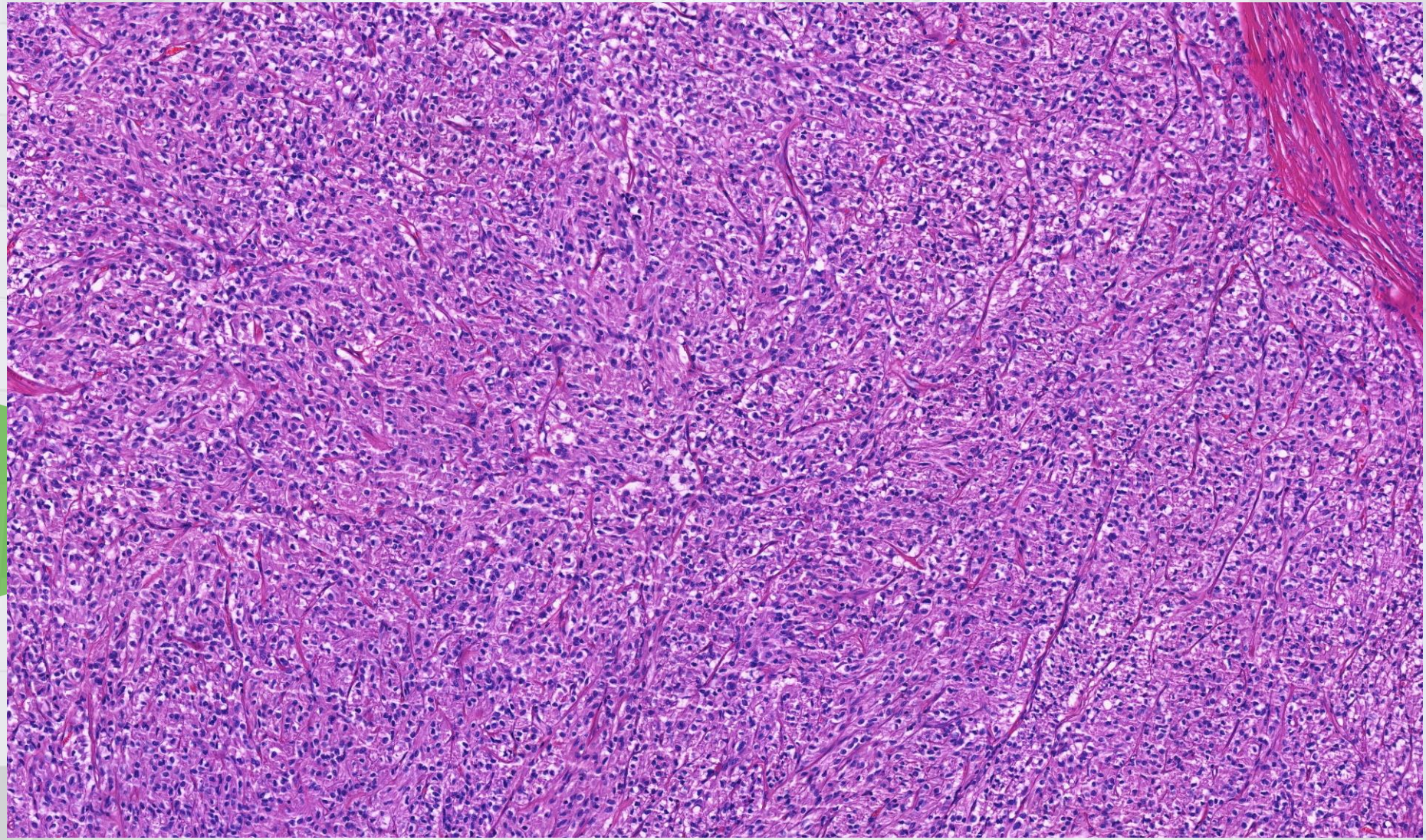
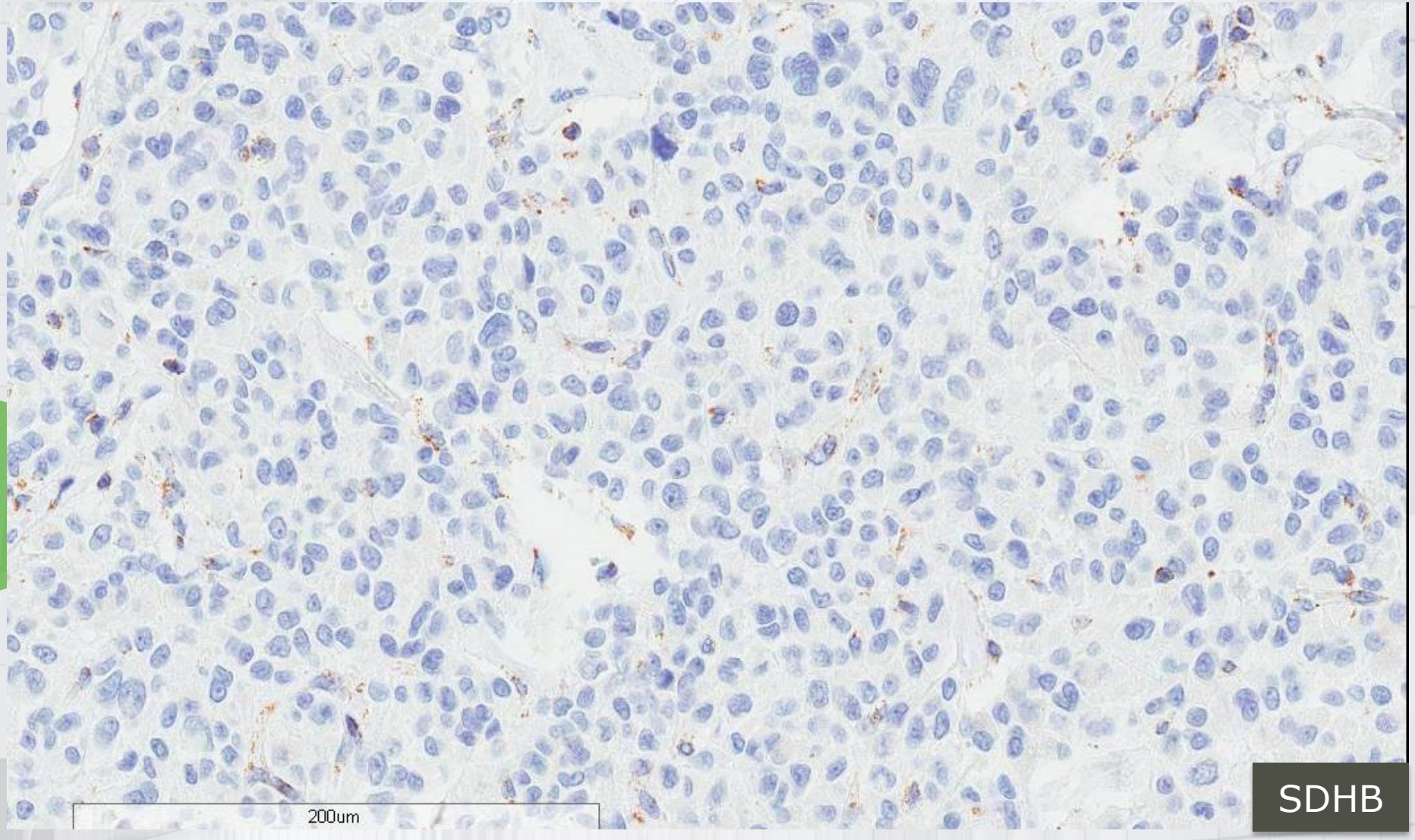
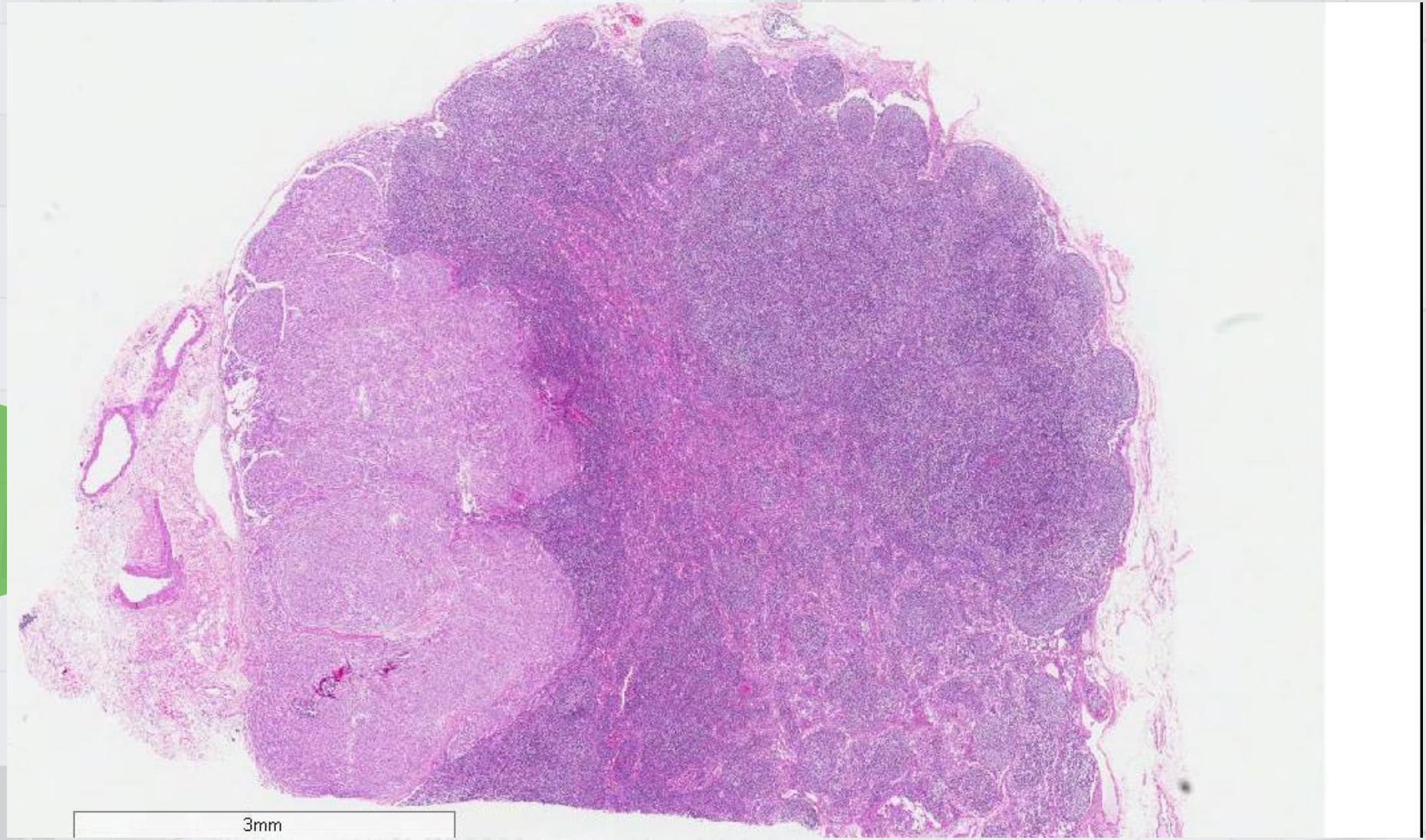
SDHB deficient 54 a female



SDHB




200um
SDHB


3mm

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SDHB immunohistochemistry has been shown a useful tool to screen for a dysfunction within any subunit of the SDH complex

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Consider SDHB deficient GIST

- In the stomach
- Predominantly in children and young adults – unifocal and multifocal
- SDHB IHC in all GIST (irrespectively of age) with multinodular/plexiform growth

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In Summary SDHB deficient GIST

- Epitheloid morphology (mixed)
- KIT and DOG1 expression
- „Dogma No“ **KIT**, **PDGFRA**, BRAF, NF1... mutations
- Riskstratification according to Miettinen -> not working
- LK metastases common
- Lymphovascular invasion can be seen
- Indolent clinically even if metastasized
- Imatinib resistent
- Association with CT and CSS
- Clinical implications

Molecular Classification of GIST

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Group A	Group B	Group C
SDHB retained by IHC	SDHB lost by IHC	
Mutations KIT PDGFRa BRAF HRAS NRAS NF-1.....	Think of SDHB deficient gastric GIST • in all patients <30a • Gists with distinctive multinodular/plexiform morphology irrespectively of age Consider Risk Stratification according to Miettinen is not working LN metastases can occur Imatinib not working.....	
No alteration in Methylation	Global tumor hypermethylation	

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Molecular Classification of

Group A

SDHB retained by IHC

Mutations
KIT
PDGFRa
BRAF
HRAS
NRAS
NF-1.....

Mutationen: ARID1B, ATR, FGFR1, LTK, SUFU, PARK2, ZNF217, EGFR .....
Fusionen: FGFR1-HOOK3 ,FGFR1-TACC1, ETV6-NTRK3, KIT-PDGFRA

Group B

SDHB lost by IHC

SDHA,B,C,D mutant Gist

Group C

SDHB lost by IHC

SDHC epimutant Gist (Promoterhype rmethylation)

Carney Triad

Carney-Stratakis Syndorme

obal tumor hypermethylation

KIT- Exon 8 (p.D419del)
KIT-Exons 9,11,13,17
PDGFRA-Exons 12,14,18

BRAF
HRAS
NRAS
KRAS
NF-1

1-3%

SDH A, B ,C ,D -> 3%
P16, PT53, RB1, NF1

Additional Mutations described:
ARID1B, ATR, FGFR1, LTK, SUFU, PARK2, ZNF217, EGFR..

Fusions:
FGFR1-HOOK3 ,FGFR1-TACC1, ETV6-NTRK3, KIT-PDGFRA

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MUG GIST panel

gene	chr	transcript	covered regions
KIT	4	NM_000222	Exon 8,9,11,12,13,17,18
PDGFRA	4	NM_006206	hotspots
PDGFRB	5	NM_002609	Exon 13,14,17,18
K-RAS	12	NM_004985	hotspots
N-RAS	1	NM_002524	hotspots
H-Ras	11	NM_005343	hotspots
BRAF	7	NM_004333	hotspots
SDHA	5	NM_004168	full coding
SDHB	1	NM_003000	full coding
SDHC	1	NM_003001	full coding
SDHD	11	NM_003002	full coding
NF1	17	NM_001042492	full coding
P16 (CDKN2A)	9	NM_000077	full coding
TP53	17	NM_000546	full coding
RB1	13	NM_000321	full coding

Ion Torrent Ampliseq technology, 248 Amplicons

Chromosome 4 KIT – Exon 11

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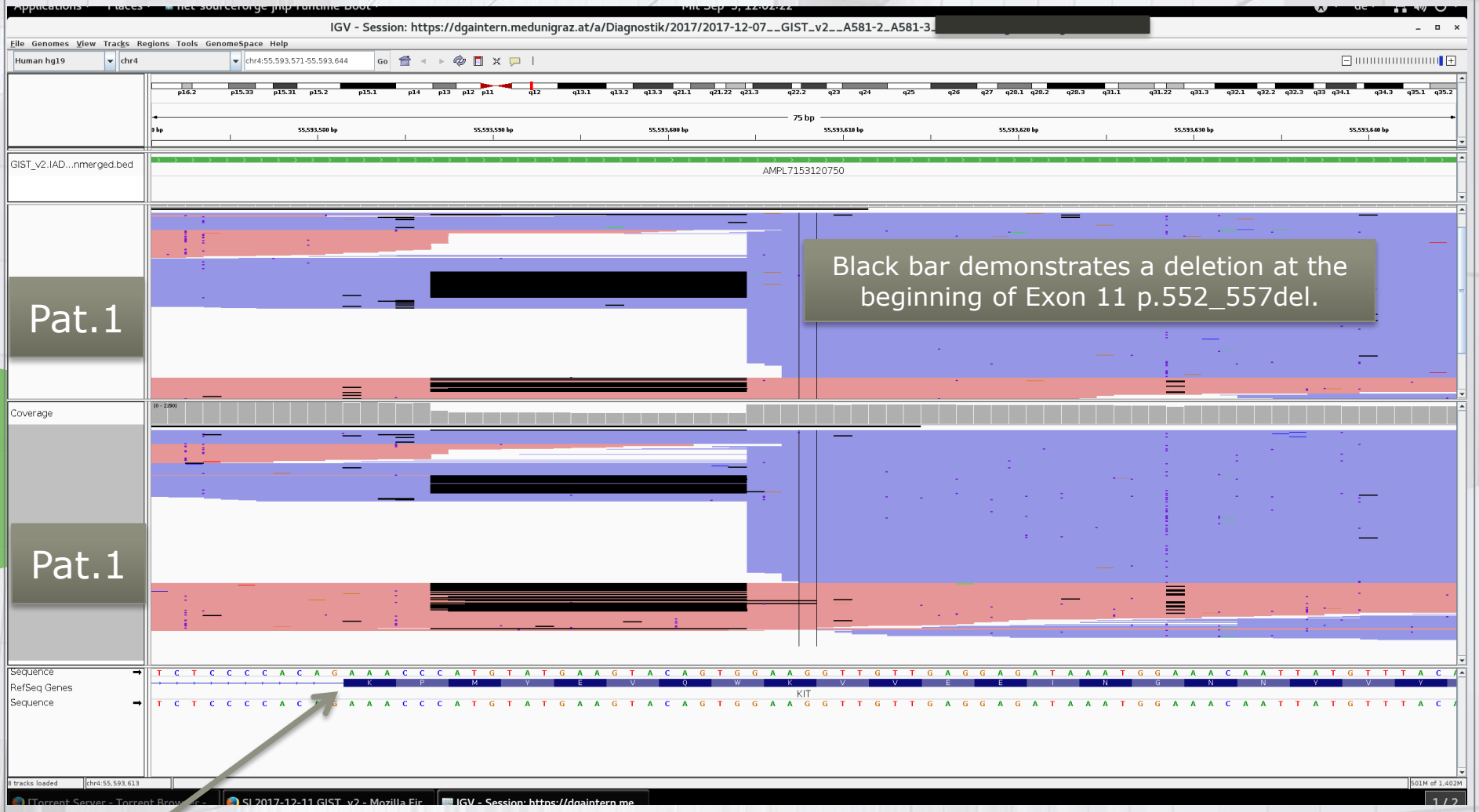
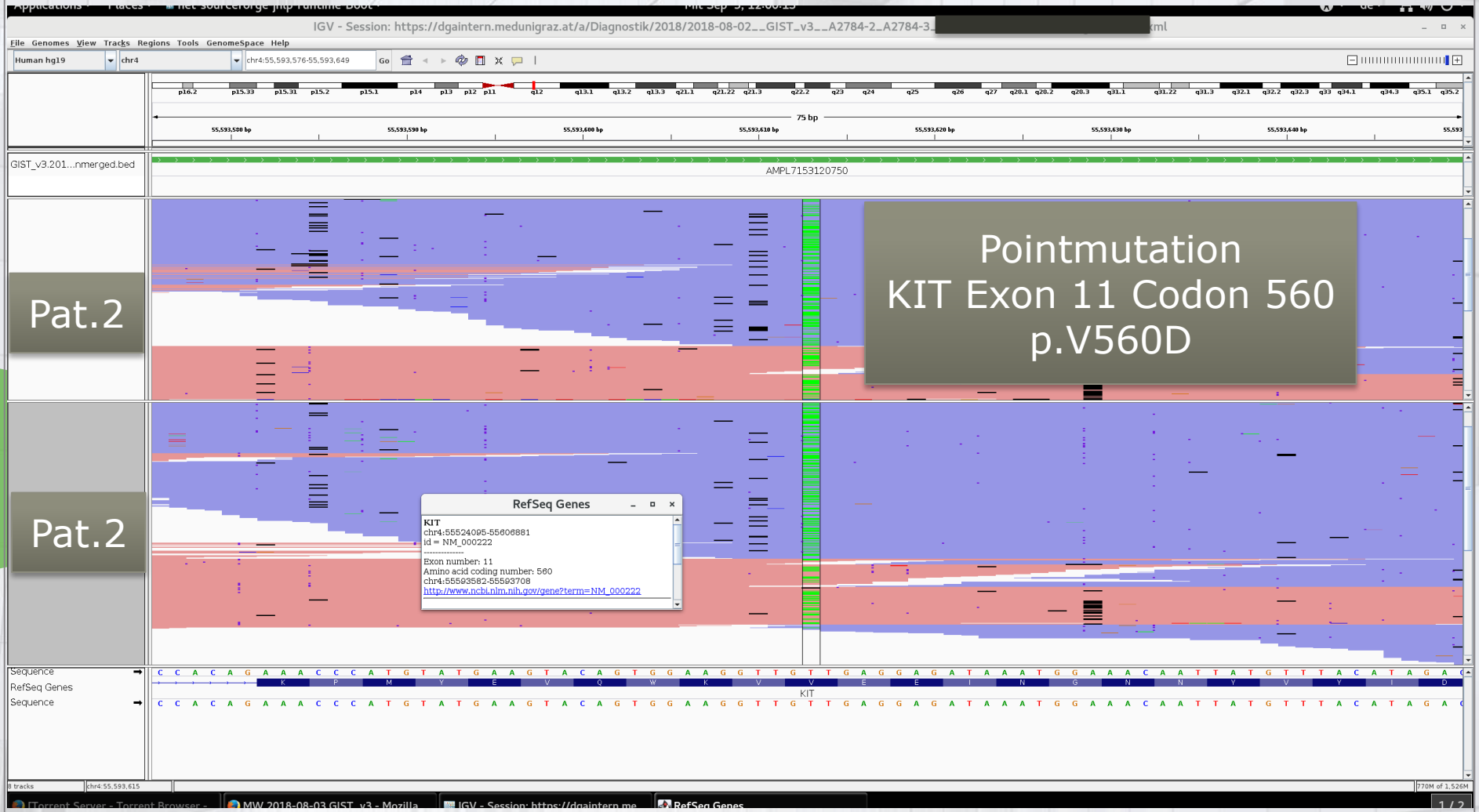


Start Exon11

Chromosome 4 KIT – Exon 11

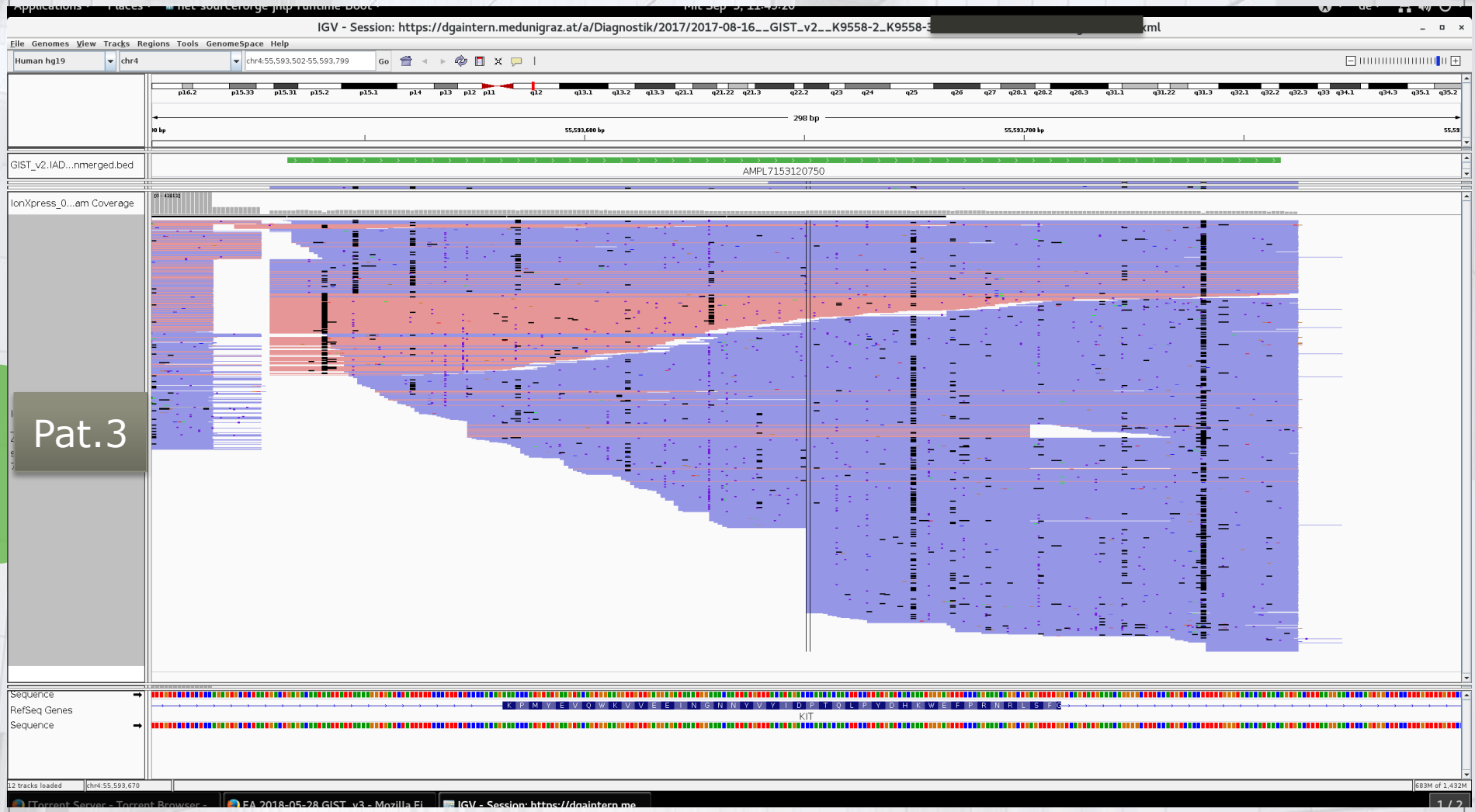


Limitations

- We are aware of limitations of NGS to detect large Insertions/Deletions => in all KIT negative GISTS we additionally test KIT Exon 11 by Sanger Sequencing

- One KIT Exon 11 Duplication (15 amino acids, 45 nucleotides) was not detected by NGS but evident in Sanger

Chromosome 4 KIT – Exon 11



Pat.3

Chromosome 4 KIT – Exon 11

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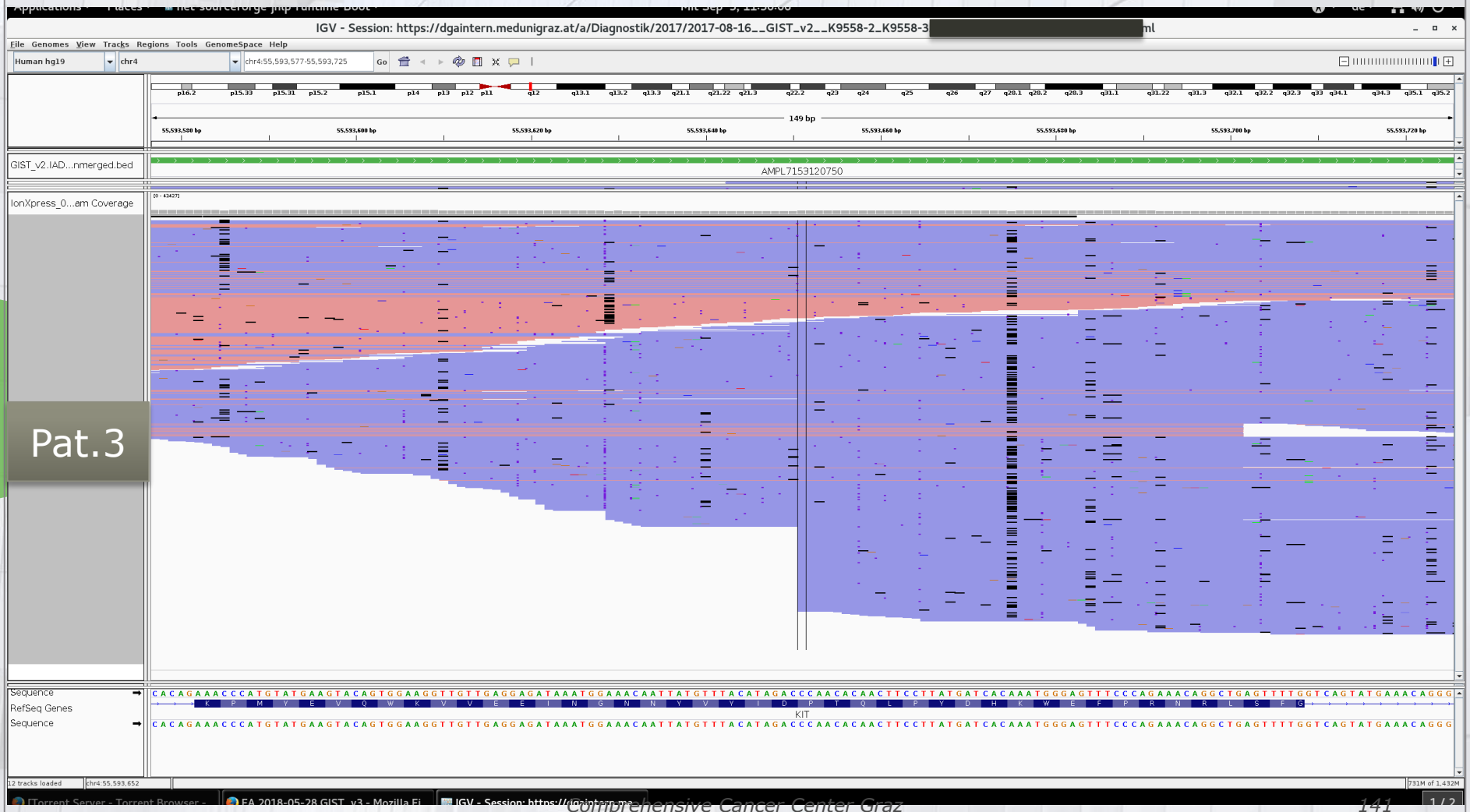

Pat.3

Chromosome 4 KIT – Exon 11

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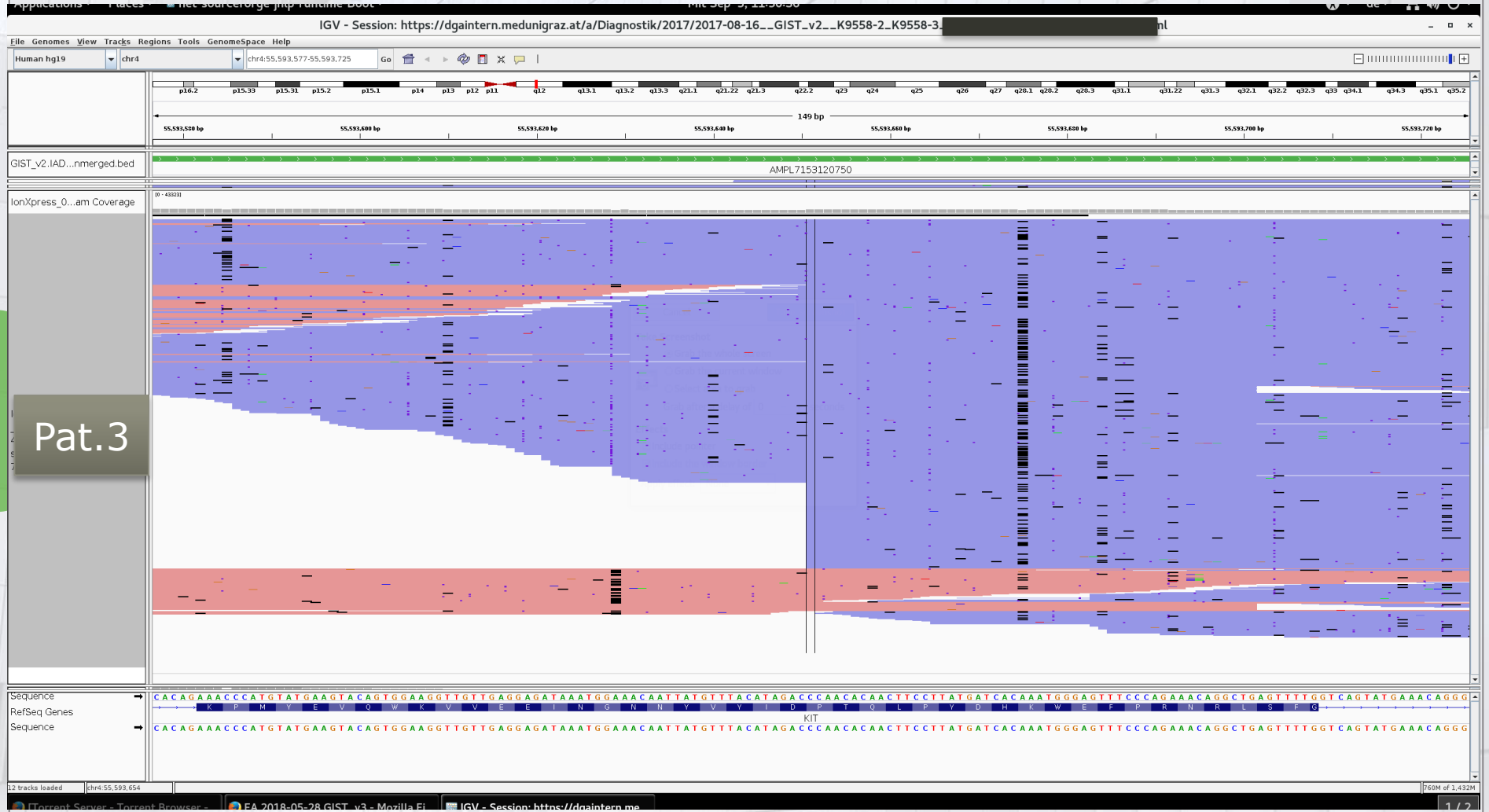

Pat.3

Chromosome 4 KIT – Exon 11

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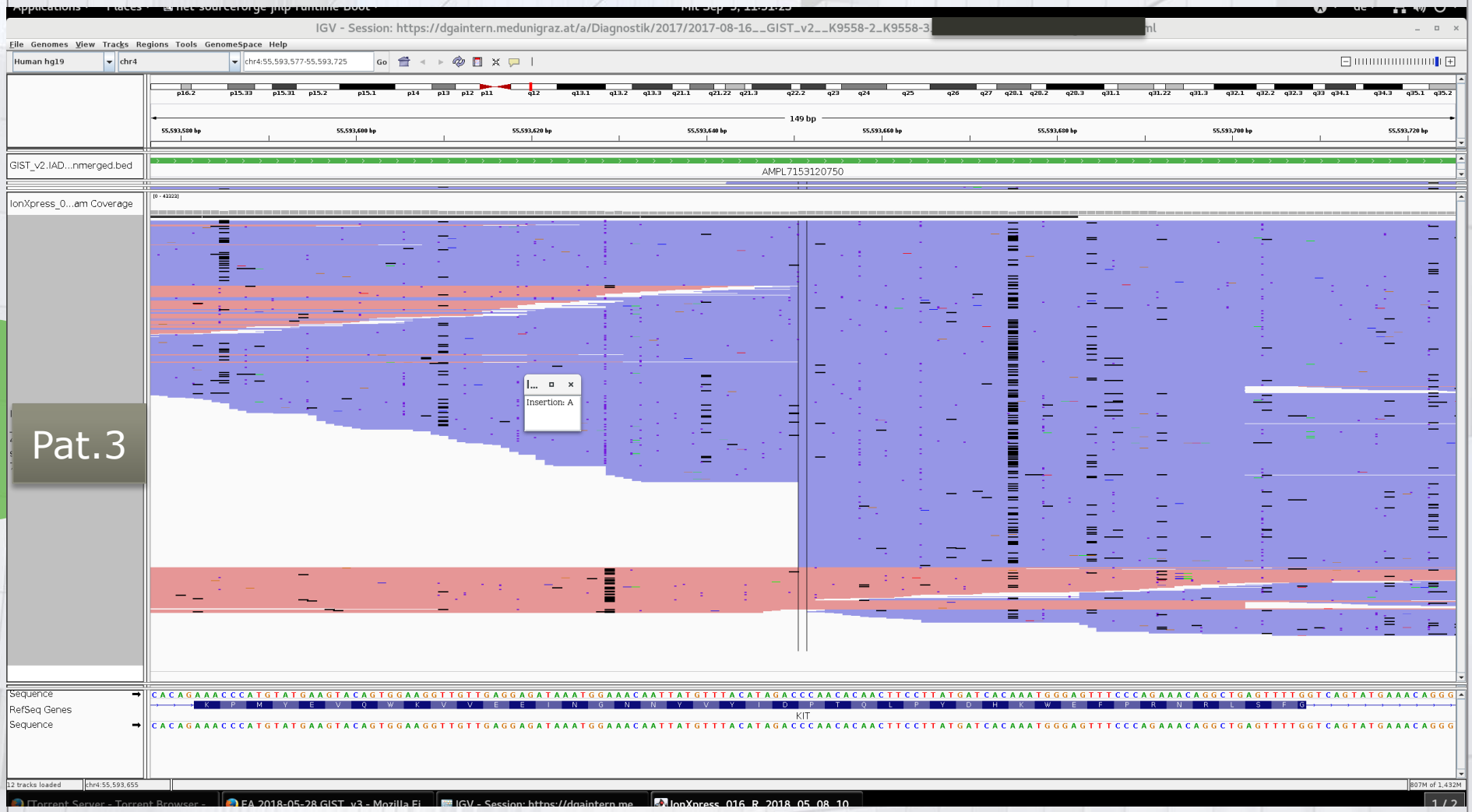

Pat.3

Chromosome 4 KIT – Exon 11

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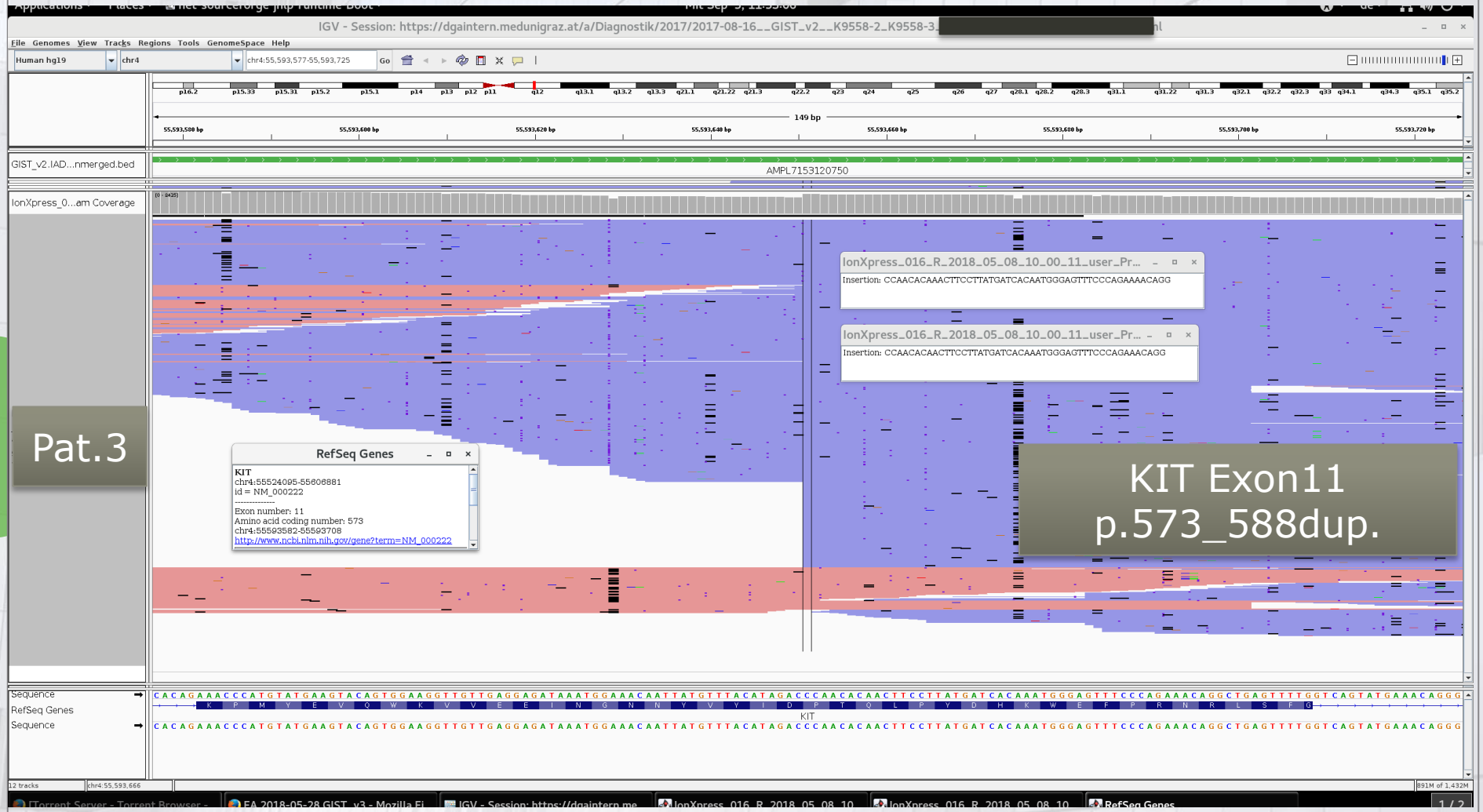
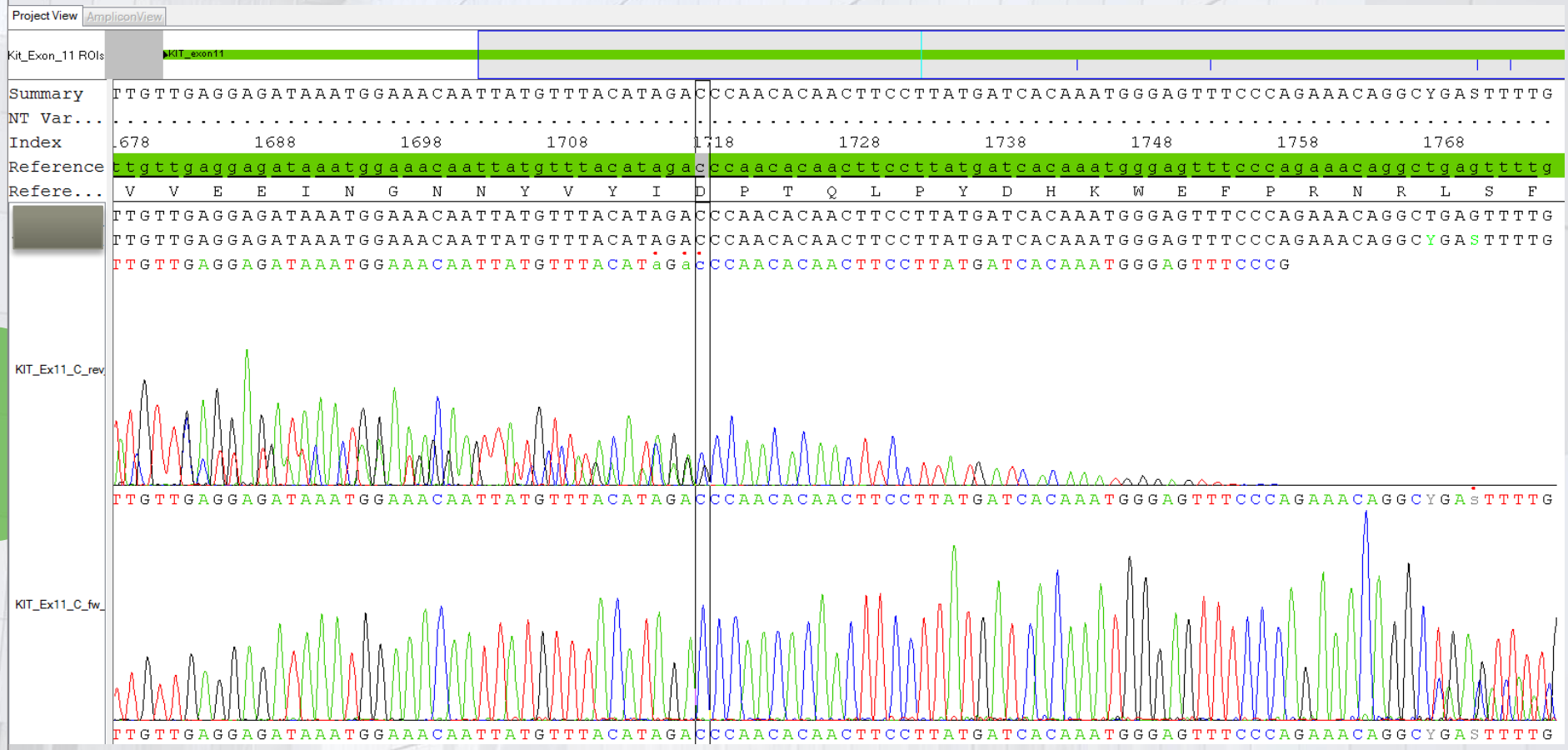


Pat.3

KIT Exon11
p.573_588dup.



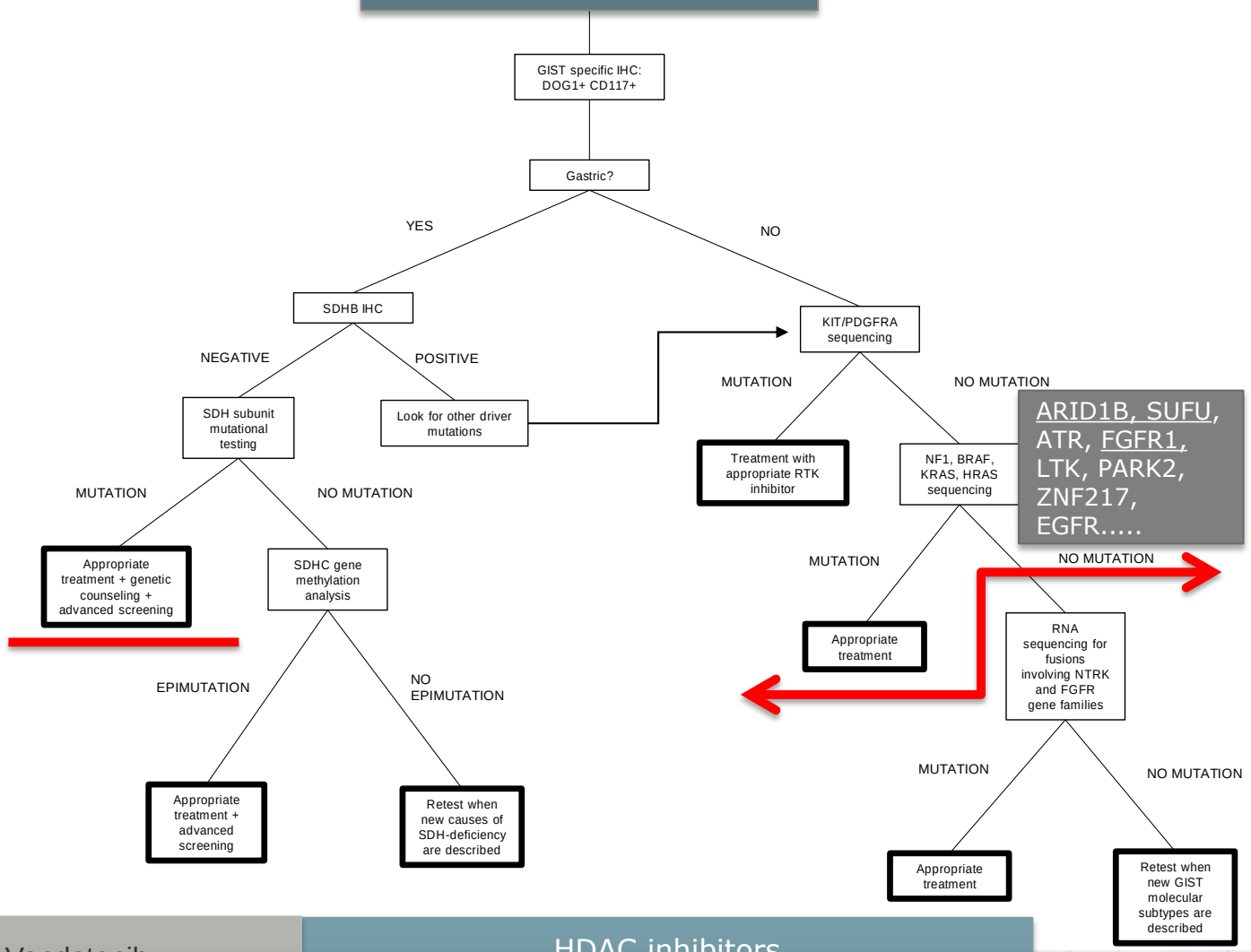
Duplication in KIT Exon11 c.1718_1765dup, p.P573_R588dup.

Chromosome 4 KIT – Exon 11

Molecular Diagnostic essential for treatment decission

737159.2017.1308826

GIST Diagnosis



Therapy Trials

VEGFR Inhibitor: Vandetanib
DNA methyltransferase inhibitors

HDAC inhibitors
FGFR TKI : Ponatinib, Pazobanib
Cancers with NTRK3 fusions -> TRK LOXO-101

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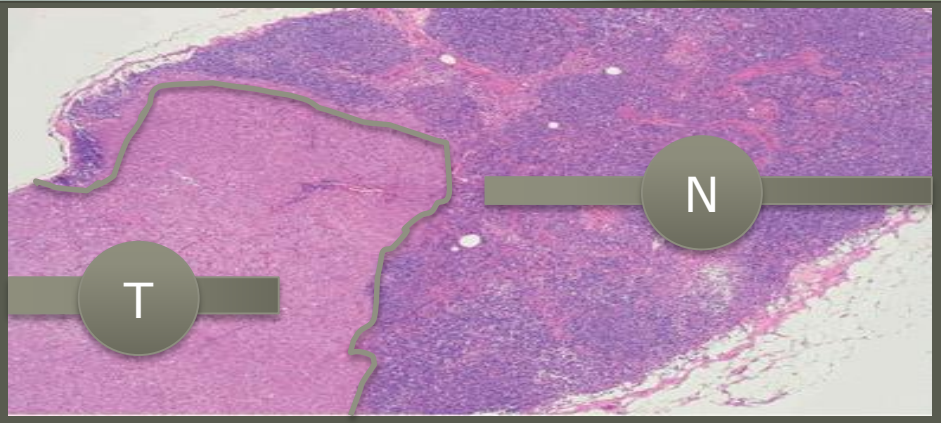
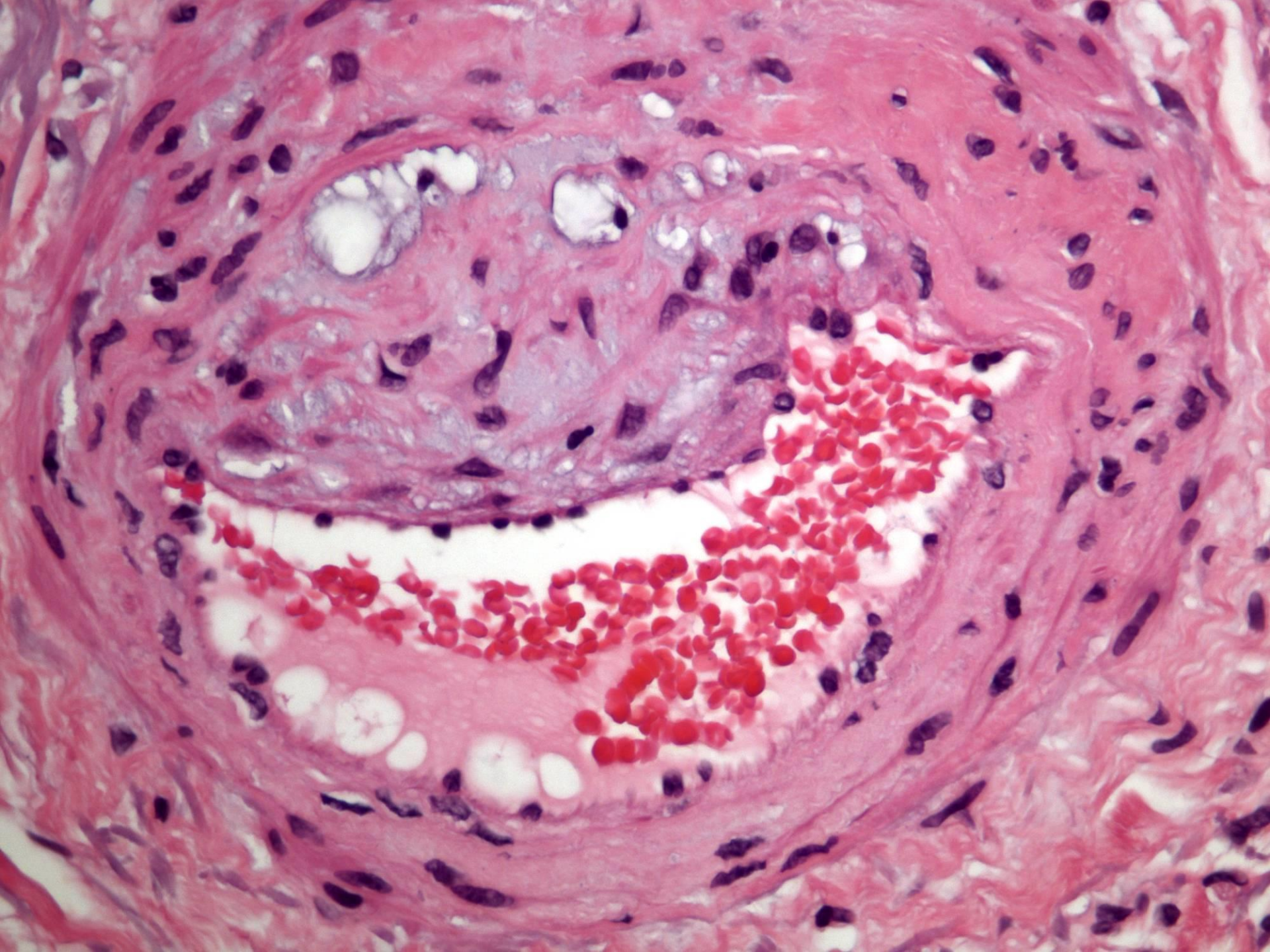
100000/18



Identify treatment targets



Statistics

- June 2017- July 2018

  - 41 GIST NGS Analyses
  - 25 KIT mutated cases (60,9%) +5%
  - 8 PDGFRa (19,5%)
  - 5 SDH A/B/C (12,2%)
  - 3 WT Gist (7,4%) -5%

  -> 2 by Sanger Sequencing long insertions/duplications in Exon 11 of the KIT

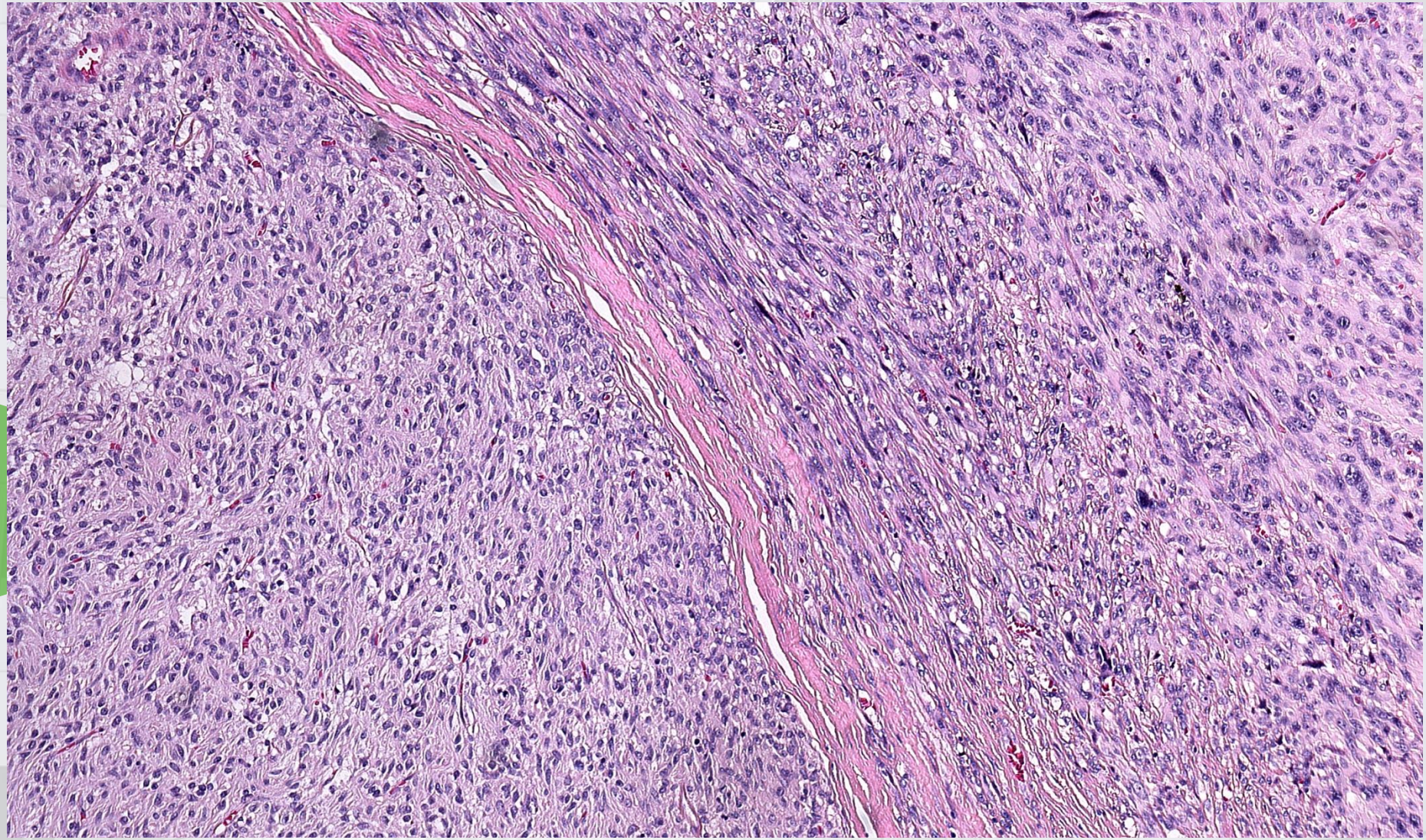
(selection bias -> consultation material)

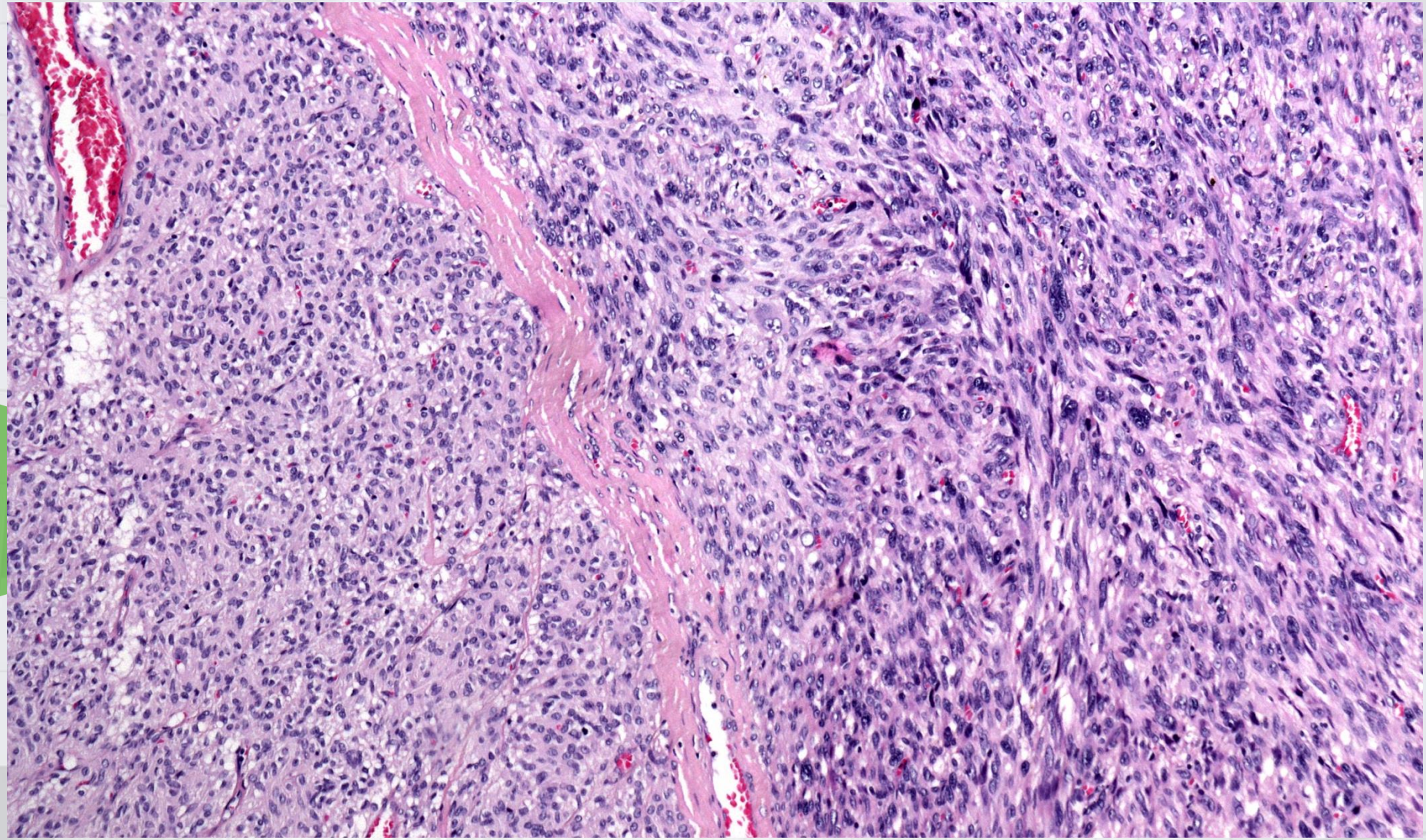
PDGFRA-mutant GIST

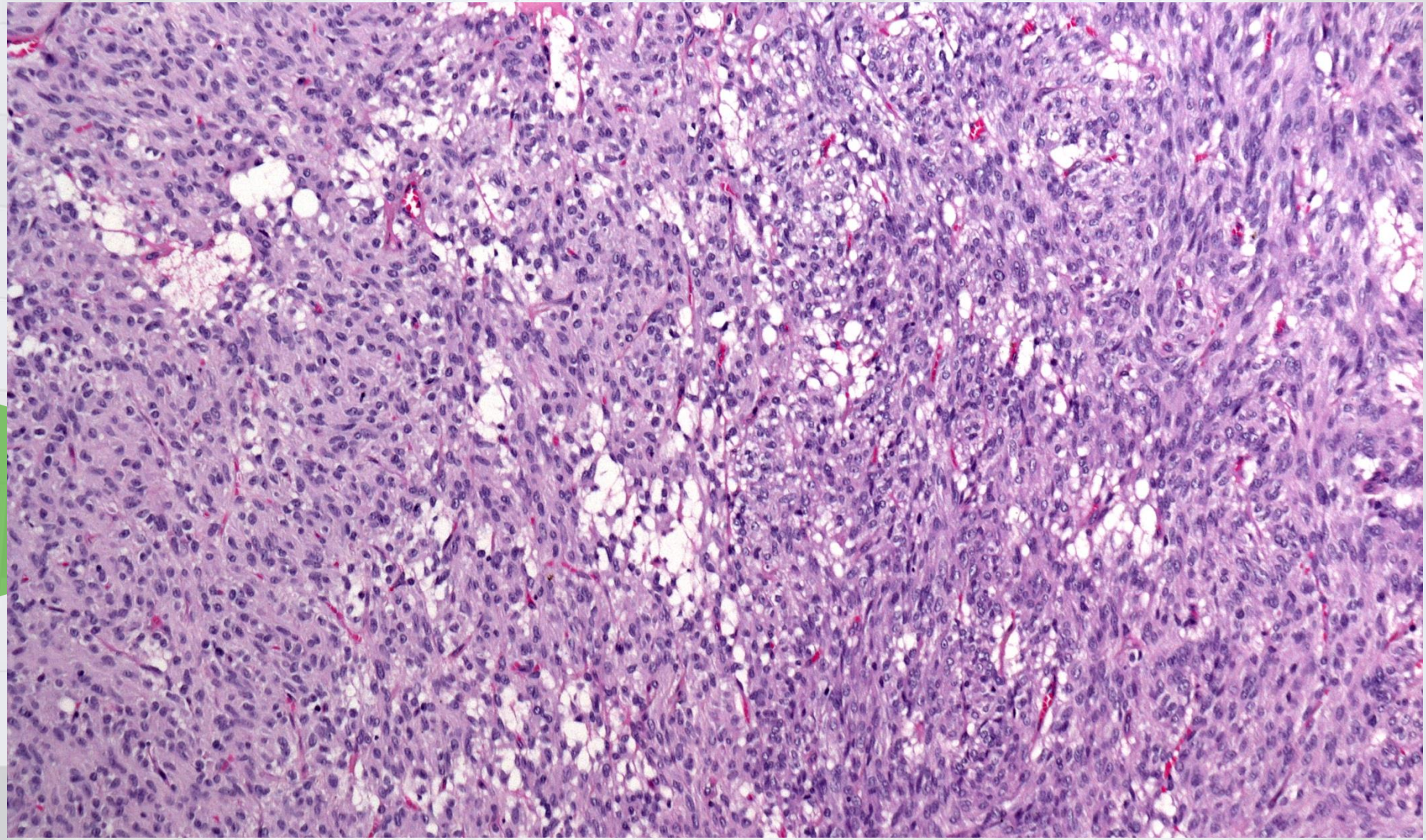
Crenolanib
BLU-285 (++)

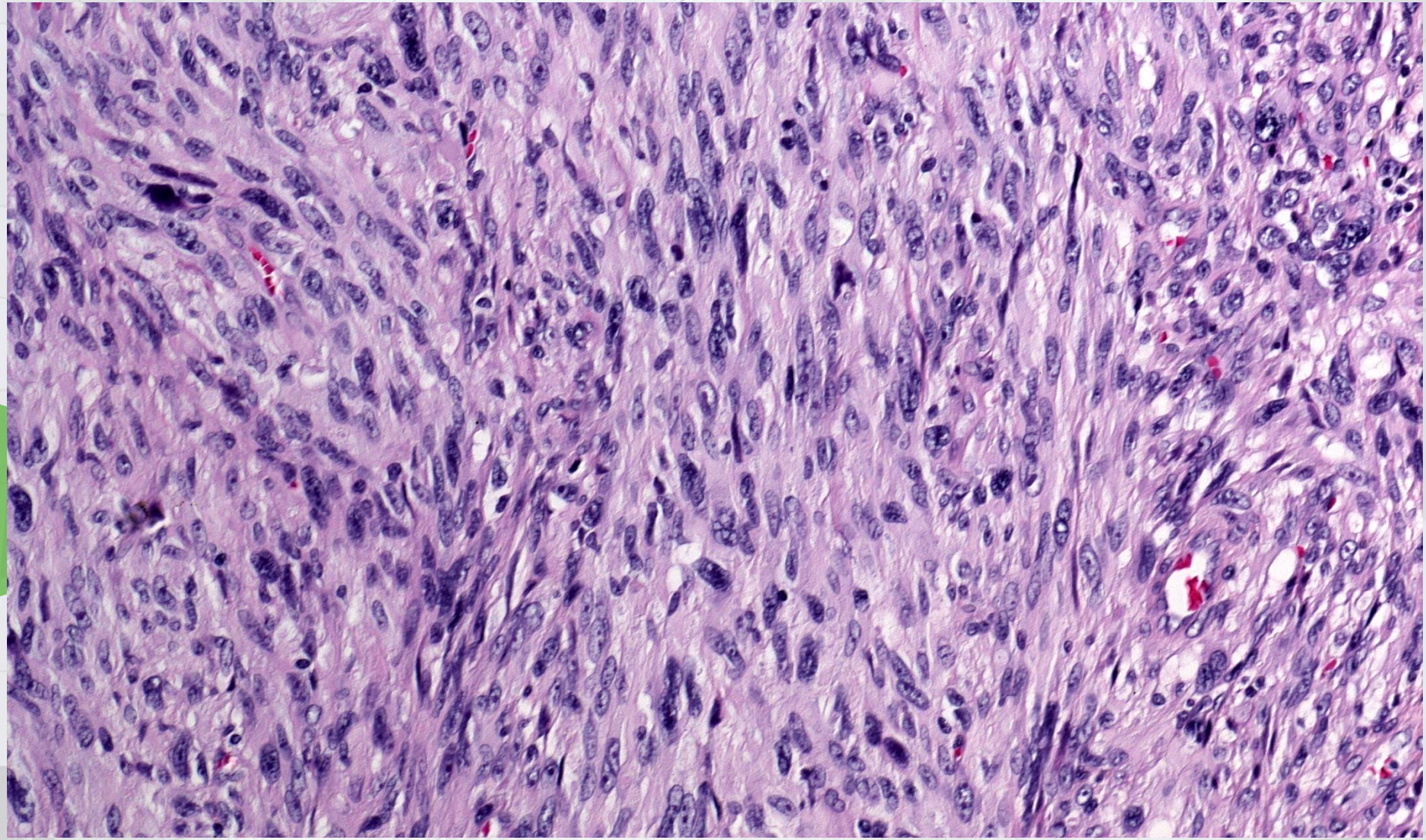
Therapy:

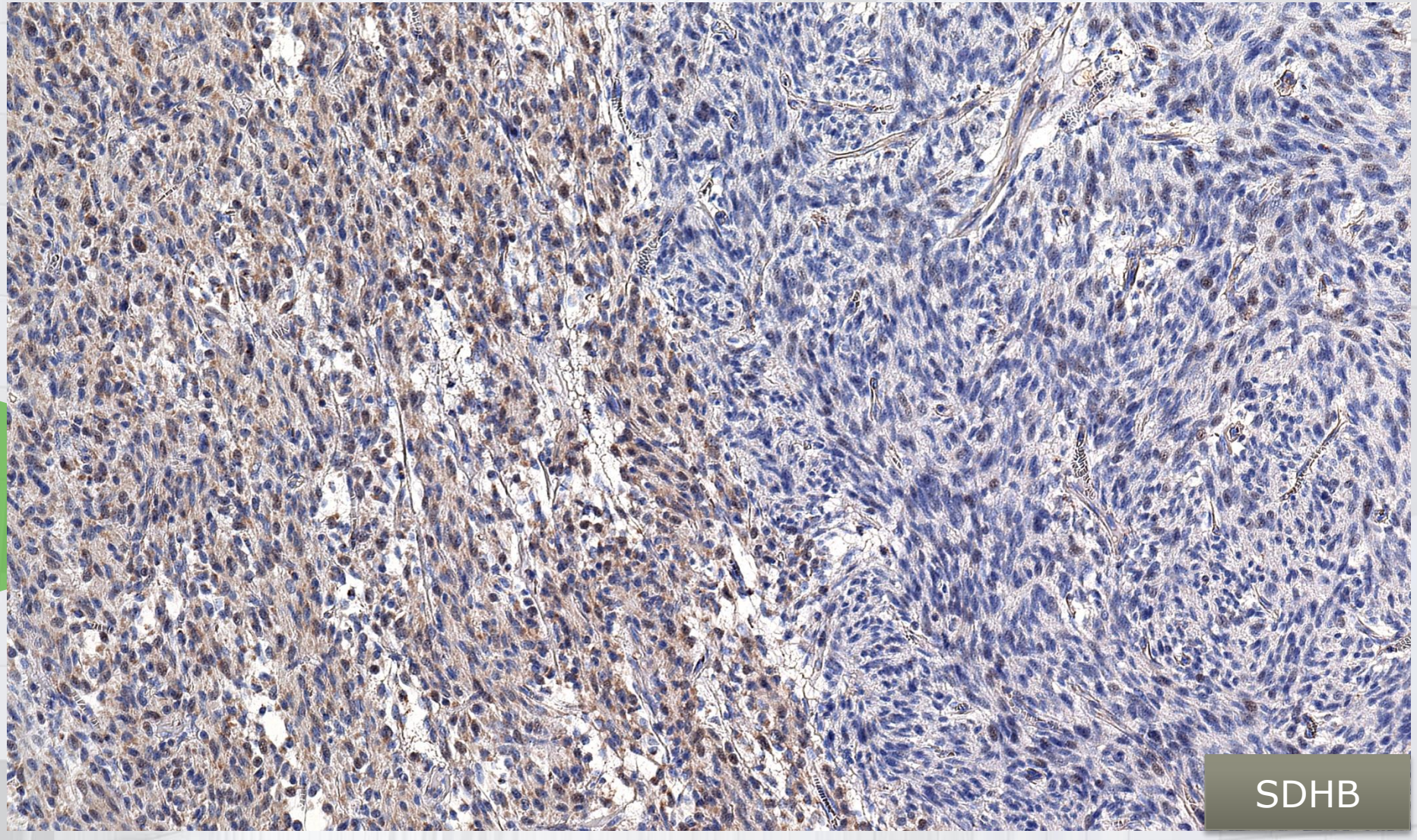
- Exon 18 D842V: Imatinib, Sunitinib, Regorafinib resistent
- *Exon 18: D846Y, N848K, Y849K IM resistent*
- Exon 12 and 14: Imatinib sensitiv
- Other Exon 18 Mutationen: described as Imatinib sensitiv (deletions in codons 842-845)










SDHB

-wild-type [WT] GIST-

Lack *KIT* and *PDGFRA* mutations

- 85% of GISTs in children
- 10% to 15% of GISTs in adults

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KIT and *PDGFRA* WT Gist Heterogenous Group

Sporadic WT

- Pat. 6LD
- NCCN Risk Strat.
- No LN metastasis
- Location (*)
- Presentation(*)
- Morphology(*)

(*)identical to mutated GIST

WT Gist in young adults Similar Clinical features as the pediatric WT GIST

NF1

- Commonly small intestine
- Multifocal
- Small
- Low mitotic rate
- Good prognosis
- IGF1R neg./ IHC
- Loss of 14q and 22q

BRAF-mut. GIST

- First discribed in 2008
- (in one case as a secondary mutation in a *PDGFRa*-mutant GIST)
- Approx. 20-30 cases reported
- Mean age 58 a
- Female=Male
- Commonly in the small bowel
- Commonly spindle cell morphology
- Clinical behaviour variable

Pediatric WT

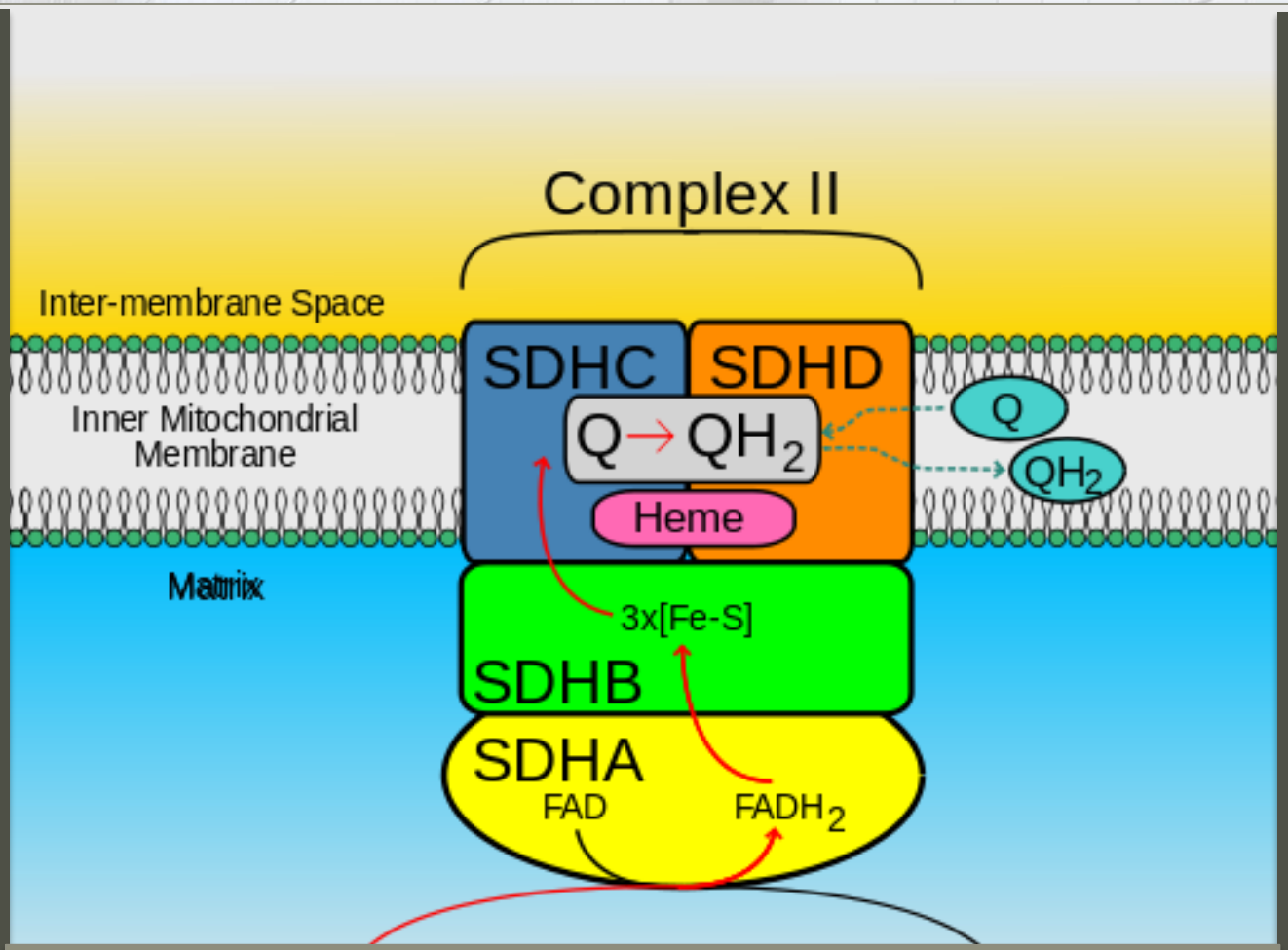
CT

CSS

- Stomach
- Female Predominance
- Commonly epitheloid morphology
- Multifocal Gist (synchronous or metachronous)
- Risk Stratification not useful to predict clinical behaviour
- LN metastases common
- Indolent clinical course in metastatic setting
- Do not response to imatinib
- IGFR1 pos./IHC

SDH

It is the only enzyme that participates in both the the electron transport chain (complex II) and the Krebs cycle



catalyzes the oxidative dehydro-genation of succinate to fumarate

SDHB IHC usefull marker to screen for SDHB deficient GIST in the stomach

Unique clinical behavior and biology

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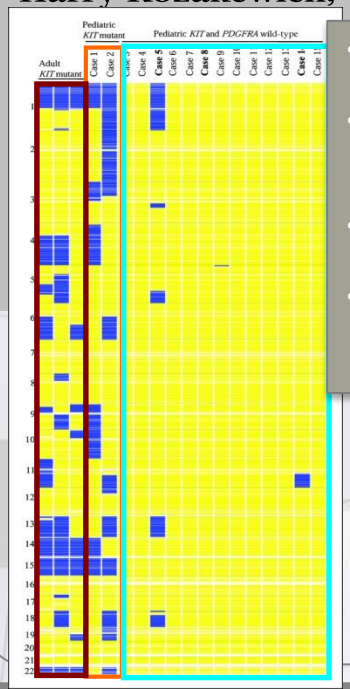
Cancer Res 2007; 67: (19). October 1, 2007

Research Article

Pediatric *KIT*–Wild-Type and Platelet-Derived Growth Factor Receptor α–Wild-Type Gastrointestinal Stromal Tumors Share KIT Activation but not Mechanisms of Genetic Progression with Adult Gastrointestinal Stromal Tumors

Katherine A. Janeway,[1,3,4] Bernadette Liegl,[4,5] Amy Harlow,[6] Claudia Le,[6] Antonio Perez-Atayde,[2] Harry Kozakewich,[2] Christopher L. Corless,[6,7,8] Michael C. Heinrich,[6,7,8] and Jonathan A. Fletcher[1,3,4]

gy, Dana-Farber Cancer Institute; [4]Department of thology, Medical University, Graz, Austria; and ience University and [8]Portland VA Medical



- KIT expression and activation of KIT downstream targets
- Pediatric GIST lack the typical cytogenetic deletions (1q, 14q, 22q) seen in mutant GIST
- Better response to second line TKI (sunitinib..)
- Distinctive transcriptional signature with overexpression of IGF1R, FGF4...

2008 May 15; 14(10): 3204–3215. doi:10.1158/1078-0432.CCR-07-1984.

Molecular Characterization of Pediatric Gastrointestinal Stromal Tumors

Narasimhan P. Agaram[1], Michael P. Laquaglia[2], Berrin Ustun[1], Tianhua Guo[1], Grace C. Wong[1], Nicholas D. Socci[4], Robert G. Maki[3], Ronald P. DeMatteo[4], Peter Besmer[5], and Cristina R. Antonescu[1,5]

BMC Medical Genetics

BioMed Central

Research article

Open Access

Mutation analysis of SDHB and SDHC: novel germline mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma

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Genetics of Carney Triad: Recurrent Losses at Chromosome 1 but Lack of Germline Mutations in Genes Associated with Paragangliomas and Gastrointestinal Stromal Tumors

Ludmila Matyakhina, Thalia A. Bei, Sarah R. McWhinney, Barbara Pasini, Silke Cameron, Bastian Gunawan, Sotirios G. Stergiopoulos, Sosipatros Boikos, Michael Muchow, Amalia Dutra, Evgenia Pak, Elias Campo, Maria C. Cid, Fulgencio Gomez, Rolf C. Gaillard, Guillaume Assie, Laszlo Füzesi, Bora E. Baysal, Charis Eng, J. Aidan Carney, and Constantine A. Stratakis

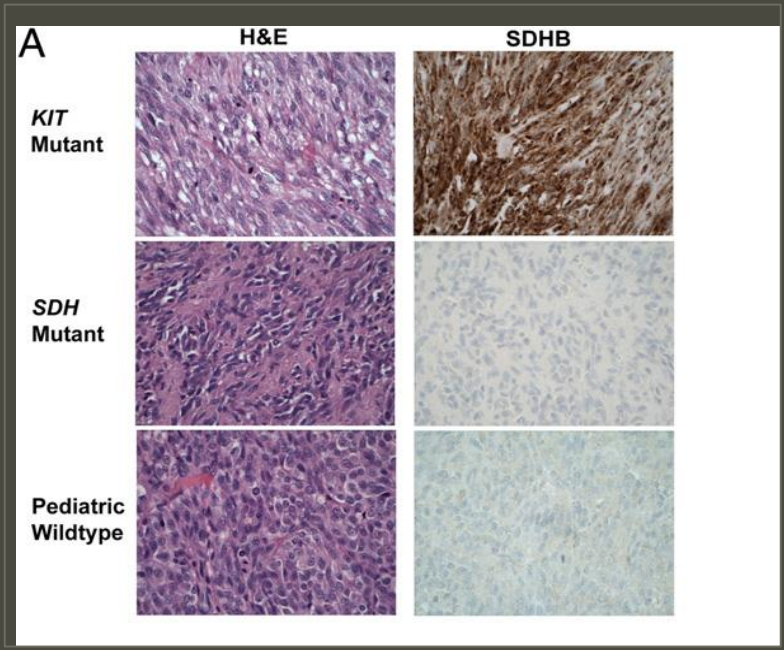
ARTICLE

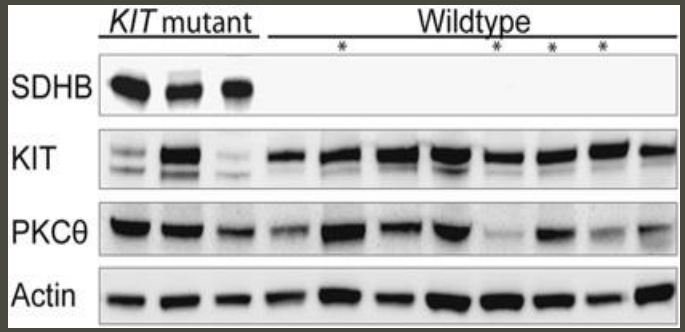
Clinical and molecular genetics of patients with the Carney–Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD

Barbara Pasini[1,16], Sarah R McWhinney[2,16], Thalia Bei[3], Ludmila Matyakhina[3], Sotirios Stergiopoulos[3], Michael Muchow[3], Sosipatros A Boikos[3], Barbara Ferrando[1], Karel Pacak[4], Guillaume Assie[5,14], Eric Baudin[6], Agnes Chompret[7], Jay W Ellison[8], Jean-Jacques Briere[9,10], Pierre Rustin[9,10], Anne-Paule Gimenez-Roqueplo[11,12,13,16], Charis Eng[2,14,16], J Aidan Carney[15,16] and Constantine A Stratakis*[3,16]

Carney Triad: Gastric GIST, pulmonary chondroma, paraganglioma

Carney-Stratakis Syndrome: Gastric GIST and paraganglioma





Janeway at al PNAS 2011

Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking *KIT* and *PDGFRA* mutations

Katherine A. Janeway[a,1,2], Su Young Kim[b,1], Maya Lodish[c], Vânia Nosé[d], Pierre Rustin[e], José Gaal[f], Patricia L. M. Dahia[g], Bernadette Liegl[h], Evan R. Ball[c], Margarita Raygada[i], Angela H. Lai[a], Lorna Kelly[j], Jason L. Hornick[k], NIH Pediatric and Wild-Type GIST Clinic[l,m,n,o,p,3], Maureen O'Sullivan[j,q], Ronald R. de Krijger[f], Winand N. M. Dinjens[f], George D. Demetri[r], Cristina R. Antonescu[s], Jonathan A. Fletcher[k], Lee Helman[b], and Constantine A. Stratakis[c]

314–318 | PNAS | January 4, 2011 | vol. 108 | no. 1

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SDHB immunohistochemistry has been shown a useful tool to screen for a dysfunction within any subunit of the SDH complex

SDHB IHC in GIST

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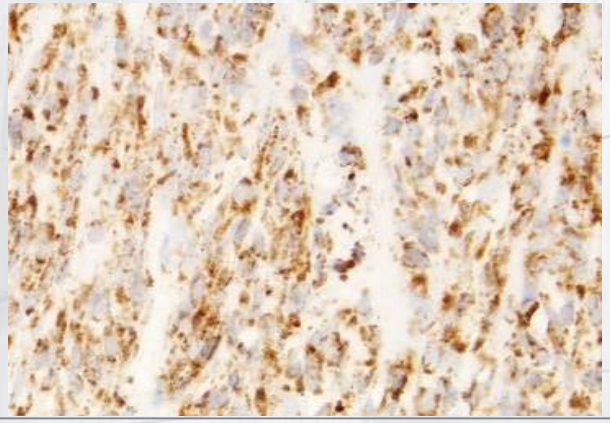
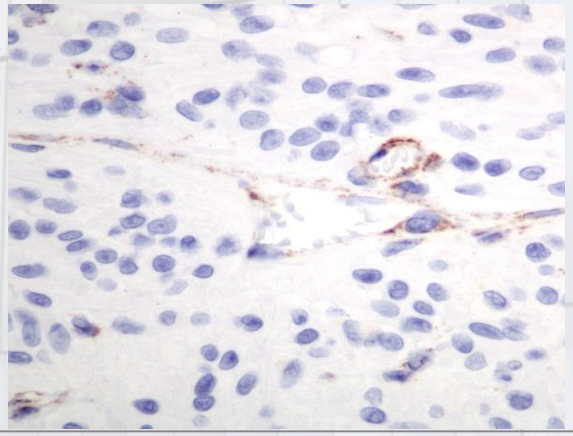
SDHB Positive „retained“

- All mutated Gists *KIT, PDGFRA, BRAF, NF1..*
- Wt-Gist in adults
- Gist in NF1



SDHB Negative „deficient“

- Wt-Gist in adults
- Wt- Gist in children
- Gist in a/w CT
- Gist in a/w CSS



SDHB IHC in GIST

SDHB Positive „retained“

- All mutated Gists *KIT, PDGFRA, BRAF, NF1..*
- Wt-Gist in adults
- Gist in NF1

SDHB Negative „deficient“

- Wt-Gist in adults
- Wt- Gist in children
- Gist in a/w CT
- Gist in a/w CSS

27% + SDHA Negative

„Young Adult“ (7% children und 40% adults 30-50a)

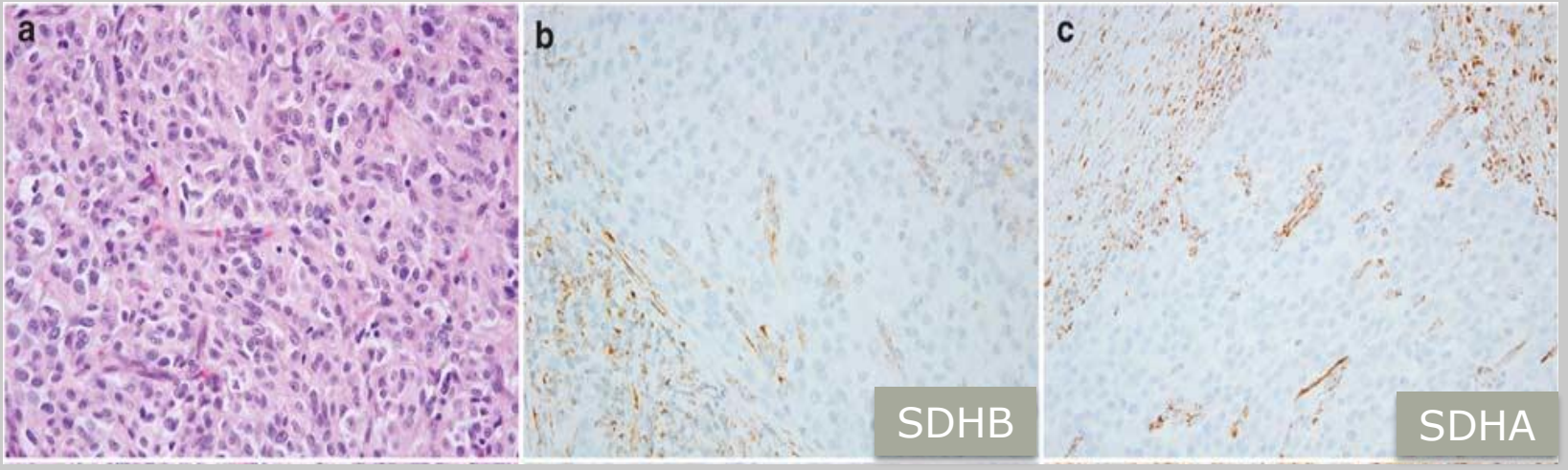
SDHB +SDHA negativ Gist

„Young Adult"
Small persentage of WT Gist in children
Rest adults 30-50a.
27% of SDH deficient GIST
Germline *SDHA* mutations
Second hit: usually somatic allelic loss or somatic second mutation

Modern Pathology (2013) 26, 289–294

Loss of expression of SDHA predicts *SDHA* mutations in gastrointestinal stromal tumors

Andrew J Wagner[1], Stephen P Remillard[1], Yi-Xiang Zhang[1], Leona A Doyle[2], Suzanne George[1] and Jason L Hornick[2]



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Original Investigation

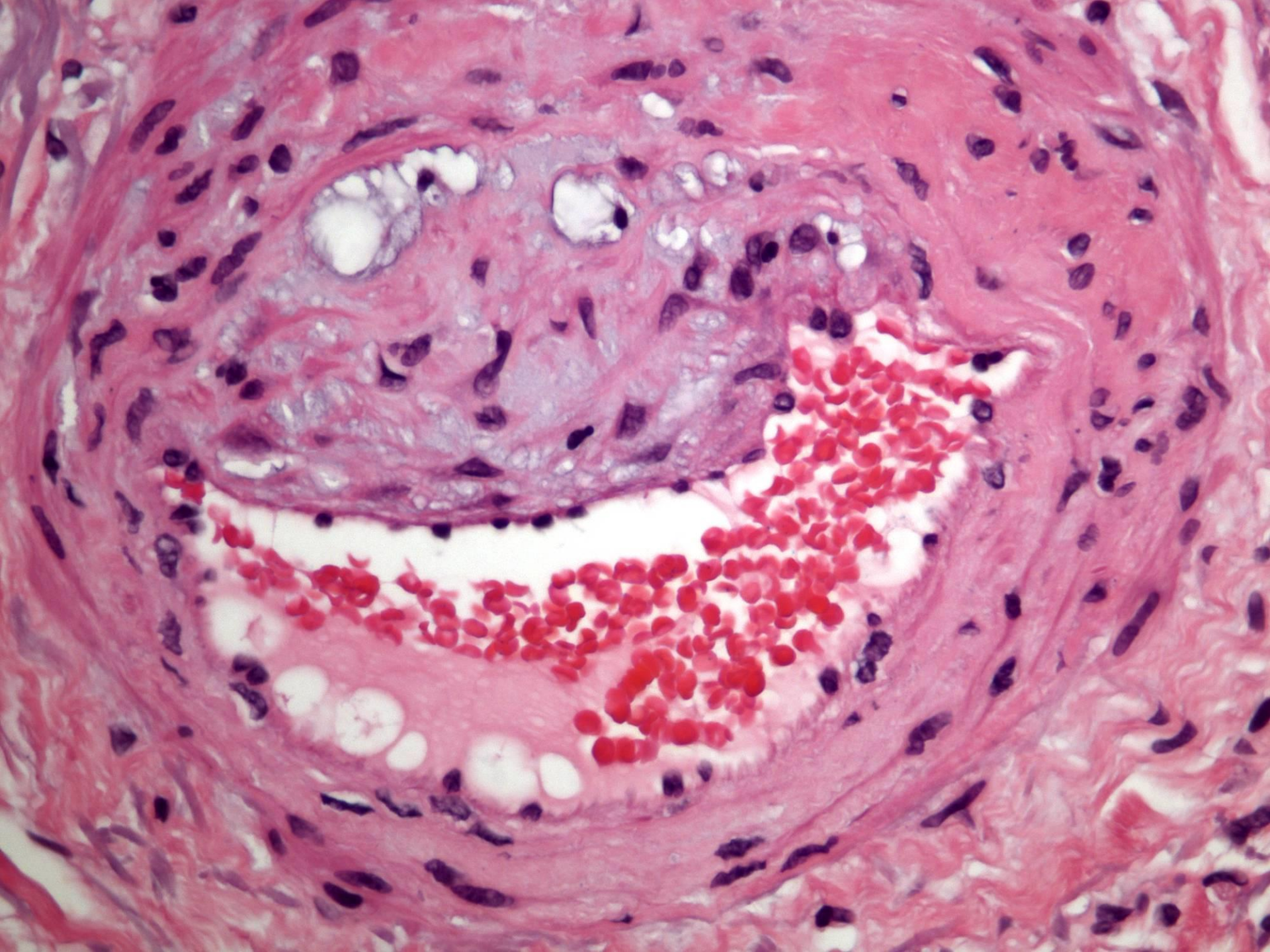
Molecular Subtypes of *KIT/PDGFRA* Wild-Type Gastrointestinal Stromal Tumors

A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic

Sosipatros A. Boikos, MD; Alberto S. Pappo, MD; J. Keith Killian, MD, PhD; Michael P. LaQuaglia, MD; Chris B. Weldon, MD; Suzanne George, MD; Jonathan C. Trent, MD, PhD; Margaret von Mehren, MD; Jennifer A. Wright, MD; Josh D. Schiffman, MD; Margarita Raygada, PhD; Karel Pacak, MD, PhD; Paul S. Meltzer, MD, PhD; Markku M. Miettinen, MD; Constantine Stratakis, MD, DSci; Katherine A. Janeway, MD; Lee J. Helman, MD

JAMA Oncology Published online March 24, 2016

NIH wt-Gist clinic: 116 patients inclusion criteria younger than 19a or wt-*KIT/ PDGFRa*.
From 95 pt. adequate tissue was available



NGS

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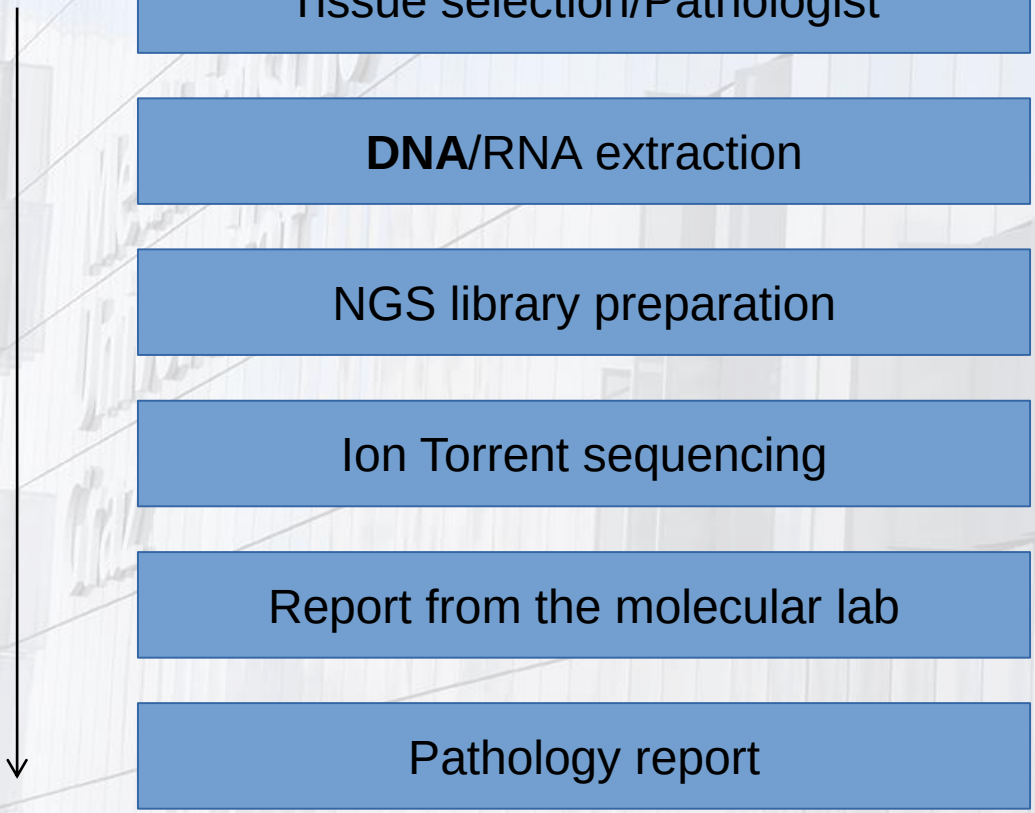
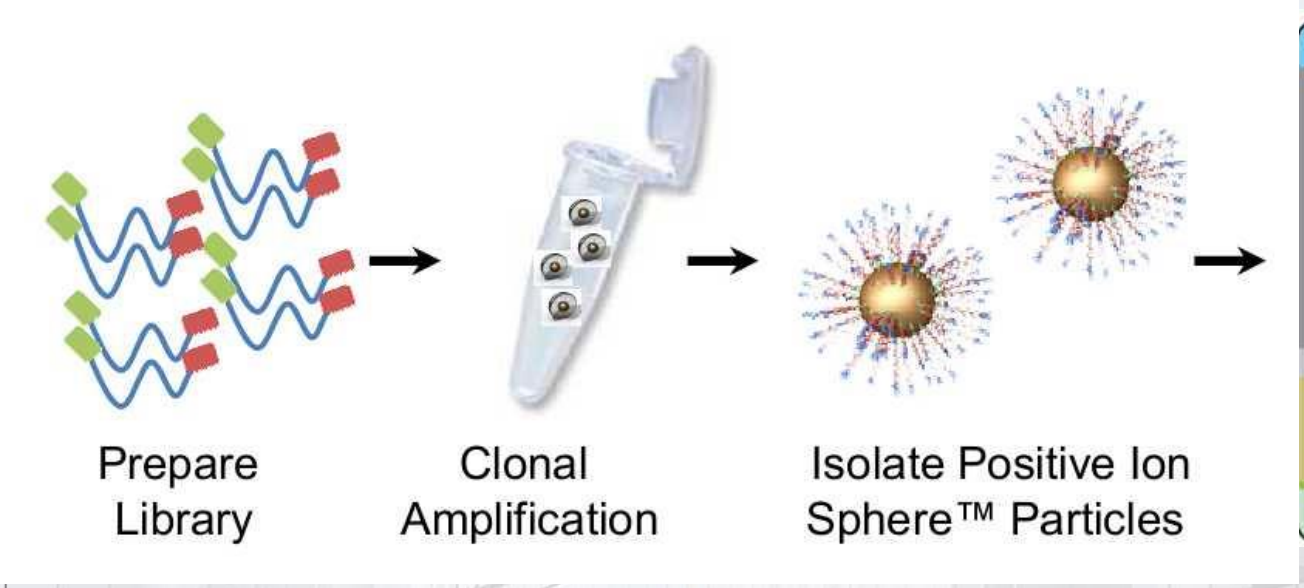
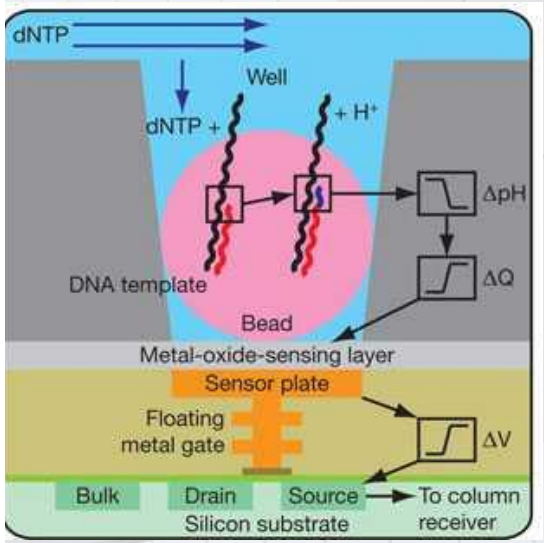


Ion Torrent Sequenzierung





Datengenerierung

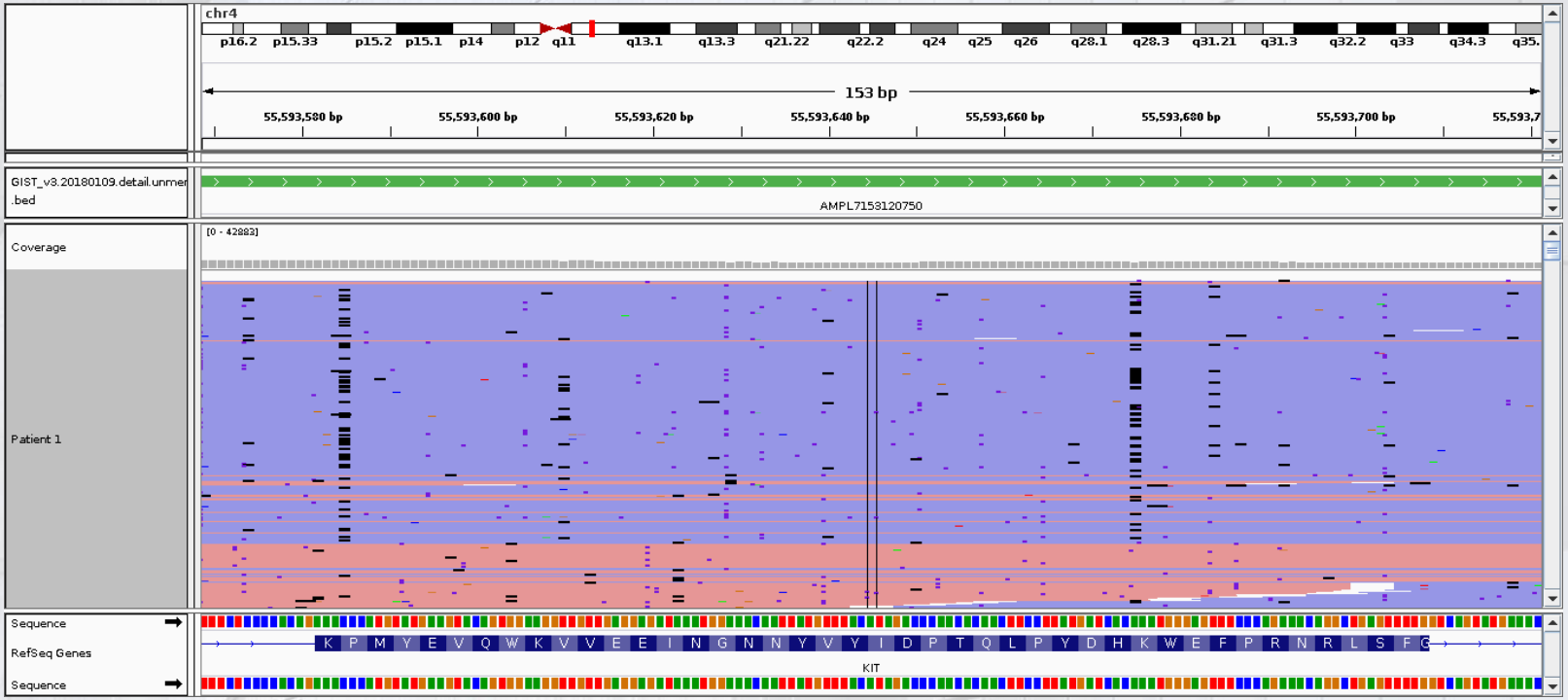
Sequenzdaten BAMfiles

↓

Variant calling

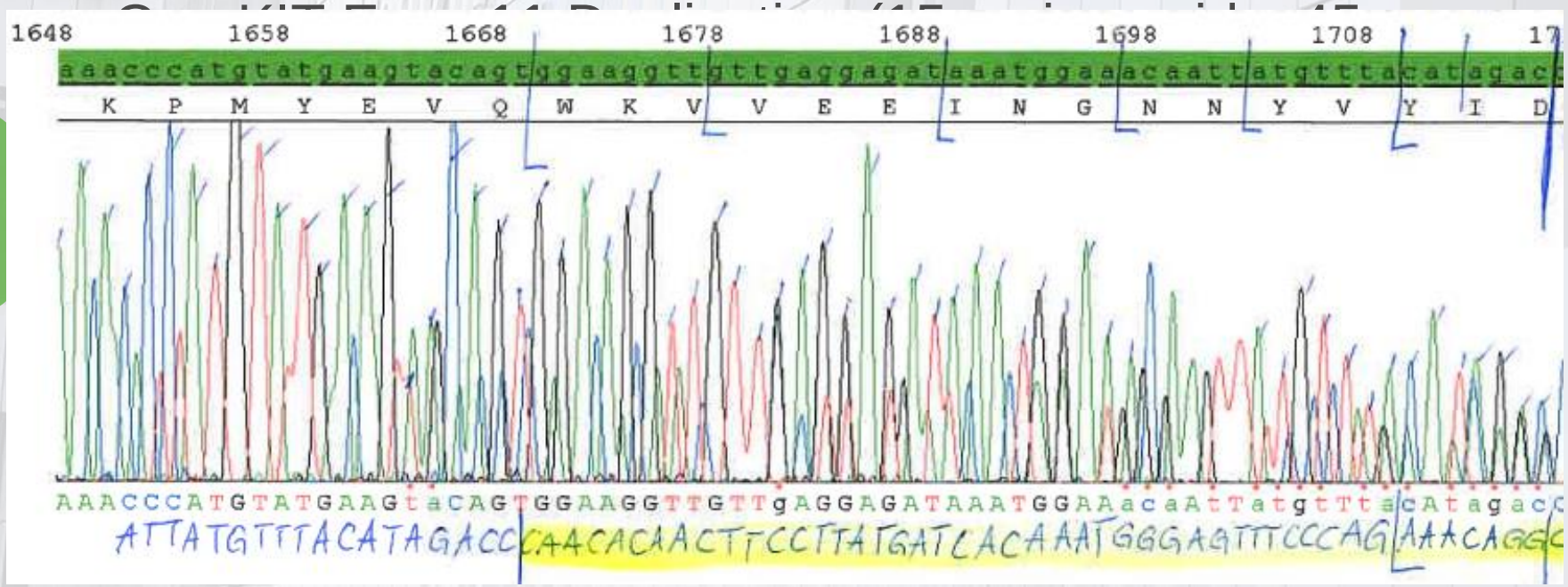
↓

Annotation


chr4
p16.2 p15.33 p15.2 p15.1 p14 p12 q11 q13.1 q13.3 q21.22 q22.2 q24 q25 q26 q28.1 q28.3 q31.21 q31.3 q32.2 q33 q34.3 q35.
153 bp
55,593,580 bp
55,593,600 bp
55,593,620 bp
55,593,640 bp
55,593,660 bp
55,593,680 bp
55,593,700 bp
GIST_v3.20180109.detail.unmer
.bed
AMPL7153120750
Coverage
[0 - 42883]
Patient 1
Sequence
RefSeq Genes
KIT
Sequence

Limitations

- We are aware of limitations of NGS to detect large Insertions/Deletions => in all KIT negative GISTS we additionally test KIT Exon 11 by Sanger Sequencing



Discuss the first 3 cases

- All of them are GISTs
- Case 1 adult (age of typical sporadic GISTS)
  - Cave if multinodular plexiform infiltrating think of SDHB deficient GIST – cost effective tool to know that you are dealing with a WT-GIST. SDHB deficient Gist only occur in the stomach...
- Case 2 kid --- pediatric Gist most commonly WT and SDHB deficient --- mainly female – CT – CSS – follow up – LN Metastases!
- Pleomorphic GIST ---- Exon 11 deletion + p53 and RB1 mutation

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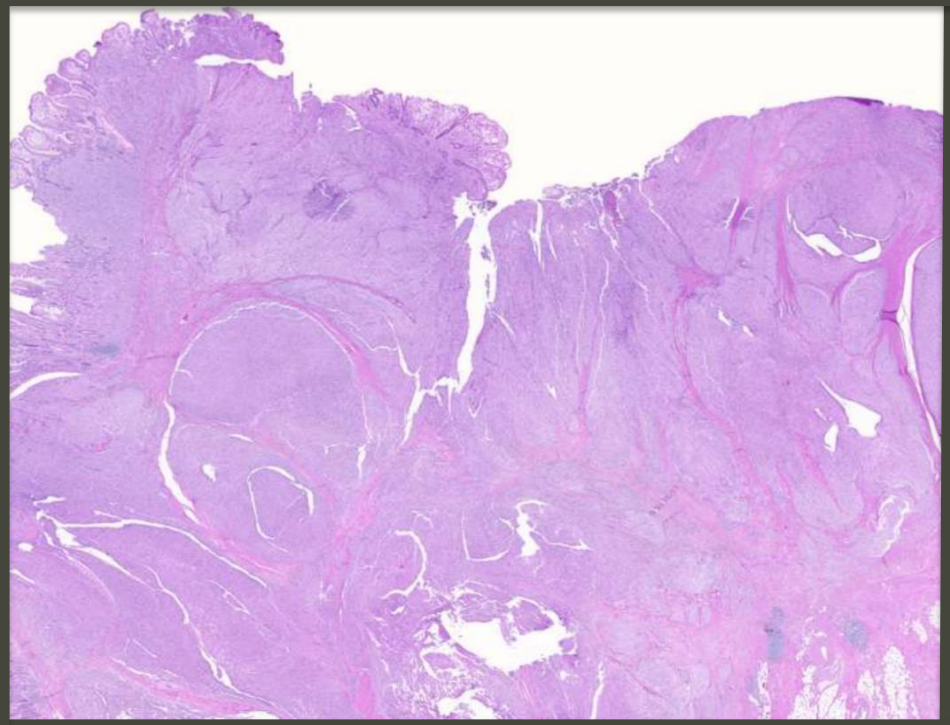
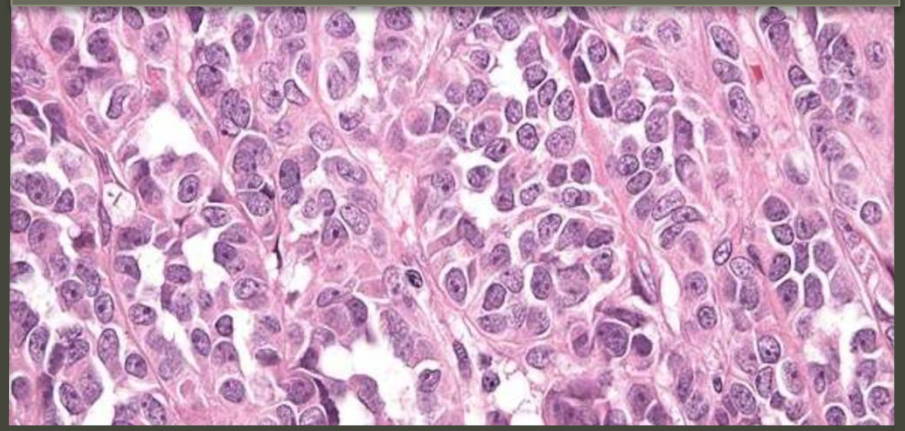
GI-Clear Cell Sarcoma-like Tumor

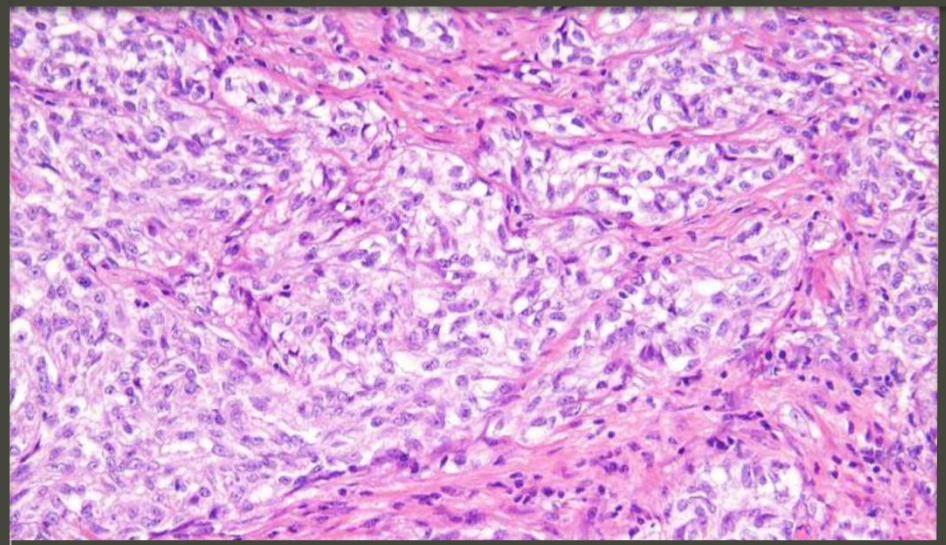
(Malignant gastrointestinal neuroectodermal tumor (GNET))

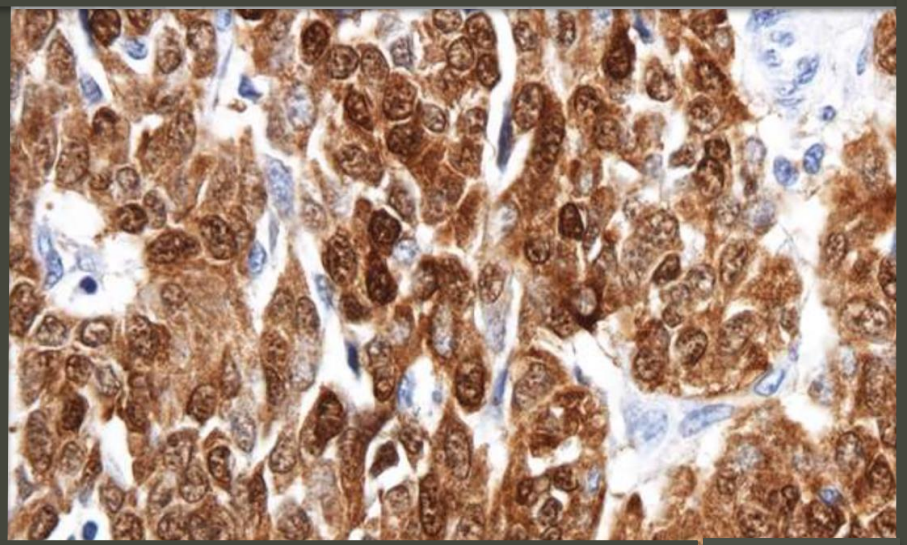


Molekularpathology:

t(12;22) with *ATF1-EWSR1* or
t(2;22) with *CREB1-EWSR1*







Images from Practical Soft Tissue Pathology: A diagnostiv Approach

S100

PLOS ONE

RESEARCH ARTICLE

Expression of cell cycle regulators and frequency of *TP53* mutations in high risk gastrointestinal stromal tumors prior to adjuvant imatinib treatment

Michaela Angelika Ihle[1☯], Sebastian Huss[2☯*], Wiebke Jeske[1], Wolfgang Hartmann[2], Sabine Merkelbach-Bruse[1], Hans-Ulrich Schildhaus[3], Reinhard Büttner[1], Harri Sihto[4], Kirsten Sundby Hall[5], Mikael Eriksson[6], Peter Reichardt[7], Heikki Joensuu[8], Eva Wardelmann[2]

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