Why Pathology & Your Pathologist Matter (or, That Mysterious Doctor You Never Meet)

Patient Summit Saturday 17 September 20

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GIST Pathology: Lecture Overview

1. **What happens to my tumor in pathology?**
2. **What information is in my pathology report?**
3. **Why is this information there?**
4. **What is the evidence that the information is useful?**

What happens to my tumor in pathology?

Tumor sample is received from the OR and logged into computer.

Tumor is examined by a pathologist.

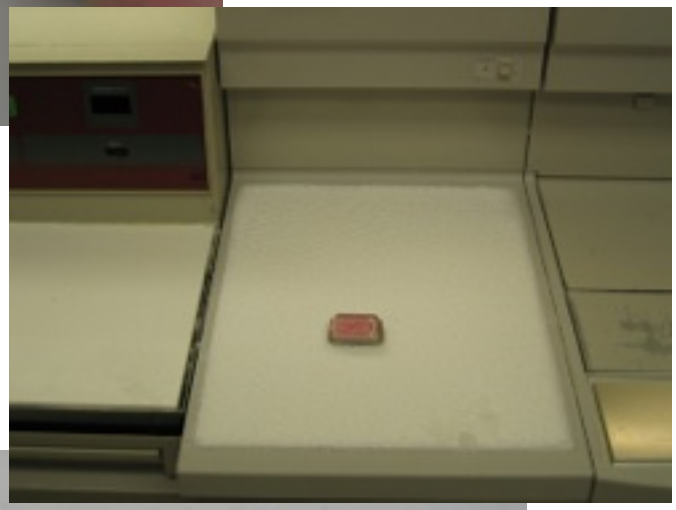
Tumor is sampled and placed in plastic cassettes for further processing.

Tumor is also given to cytogenetics, tumor bank, molecular diagnosis and electron microscopy when appropriate.

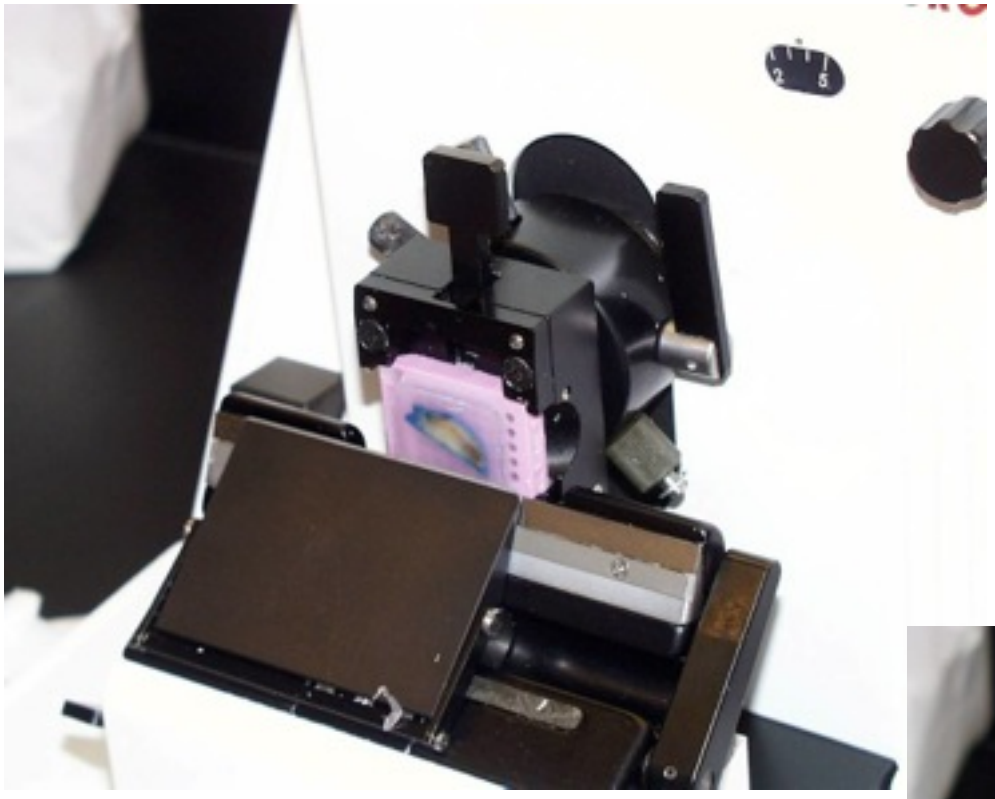
The tissue blocks are fixed in formalin and then loaded on a tissue processor overnight.

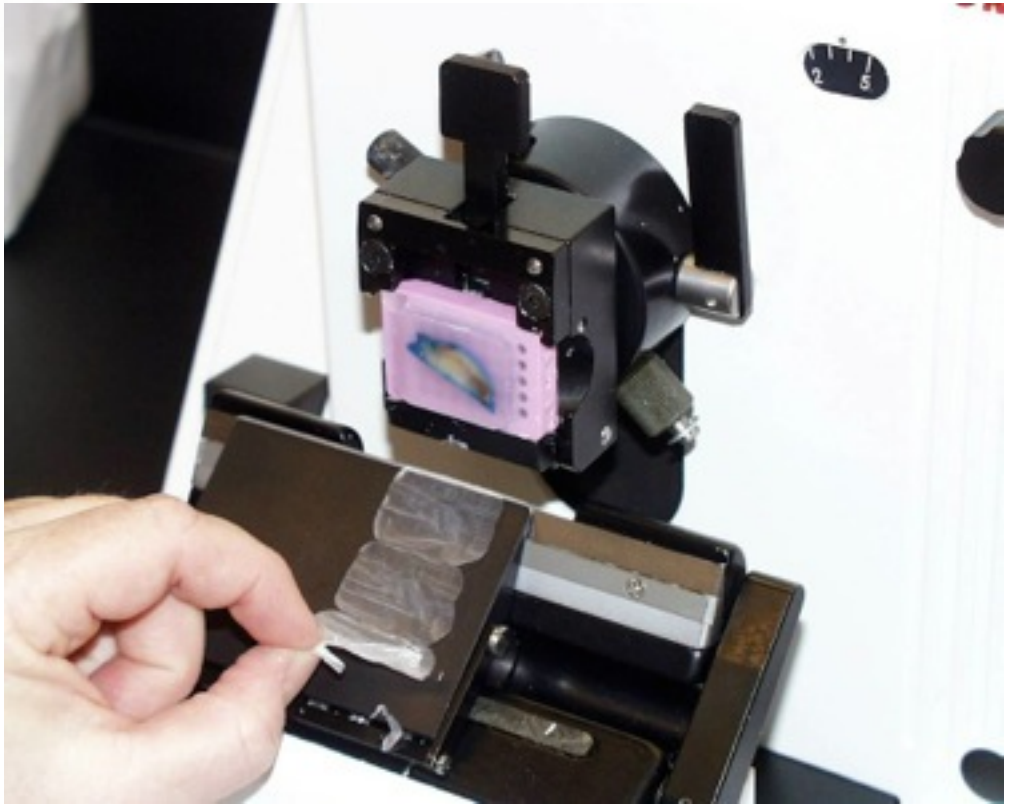
Tissue processing is done overnight and utilizes graded treatments of formalin, ethanc xylene and paraffin.

Blocks are retrieved from the tissue processor.



The tissue fragments are embedded in a paraffin mold and cooled – resulting in a tissue block.

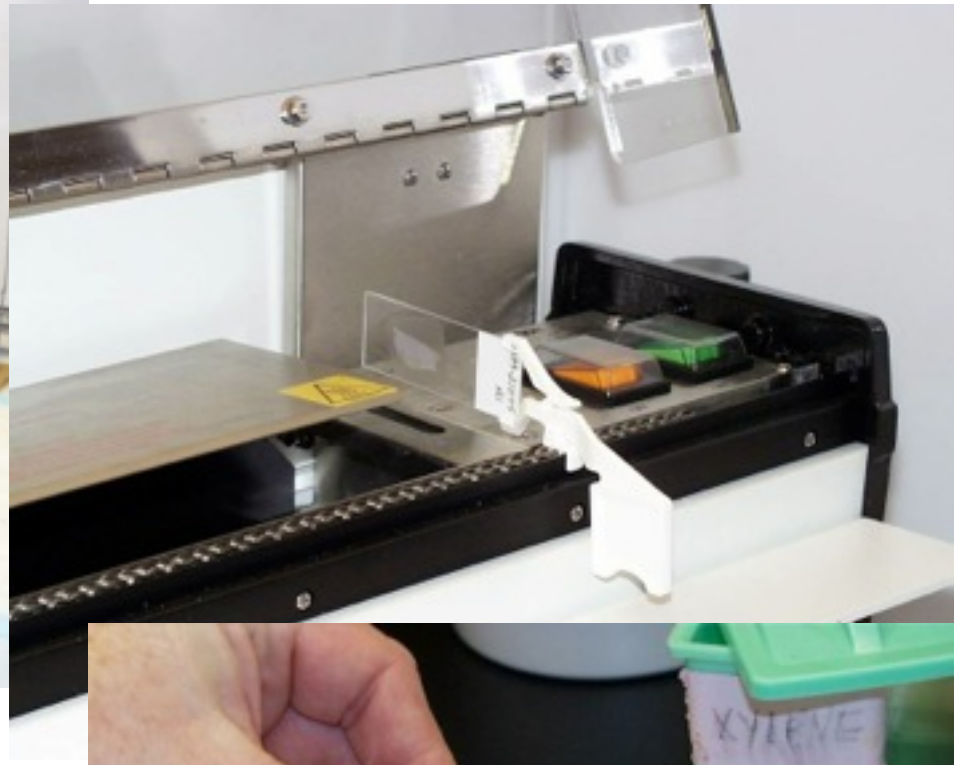




The paraffin-embedded blocks are loaded and cut using a microtome.

Tissue paraffin ribbons are placed in a warm waterbath and then picked up on glass slides.

The unstained slides can be used for H&E, special stains, immuno-histochemistry, molecular studies, etc.



Most slides are H&E (hemotoxlin & eosin) stained, given coverslips, organized and delivered to the proper pathologist.

Additional unstained slides can be cut at a later time.

After final diagnosis, both slides and the paraffin blocks from which they are cut are cataloged and stored for future use.

What information is in my pathology report?

Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST)

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedures
- Biopsy
- Resection

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Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

GASTROINTESTINAL STROMAL TUMOR (GIST): Resection

Select a single response unless otherwise indicated.

Procedure
___ Excisional biopsy
___ Resection
Specify type (eg, partial gastrectomy): _____
___ Metastasectomy
___ Other (specify): _____
___ Not specified

Tumor Site
Specify (if known): _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see "Comment")

Tumor Focality
___ Unifocal
___ Multifocal
Specify number of tumors: _____
Specify size of tumors: _____

GIST Subtype
___ Spindle cell
___ Epithelioid
___ Mixed
___ Other (specify): _____

Mitotic Rate

Specify: ___ /50 HPF

Note: The required total count of mitoses is per 5 mm² on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm². Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm². If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm².

+ Necrosis

+ ___ Not identified
+ ___ Present
    + Extent: ___%
+ ___ Cannot be determined

Histologic Grade (Note B)
___ GX: Grade cannot be assessed
___ G1: Low grade; mitotic rate ≤5/50 HPF
___ G2: High grade; mitotic rate >5/50 HPF

Risk Assessment (Note C)
___ None
___ Very low risk
___ Low risk
___ Intermediate risk
___ High risk
___ Overtly malignant/metastatic
___ Cannot be determined

Margins
___ Cannot be assessed
___ Negative for GIST
Distance of tumor from closest margin: ___ mm or ___ cm
___ Margin(s) positive for GIST
Specify margin(s): _____

Pathologic Staging (pTNM) (Note G)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence for primary tumor
___ pT1: Tumor 2 cm or less
___ pT2: Tumor more than 2 cm but not more than 5 cm
___ pT3: Tumor more than 5 cm but not more than 10 cm
___ pT4: Tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (pN) (Note D)
___ Not applicable
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

Distant Metastasis (pM) (Note D)
___ Not applicable
___ pM1: Distant metastasis
+ Specify site(s), if known: _____

+ Additional Pathologic Findings
+ Specify: _____

Ancillary Studies (select all that apply) (Note E)

Immunohistochemical Studies
___ KIT (CD117)
    ___ Positive
    ___ Negative
___ Others (specify): _____
___ Not performed

Molecular Genetic Studies (eg, *KIT* or *PDGFRA* mutational analysis)
___ Submitted for analysis; results pending
___ Performed, see separate report: _____
___ Performed
    Specify method(s) and results: _____
___ Not performed

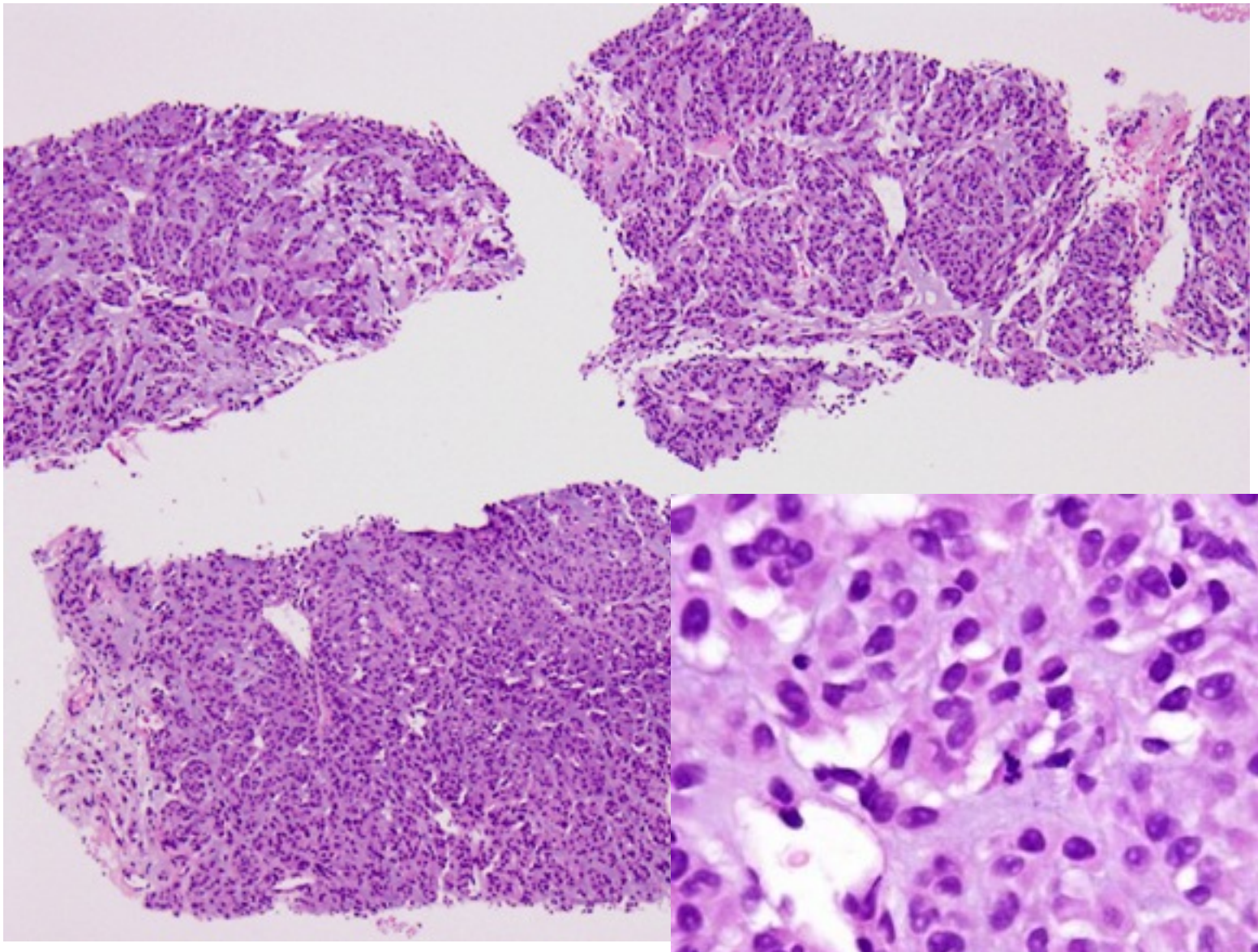
Preresection Treatment (select all that apply)
___ No therapy
___ Previous biopsy or surgery
    Specify: _____
___ Systemic therapy performed
    Specify type: _____
___ Therapy performed, type not specified
___ Unknown

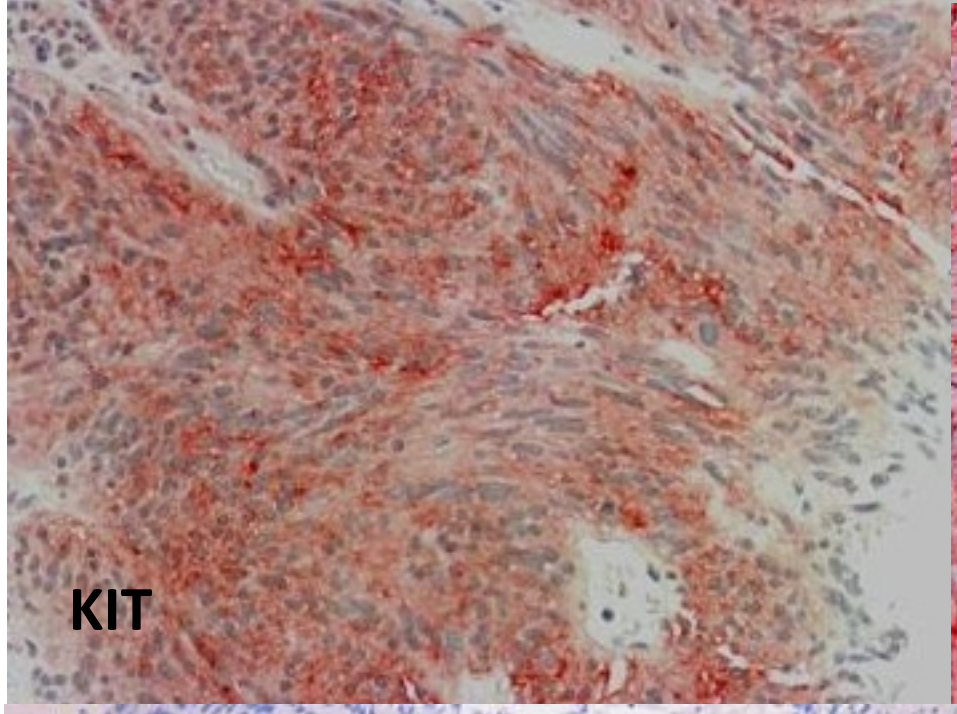
+ Treatment Effect (Note F)
+ Specify percentage of viable tumor: ___%

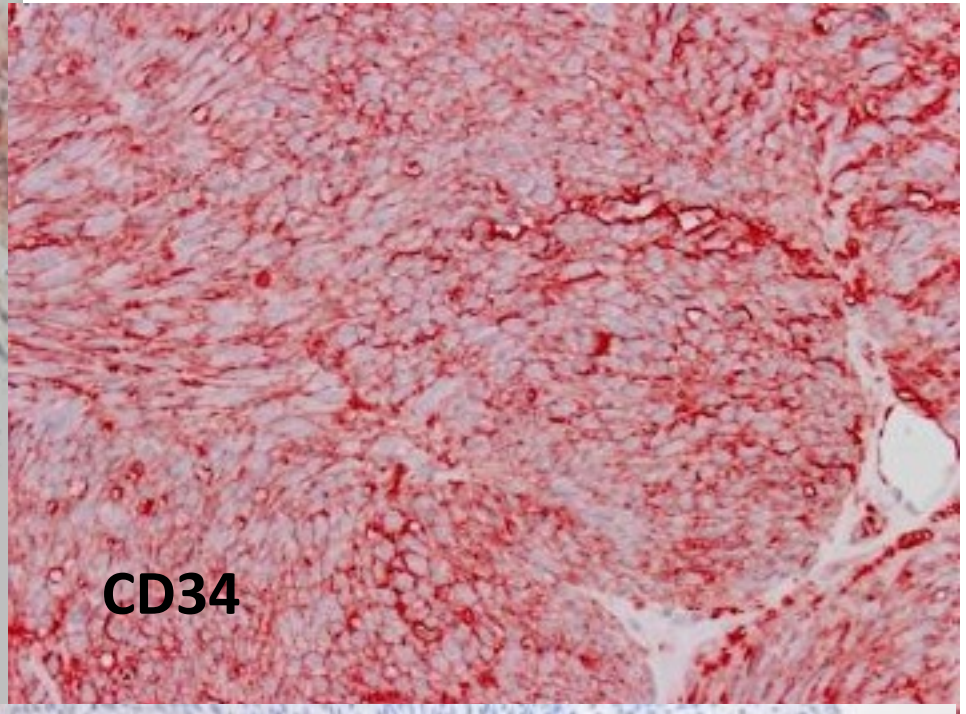
+ Comment(s)

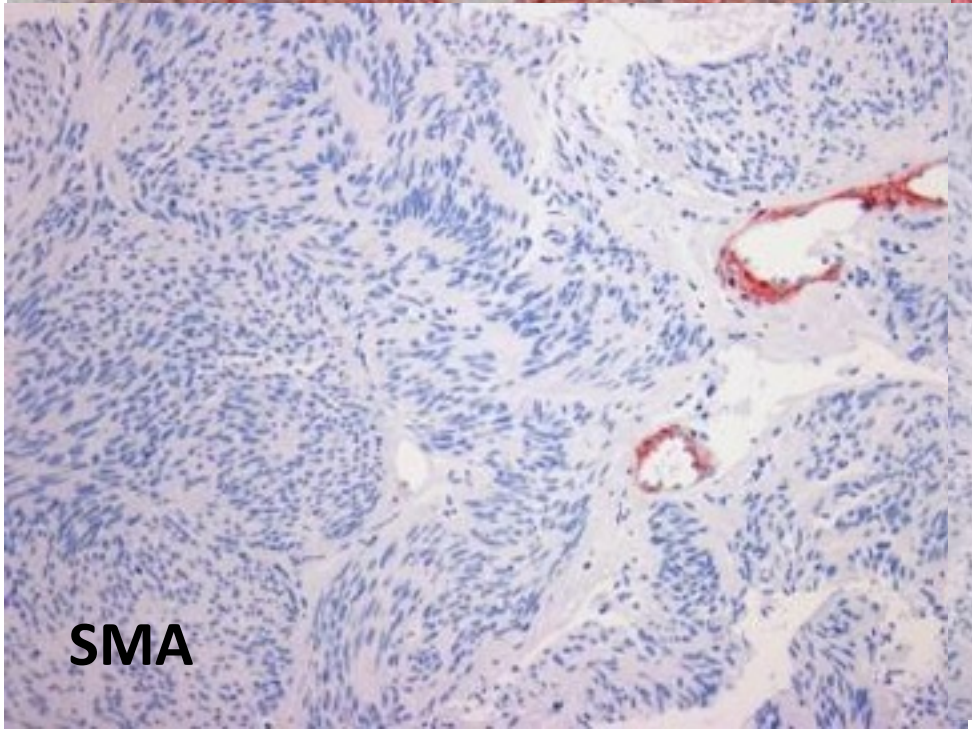
Getting the diagnosis right

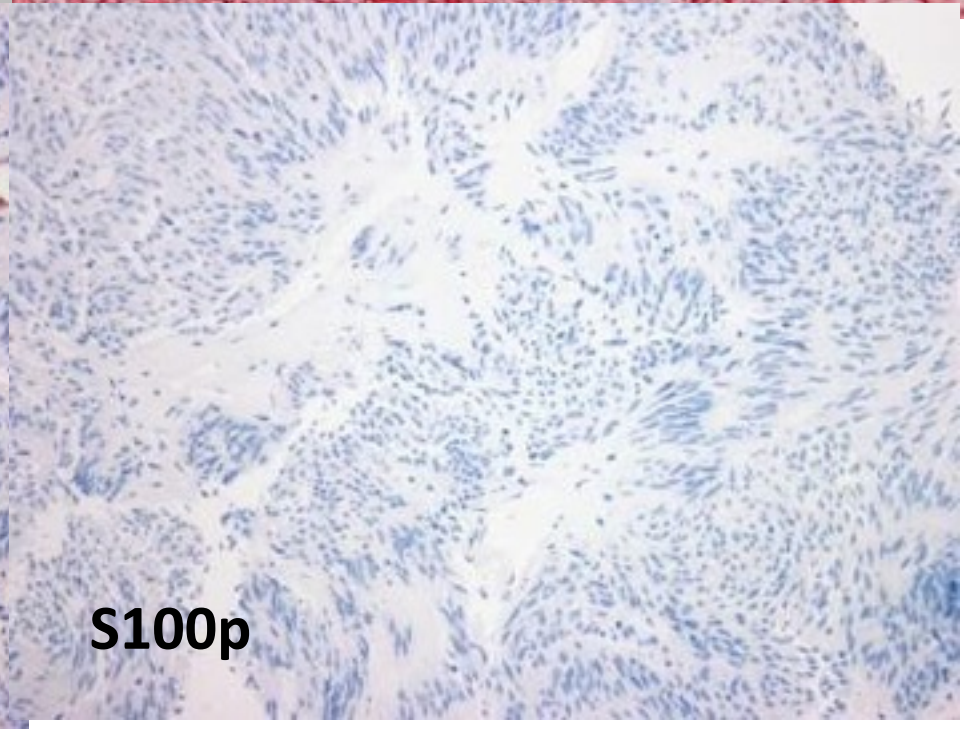
Case 1



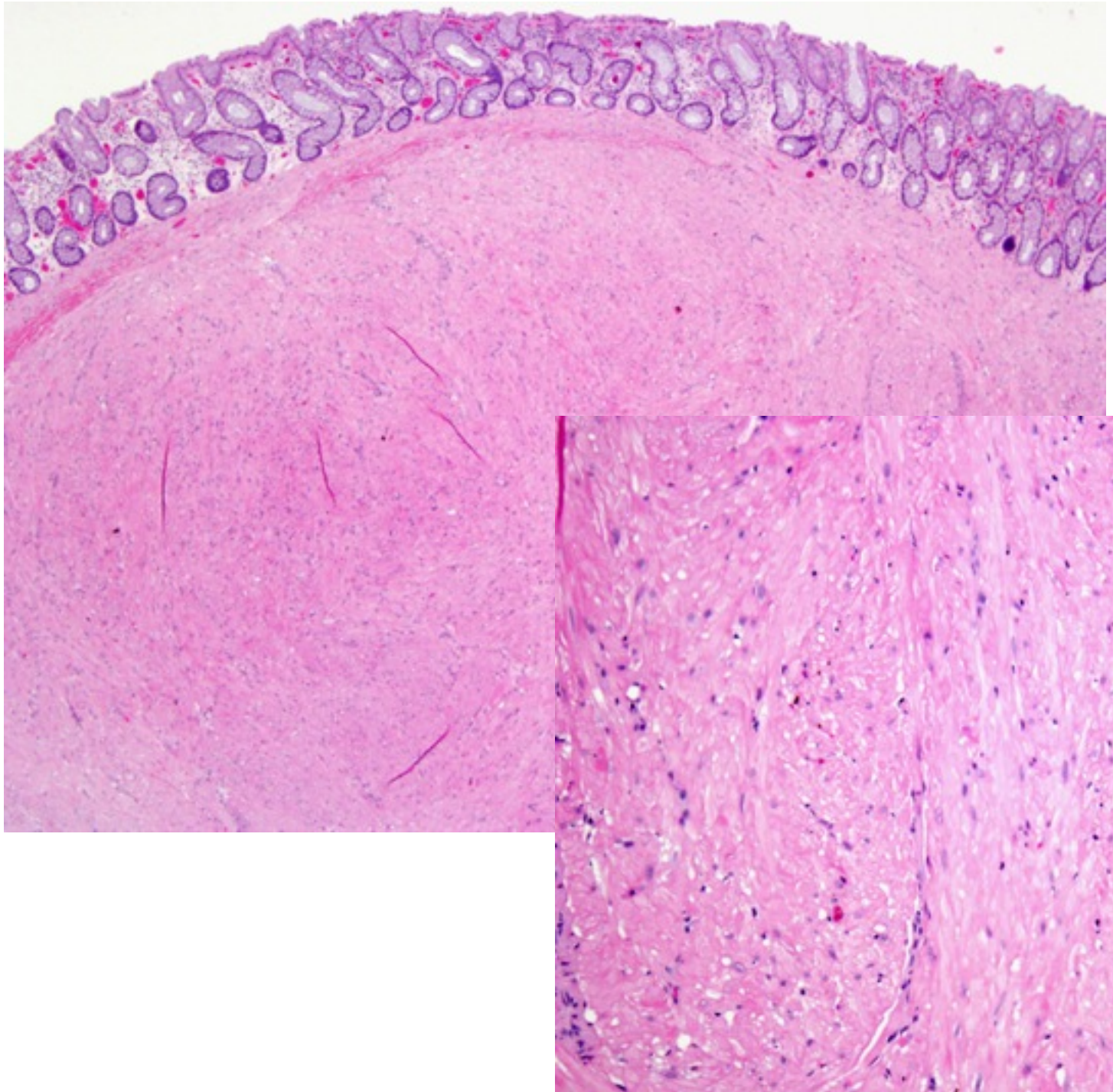

KIT

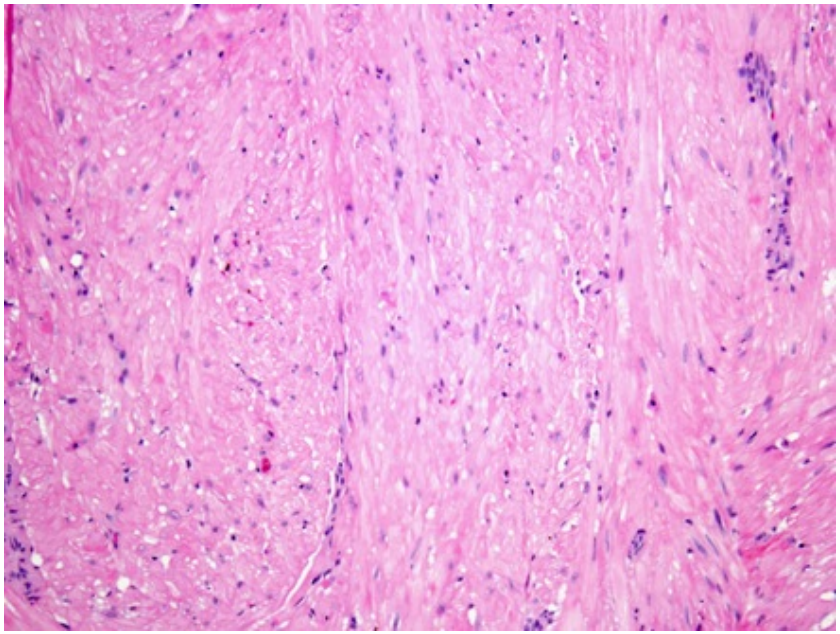

CD34

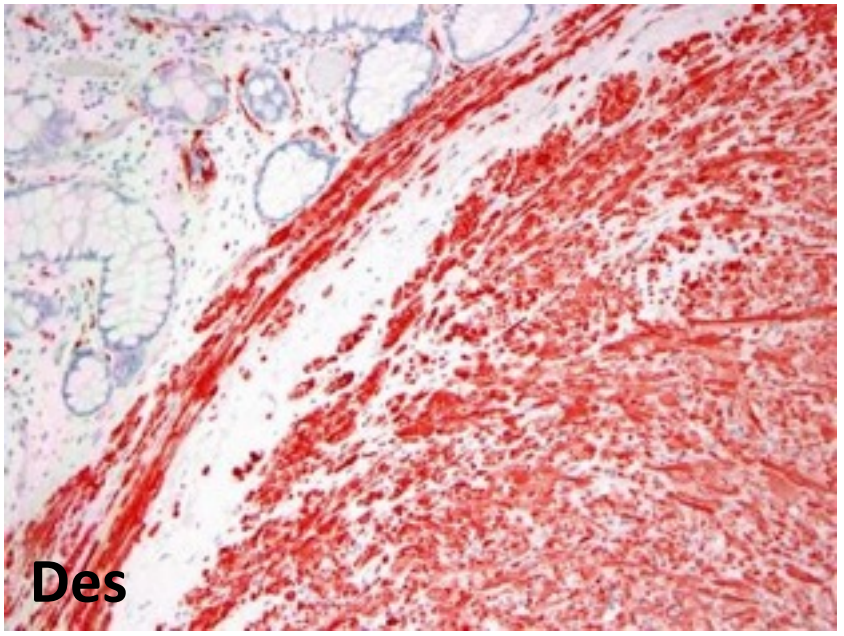

SMA

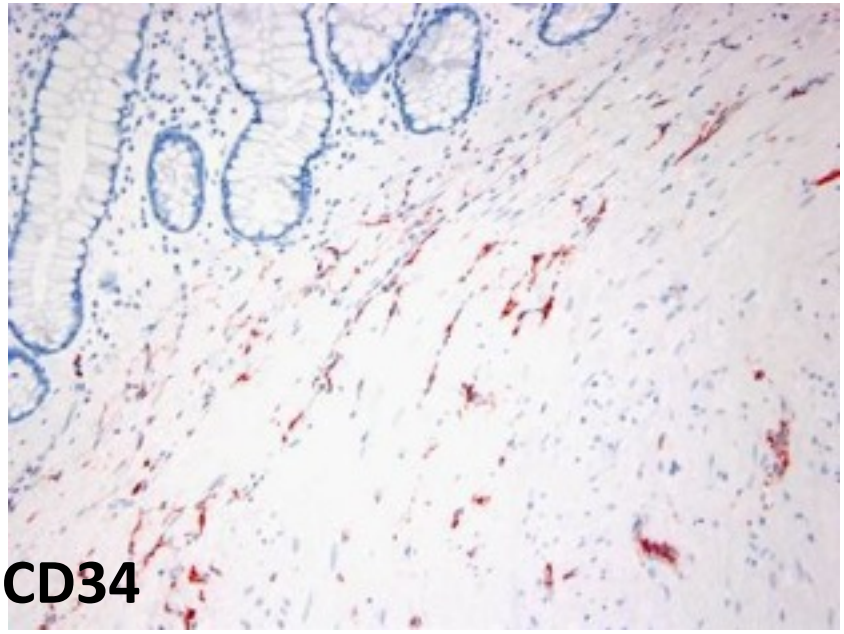

S100p

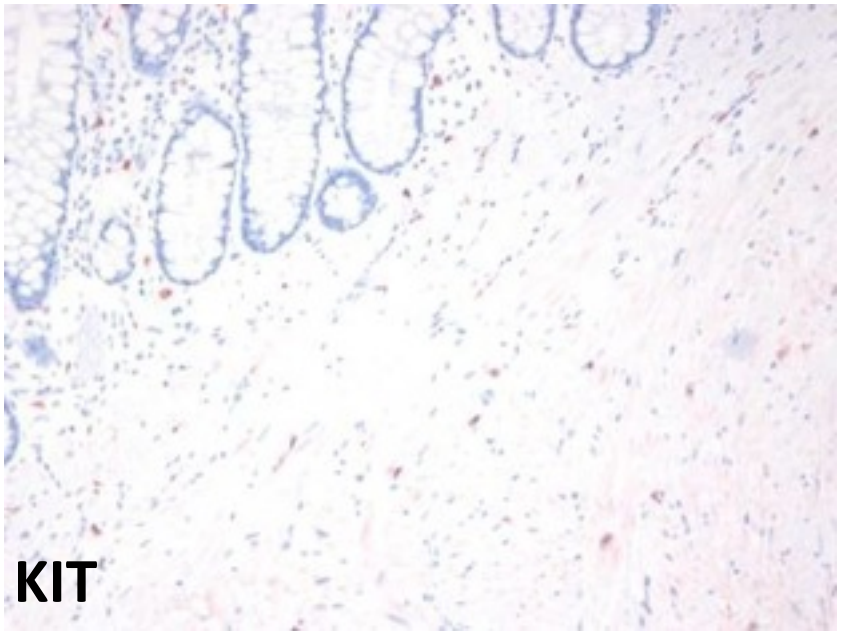
Case 2



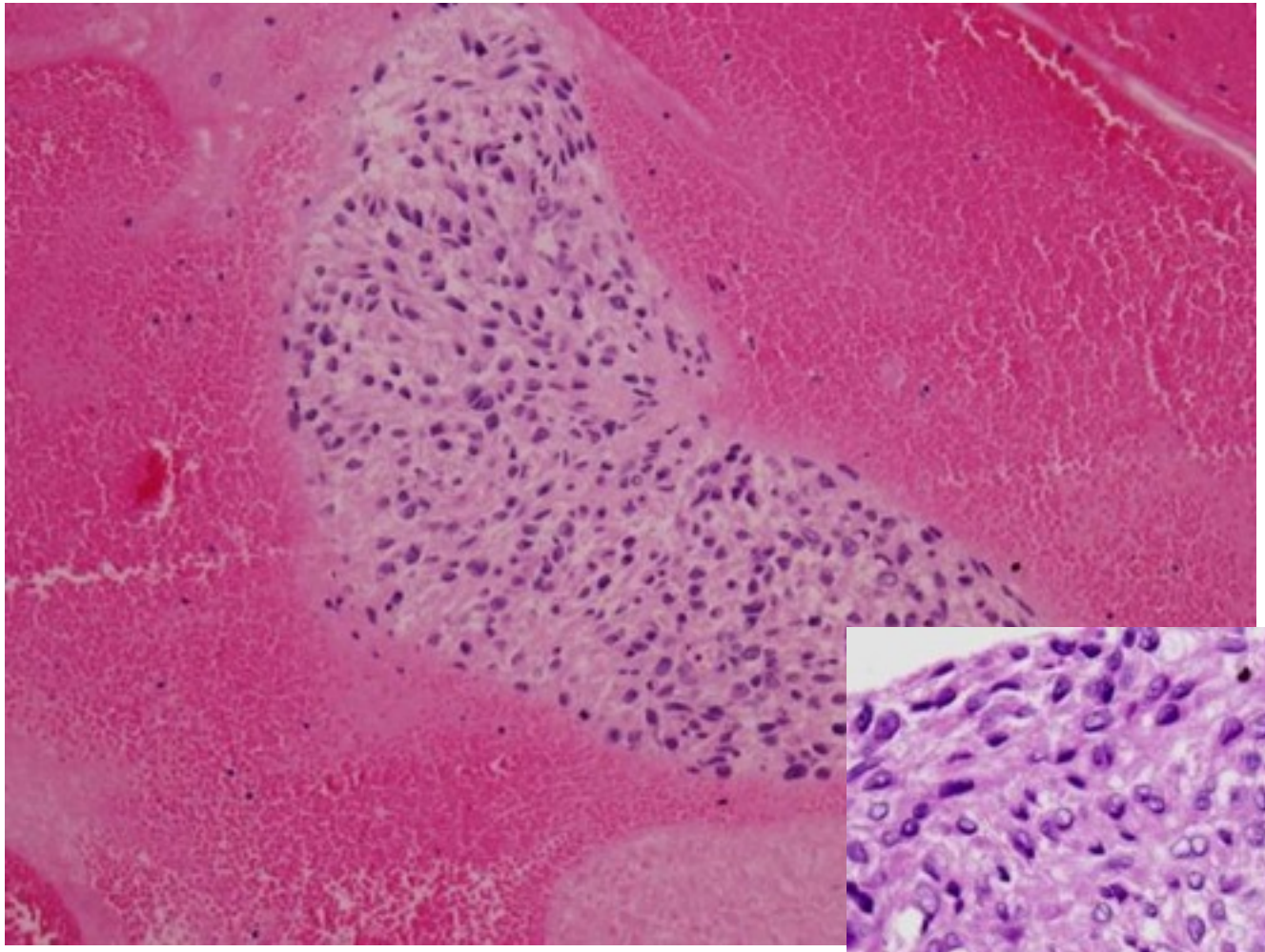


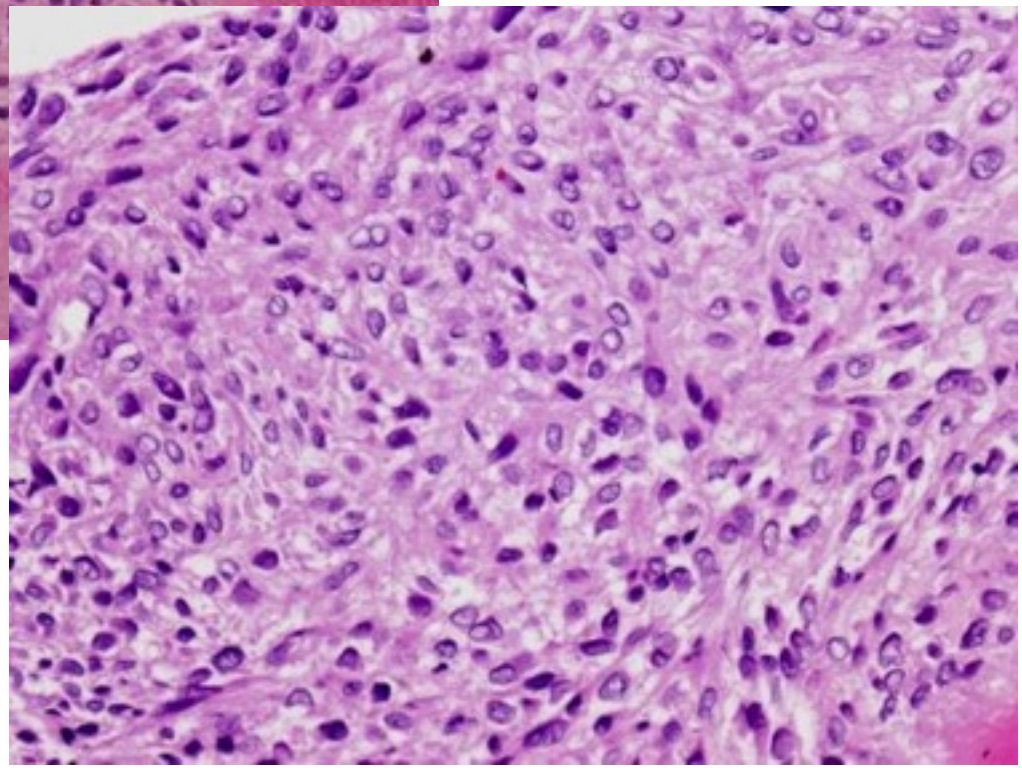

Des

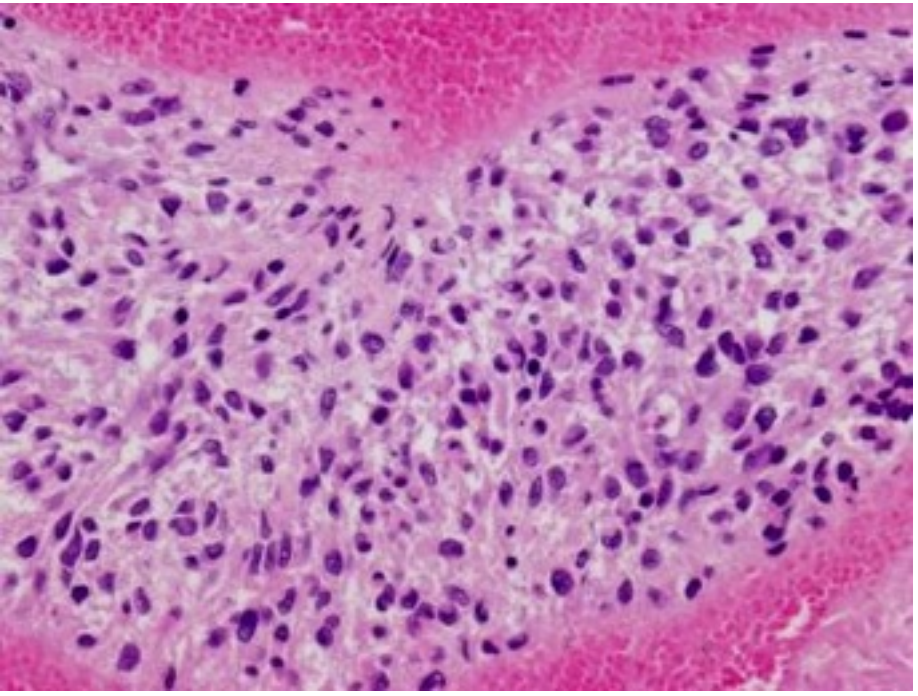

CD34

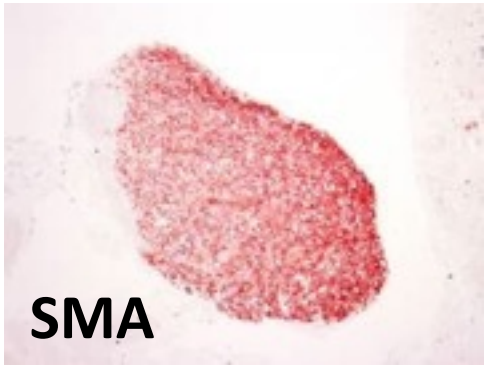

KIT

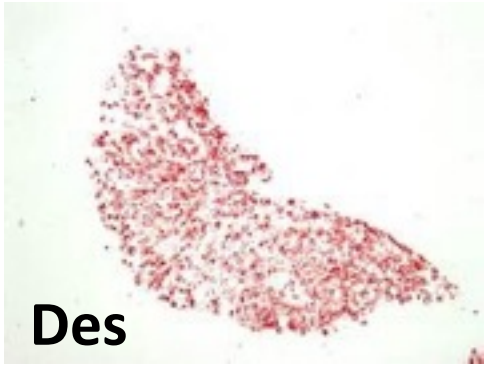
Case 3

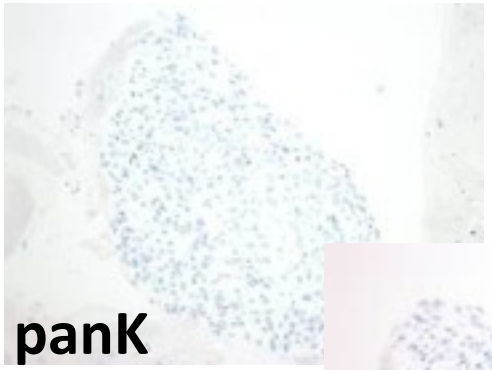


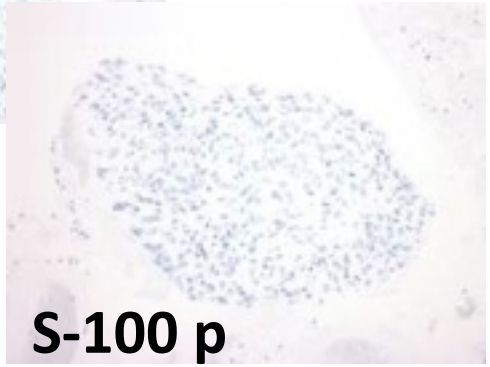




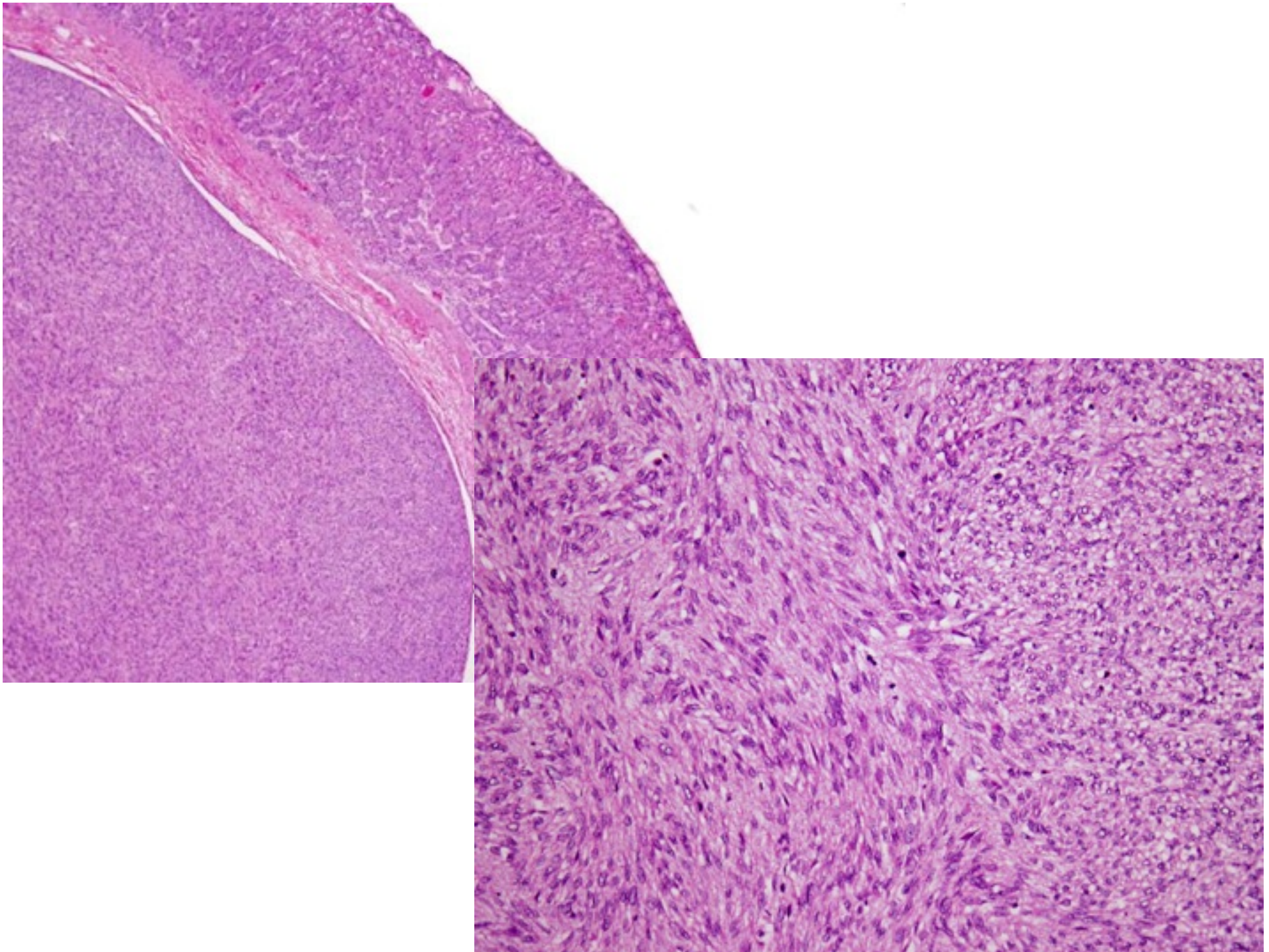

SMA

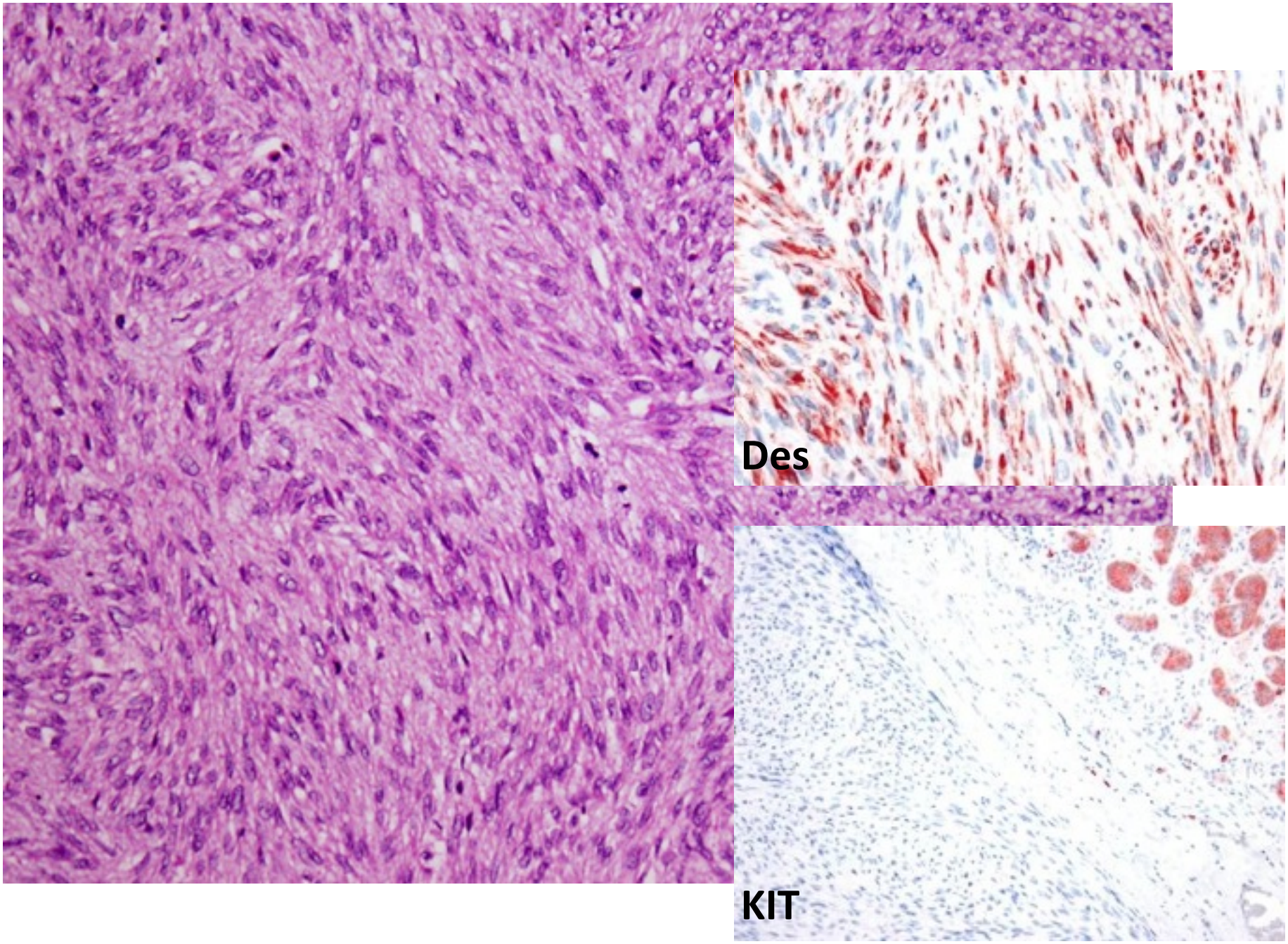

Des

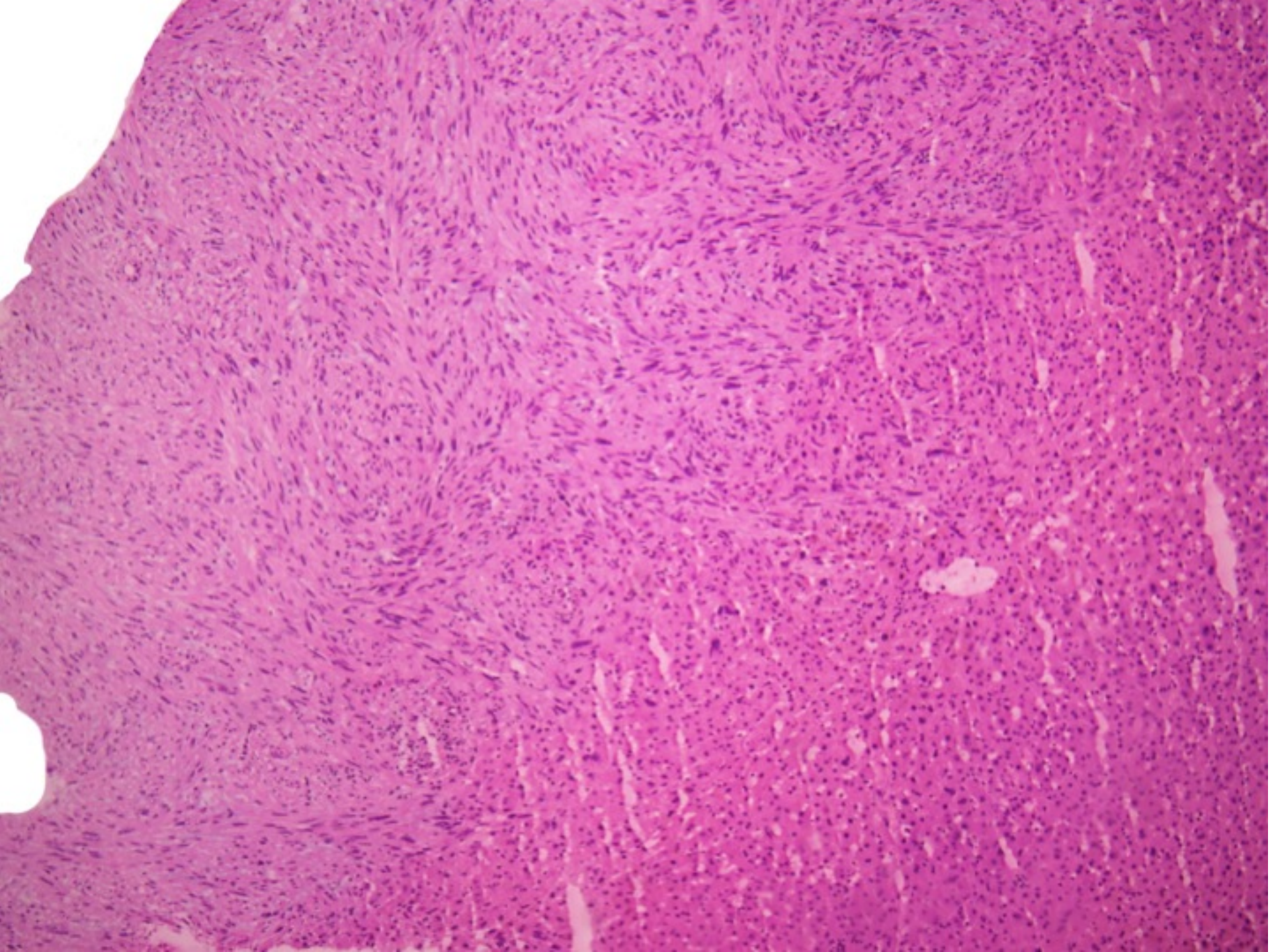

panK


S-100 p

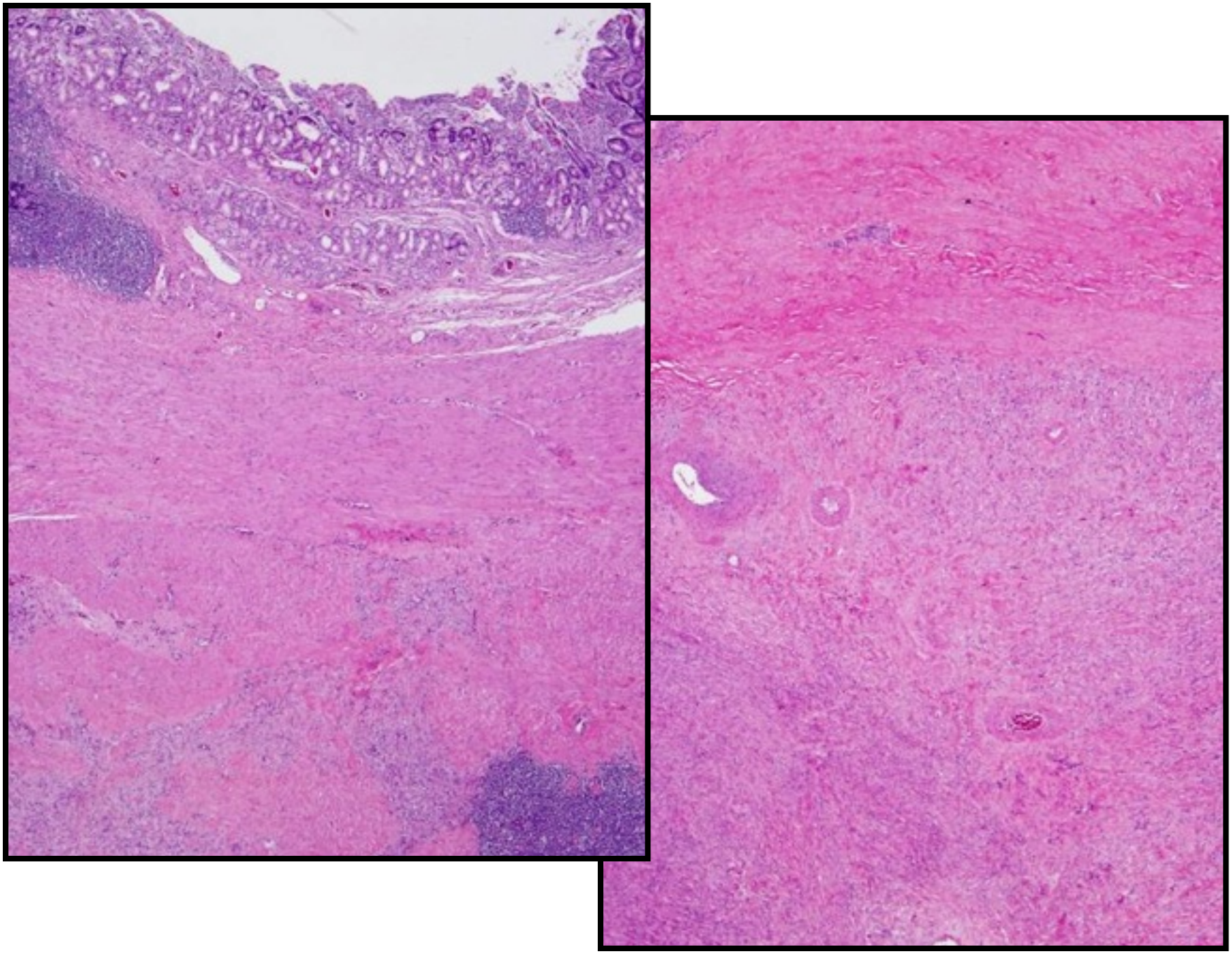

KIT

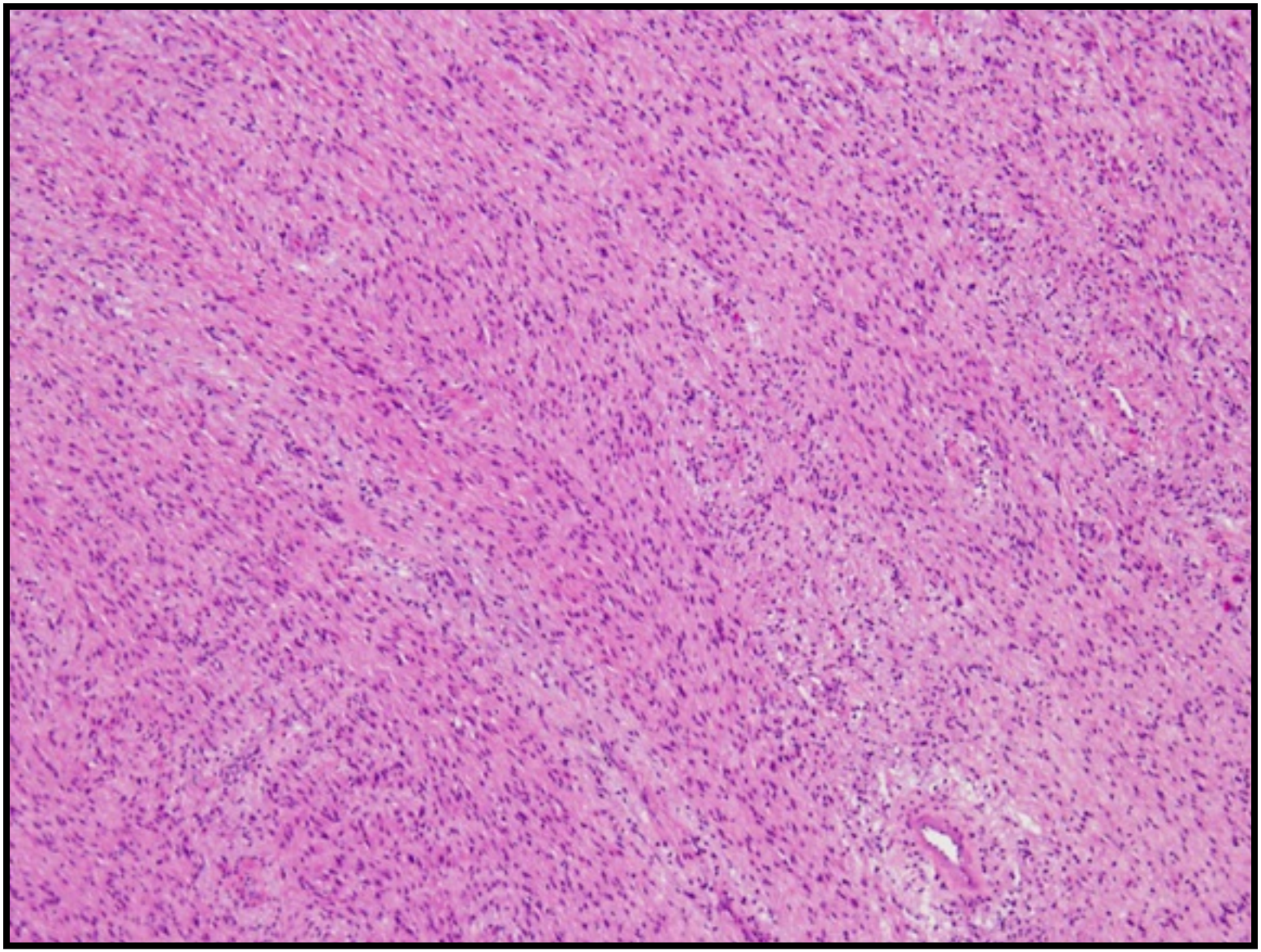


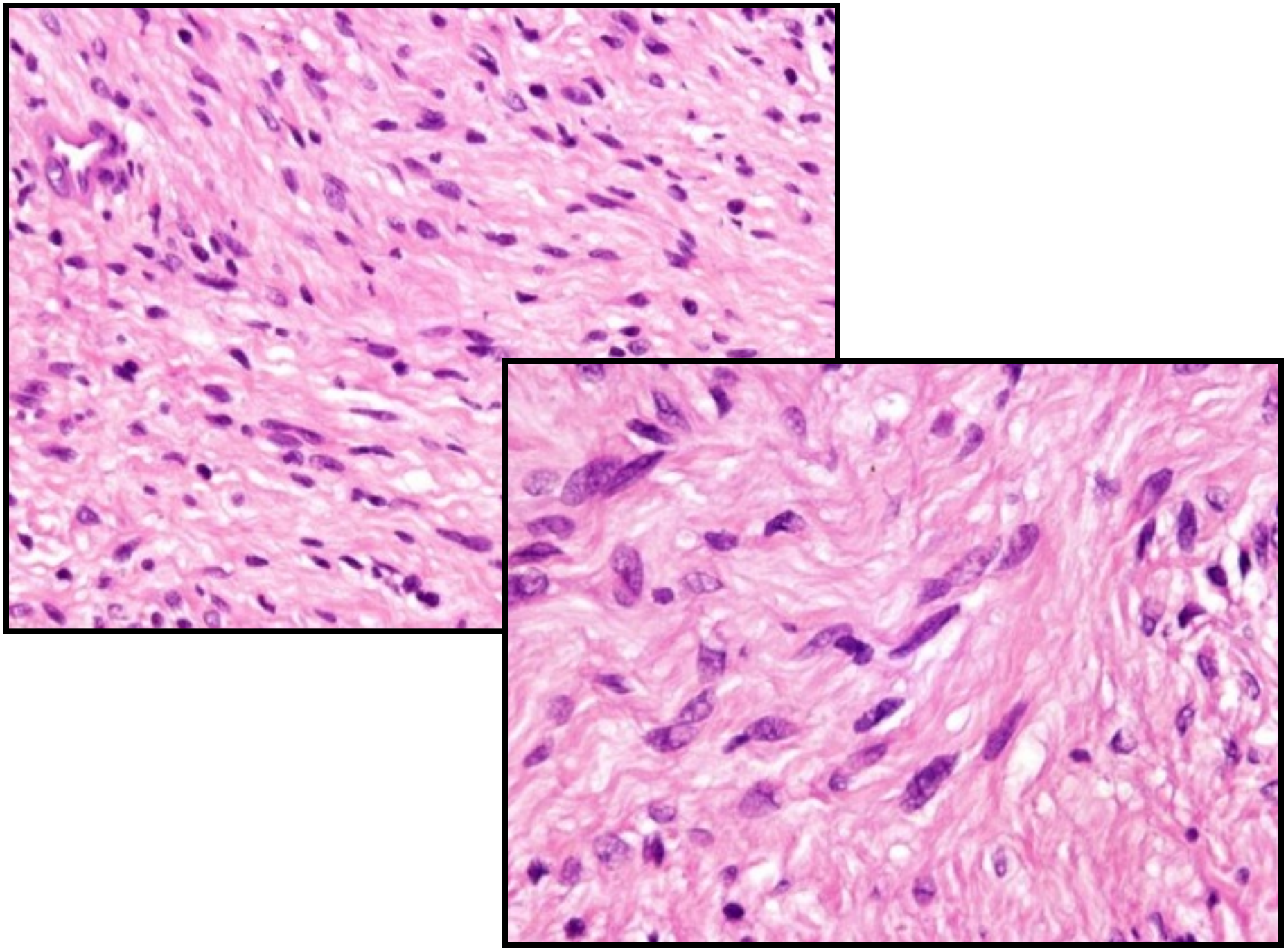

Des
KIT



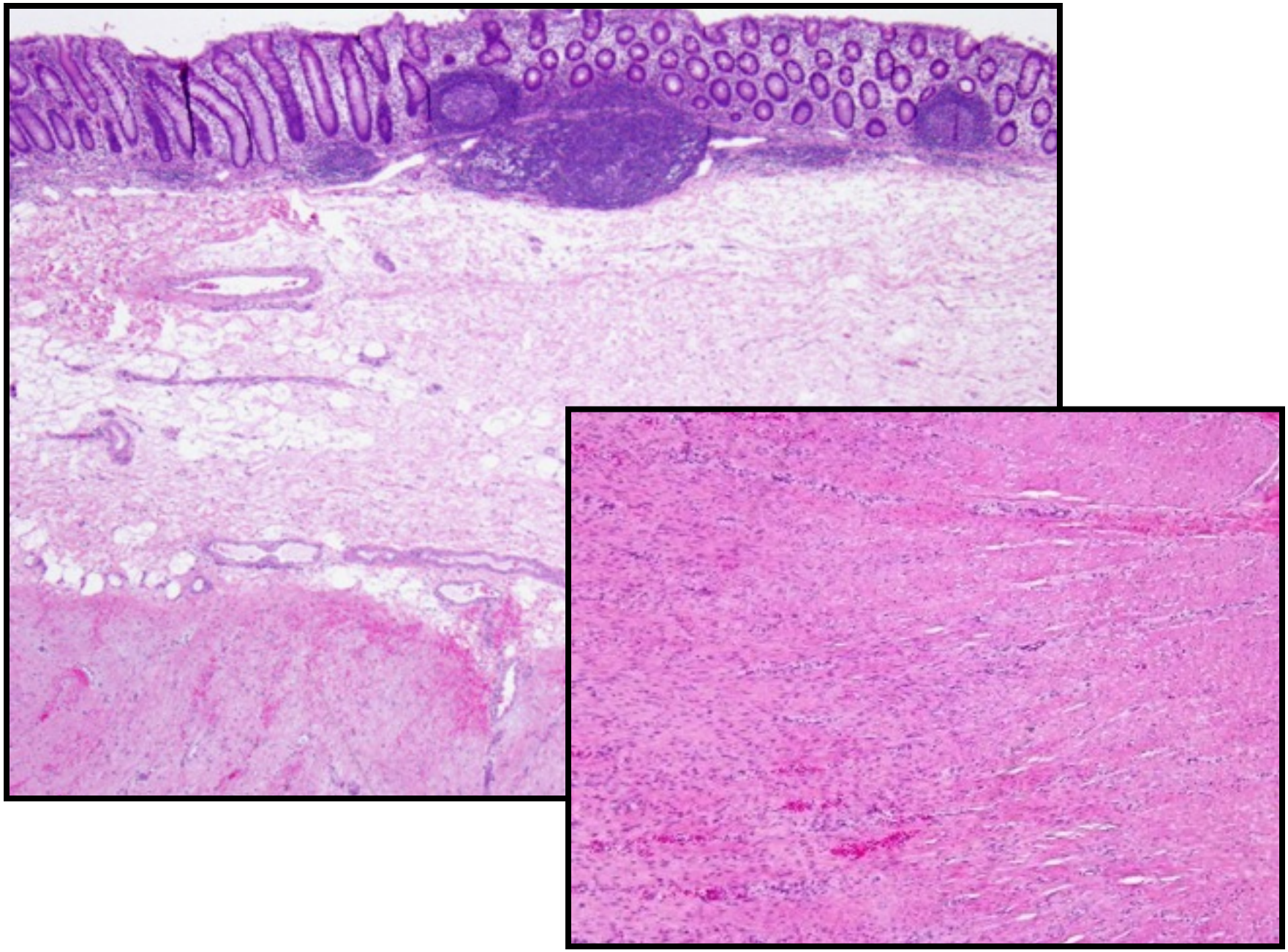
Case 4

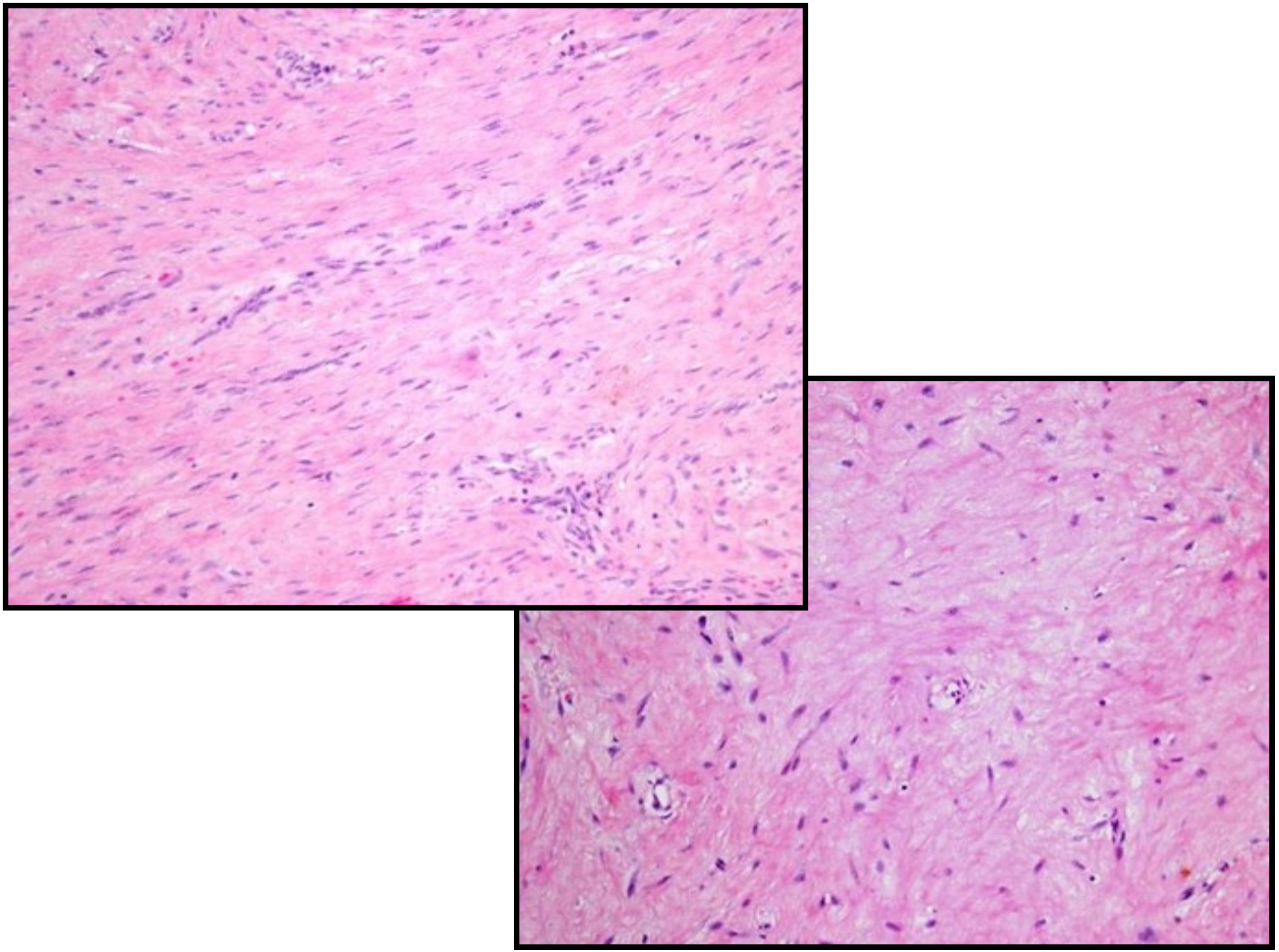


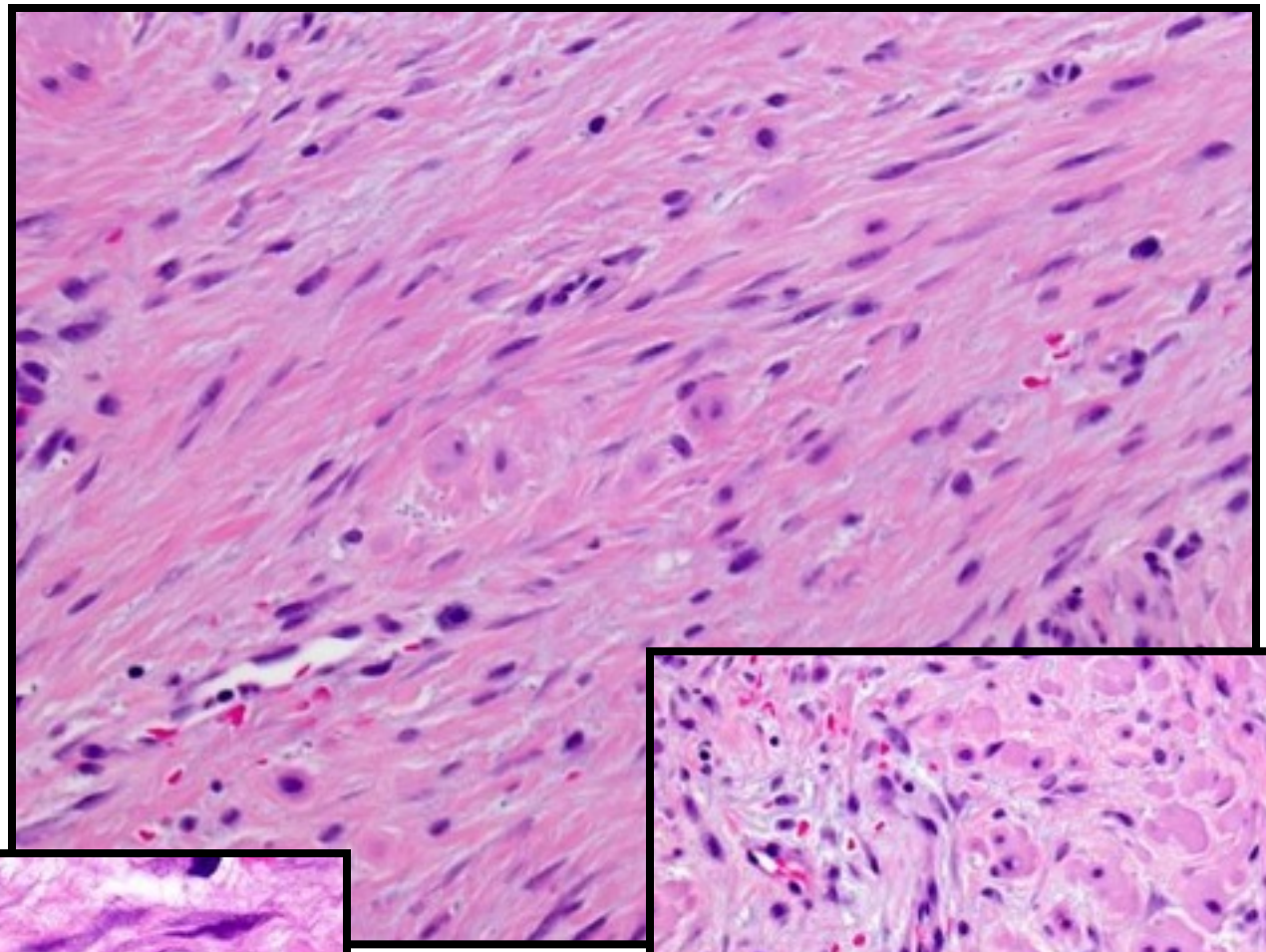


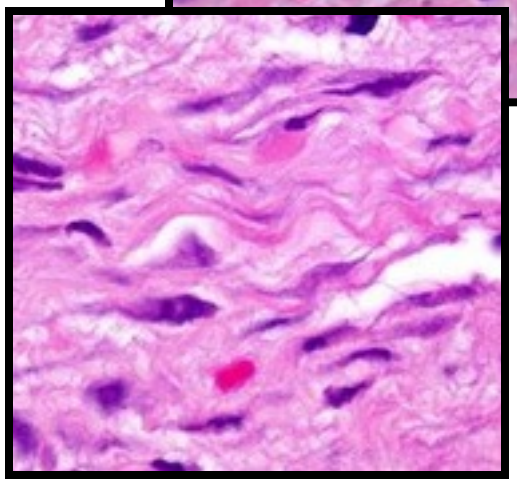


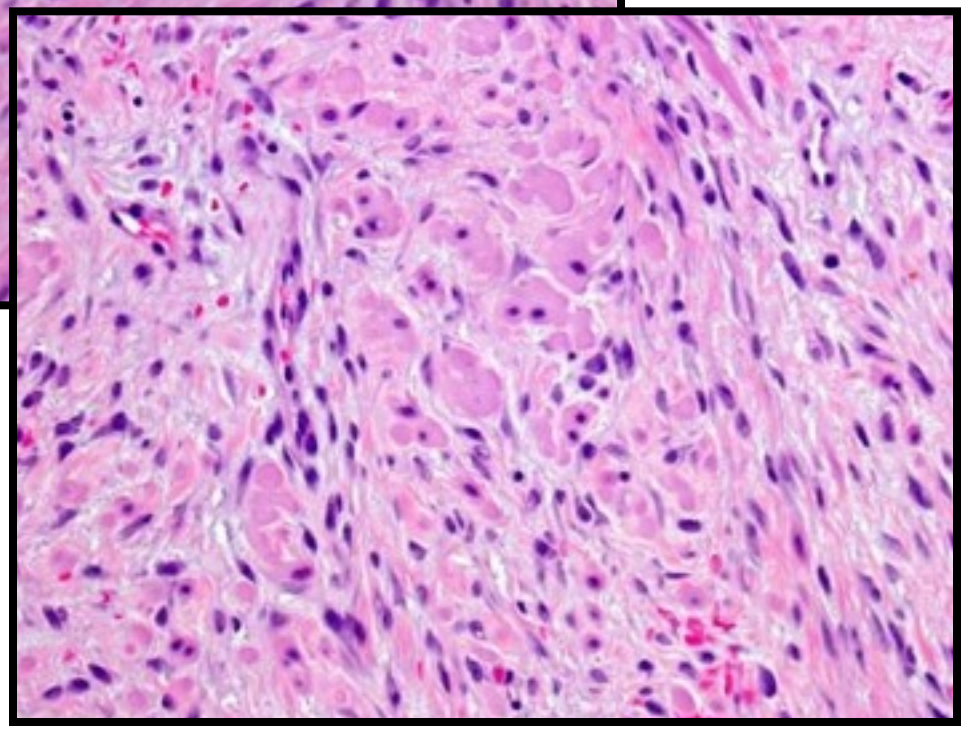
Case 5

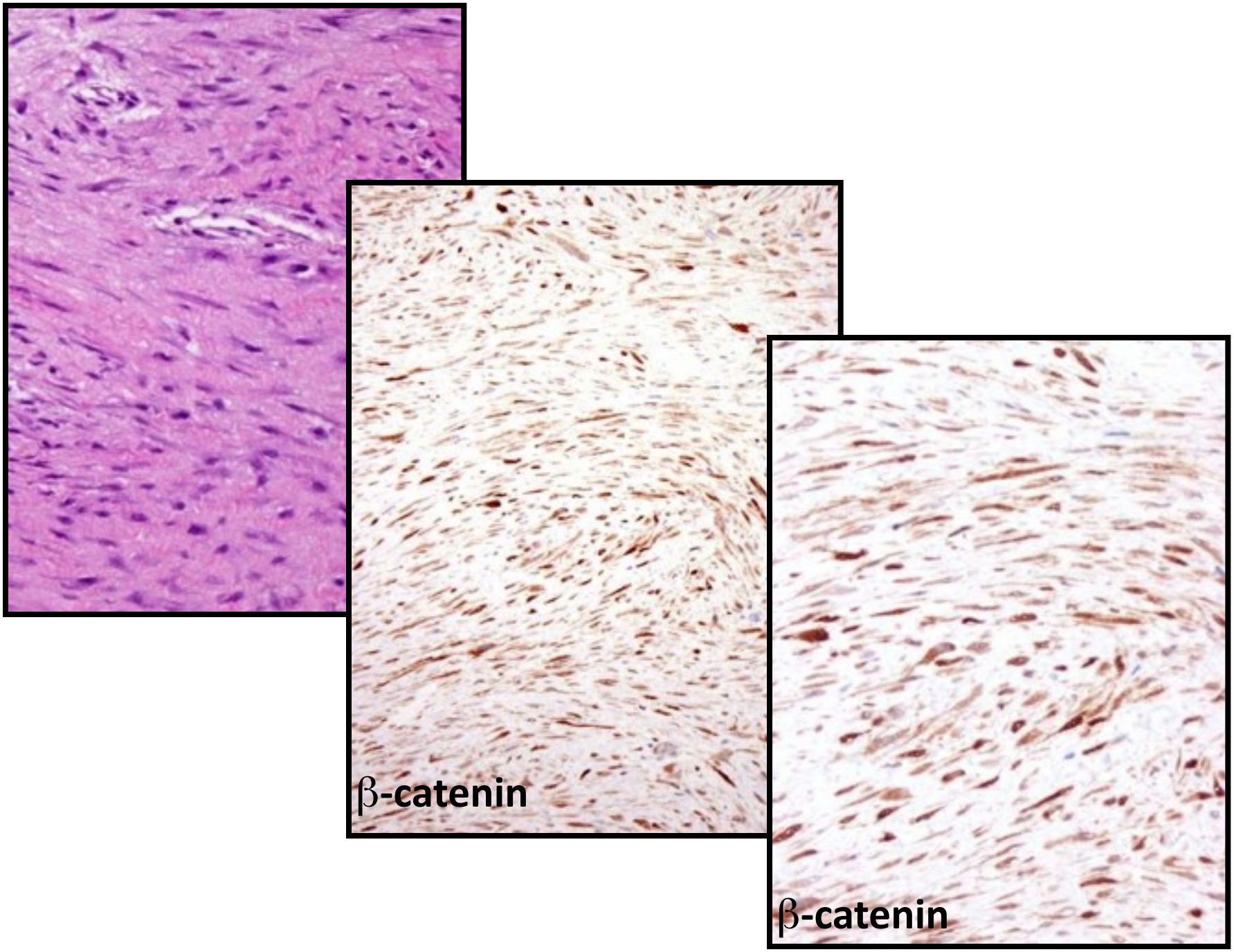


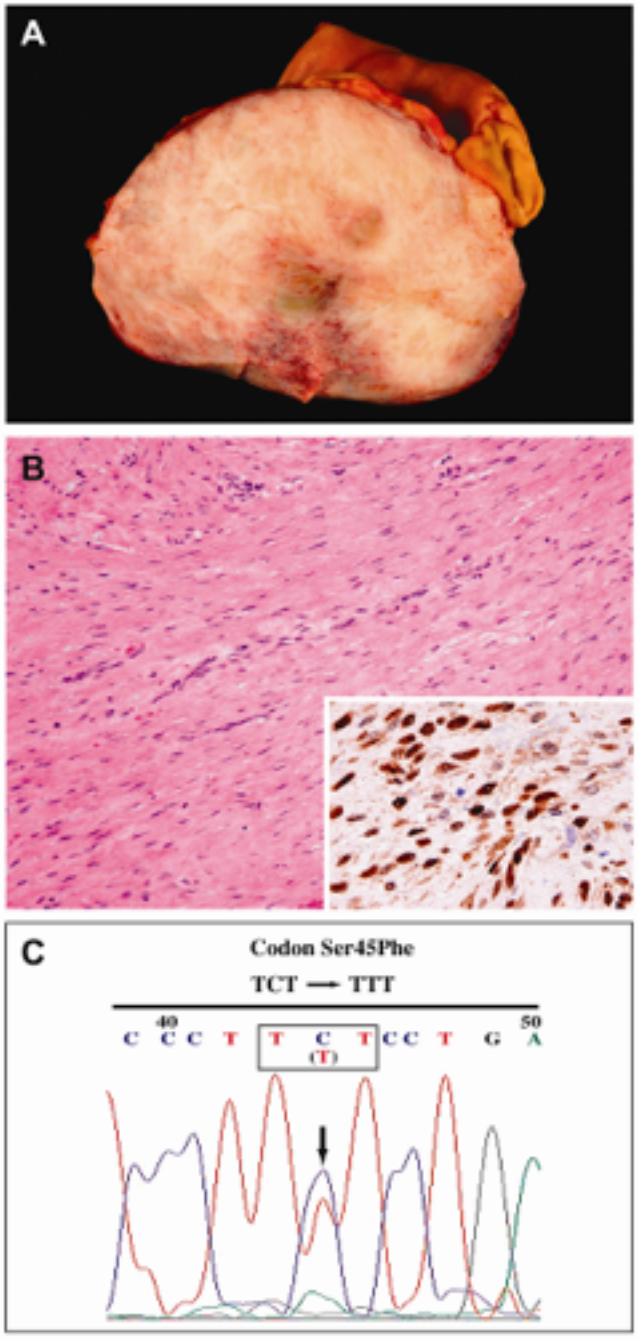








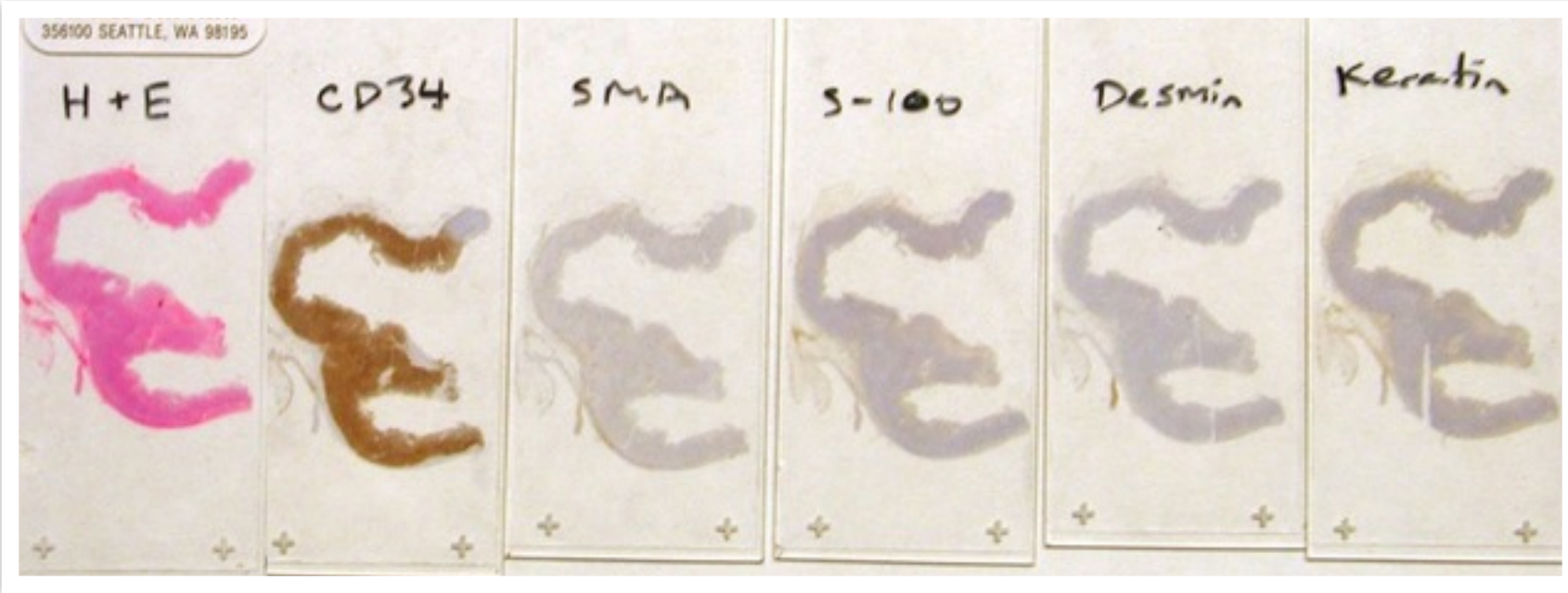

β-catenin
β-catenin


A
B
C
Codon Ser45Phe
TCT → TTT
40
C C C T T C T C C T G 50
A
(T)

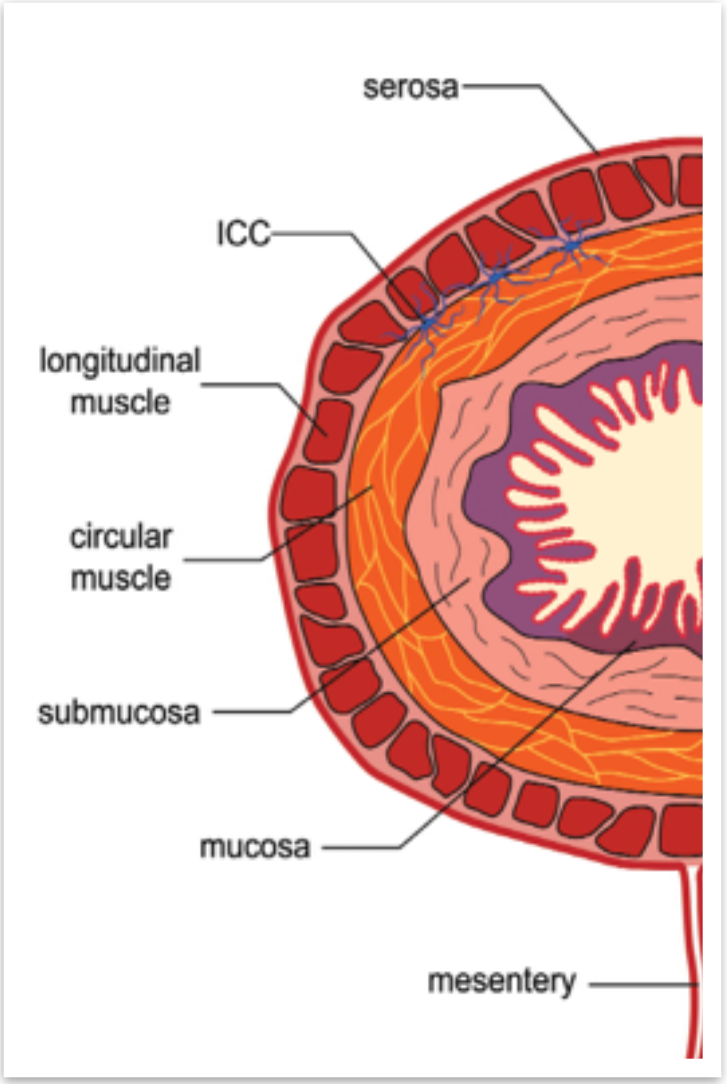
Immunohistochemical Scheme

DIAGNOSIS	KIT	CD34	Ker	SMA	DES	S-100
GIST	+	+(70%)	-	+(40%)	-	-
Carcinoma	-	-	+	+(sar)	-	-
Melanoma	+/-	-	-	-	-	+
Leiomyoma	-	+/-	+/-	+	+	-
Leiomyosarcoma	-	+/-	+/-	+	+/-	-

Immunohistochemical Profile of GISTs (Circa 1997 and prior)

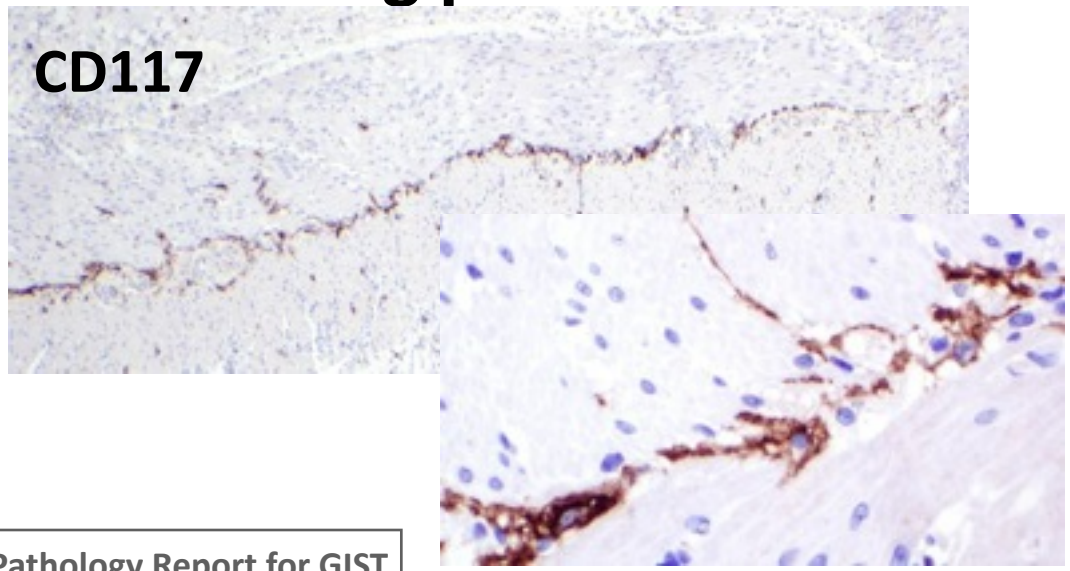


Gastrointestinal Stromal Tumor



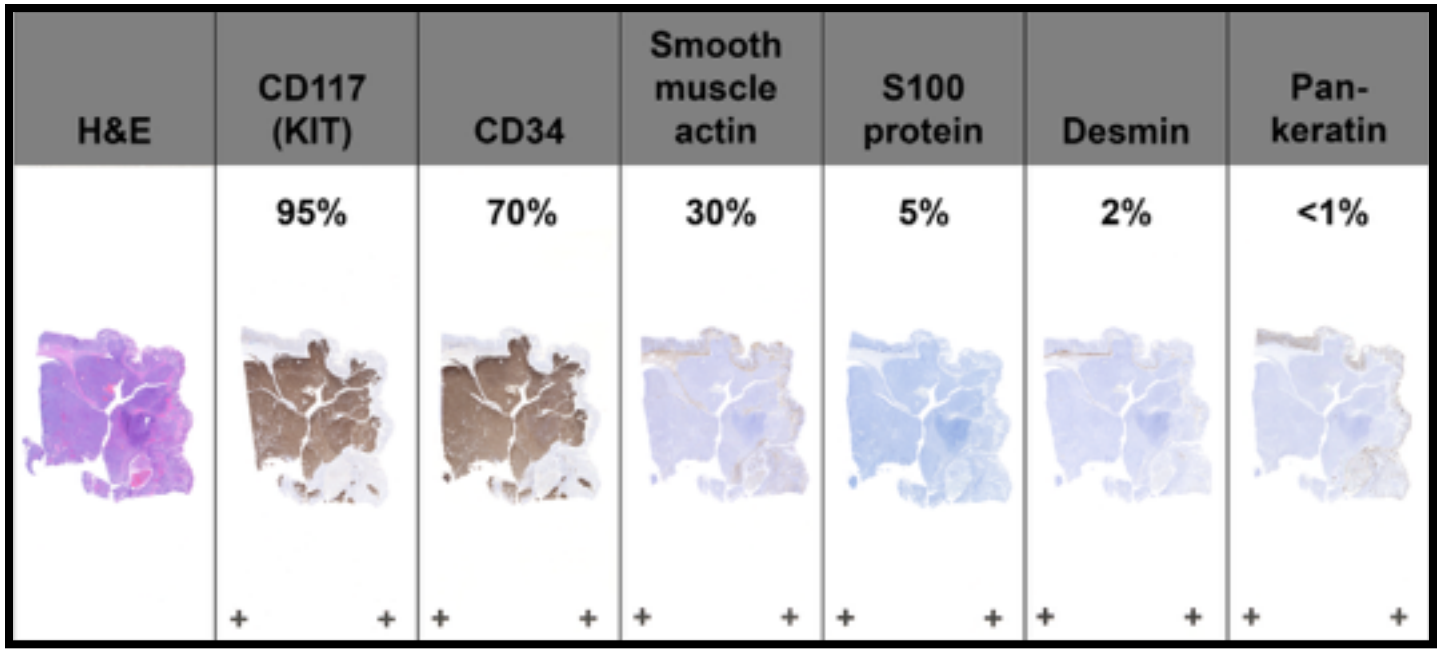
- **Arise from the interstitial cells of Cajal (ICC)**

- **ICC have a "pacemaker" function and are important in coordinating peristalsis**



Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST

Immunohistochemical Profile of GIST



KIT (CD117) +ve (95%)

CD34 +ve (70%)

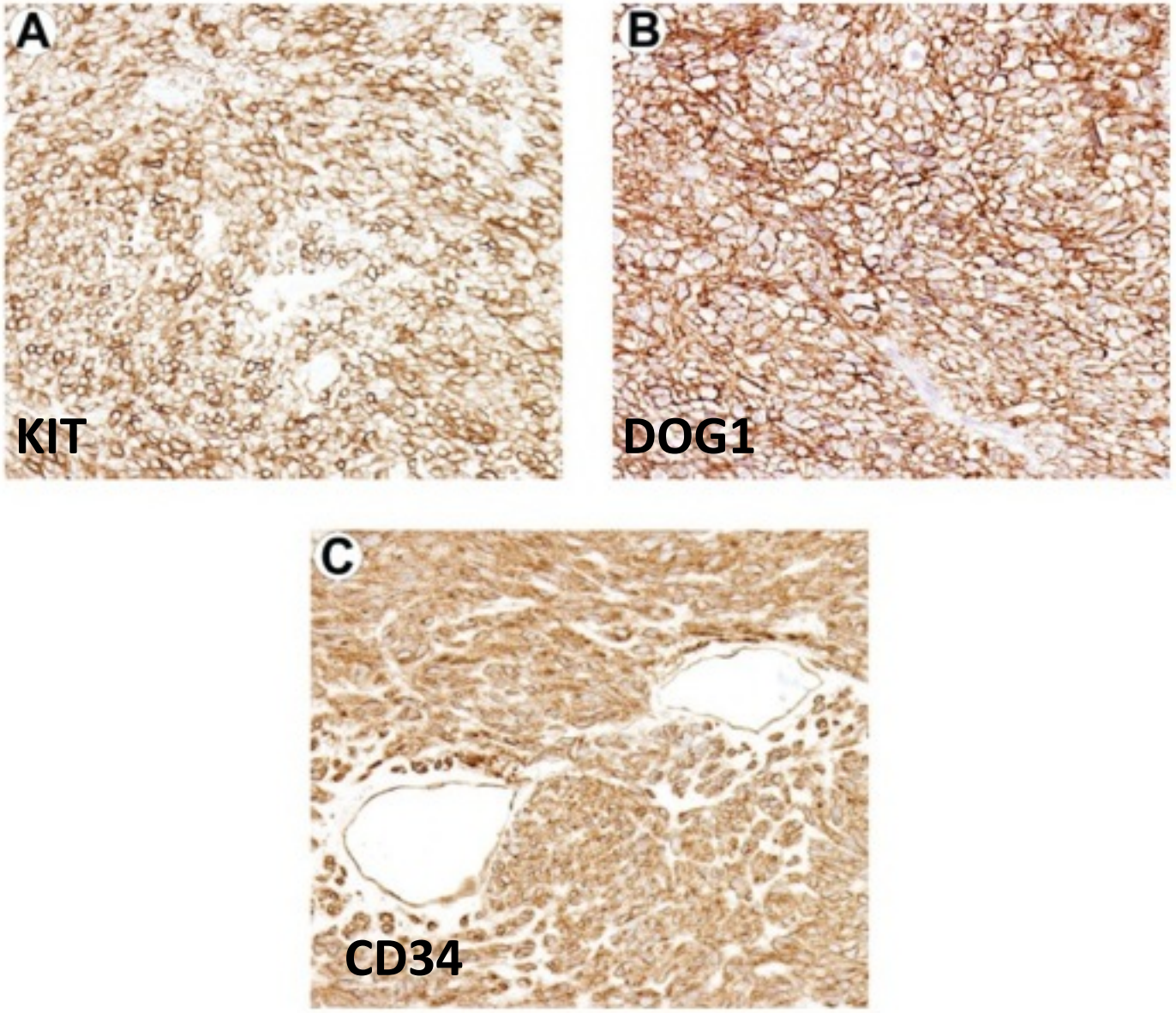
SMA +ve (30-40%)

Desmin –ve

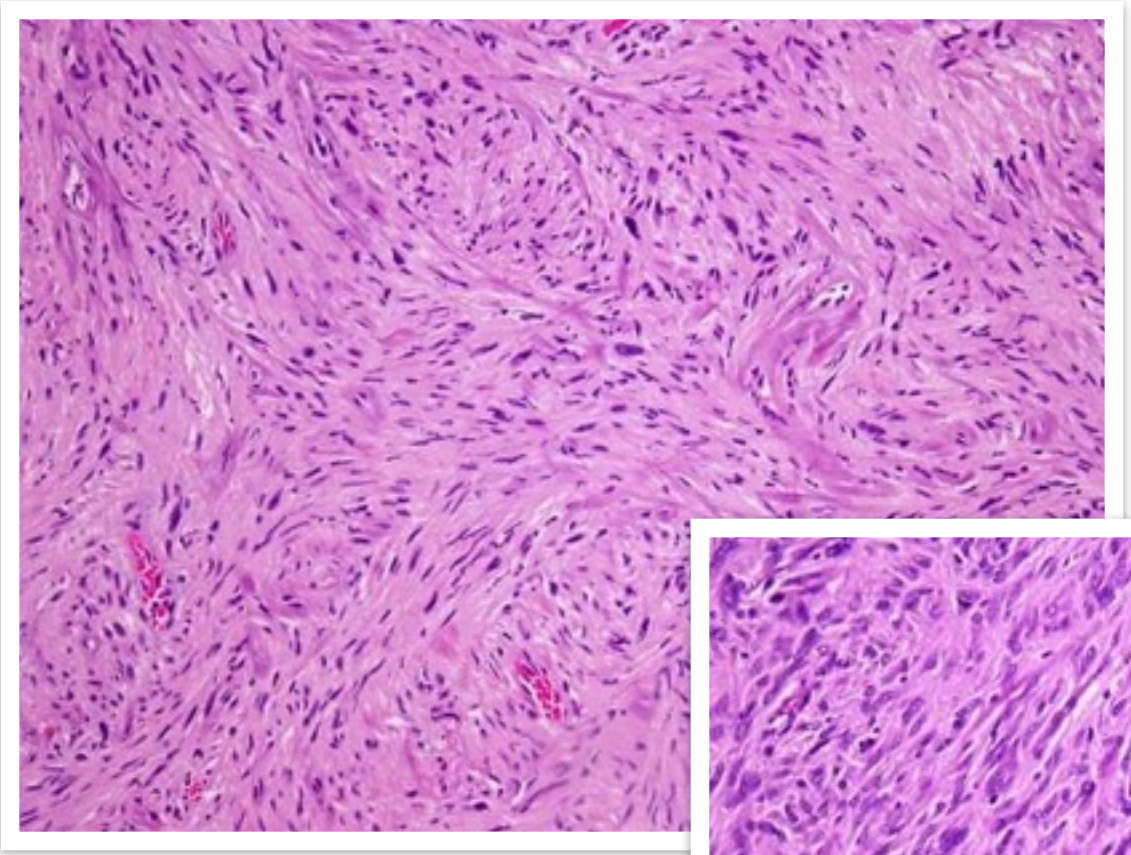
S-100 protein –ve

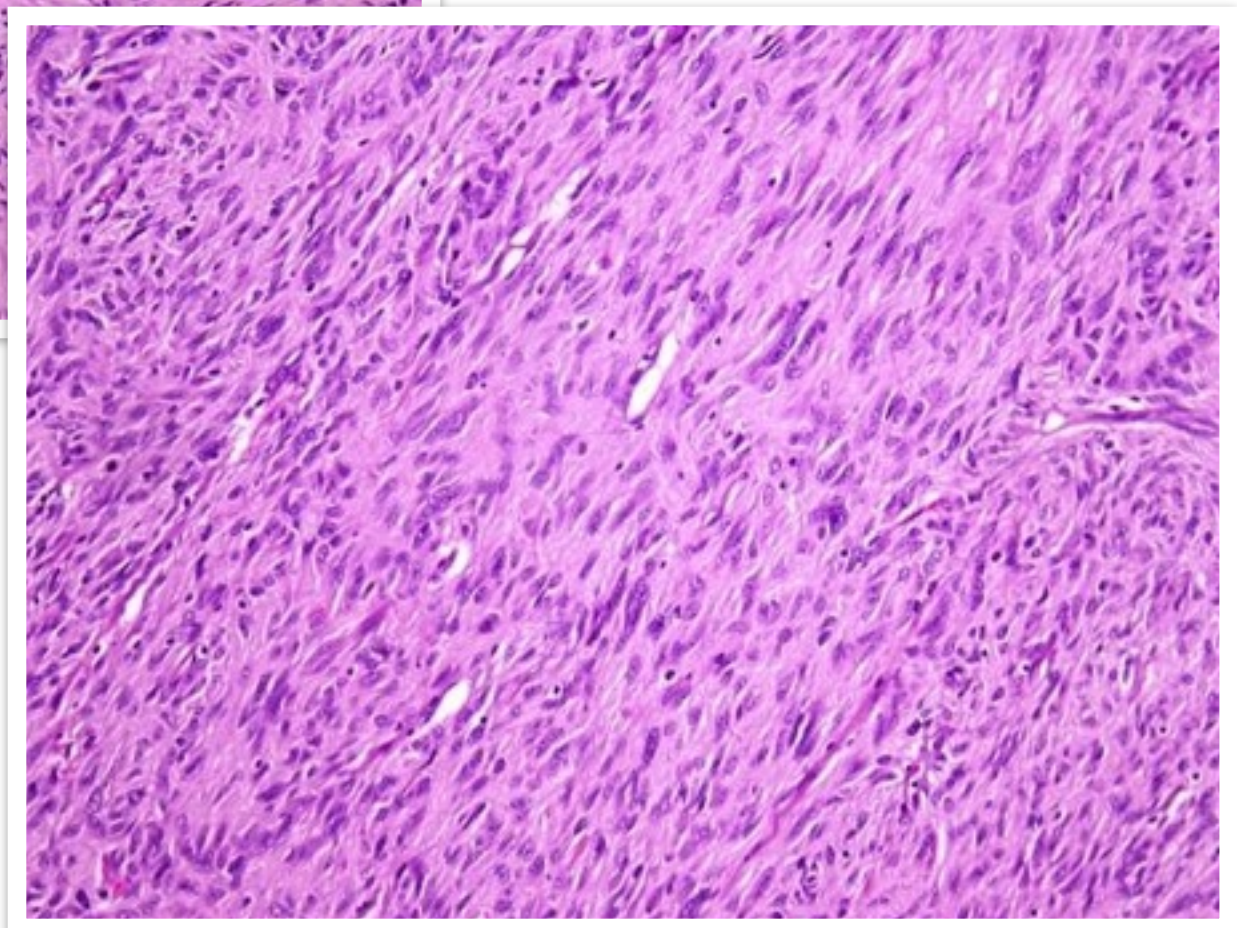
Keratin –ve

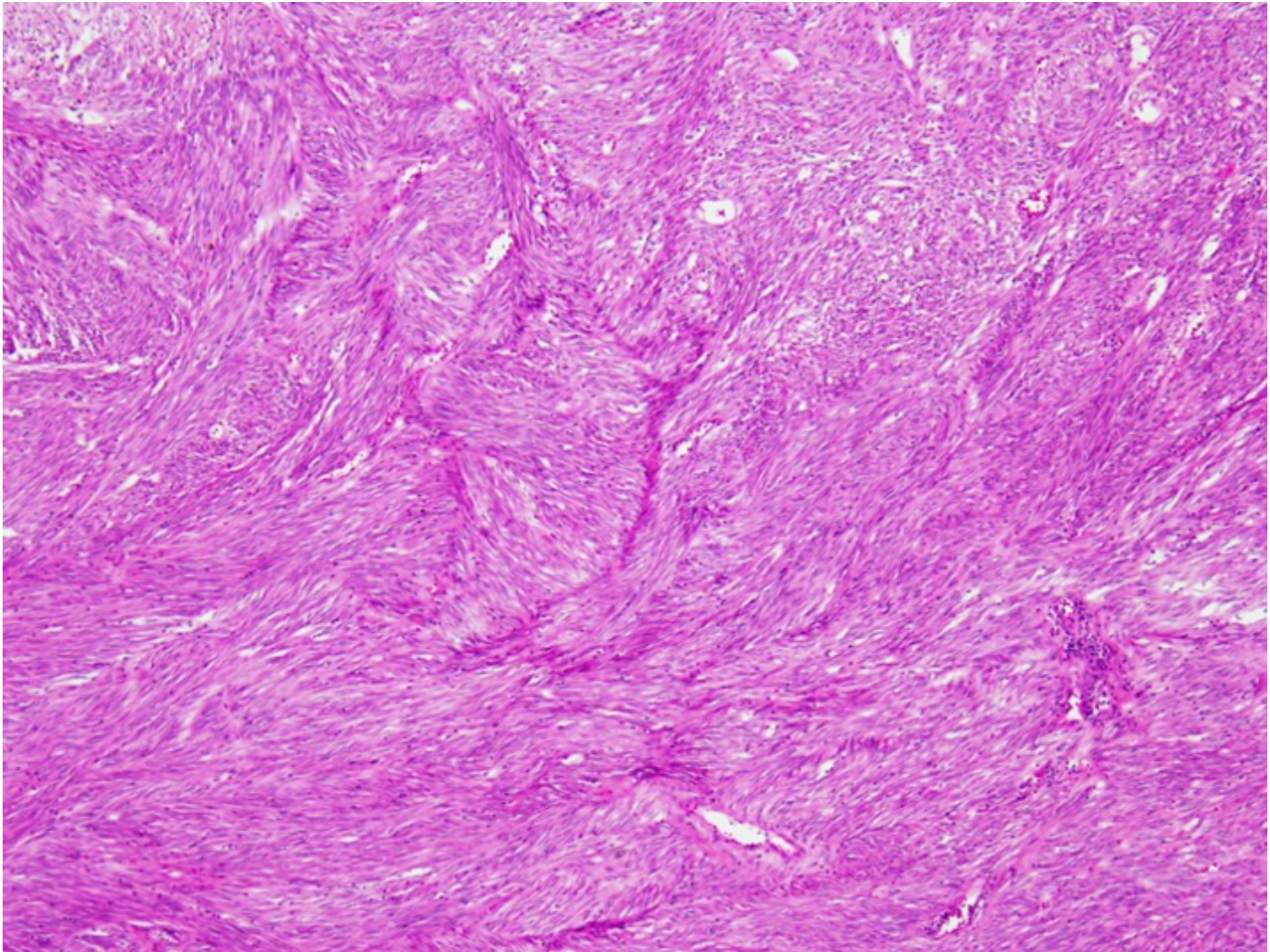
Liegl B et al. Hematol Oncol Clin North Am 2009; 23:49-68

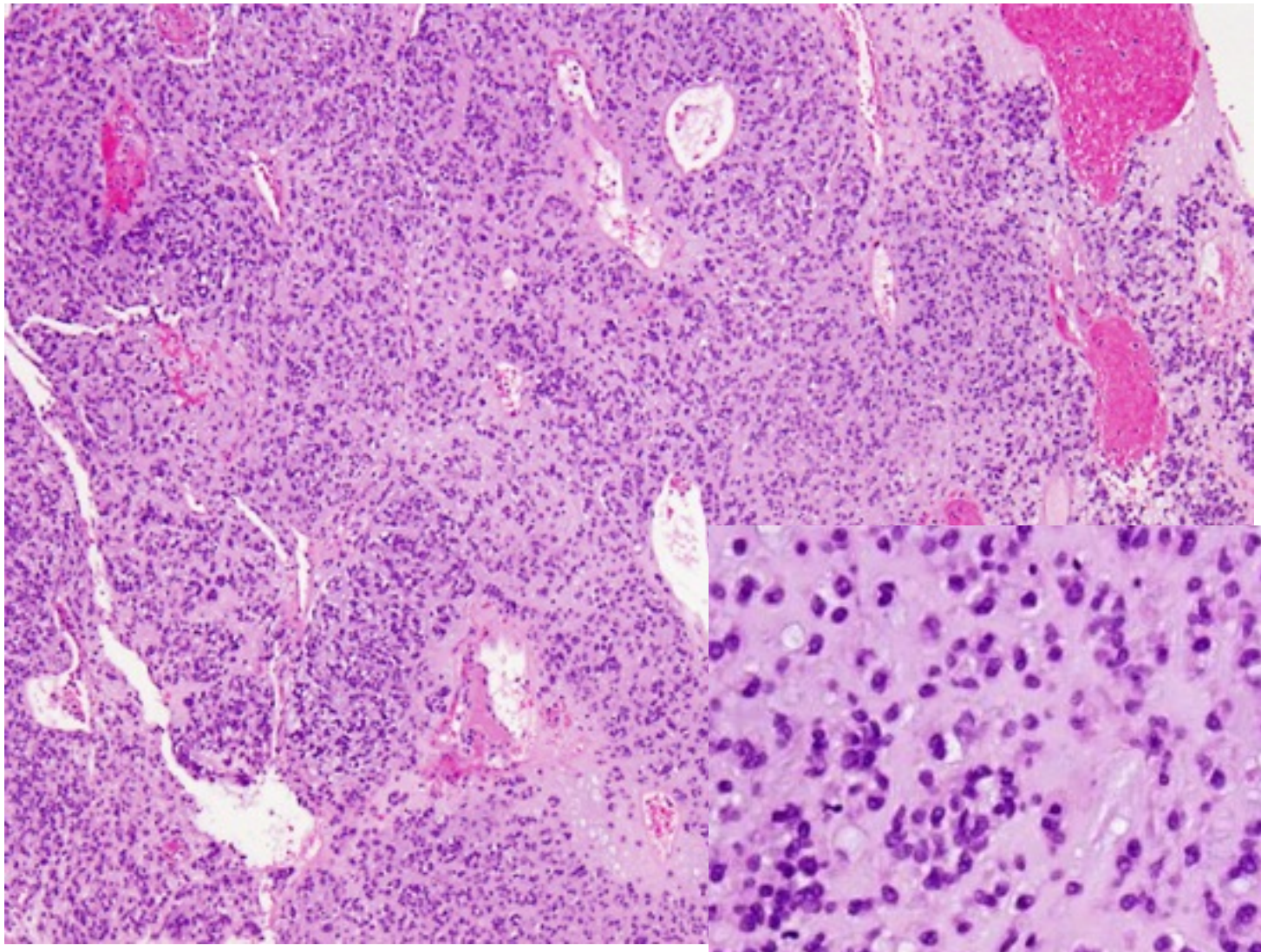

A
KIT
B
DOG1
C
CD34

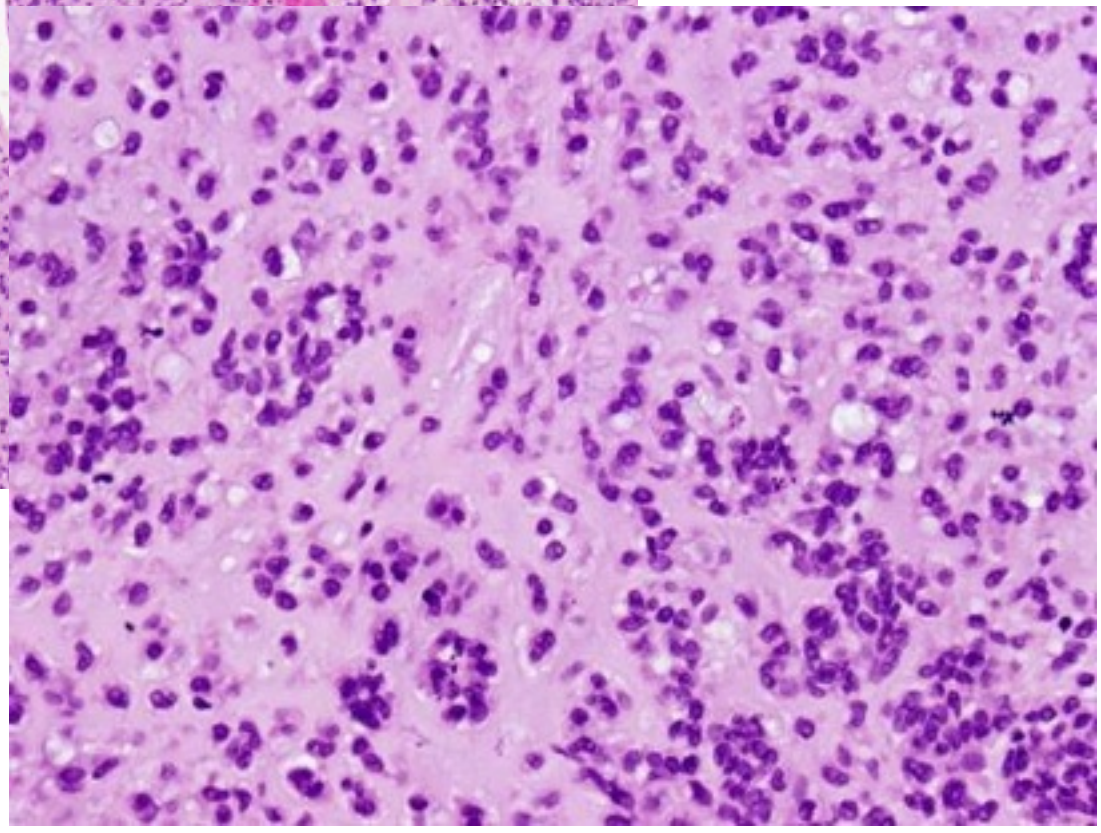
The many faces of GIST.

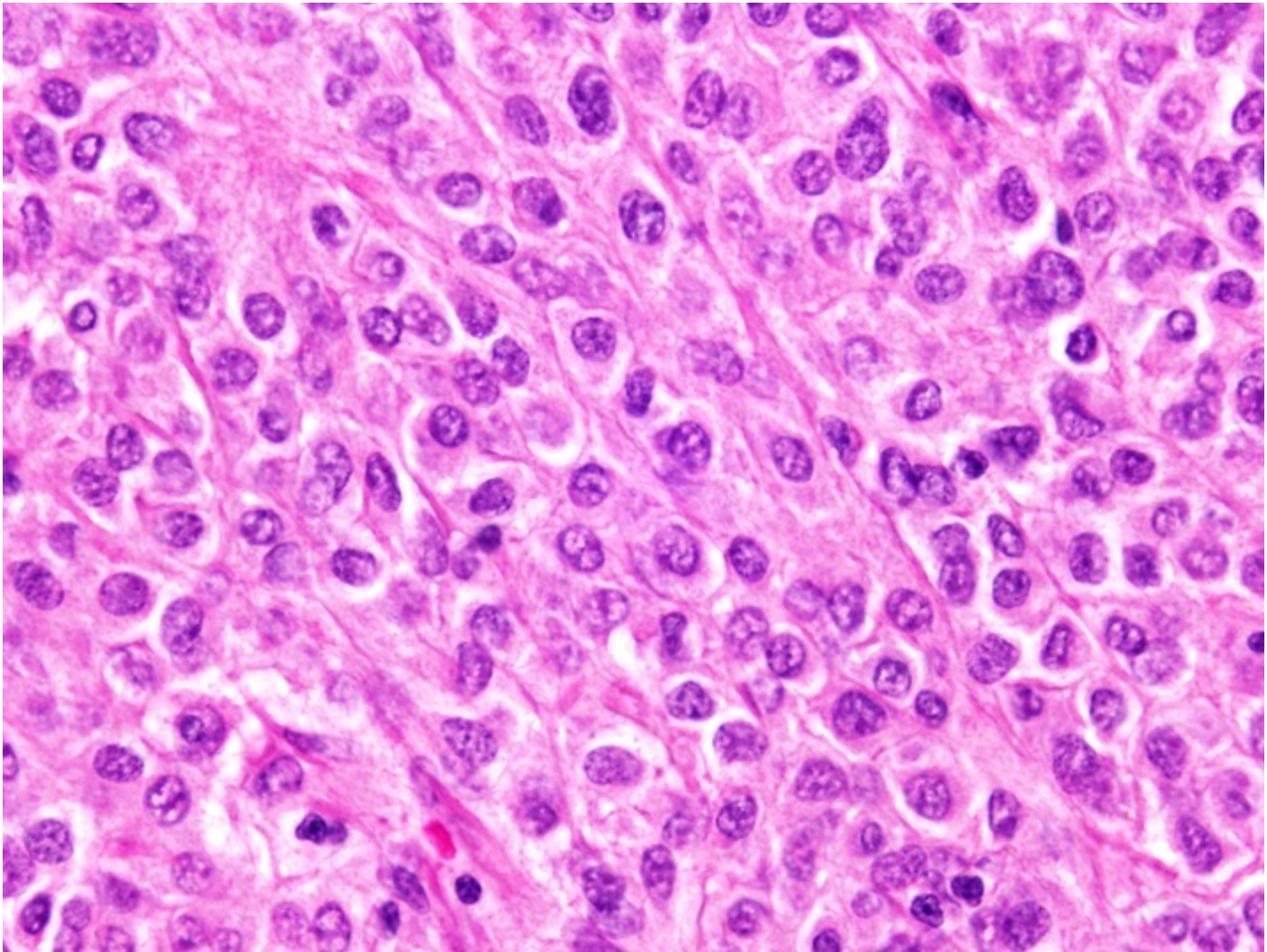


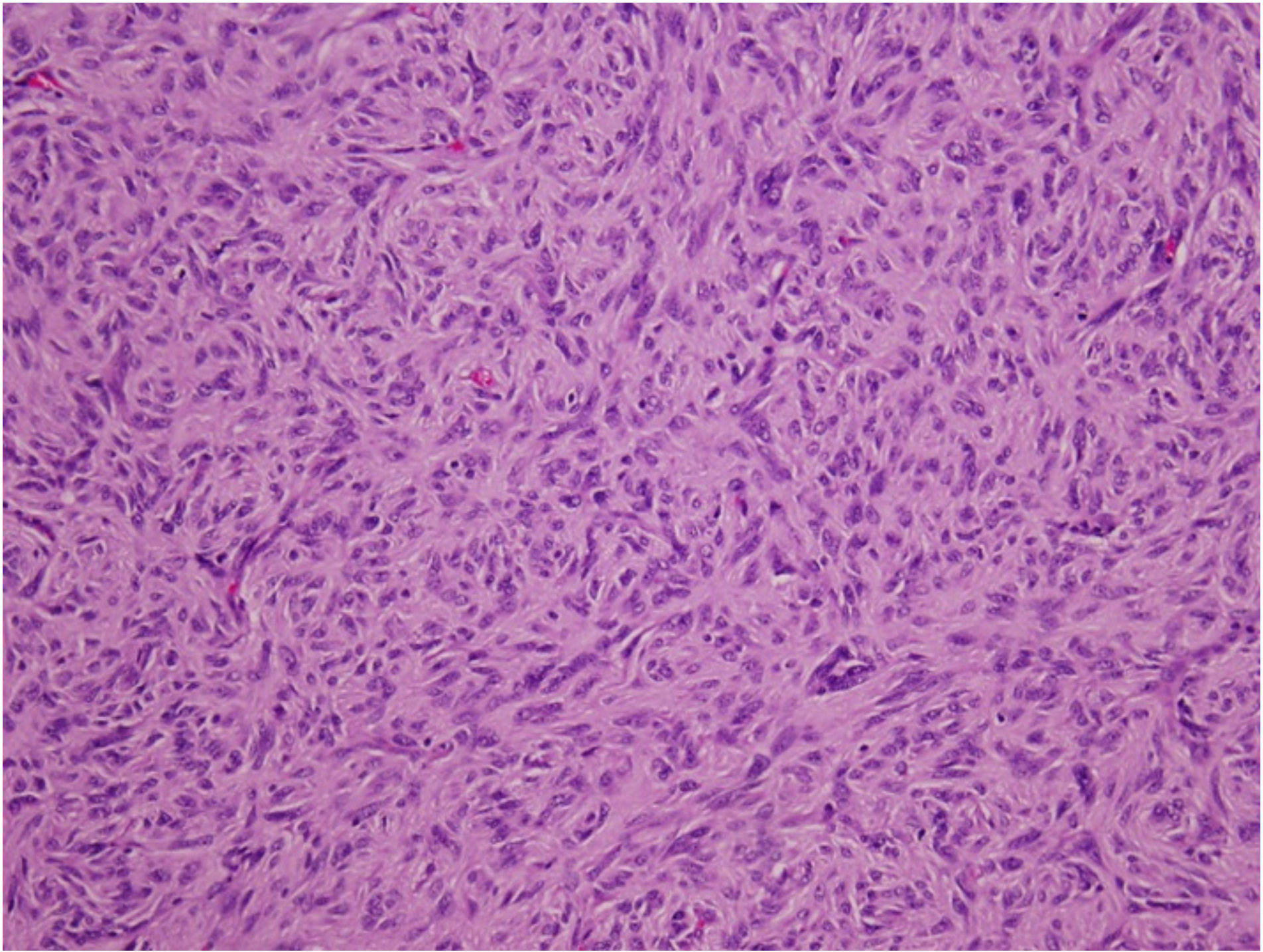


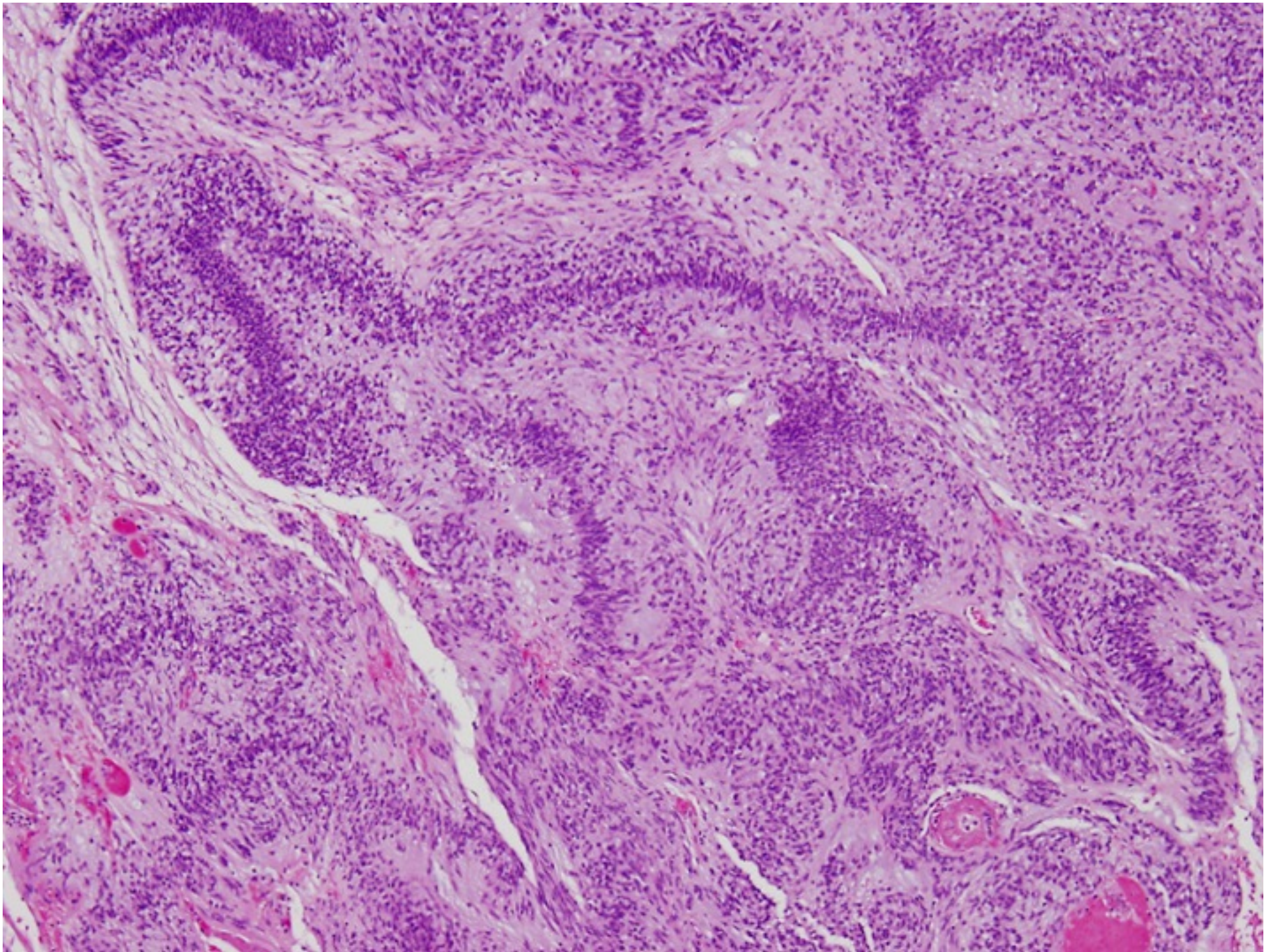


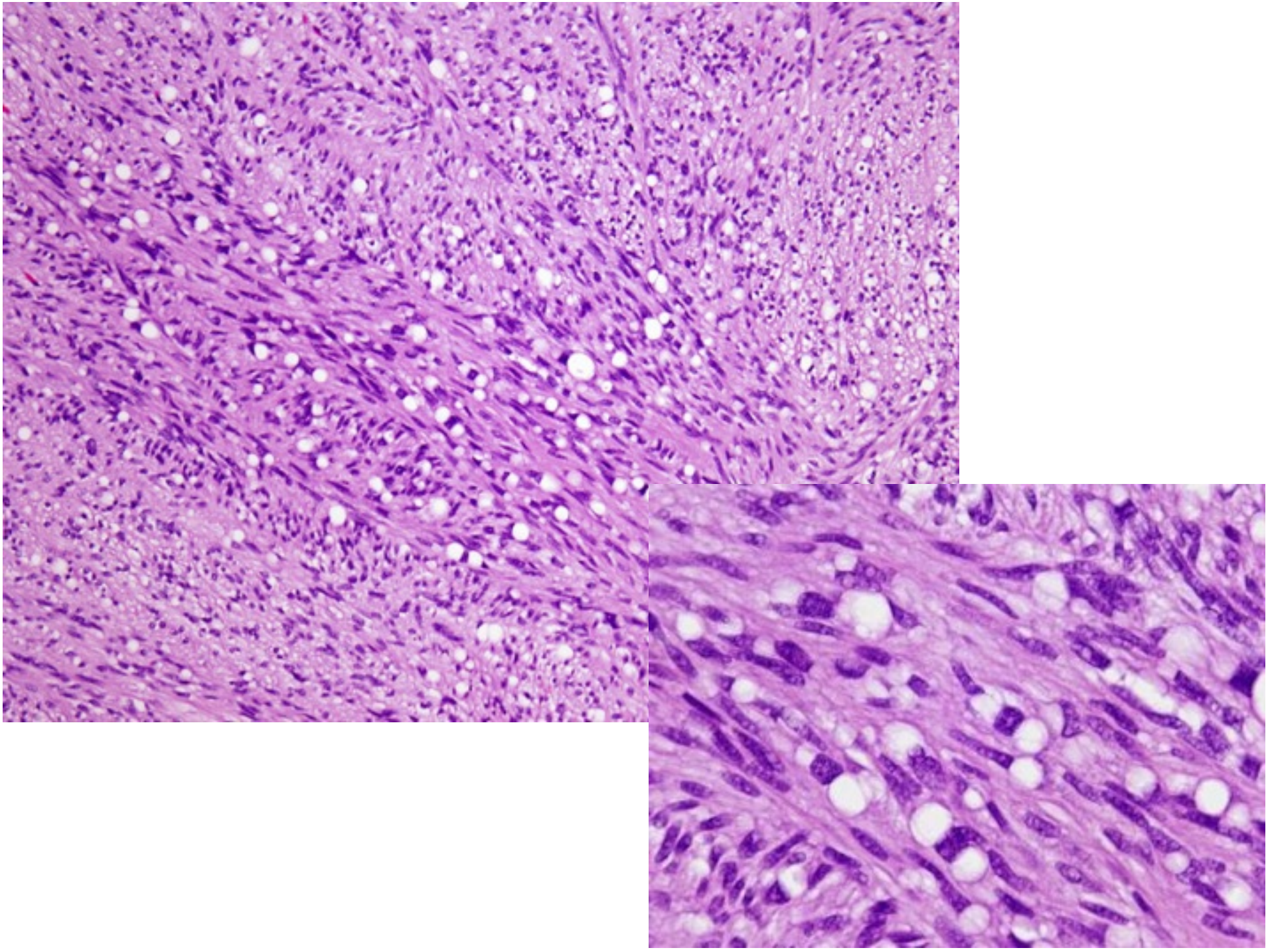


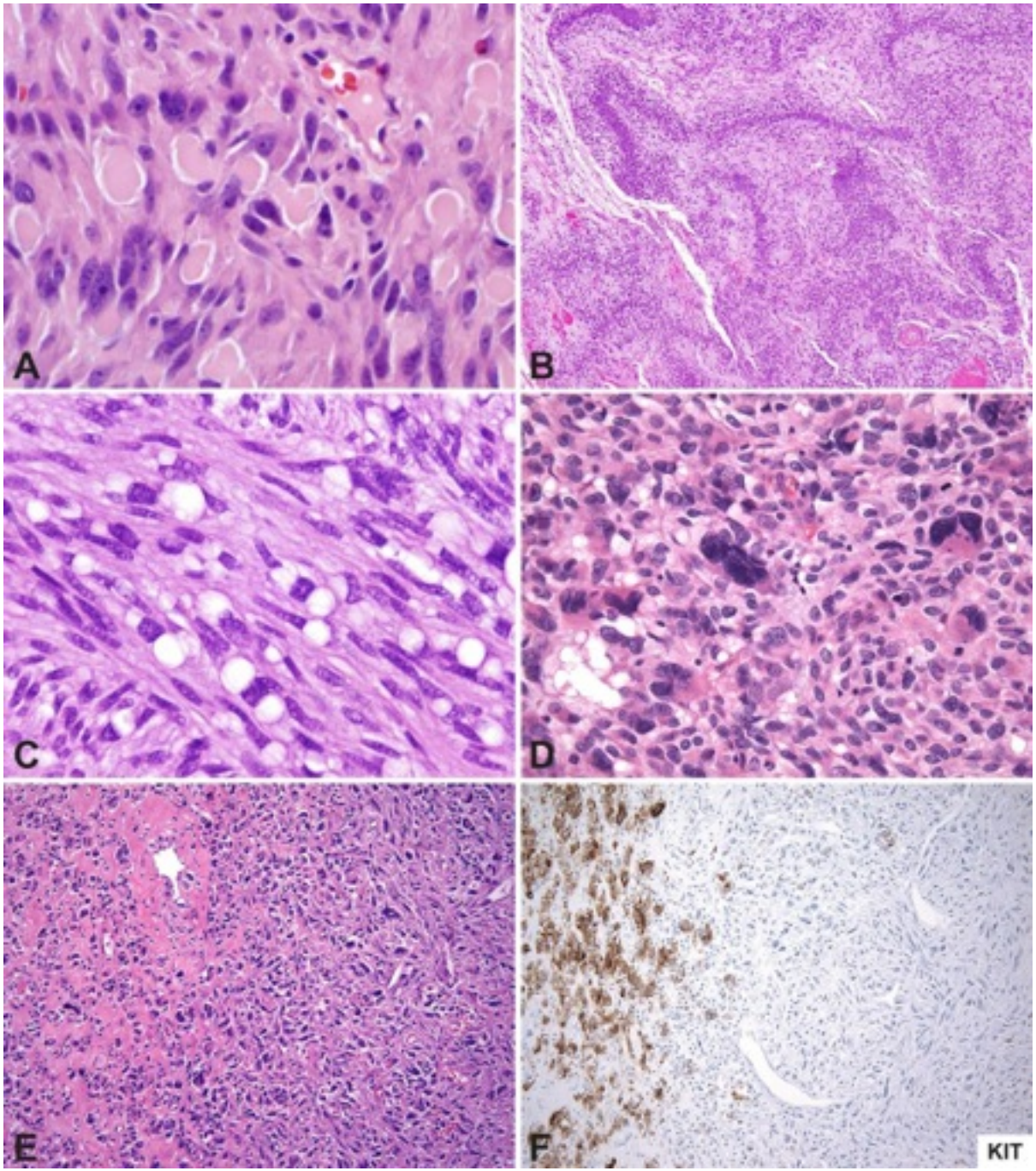


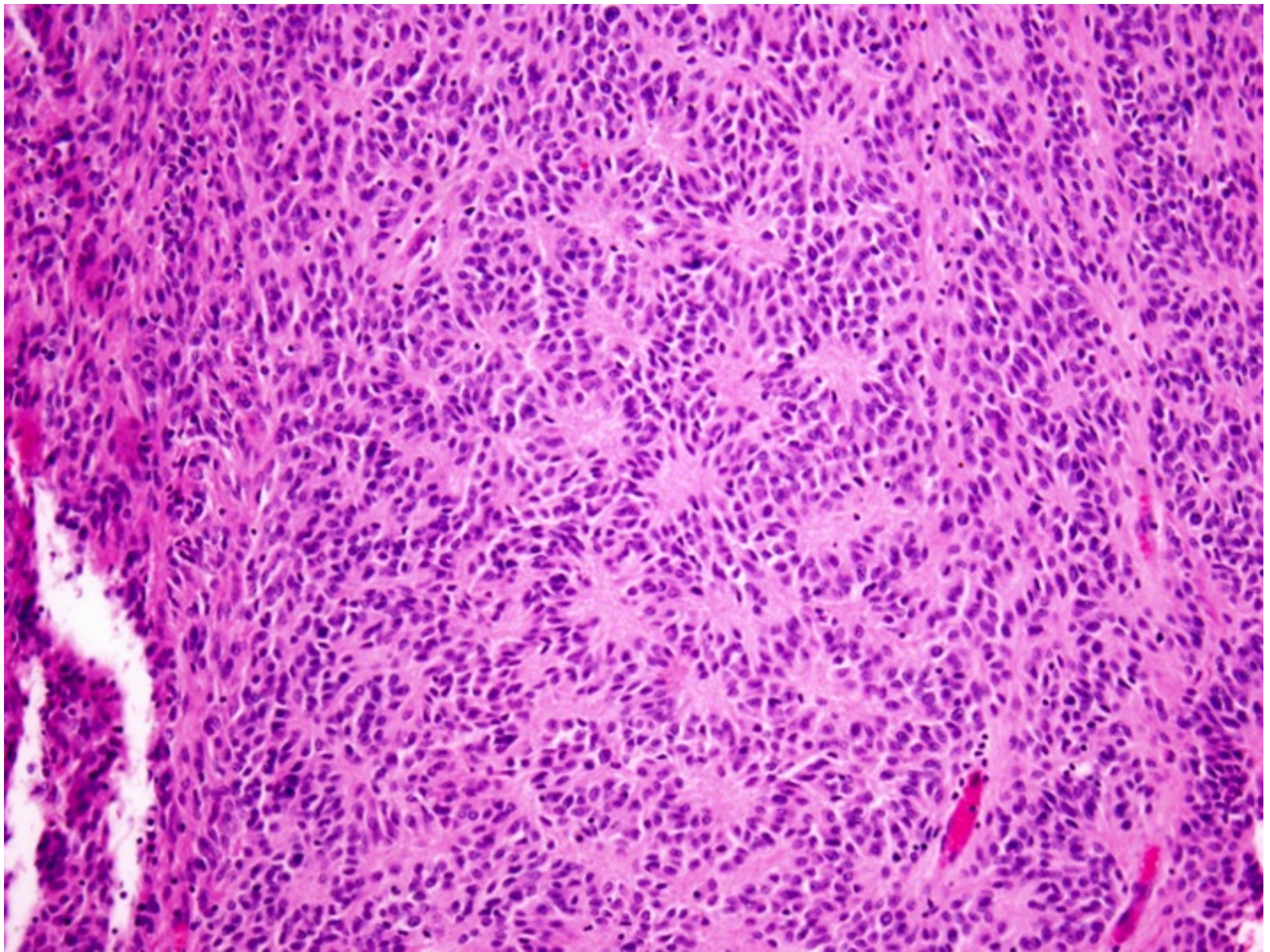









A
B
C
D
E
F
KIT



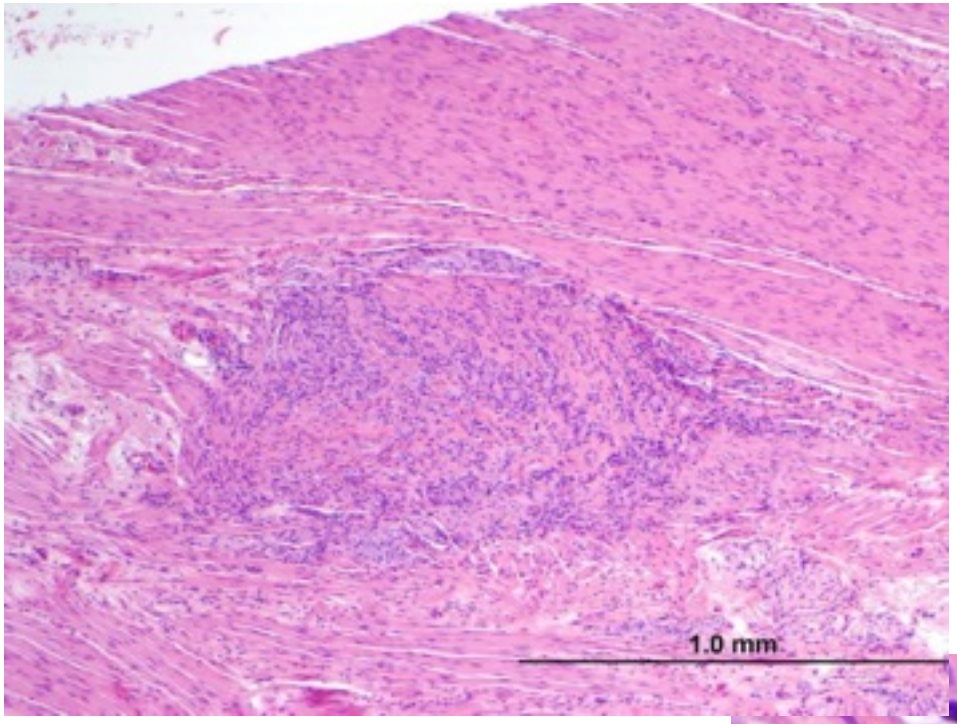
Clinical Characteristics of GIST

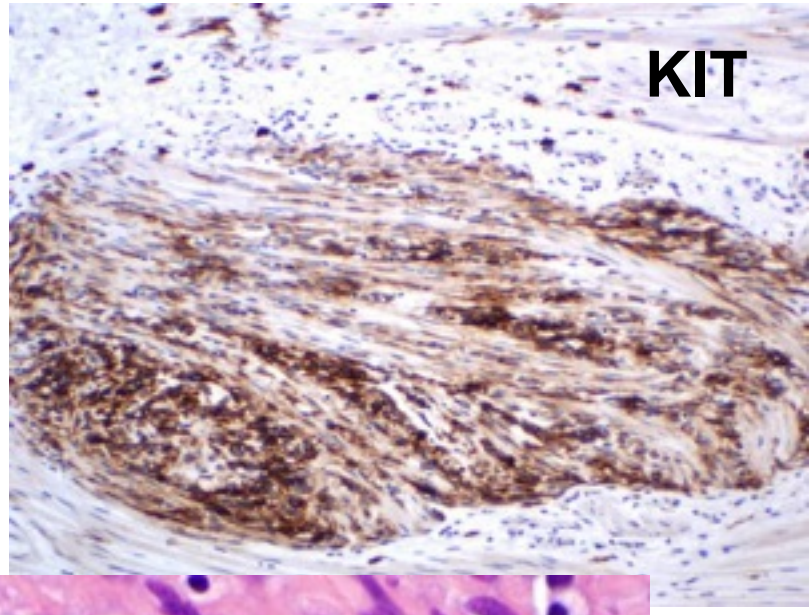
Wide age range – peak in 5^{th}-7^{th} decade

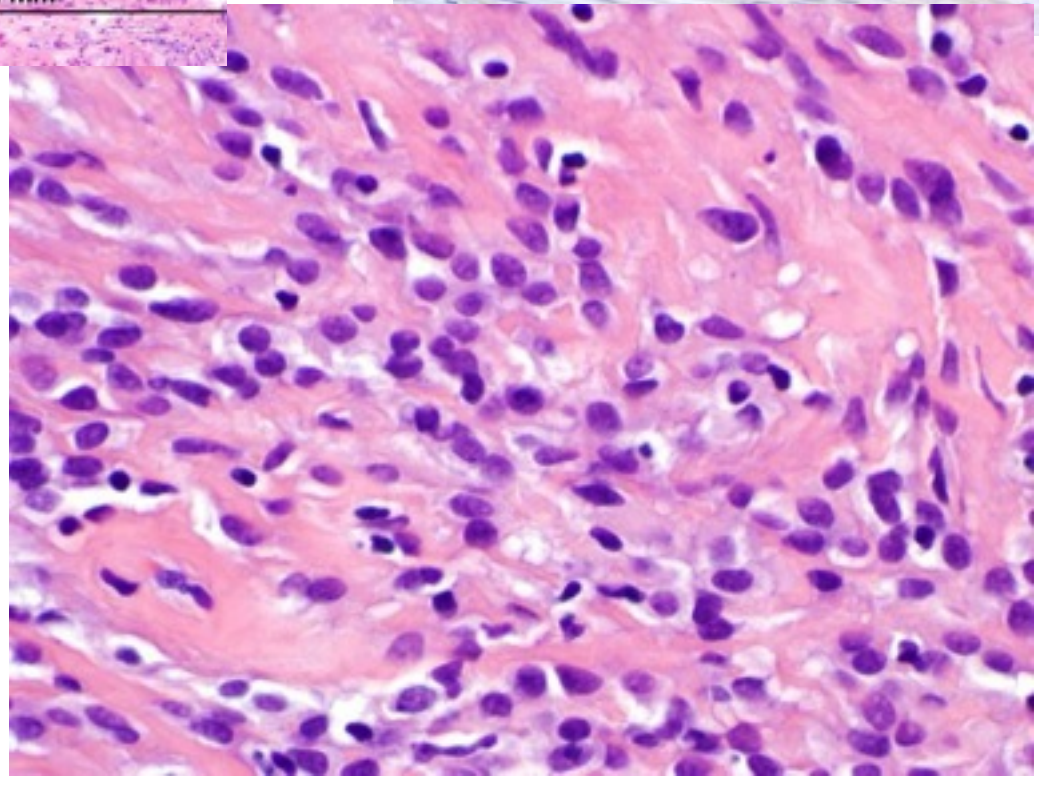
M = F

Small lesions = "incidentalomas"

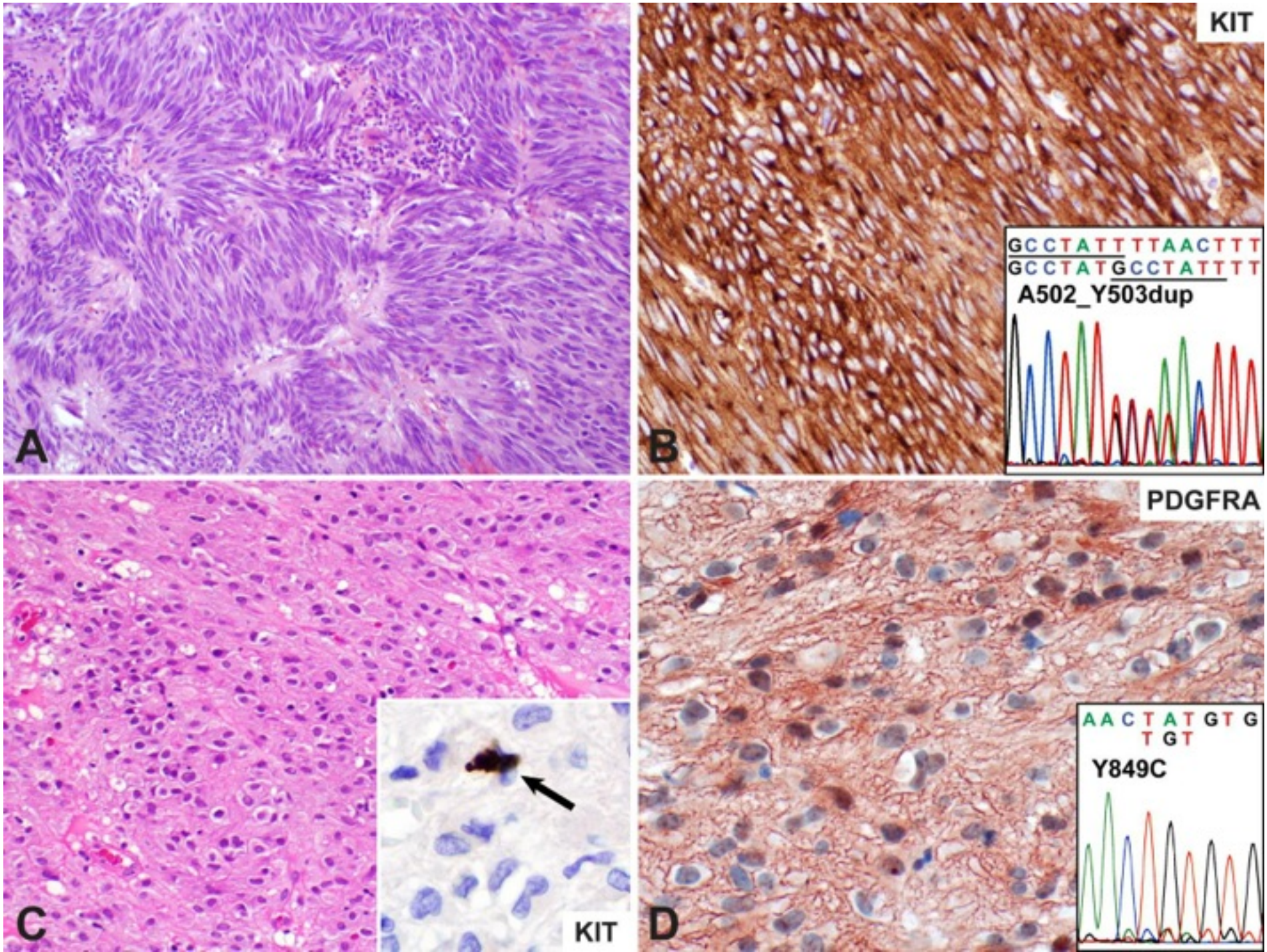
Presenting symptoms include:
abdominal pain,
gastrointestinal bleeding,
early satiety,
symptoms referable to a mass

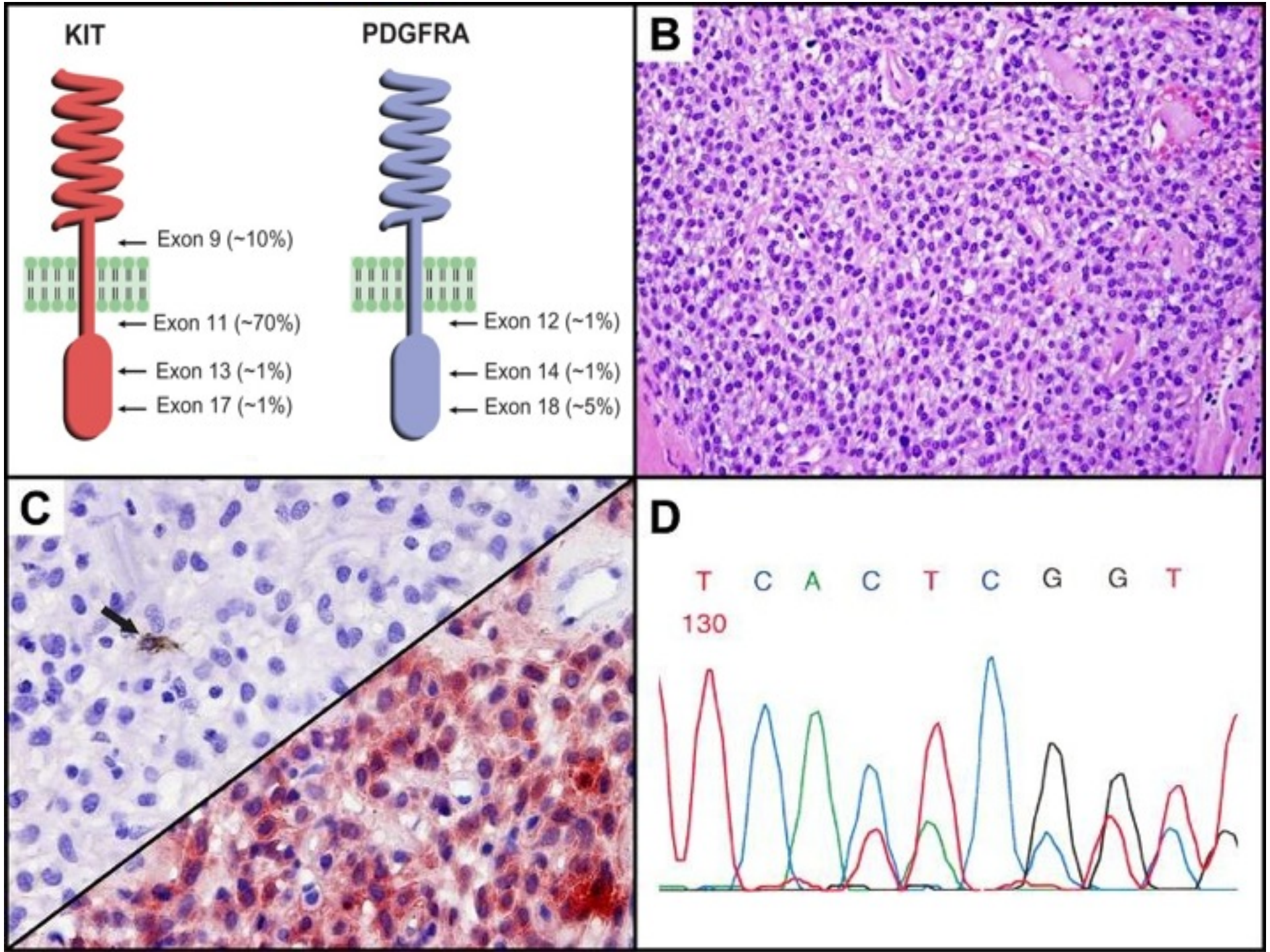






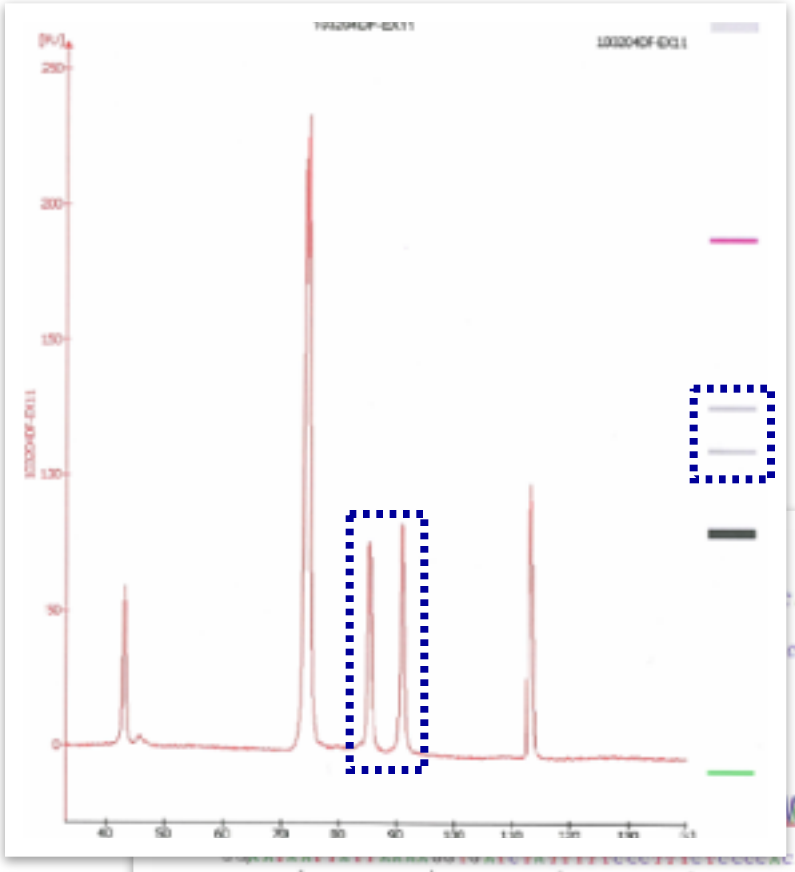
courtesy of Susan Abraham, UTMDACC, Houston, TX

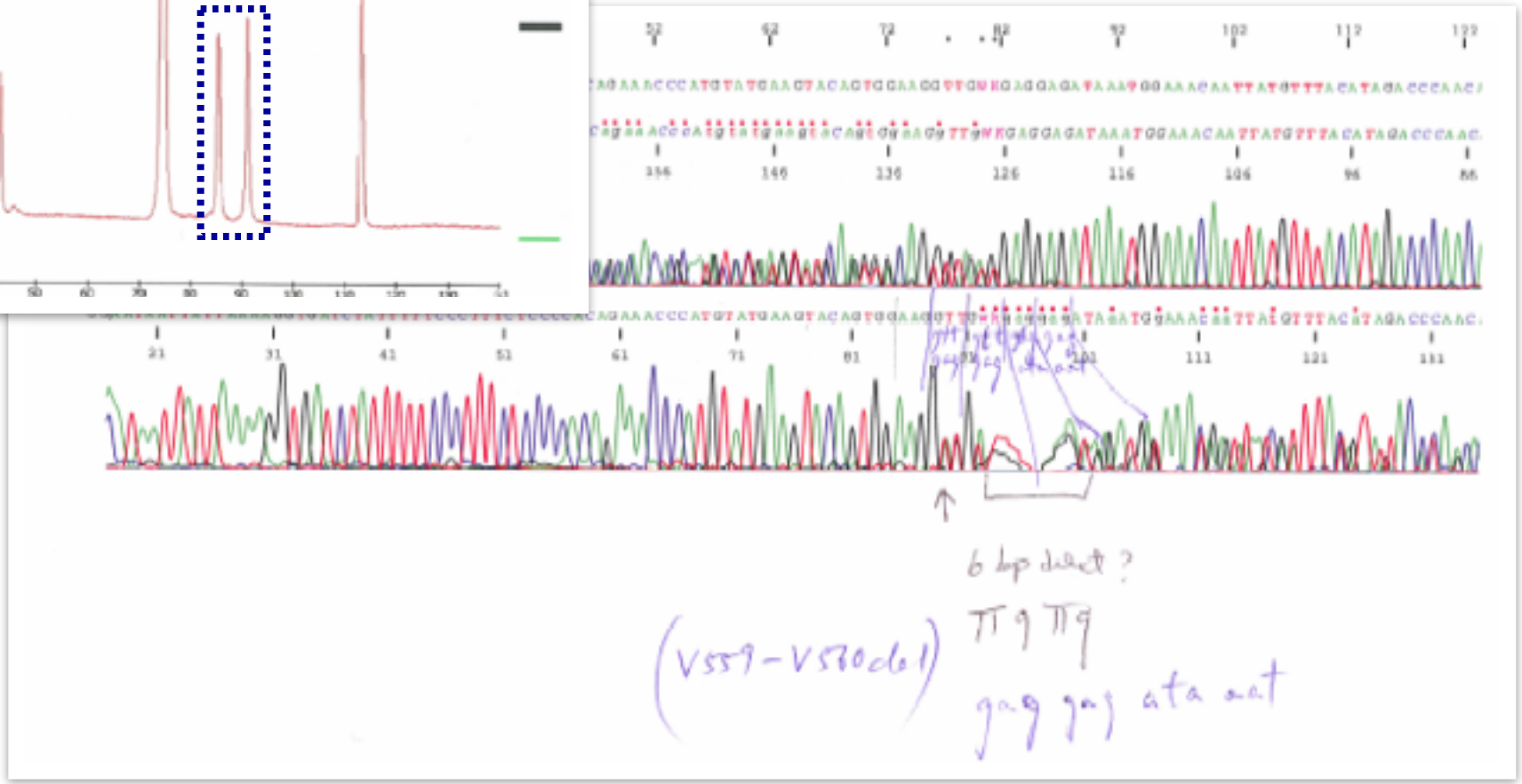

A
B
KIT
GCCTATTTTAACTTT
GCCTATGCCTATTTTT
A502_Y503dup
C
KIT
D
PDGFRA
AACTATGTG
TGT
Y849C


KIT
PDGFRA
Exon 9 (~10%)
Exon 11 (~70%)
Exon 13 (~1%)
Exon 17 (~1%)
Exon 12 (~1%)
Exon 14 (~1%)
Exon 18 (~5%)
B
C
D
T C A C T C G G T
130

Exon 11

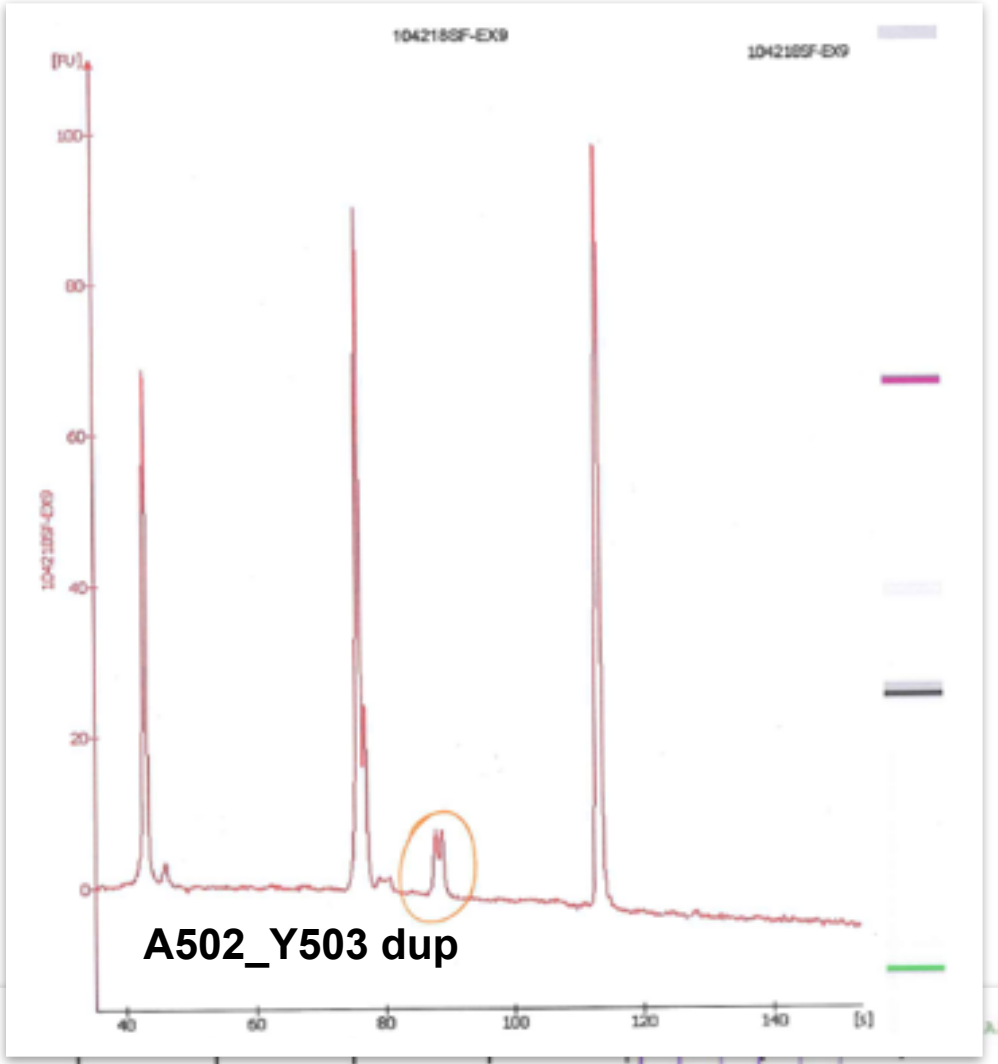
V559_V560del

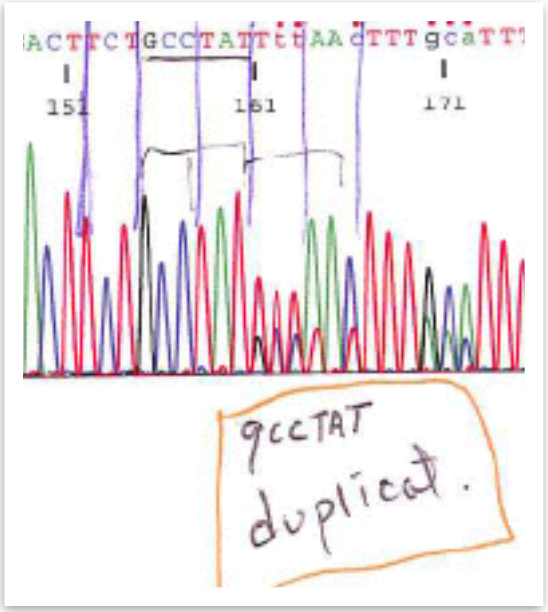


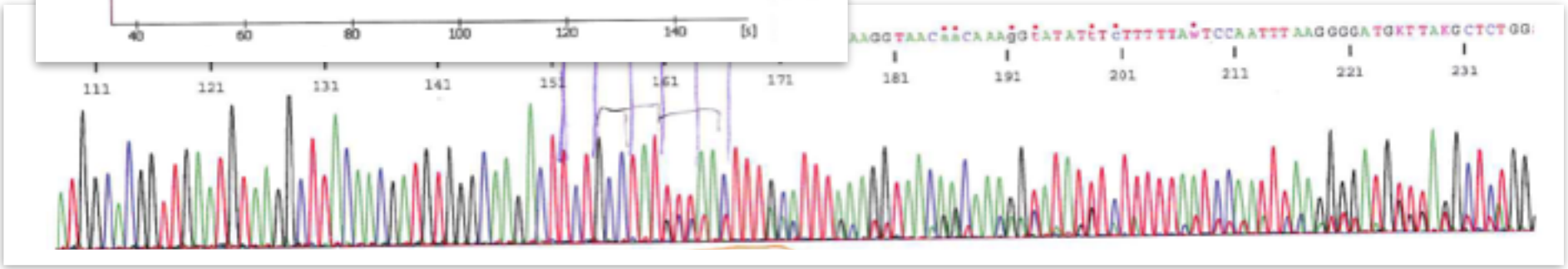


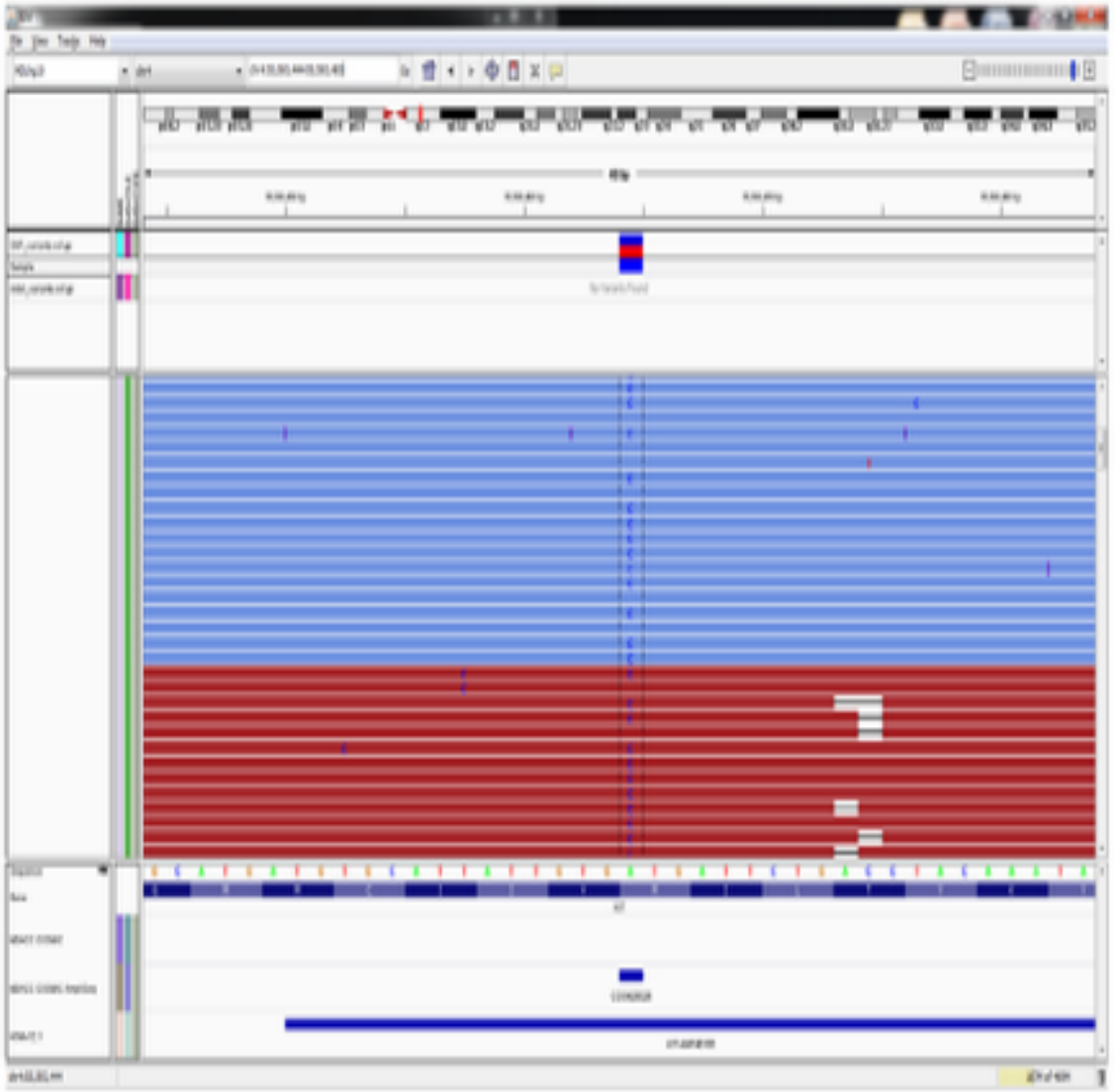
Exon 9

A502_Y503dup

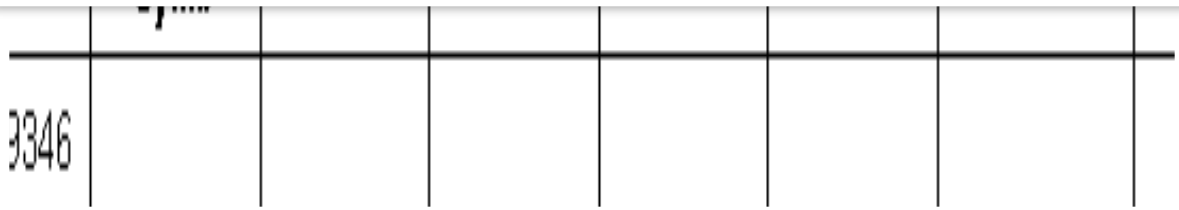




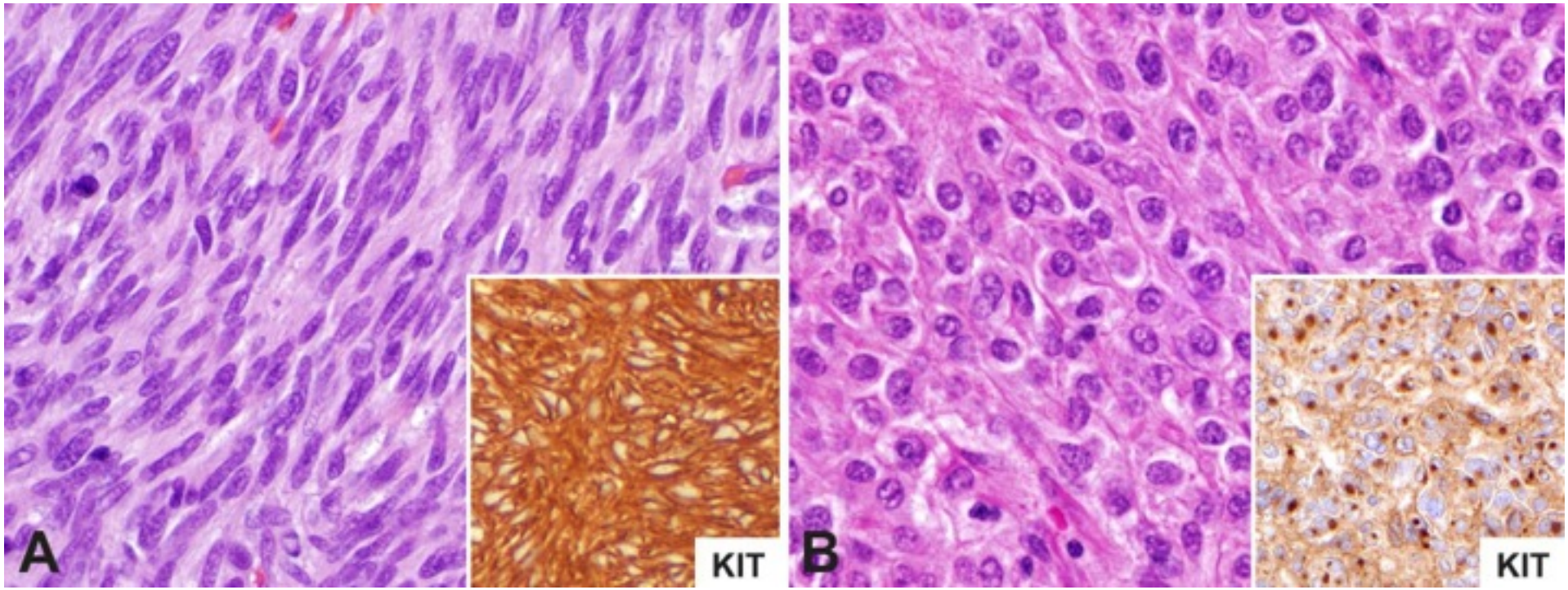




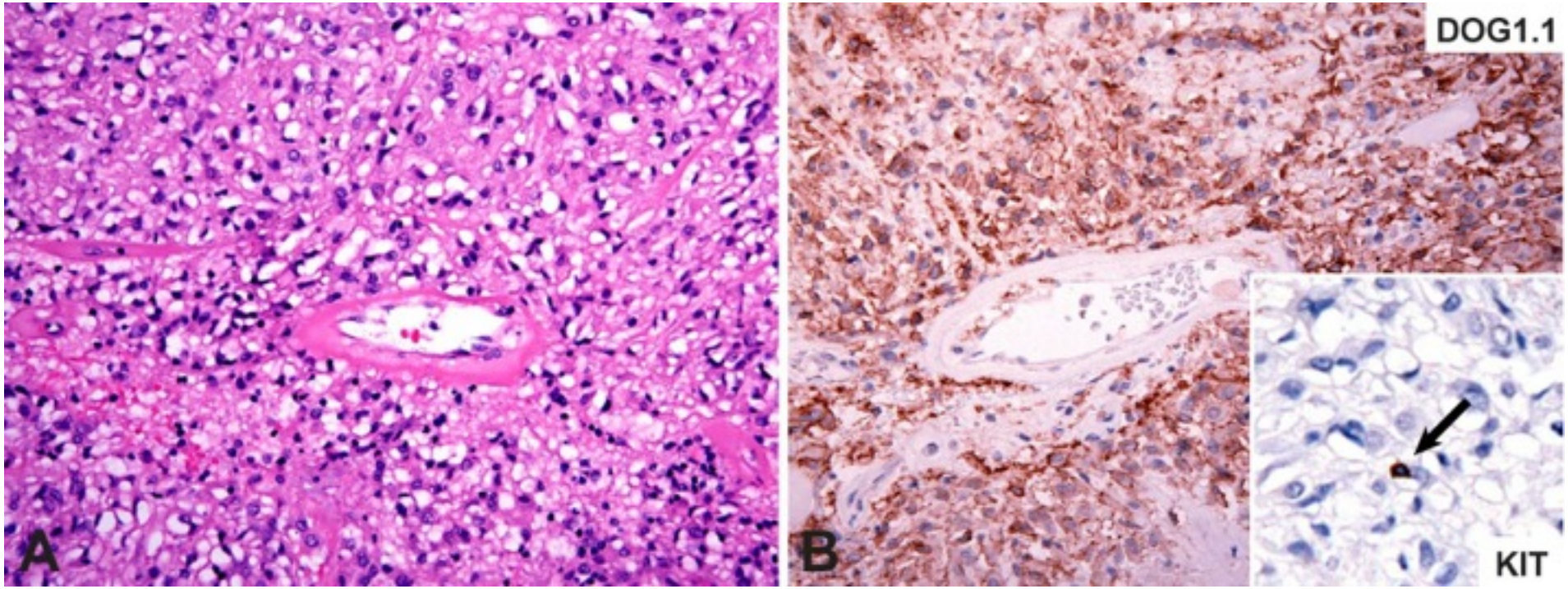
Detection of SNV in KIT Exon 10,



KIT immunoreactivity in GIST



KIT-negative GIST



Gastric GISTs with Distinctive Histology (Multinodular/Plexiform)

- **Pediatric GISTs**
  - **Female predominance (peak 2nd decade)**
  - **Indolent, but late metastases common**
  - **Molecular genetic basis unknown**

Carney Triad

- **Gastric GIST, pulmonary chondroma, paraganglioma**
- **Molecular genetic basis unknown**

Carney-Stratakis Syndrome

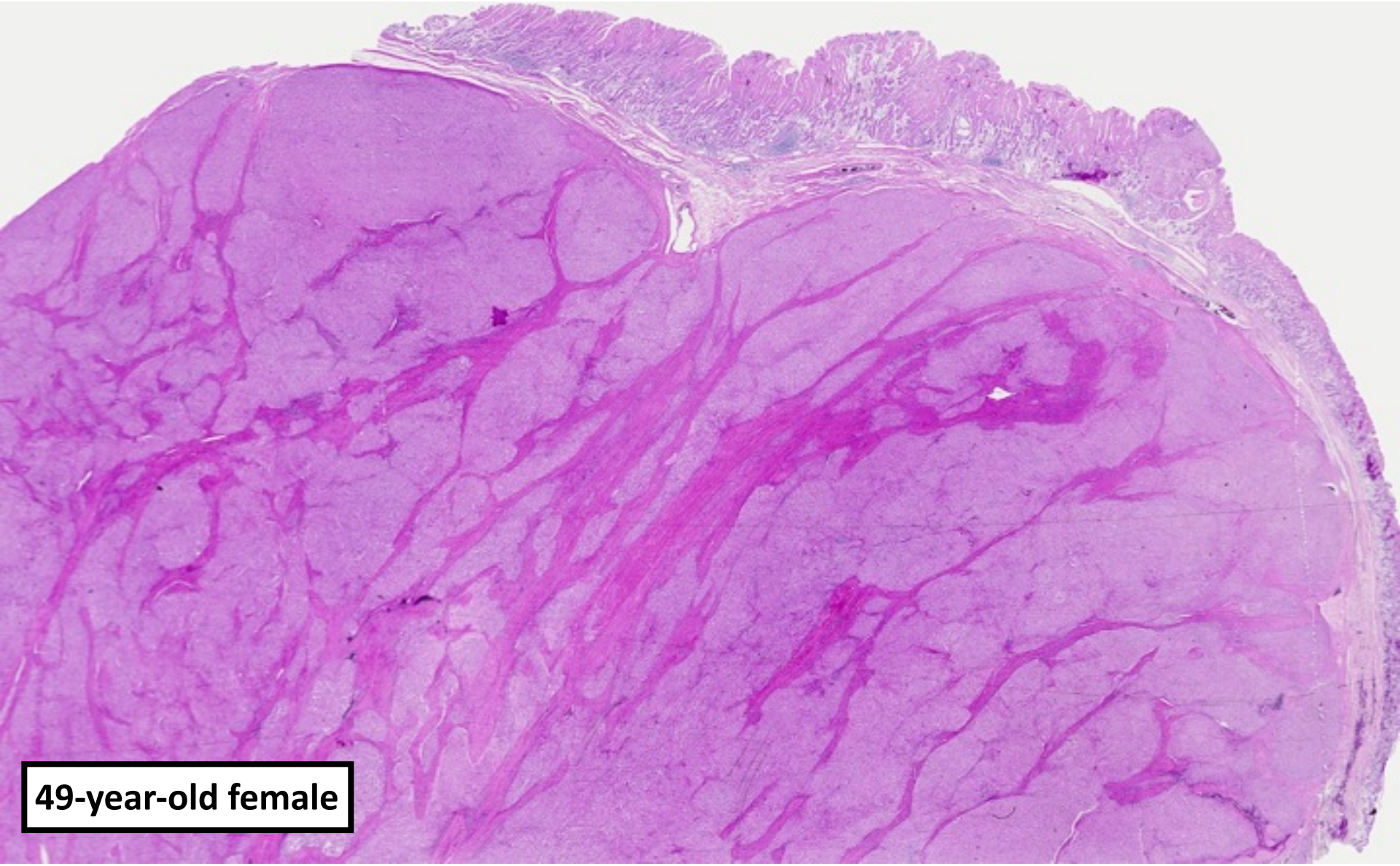
- **Gastric GIST and paraganglioma**
- **Germline mutations in succinate dehydrogenase subunit genes (*SDHA*, *SDHB*, *SDHC*, or *SDHD*)**

GIST with Distinctive Histology

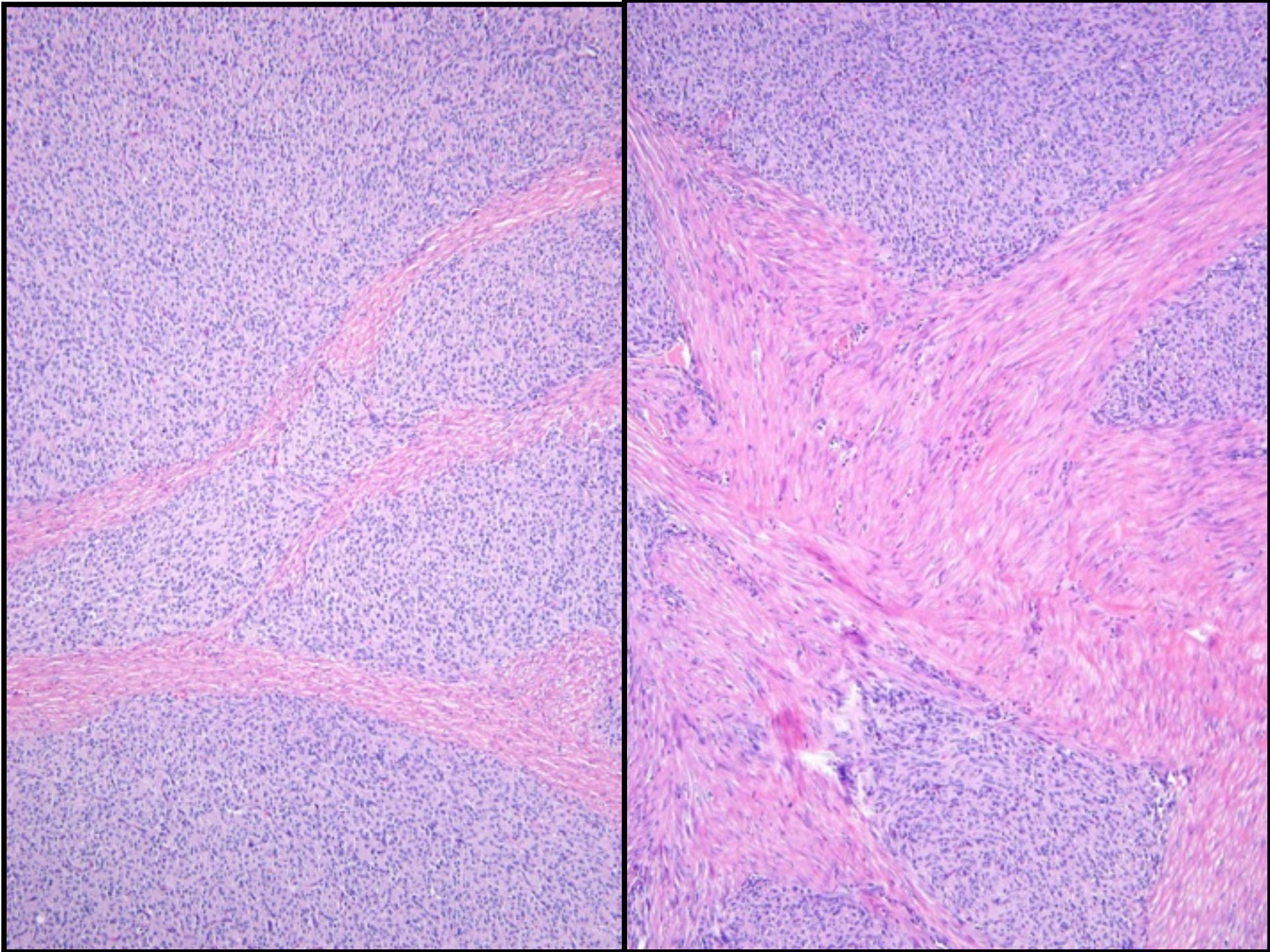
- **Multinodular/plexiform growth pattern**
- **Epithelioid or mixed morphology**
- **“Pediatric-type” or “type 2” GISTs**
- **Loss of SDHB staining by IHC**
- **Lymph node metastases common**
- **Distant metastases common – clinically indolent**
- **Current risk assessment criteria do not reliably predict behavior**
- **No response to imatinib**

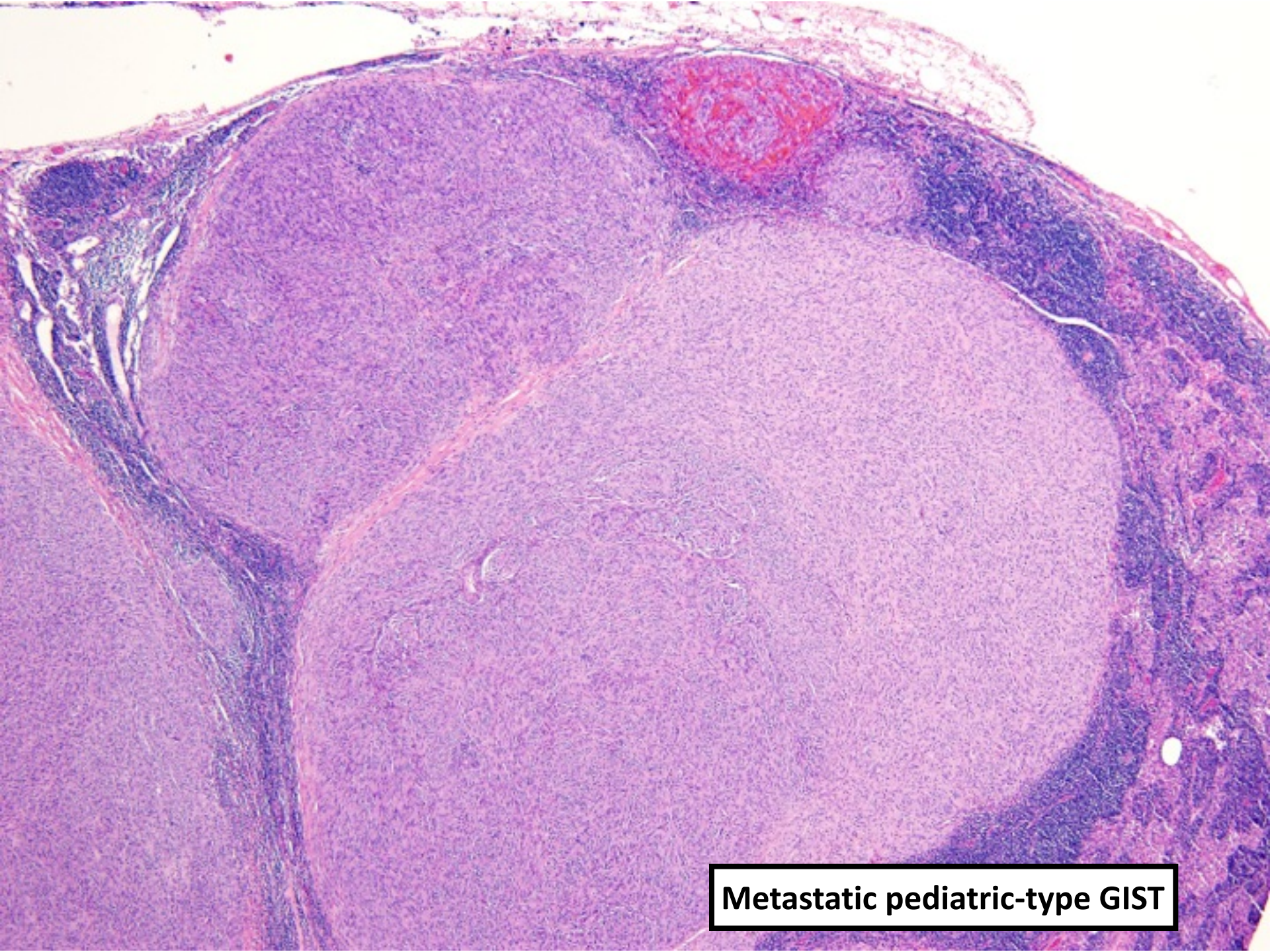
Courtesy of Jason Hornick, BWH/Harvard, Boston, MA

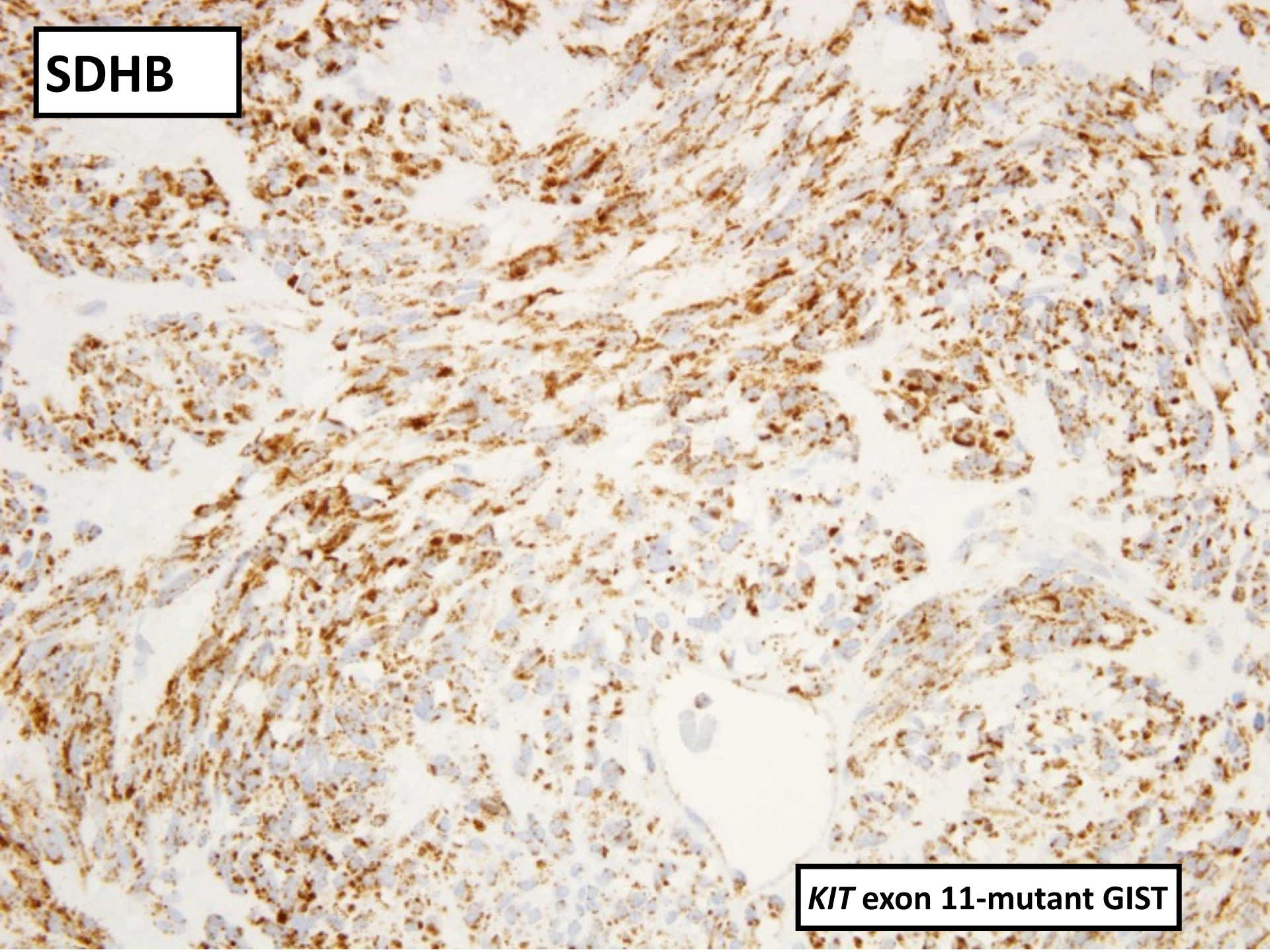
Pediatric-type GIST in an Adult

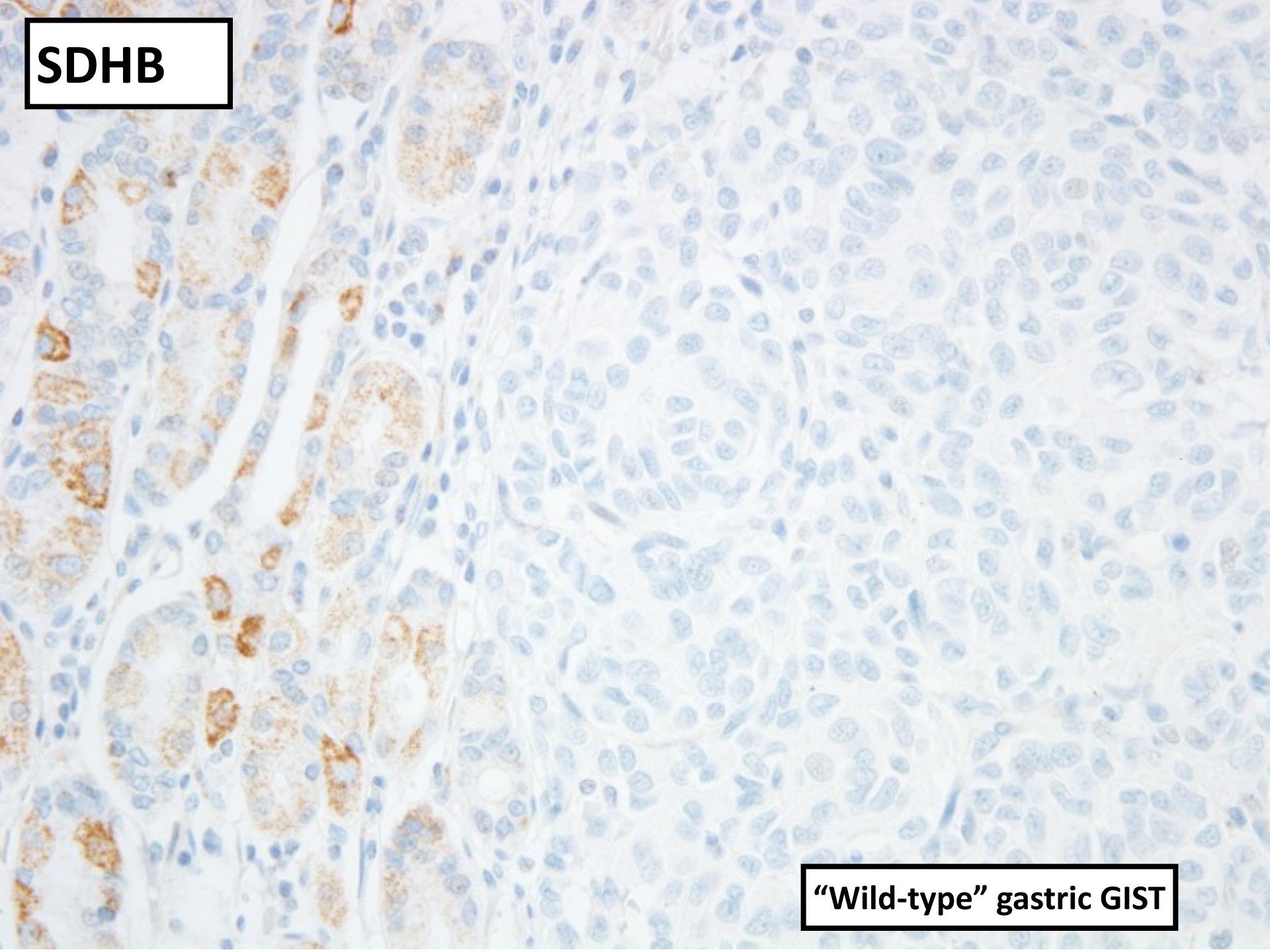


Courtesy of Jason Hornick, BWH/Harvard, Boston, MA




Metastatic pediatric-type GIST


SDHB
KIT exon 11-mutant GIST


SDHB
“Wild-type” gastric GIST

Risk assessment in GIST

GIST – Prognostic Factors

Size

Mitotic Rate

Anatomic Location

Pleomorphism

Cellularity

Necrosis

Mucosal Invasion

Proliferation Markers (Ki-67, Mib-1, PCNA, etc)

DNA Flow Cytometry

Image Analysis

Nuclear Organizer Regions

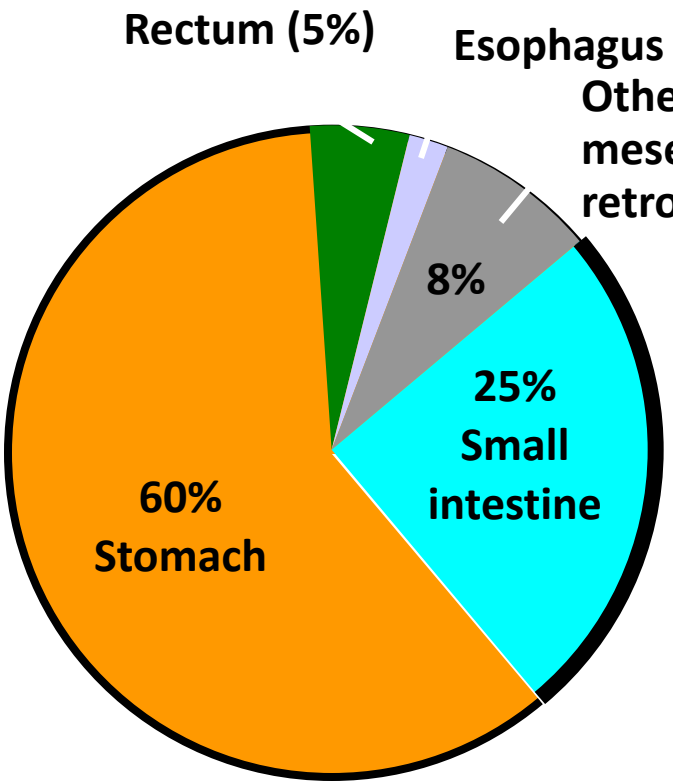
Problem – Small GISTs without mitoses can metastasize!

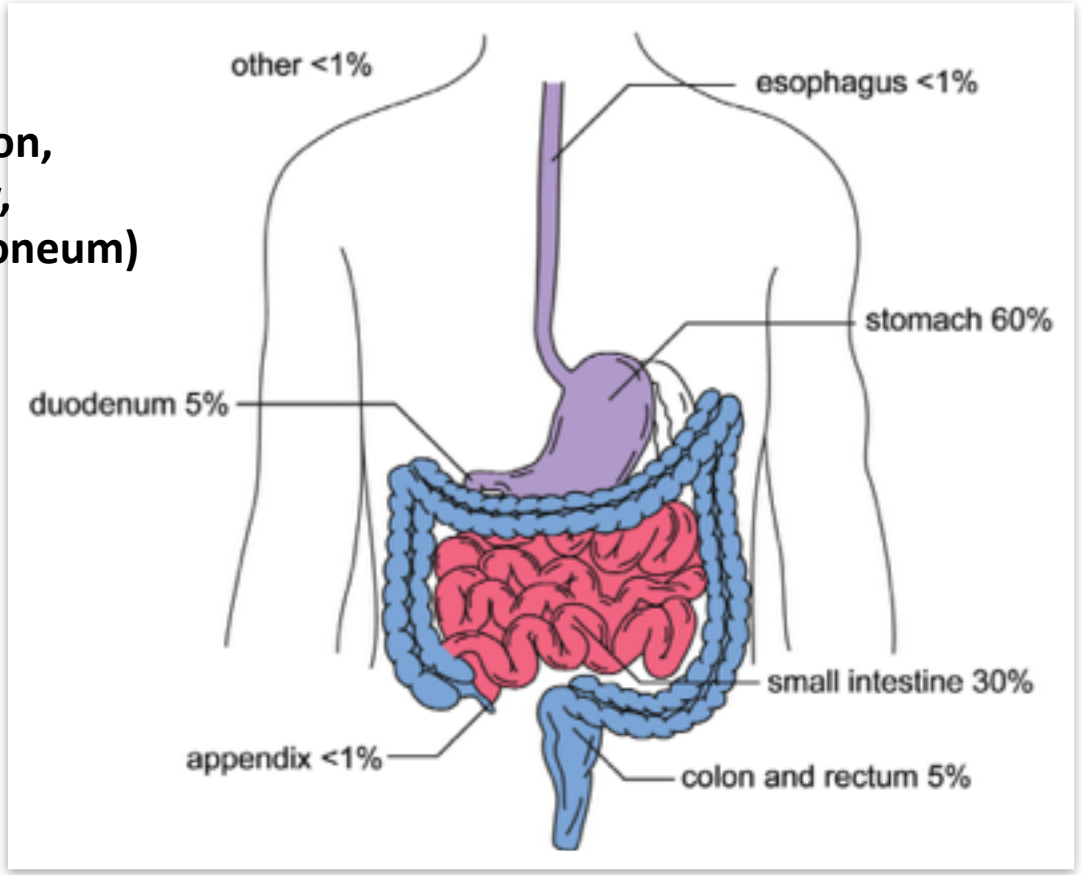
NIH Consensus Risk Assessment

	Size	Mitotic Count
Very Low Risk	< 2 cm	< 5/50 HPF
Low Risk	2-5 cm	< 5/50 HPF
Intermediate Risk	< 5 cm	6-10/50 HPF
	5-10 cm	< 5/50 HPF
High Risk	> 5 cm	> 5/50 HPF

Fletcher et al., Hum Pathol, 2002

GIST: Sites of Involvement





Omentum, mesentery, pelvis and retroperitoneum = EGIST (<1%)

Hornick & Lazar. GSI website: Understanding Your Pathology Report for GIST.

*2007/2010/2014 NCCN GIST Risk Assessment Guidelines****

Tumor	Parameters	Risk of	Progressive	Disease	
	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
Mitotic	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
Index	> 2 ≤ 5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
≤ 5 per 50 hpf	> 5 ≤ 10 cm	Low (3.6%)	(Insuff. data)	Moderate (24%)	(Insuff. data)
	> 10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
Mitotic	≤ 2 cm	None*	(Insuff. data)	High*	High (54%)
Index	> 2 ≤ 5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
> 5 per 50 hpf	> 5 ≤ 10 cm	High (55%)	(Insuff. data)	High (85%)	(Insuff. data)
	> 10 cm	High (86%)	High (86%)	High (90%)	High (71%)

Lasota, *Semin Diagn Pathol*, 2006 by Dr. Chris Corless, OHSU

-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST

Miettinen *et al*. 2005 and 2006

GIST - Gross Appearance

Courtesy of Brian Rubin, Cleveland Clinic

*2007/2010/2014 NCCN GIST Risk Assessment Guidelines****

Tumor	Parameters	Risk of	Progressive	Disease	
	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
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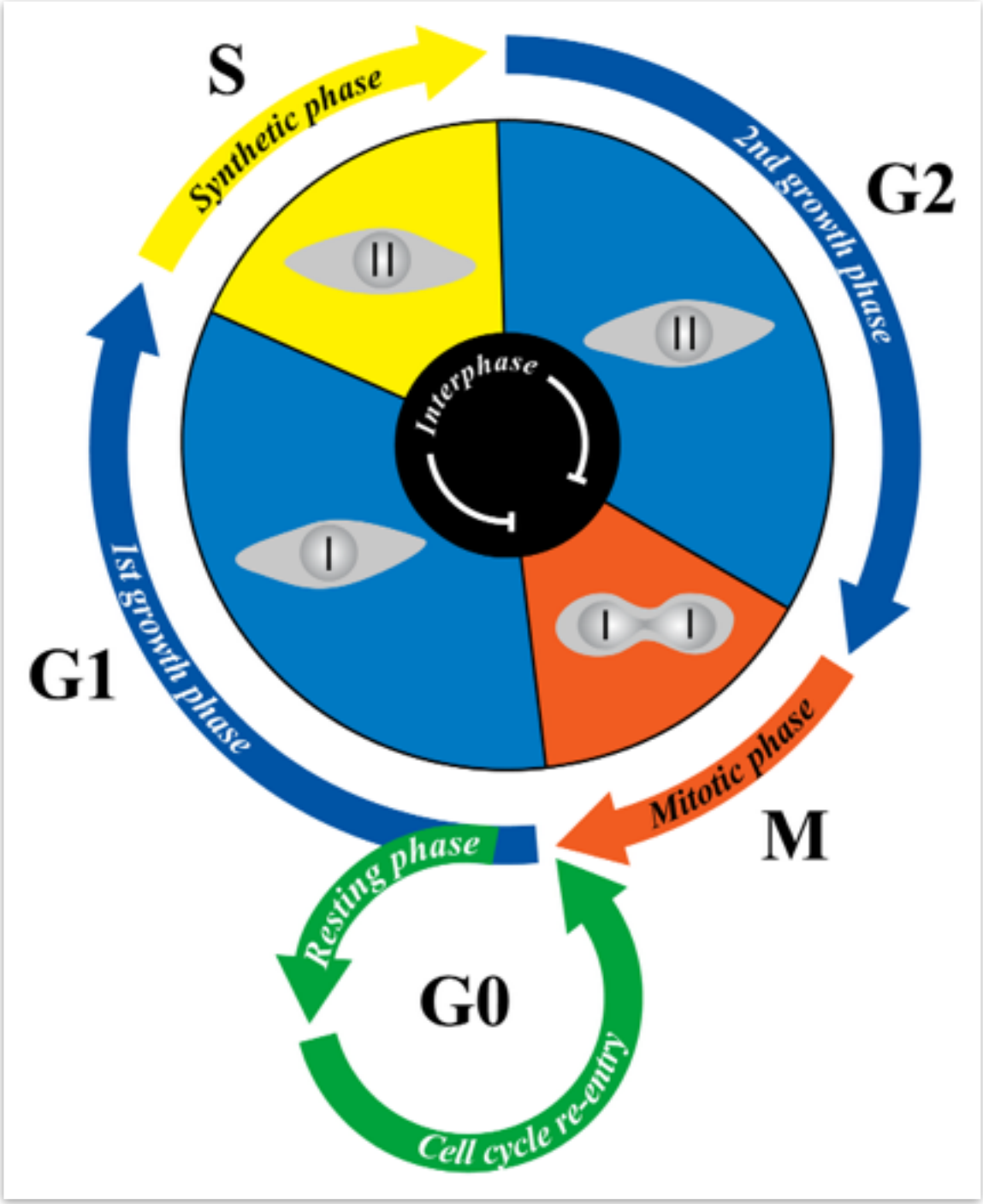
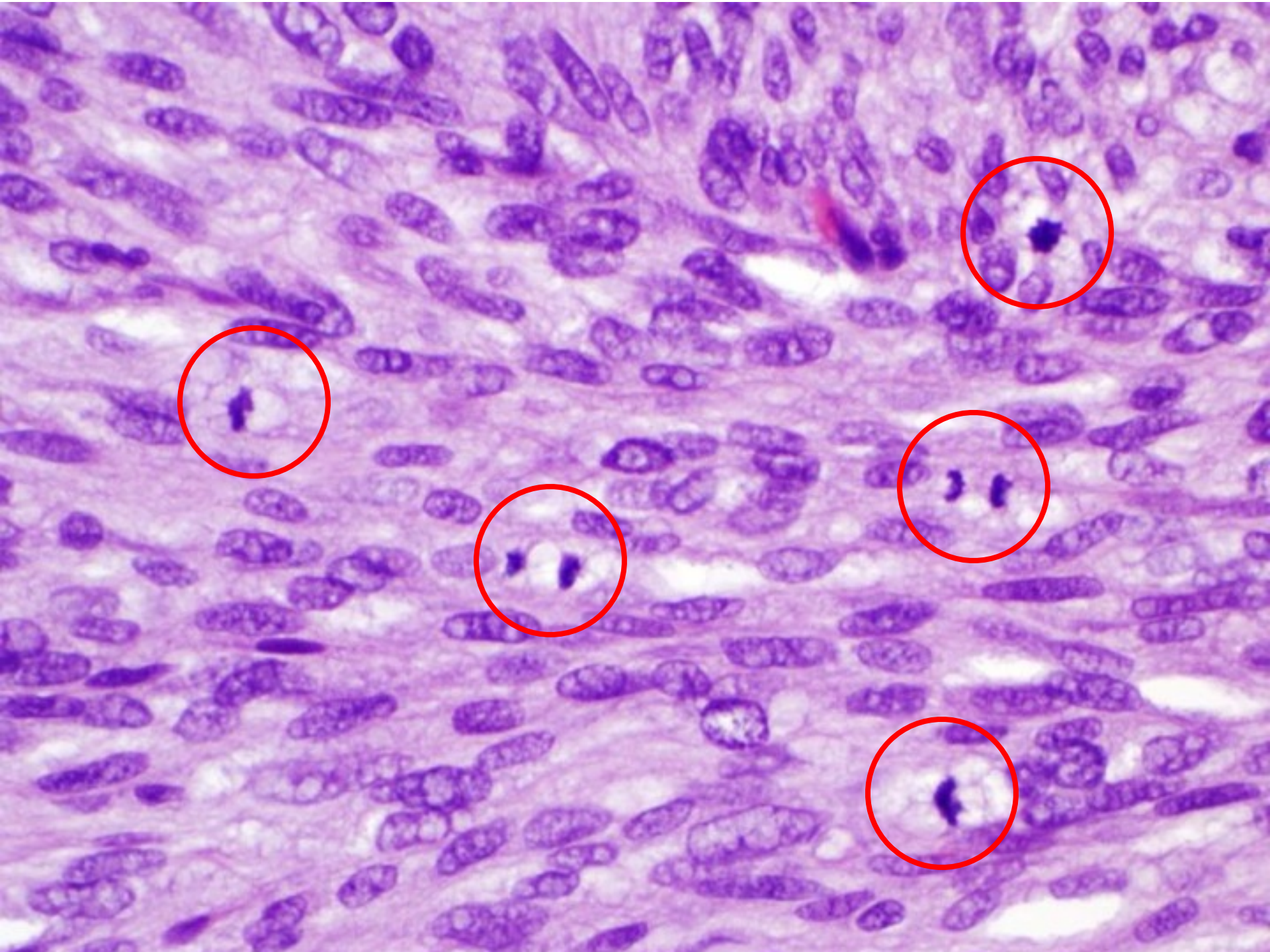
> 5 per 50 hpf	> 5 ≤ 10 cm	High (55%)	(Insuff. data)	High (85%)	(Insuff. data)
	> 10 cm	High (86%)	High (86%)	High (90%)	High (71%)

***Modified from Miettinen & Lasota, *Semin Diagn Pathol*, 2006 by Dr. Chris Corless, OHSU

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST

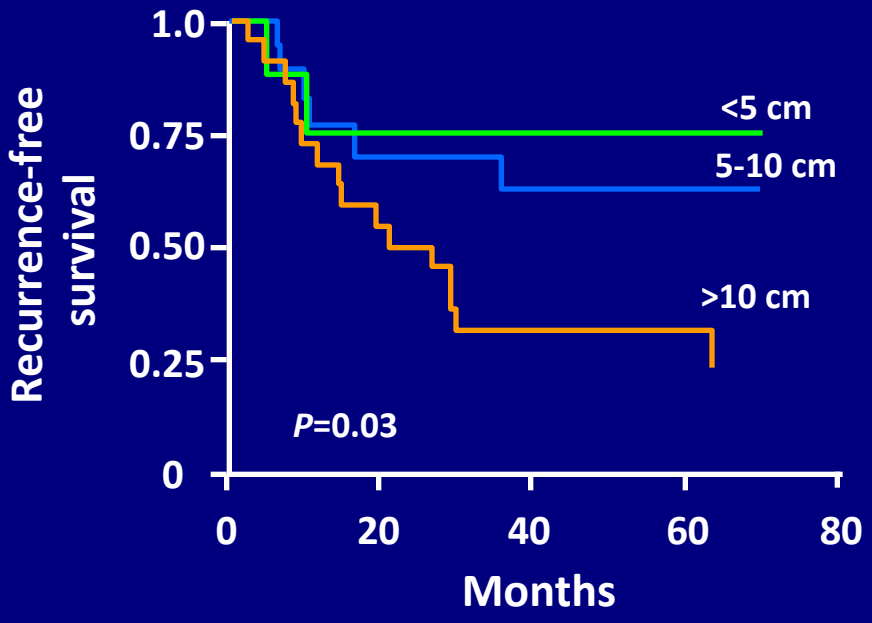
Miettinen *et al*. 2005 and 2006

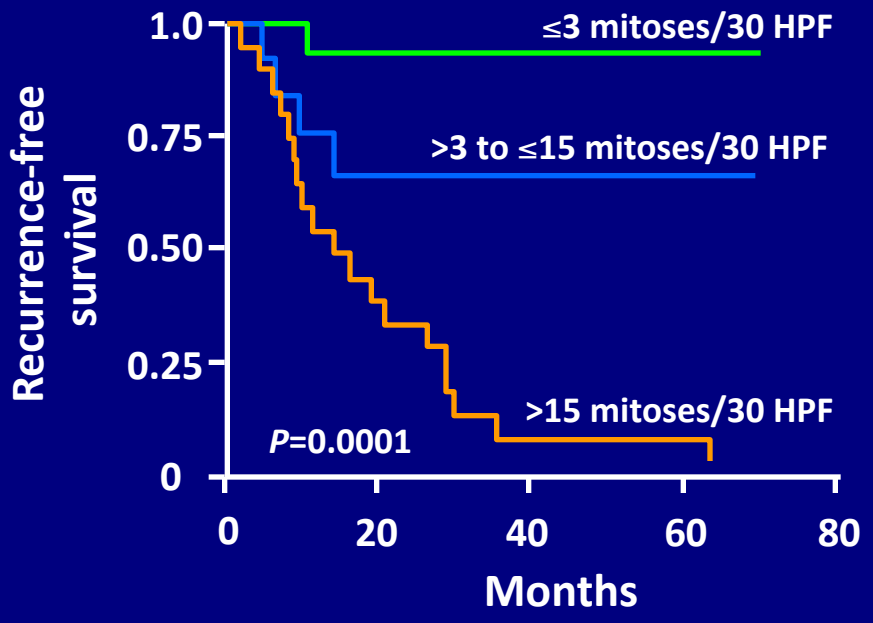

S
Synthetic phase
2nd growth phase
G2
Interphase
1st growth phase
G1
Mitotic phase
M
Resting phase
G0
Cell cycle re-entry



GIST - Recurrence-Free Survival Following Surgical Treatment of Primary GIST

- **Recurrence-free survival is predicted by tumor size and mitotic index**





Singer et al. *J Clin Oncol.* 2002;20:3898

FNCLCC Grading

- **All three numbers are summated to determine degree of differentiation**

Grade 1 : 2-3

Grade 2 : 4-5

Grade 3 : 6-8

- **Proven to correlated well with survival**

- ***Mitotic Count.*** **In the most mitotically active area, ten successive high-power fields (at 400x magnification=0.1734 mm^2) using a 40x objective.**

1. **0-9 mitoses per 10 HPFs**
2. **10-19 mitoses per 10 HPFs**
3. **>20 mitoses per 10 HPFs**

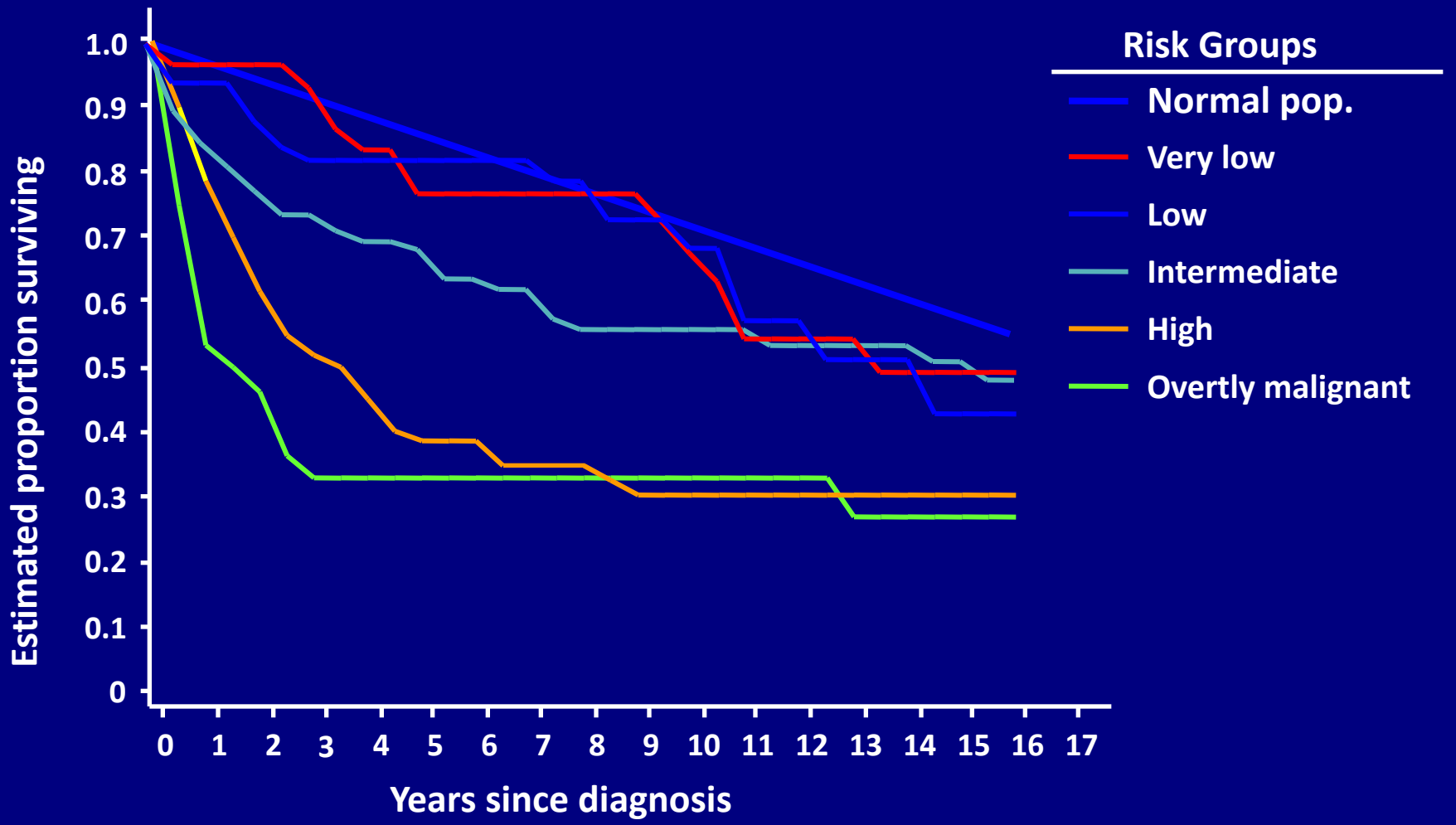
- ***Tumor necrosis.*** **Evaluated on gross examination and validated with histological sections**

0 **No tumor necrosis**

1. **<50% tumor necrosis**
2. **>50% tumor necrosis**

- ***Degree of Differentiation.*** **1-3**

GIST - Overall Survival by Risk Group



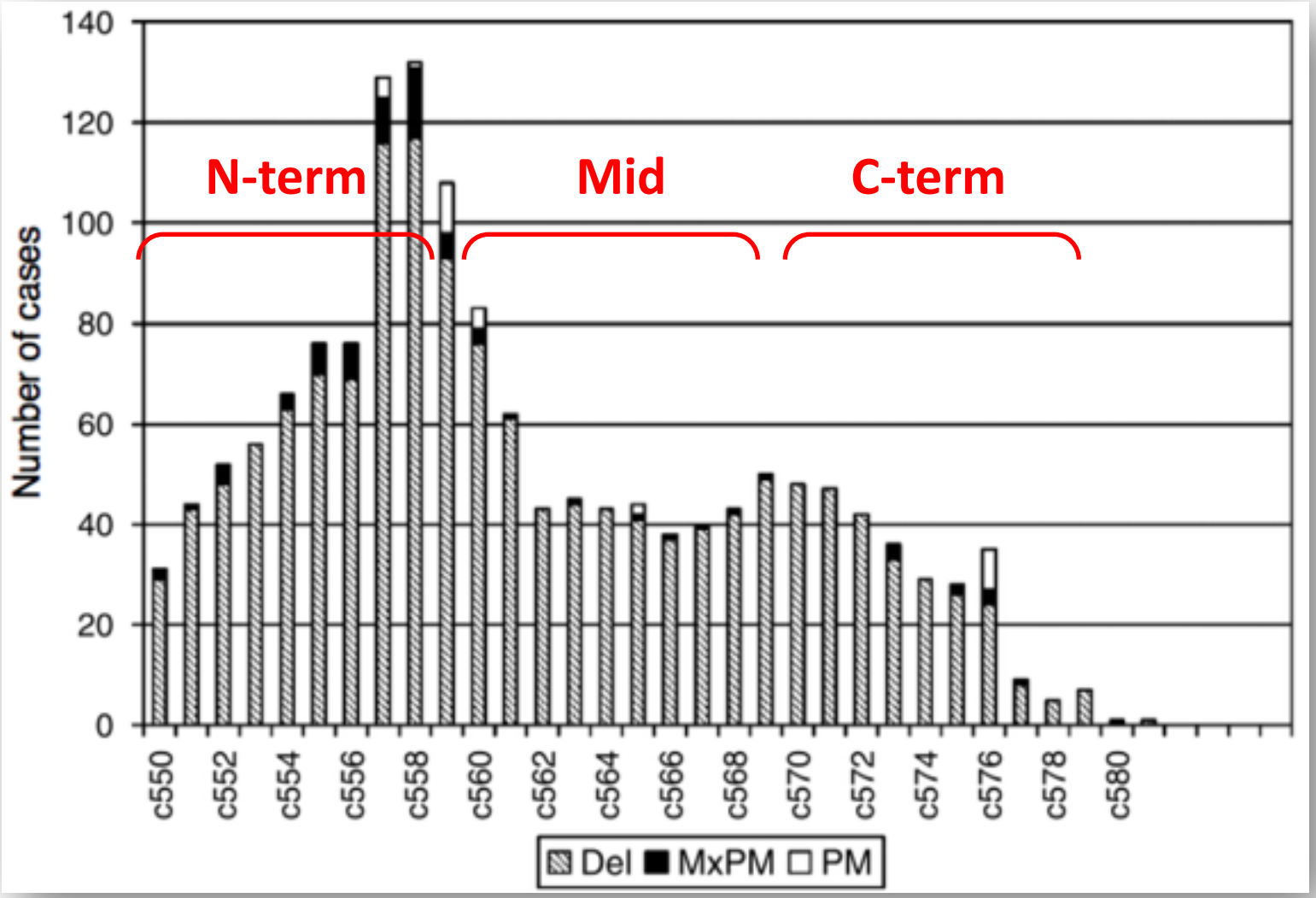
Kindblom. at: http://www.asco.org

Genomic complexity and prognosis
Possible approaches

- **(Histological grading)**
- **Histologic grading +**
- **Array-CGH**
- **Carter signature**
- **Next generation Sequencing**

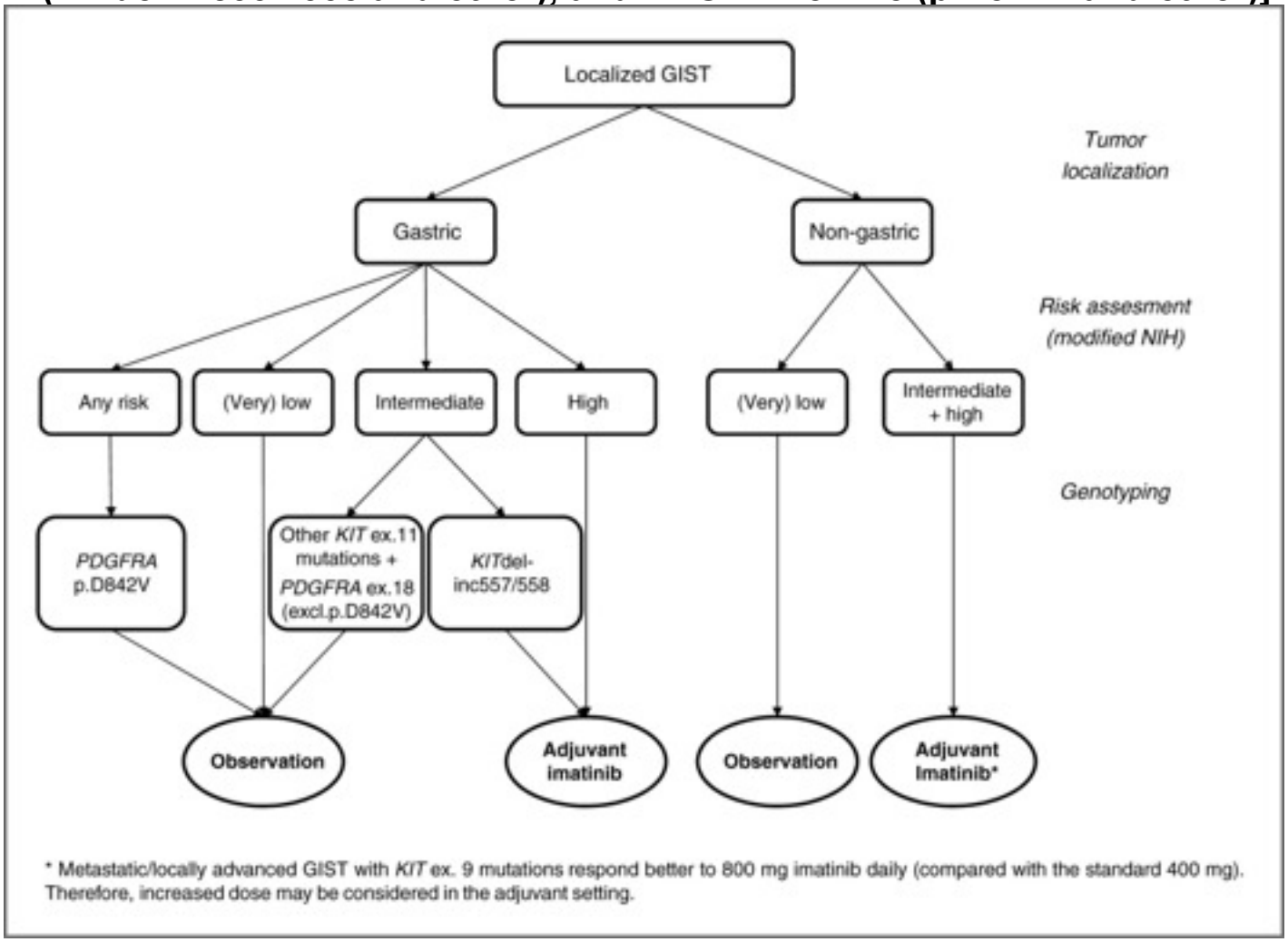
Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

Spectrum of KIT Exon 11 Mutations



Debiec-Rychter et al., J Pathol, 2004.

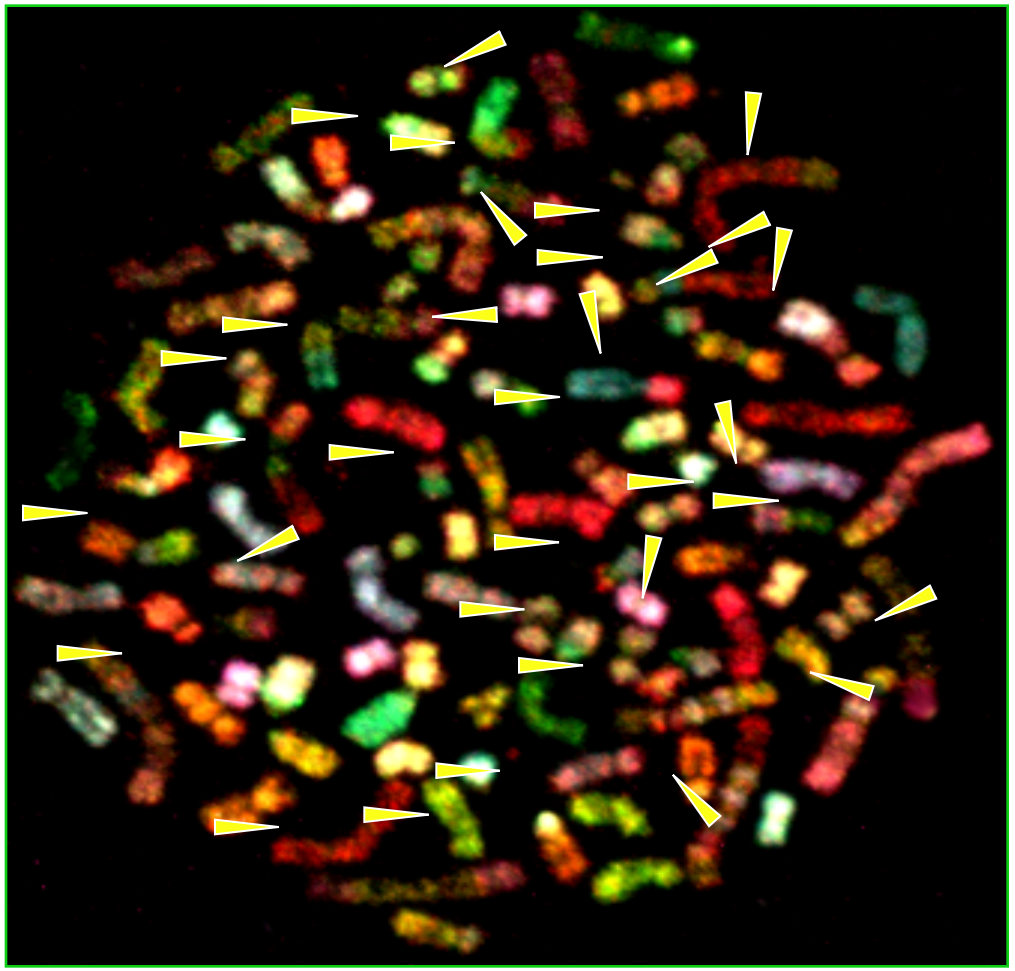
The recommendations for adjuvant imatinib therapy by integration of the risk assessment (based on modified NIH classification) and tumor genotype [KIT ex. 9 p.A502_Y503dup, KIT ex. 11 (KITdel-inc557/558 and other), and PDGFRA ex. 18 (p.D842V and other)] in ...



Agnieszka Wozniak et al. Clin Cancer Res 2014;20:6105-6116

Clinical Cancer Research
AACR

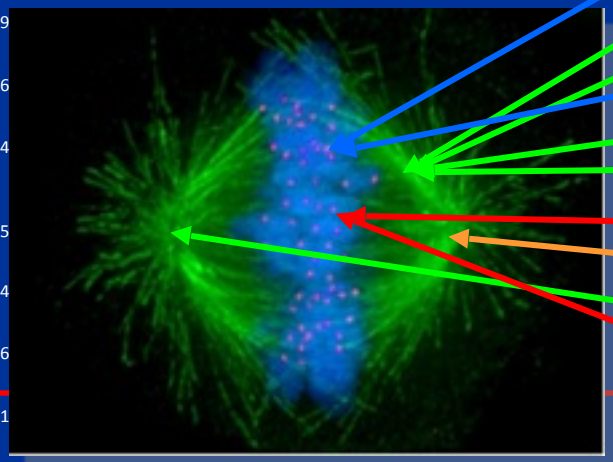
Chromosomal complexity and prognosis



97 chromosomes and more than 50 translocations

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

CINSARC : GO analysis of the 67 significant genes



GO.ID	selection	array	pValue	Z-Score	GO.Term
GO:0000775	10	37	1,06E-14	23,58	chromosome, pericentric region
GO:0005819				27,03	spindle
GO:0005876				25,02	spindle microtubule
GO:0005694				12,73	chromosome
GO:0005875				11,42	microtubule associated complex
GO:0005874				7,88	microtubule
GO:0000776				12,42	kinetochore
GO:0005871				10,67	kinesin complex
GO:0005813	4	48	0,0001	7,96	centrosome
GO:0000940					some
GO:0030496					
GO:0005657					
GO:0005814	2	9	0,0012	9,52	centriole
GO:0015630	2	13	0,0022	7,84	microtubule cytoskeleton
GO:0000922	2	16	0,0032	7,02	spindle pole
GO:0000785	3	75	0,0059	4,47	chromatin
GO:0000786	2	32	0,0111	4,77	nucleosome
GO:0001939	1	3	0,0187	8,30	female pronucleus
GO:0005816	1	3	0,0187	8,30	spindle pole body

CINSARC is a signature related to chromosome management and mitosis control associated with genome complexity

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

Chromosomal complexity in sarcomas

- Alain Aurias and Frédéric Chibon
- Sarcomas with a complex genetic profile
- Array-CGH and expression profile analyses
- Which genes / pathways are related to the chromosomal complexity ?
- Is there a link between chromosomal complexity and prognosis ?

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

Chromosomal instability signature

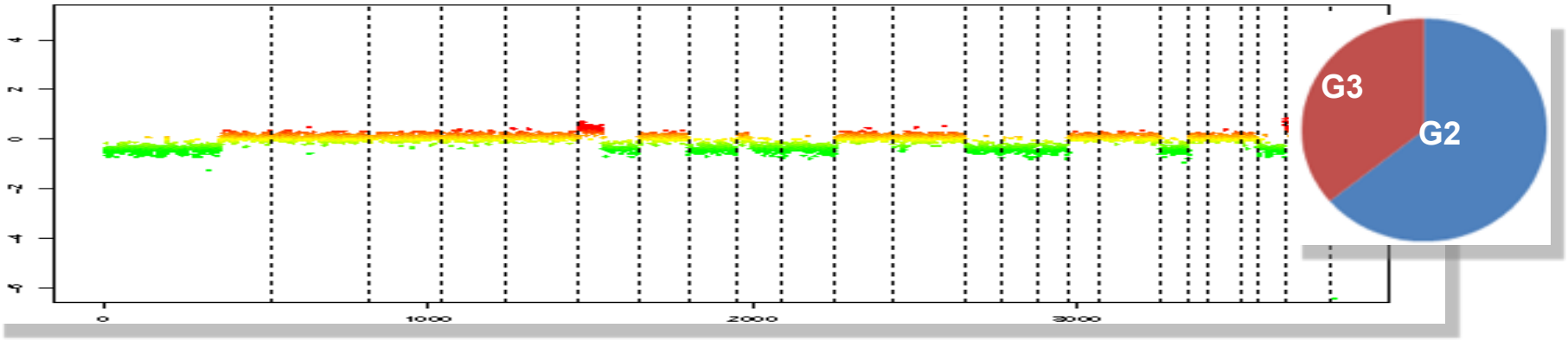
Carter et al Nat Genet 2002

- **Computational method for evaluating aneuploidy**
- **Analysis of genes differentially expressed according to the level of aneuploidy**
- **Aneuploidy is a consequence of chromosomal instability (CIN)**
- **CIN70 signature predicts survival in several types of cancers**
- **No prediction in our series of sarcomas**

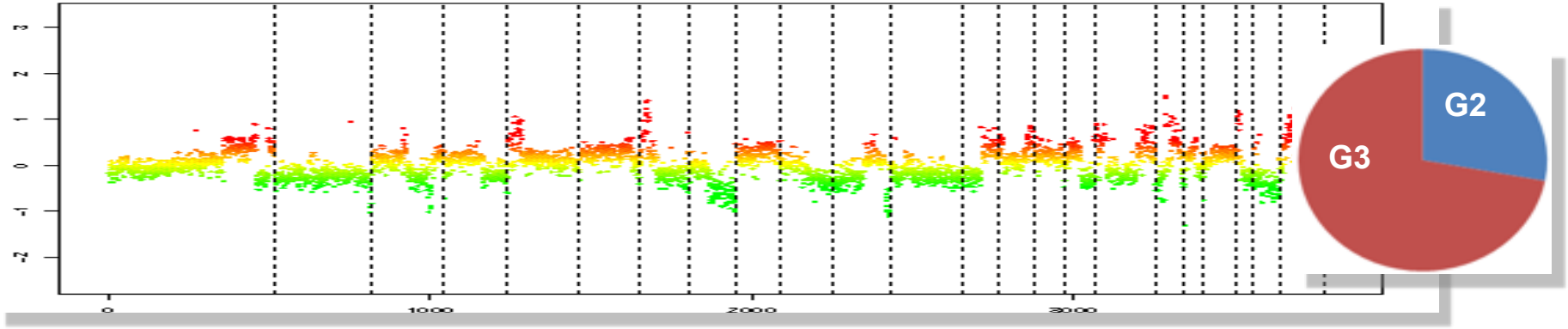
Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

CINSARC : arrayCGH analysis and correlation with FNCLCC grading

« Arm » Profile



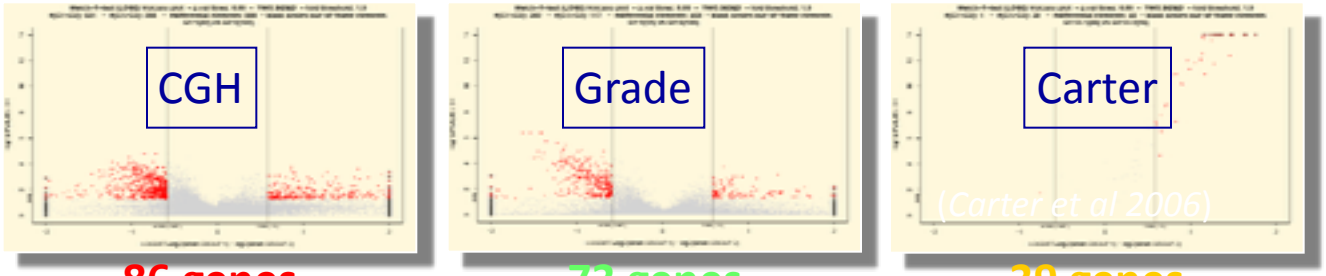
« Rearranged » Profile



Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

Molecular grading in sarcomas

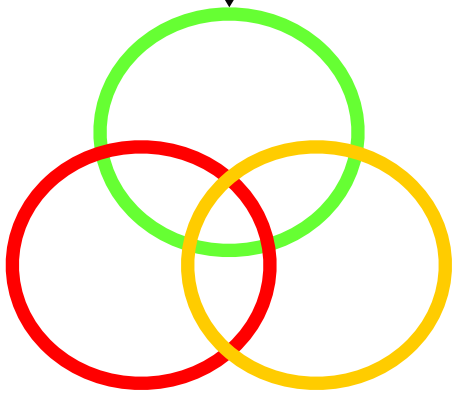
3 tests to compare the expression profiles of tumors classified according to:



86 genes | 73 genes | 39 genes

GO analysis:
To identify the underlying pathways
Selection of genes involved in the most significantly overrepresented pathways ($p<10^{-5}$)

37 genes | 18 genes | 39 genes



67 genes

Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

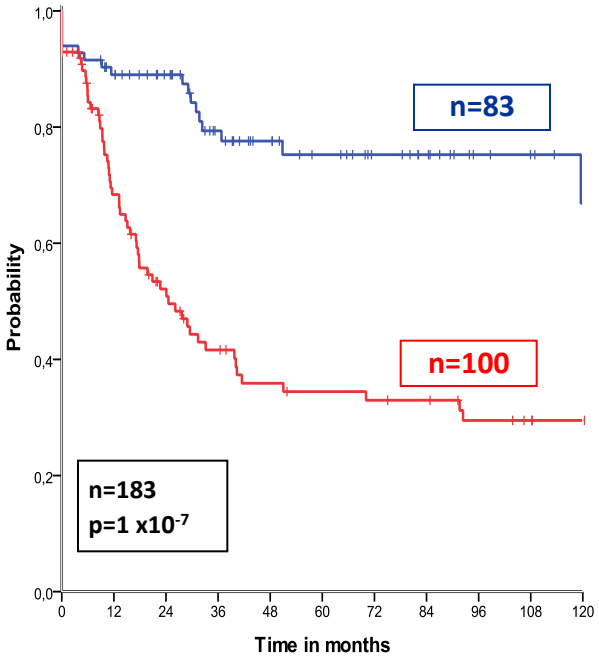
Complexity INdex In SARComas
CINSARC

Chibon et al, Nat Med 2010; 16: 781-7

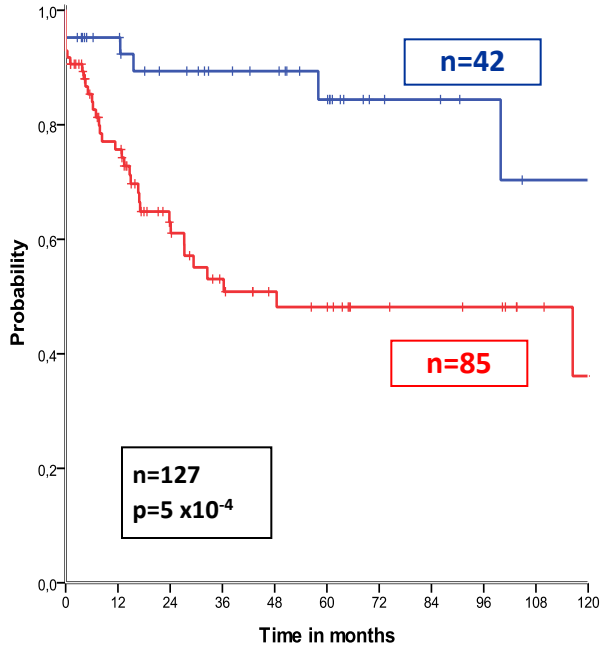
CINSARC: Prognostic signature ?

Prognostic value of CINSARC: Metastasis free survival

Cohort 1



Cohort 2



Multivariate analysis

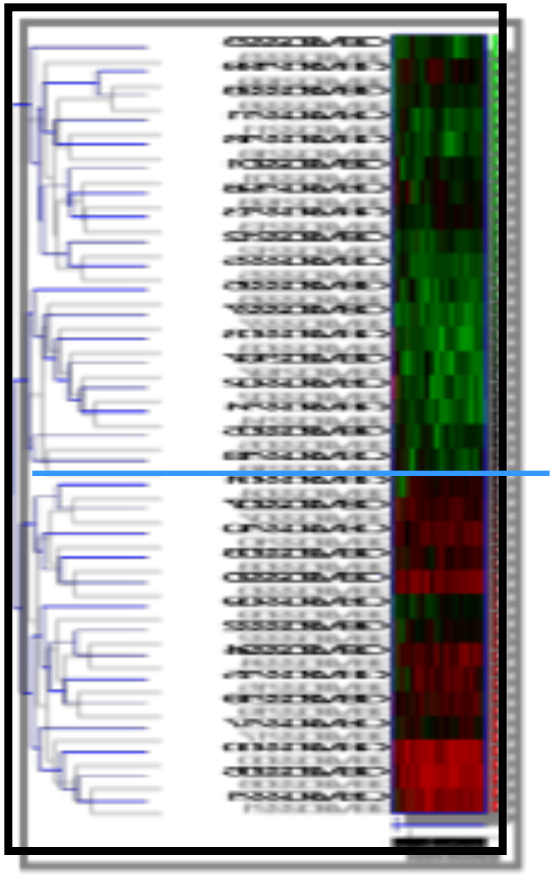
CINSARC is an independent prognostic factor

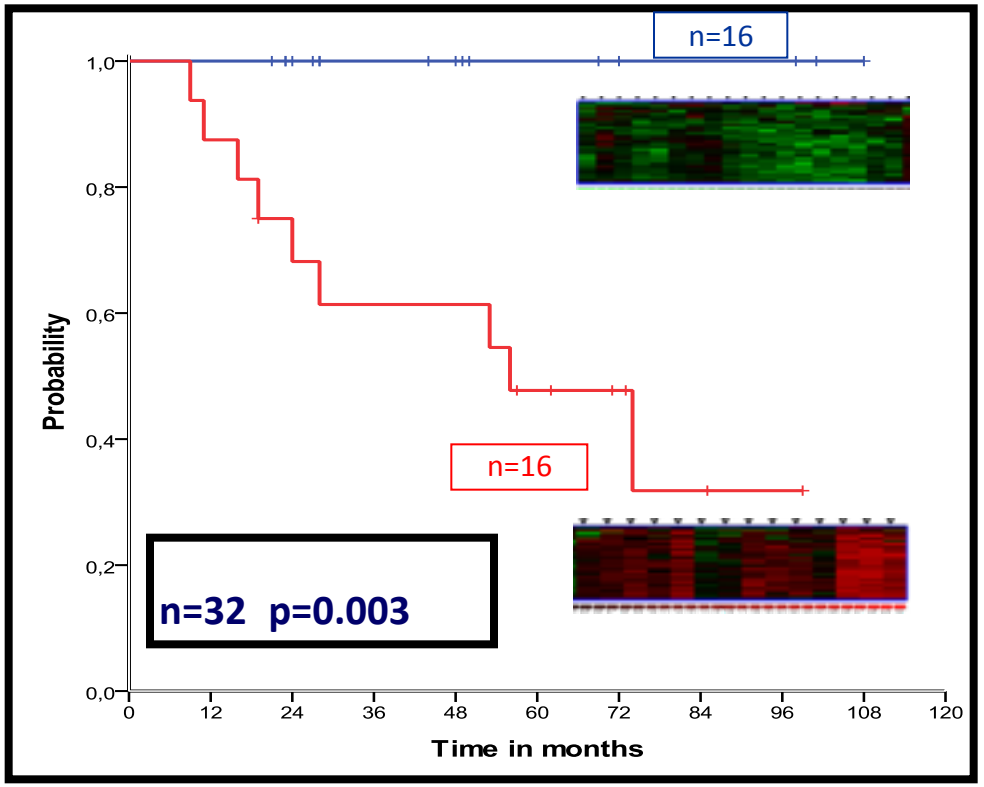
Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

CINSARC and GIST

In-silico study of 32 GISTs

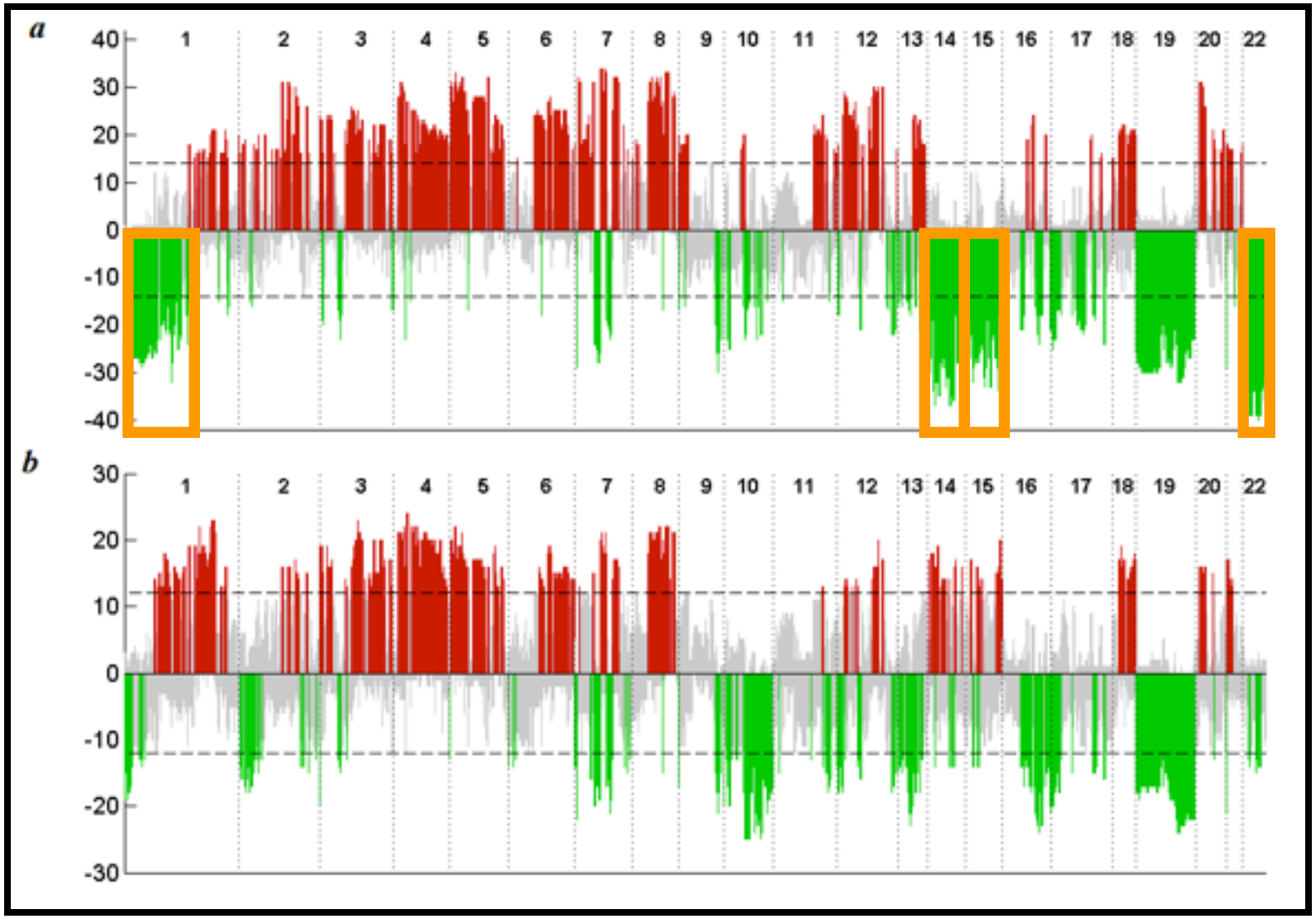
(Yamaguchi *et al* 2008)





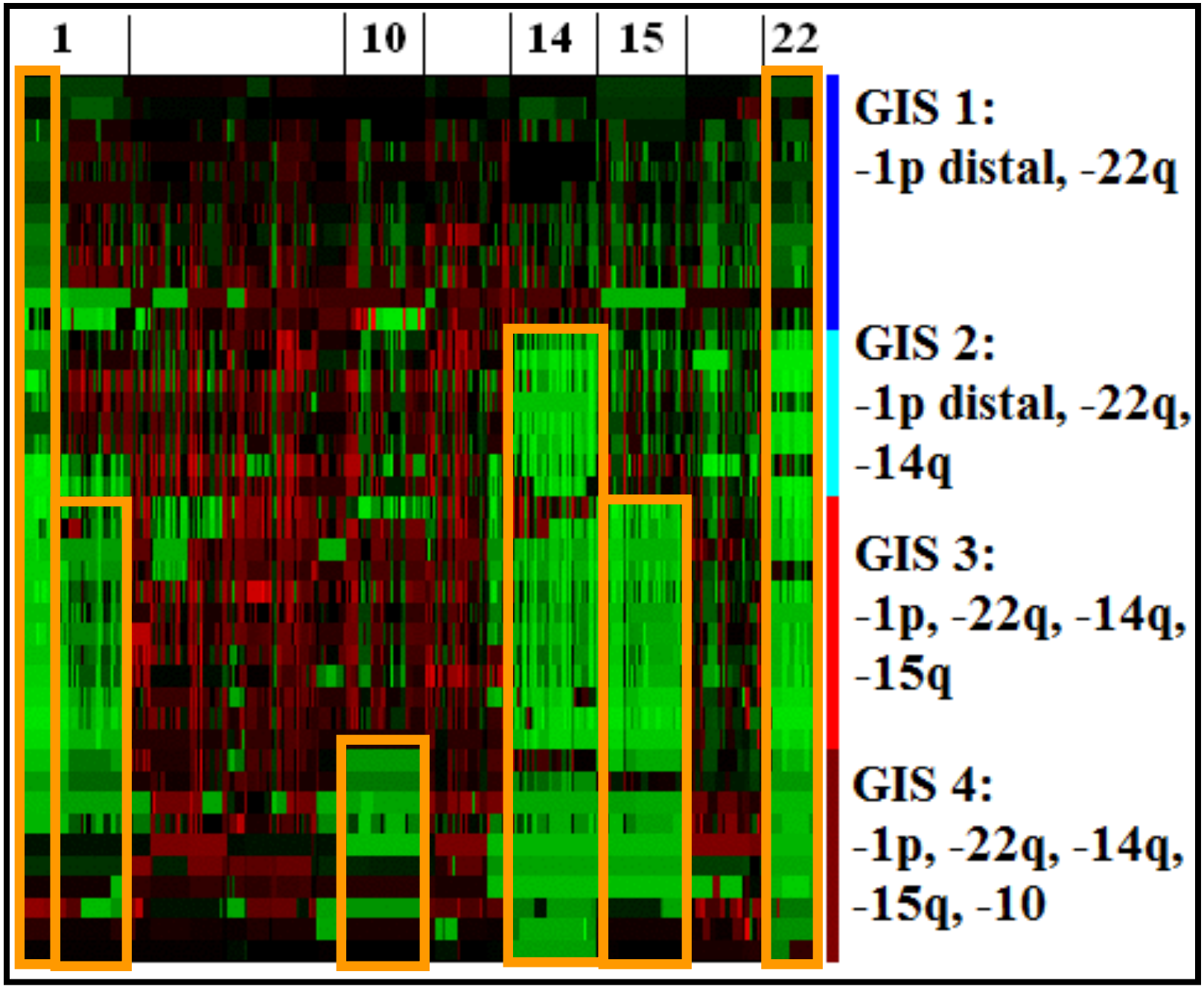
Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

GIST (n=42)

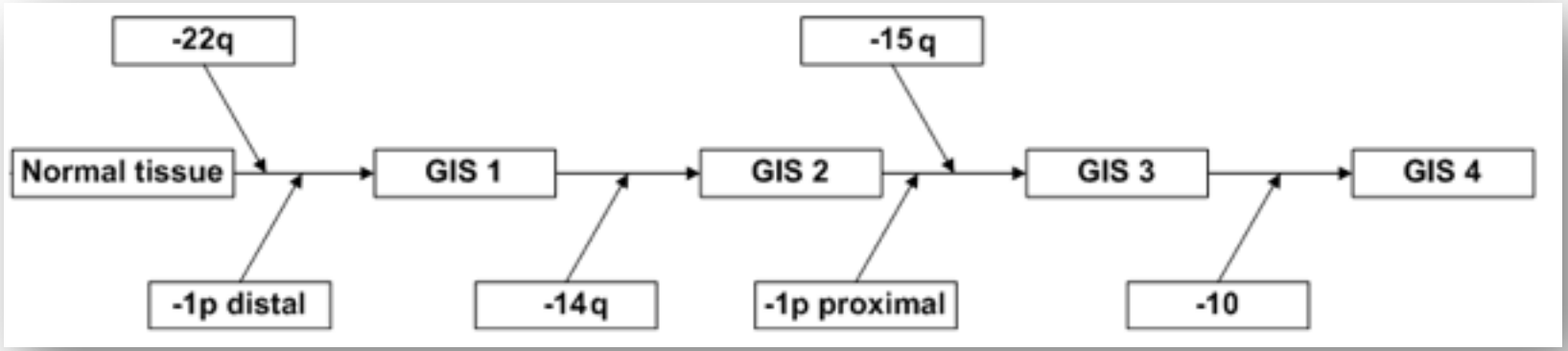


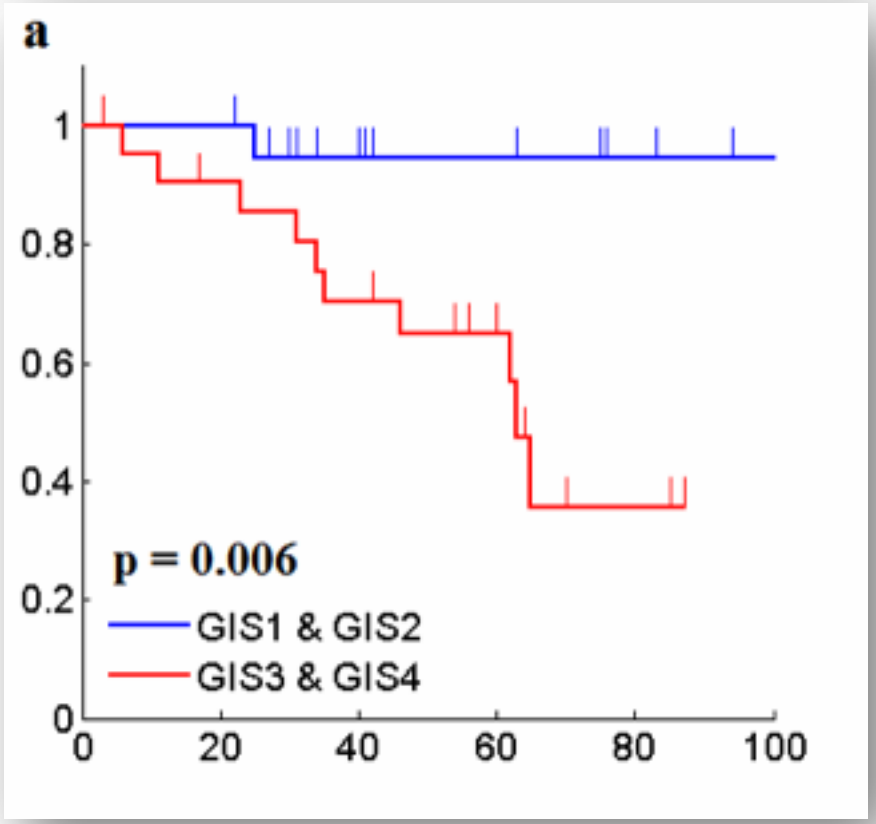
LMS (n=30)

Ylipää A, et al. Cancer 2011 117(2)380-9, 2011



Ylipää A, et al. Cancer 2011 117(2)380-9, 2011



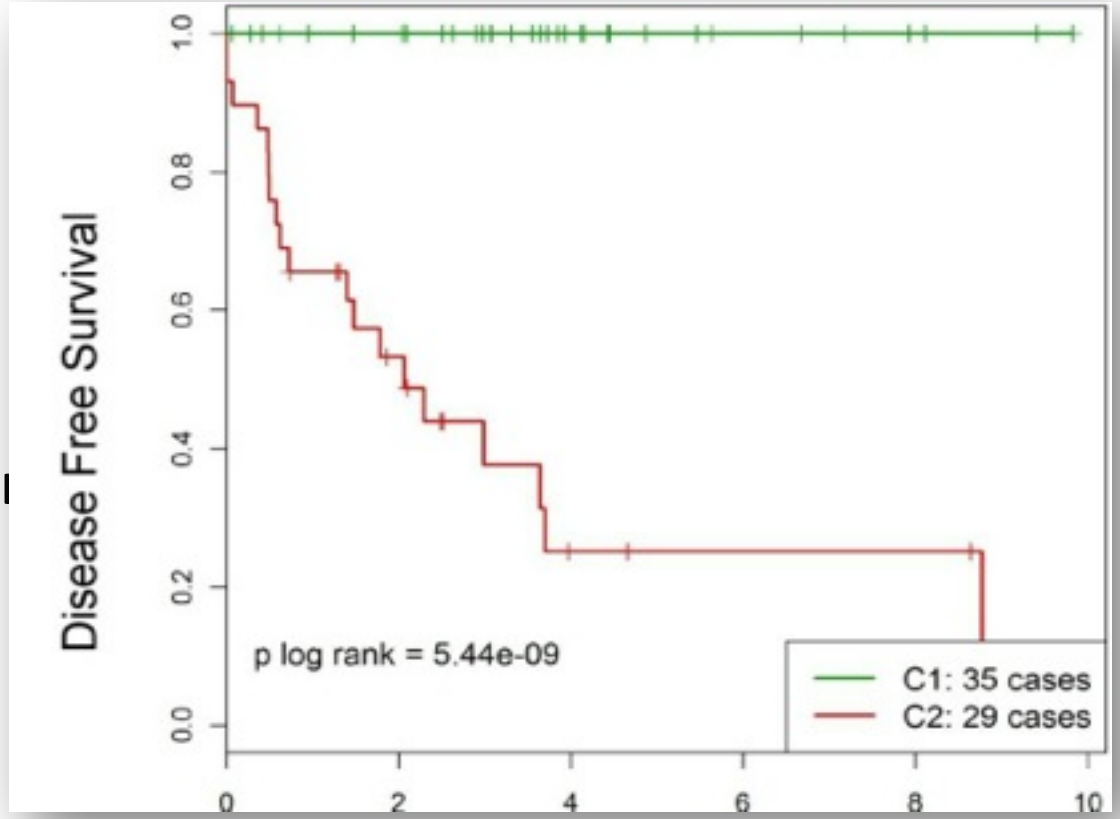


Ylipää A, et al. Cancer 2011 117(2)380-9, 2011

GIST and molecular signature

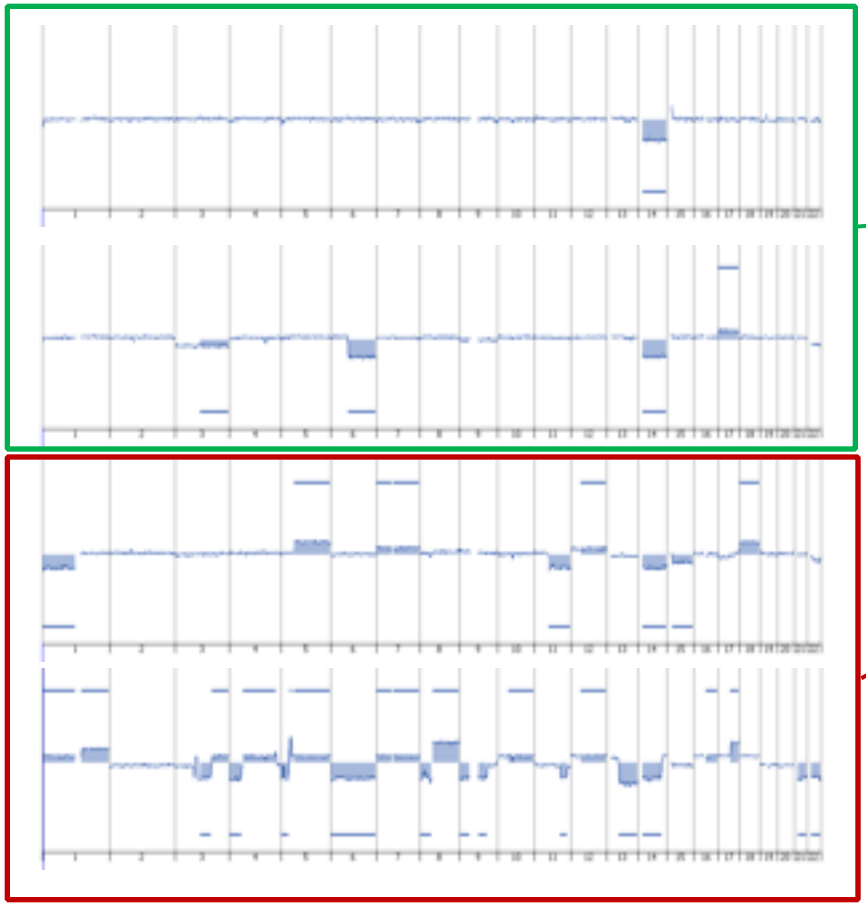
(Lagarde et al. Clin Cancer Res 2012;18: 826-838)

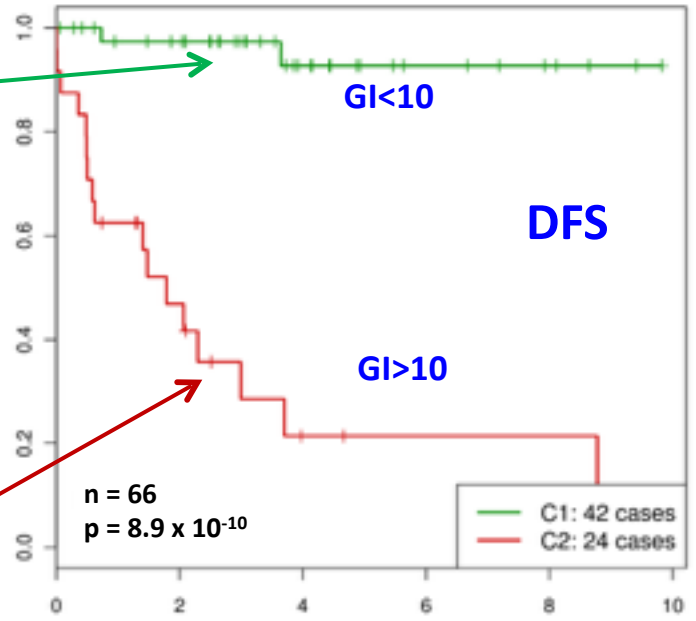
- 67 patients (Leuven + Bordeaux)
- Localised GIST
- No adjuvant treatment
- Frozen tissue from prima
- Miettinen classification
- Follow-up



Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

Genomic Index (GI) is a prognostic factor in GIST…

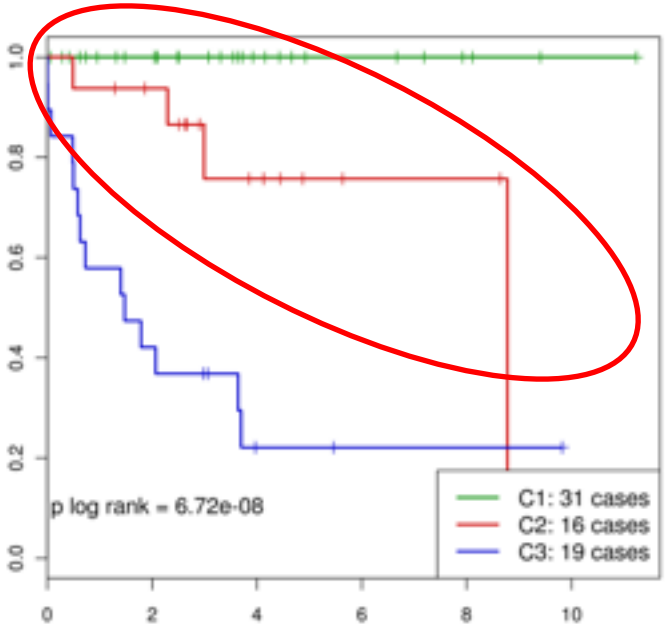


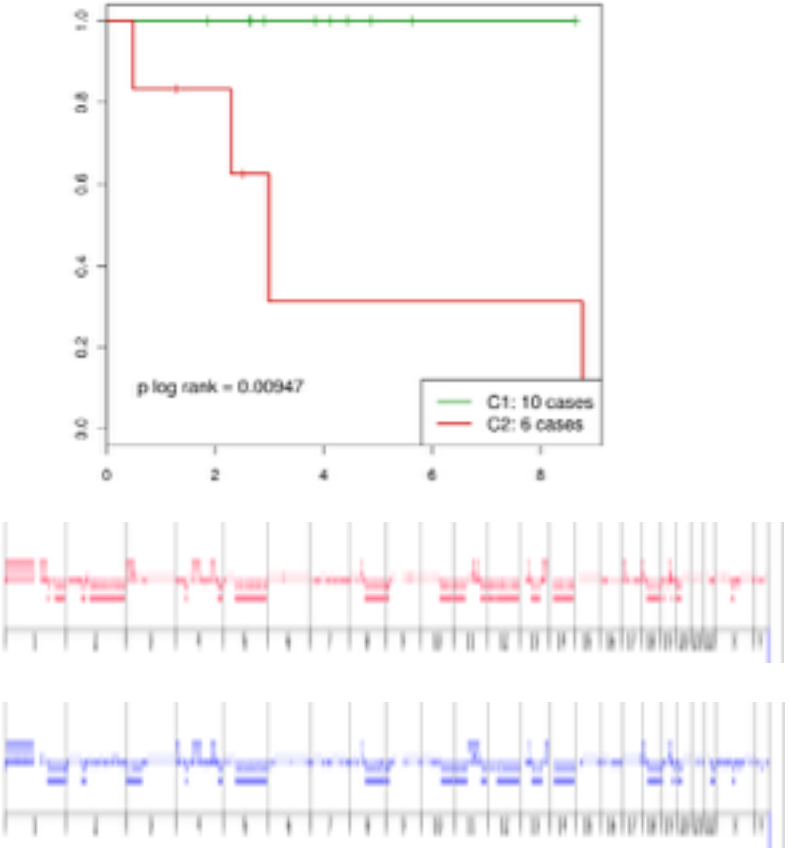


Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

GIST and molecular signature

(Lagarde et al. Clin Cancer Res 2012;18: 826-838)

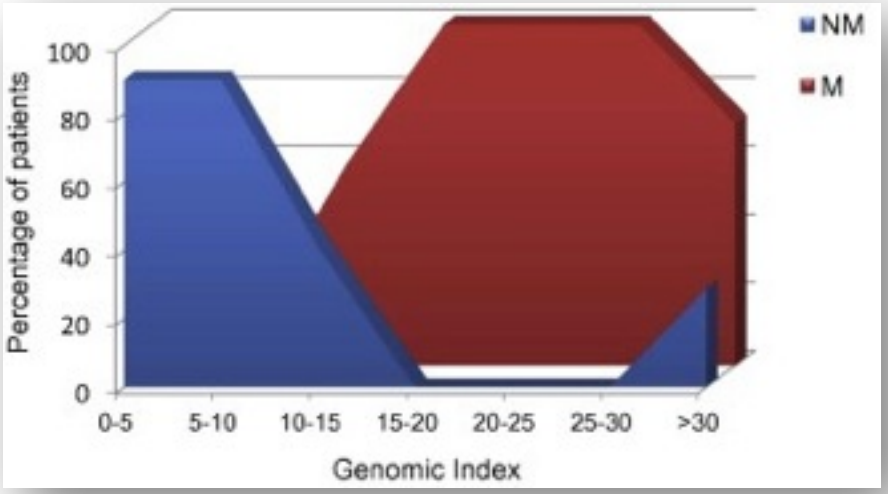




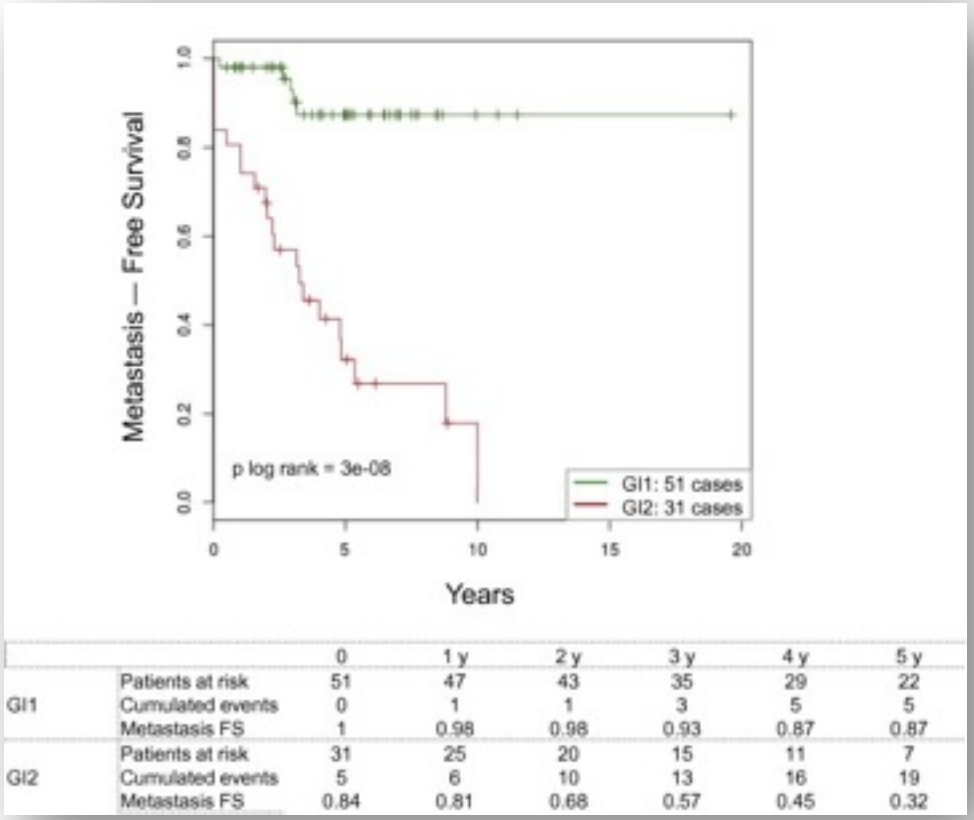
Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

Latest Data

82 intermediate-risk (AFIP) GISTS
Array CGH from FFPE blocks



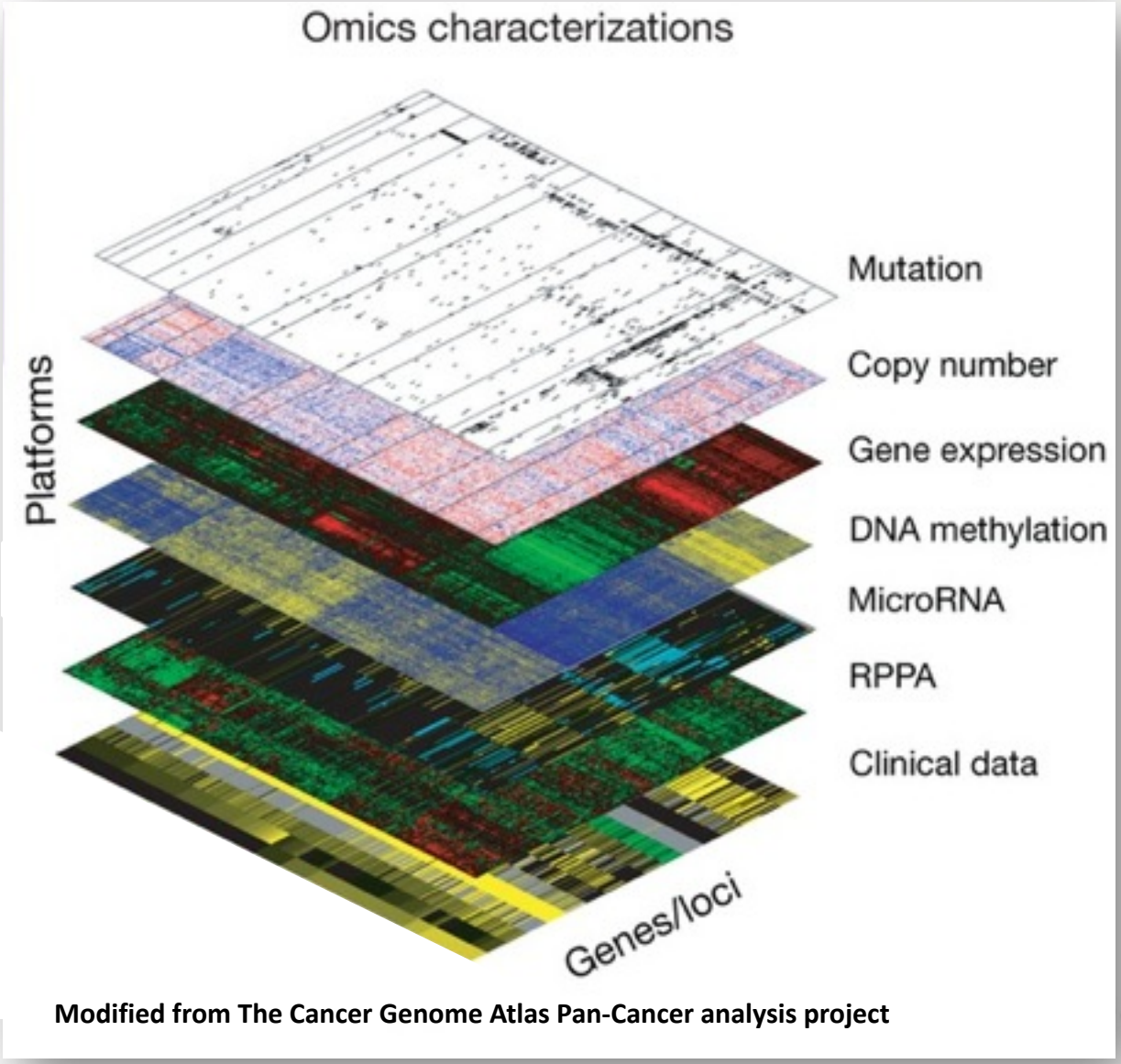
- Leuven (M Debiec-Rychter)
- Köln (E Wardelmann)
- Warsaw (P Rutkowski)
- Treviso (AP Dei Tos)
- French Sarcoma Group



		0	1 y	2 y	3 y	4 y	5 y
GI1	Patients at risk	51	47	43	35	29	22
	Cumulated events	0	1	1	3	5	5
	Metastasis FS	1	0.98	0.98	0.93	0.87	0.87
GI2	Patients at risk	31	25	20	15	11	7
	Cumulated events	5	6	10	13	16	19
	Metastasis FS	0.84	0.81	0.68	0.57	0.45	0.32

Chibon & Colleagues. Eur J Cancer 2014; 51(1):75-83.

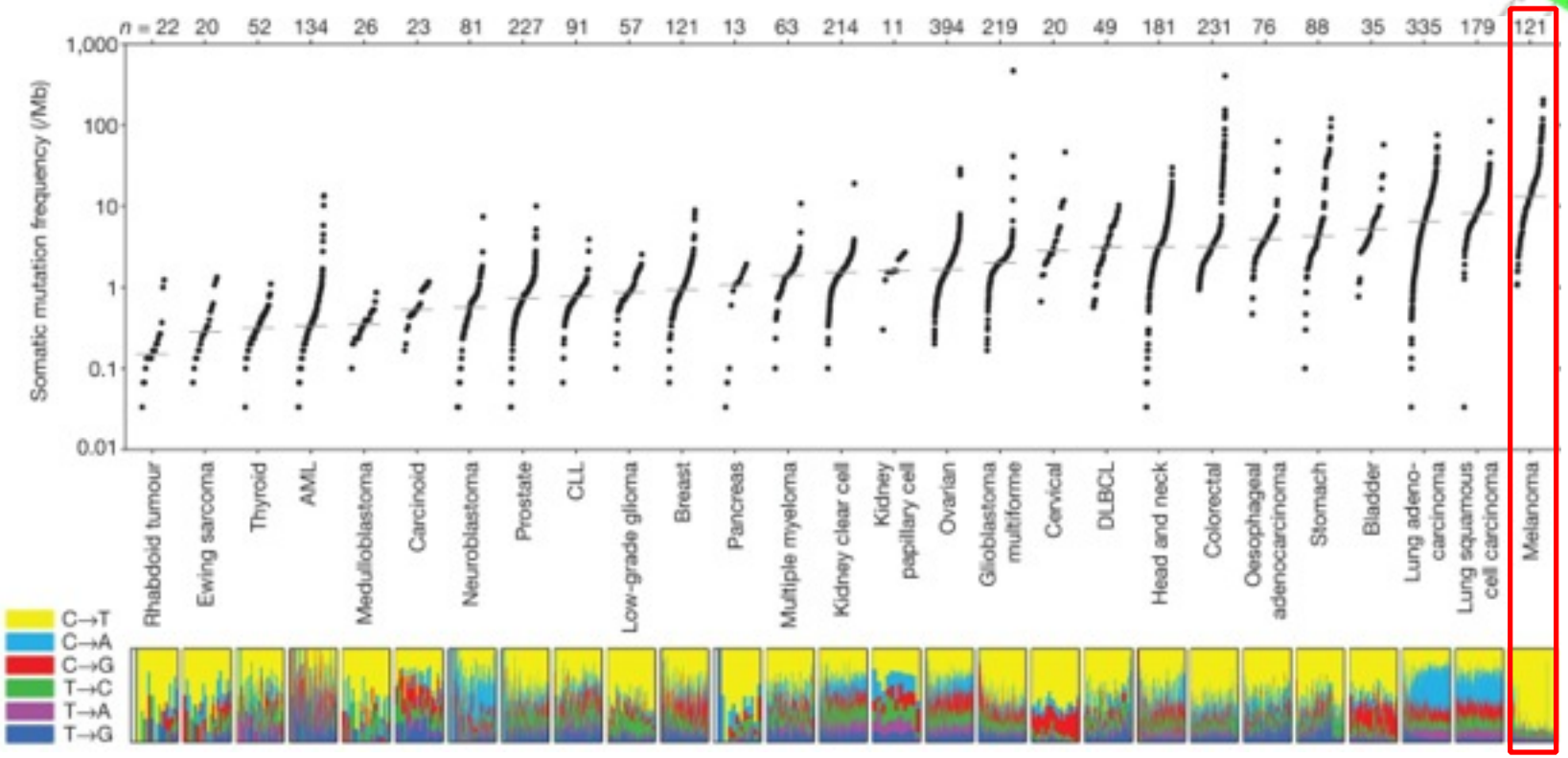
Cutaneous Melanoma Integrative Analysis



Modified from The Cancer Genome Atlas Pan-Cancer analysis project

Genome Atlas

Whole Exome Sequencing (WES): Melanoma has the Highest Mutation Rate of Cancers Sequenced to Date

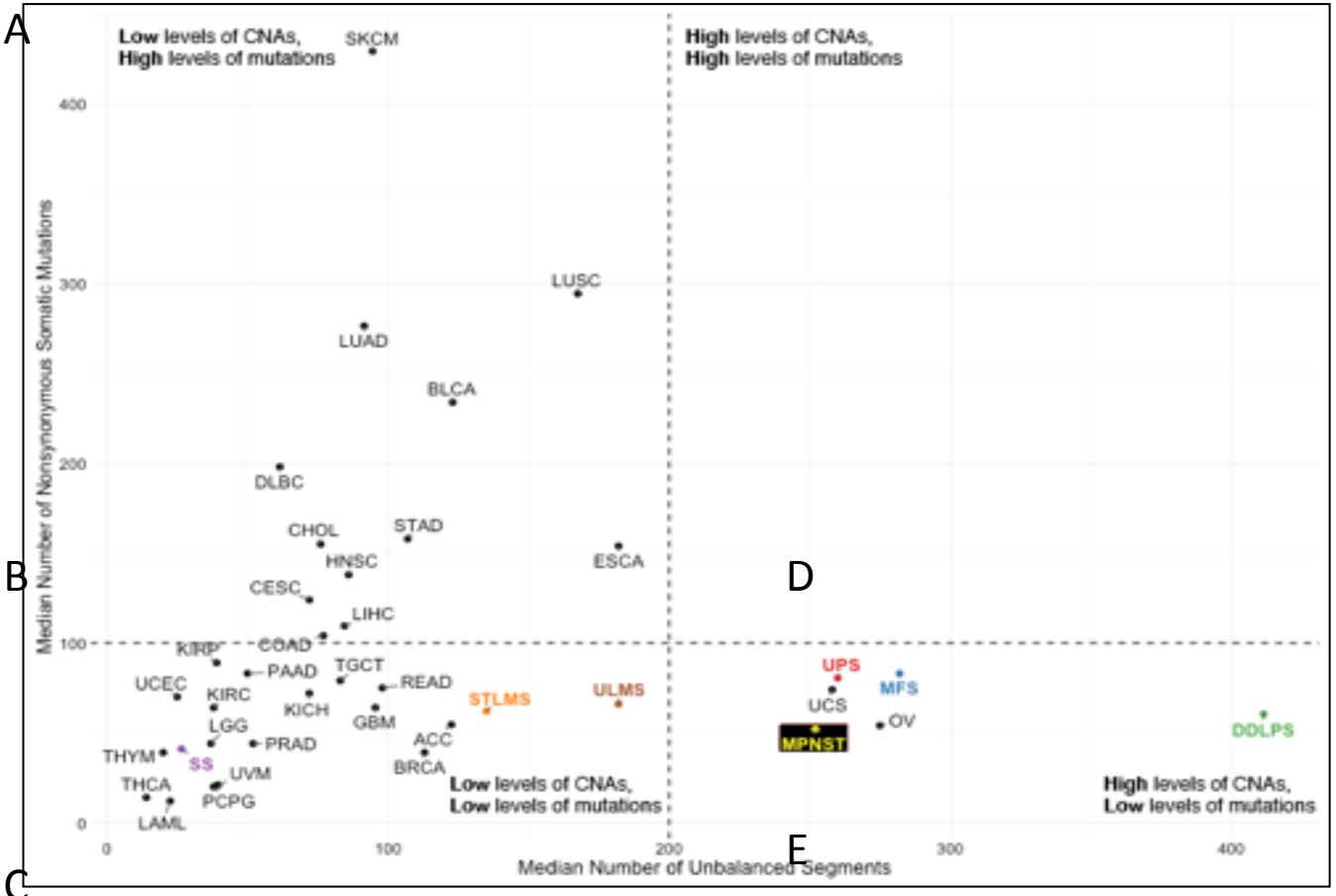


Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.

Broad Institute
Mike Lawrence
Gad Getz
Nature, 2013

The Cancer Genome Atlas

A

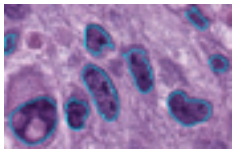


B

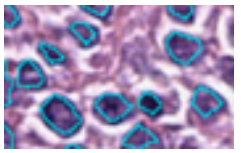
C

D

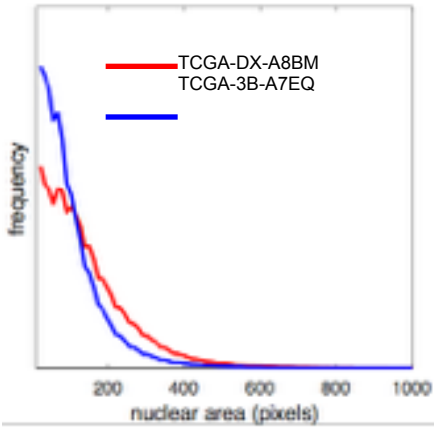
E

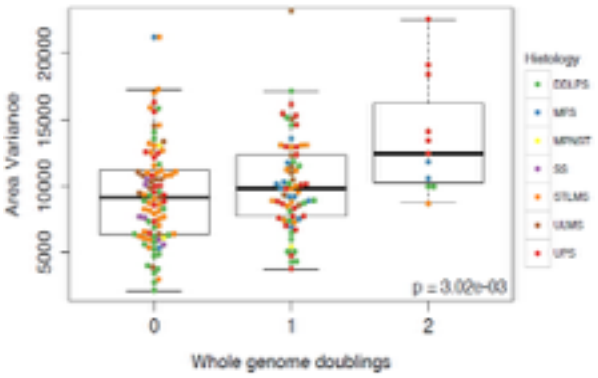


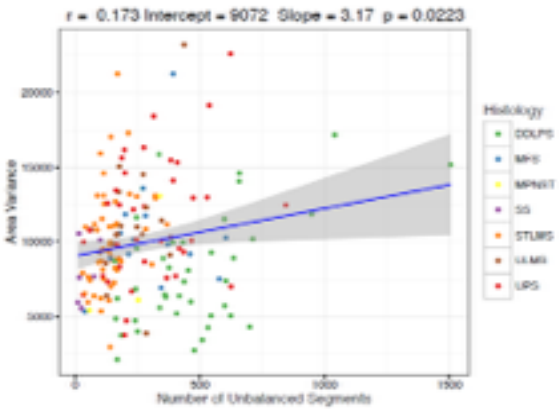
TCGA-DX-AM

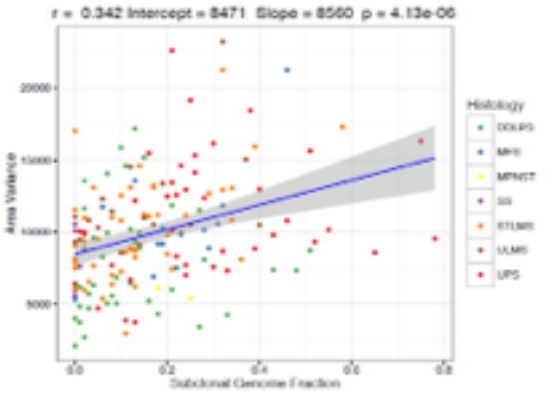


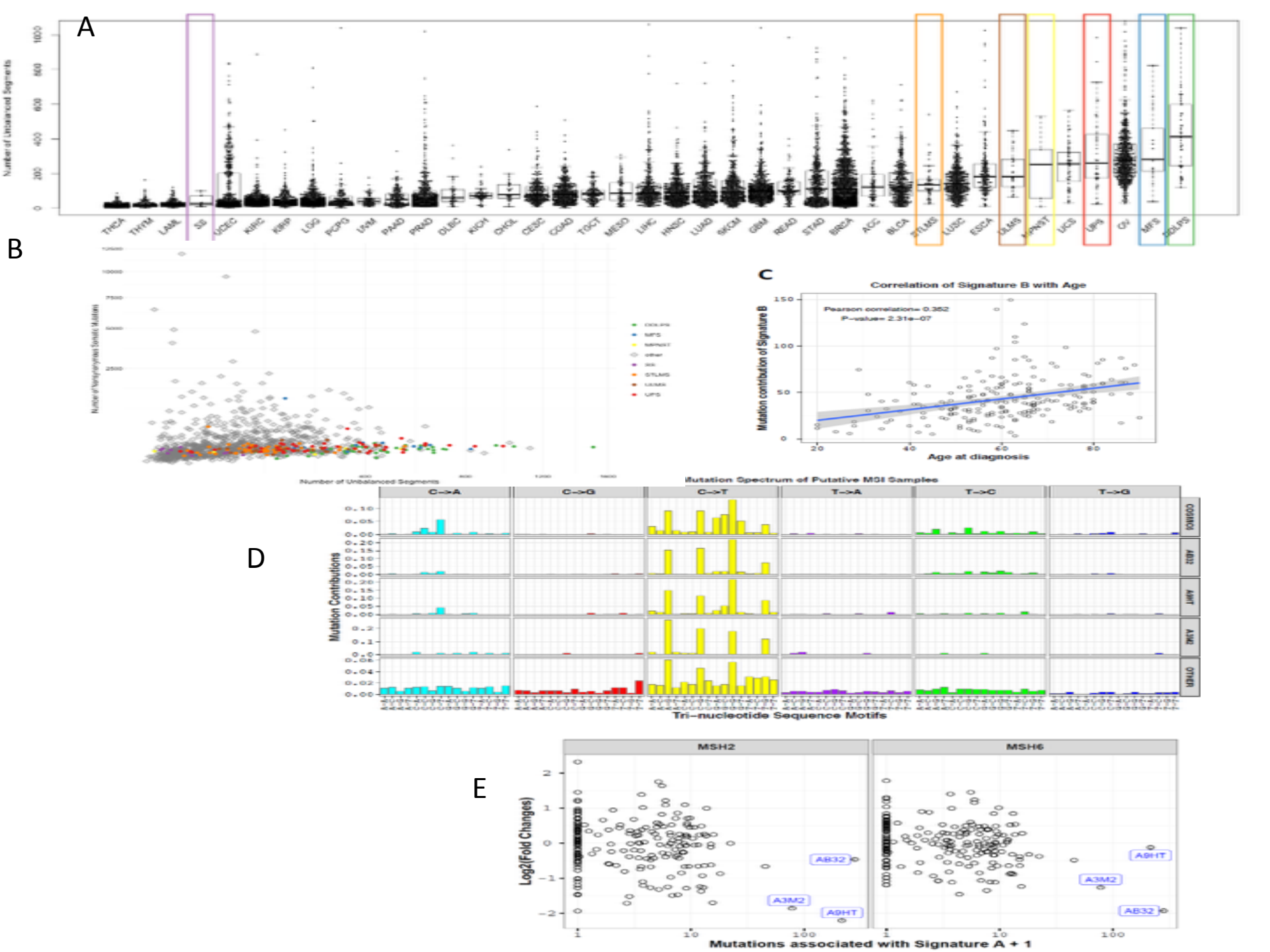
TCGA-DX-A7EQ





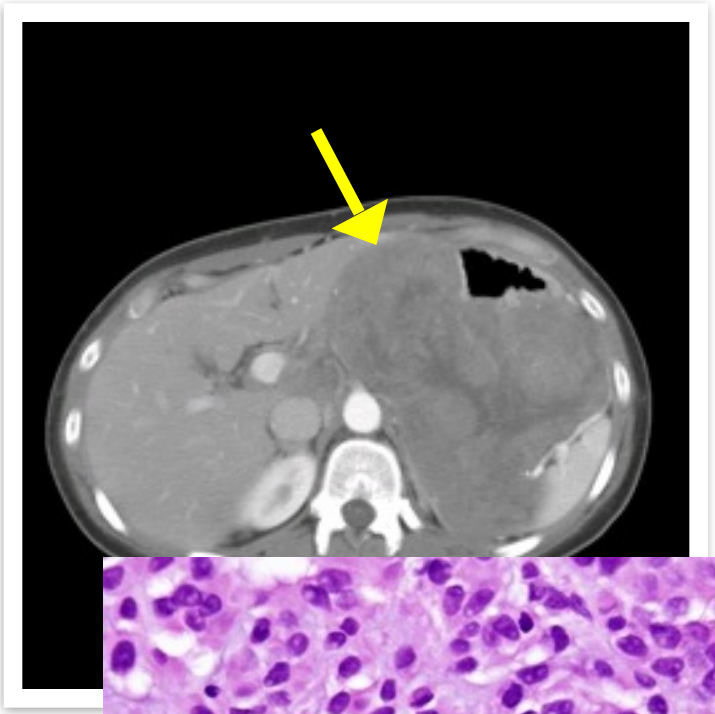


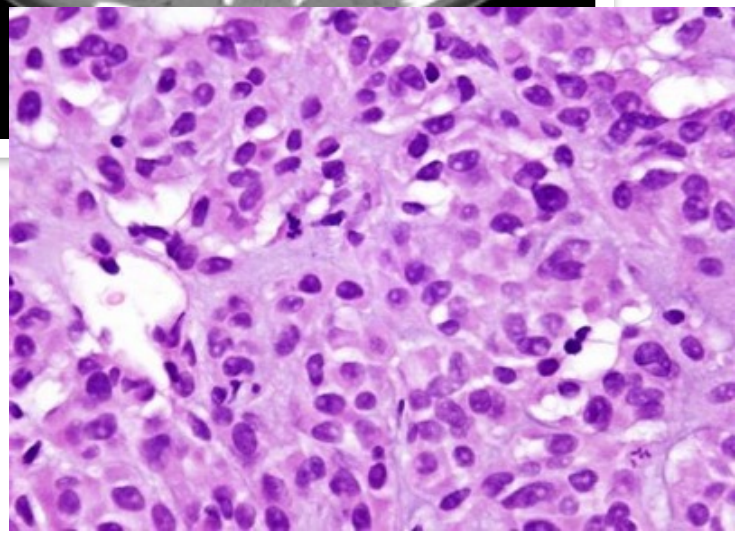



A
Number of Unbalanced Segments
THCA
THYM
LAML
SB
UCEC
KIRC
KIRP
LGG
PCPG
UVM
PAAD
PRAD
DLBC
KICH
CHOL
CESC
COAD
TGCT
MESO
LIHC
HNSC
LUAD
SKCM
GBM
READ
STAD
BRCA
ACC
BLCA
STLMS
LUSC
ESCA
ULMS
MPNST
UCS
UPS
OV
MFS
DDLPS
B
Number of Unbalanced Segments
C
Correlation of Signature B with Age
Pearson correlation= 0.352
P-value= 2.31e-07
Mutation contribution of Signature B
Age at diagnosis
D
Mutation Spectrum of Putative MSI Samples
C->A
C->G
C->T
T->A
T->C
T->G
COSMIC
AB32
A9HT
A3M2
OTHER
Mutation Contributions
Tri-nucleotide Sequence Motifs
E
MSH2
MSH6
Log2(Fold Changes)
AB32
A3M2
A9HT
Mutations associated with Signature A + 1

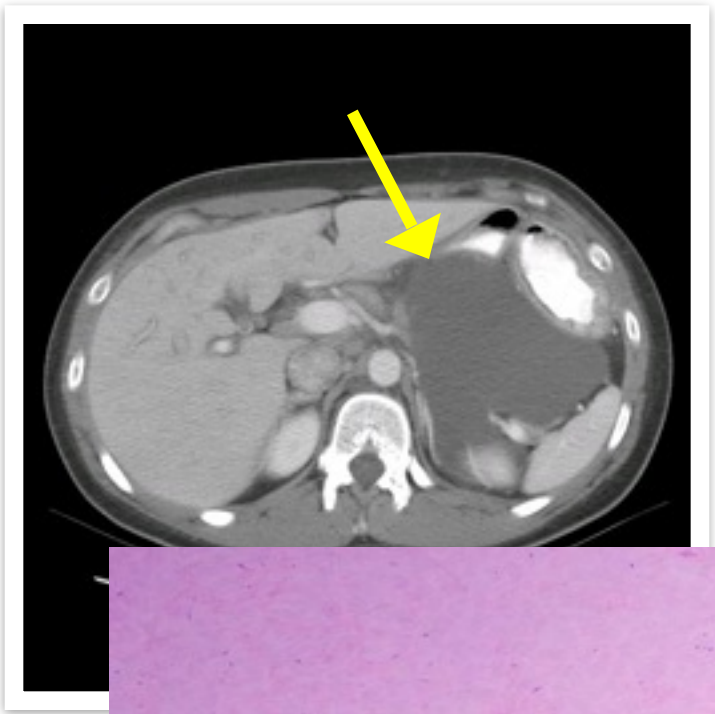
Treatment can cause big changes.

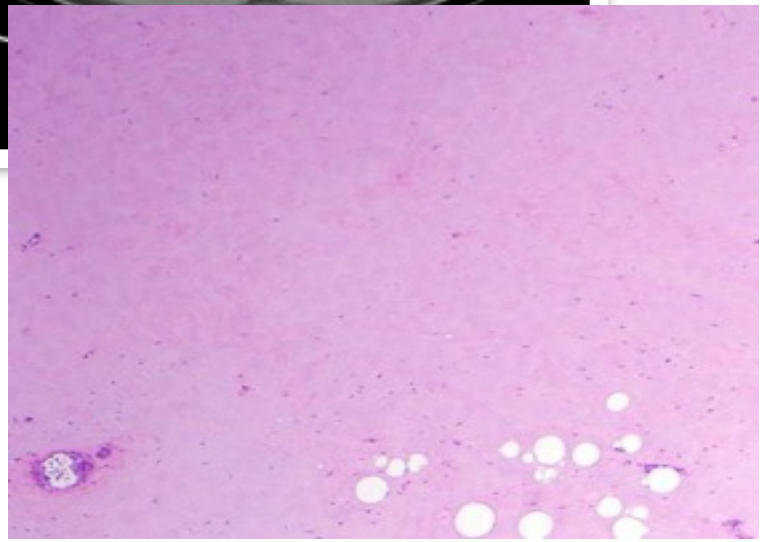
Treatment effect



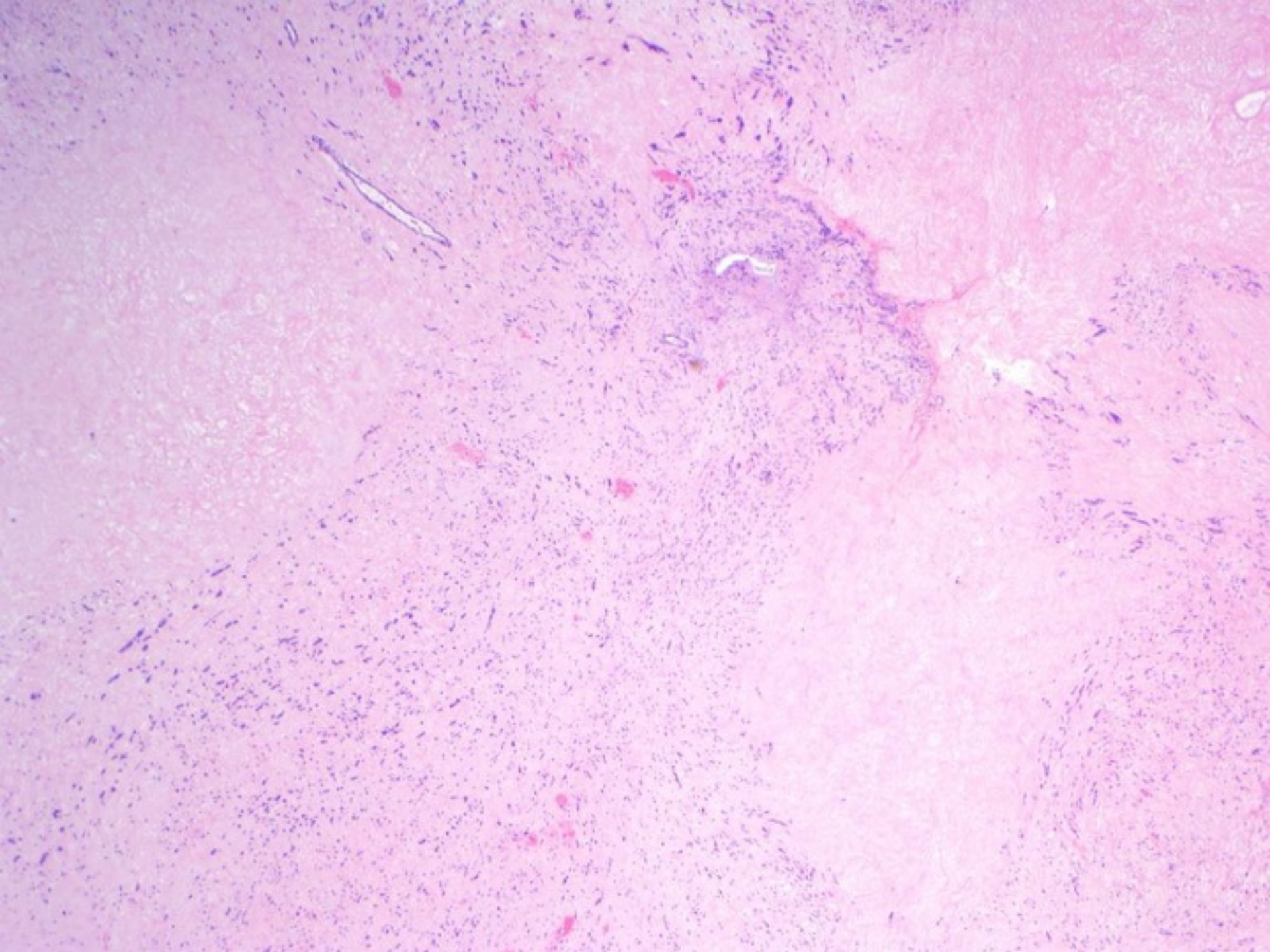


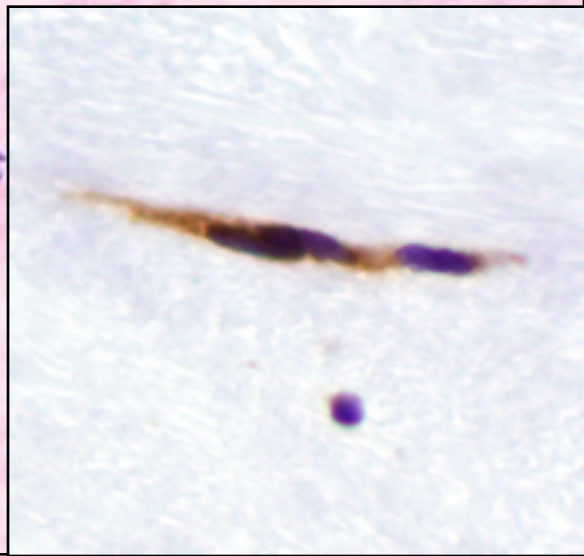
Pre-Imatinib



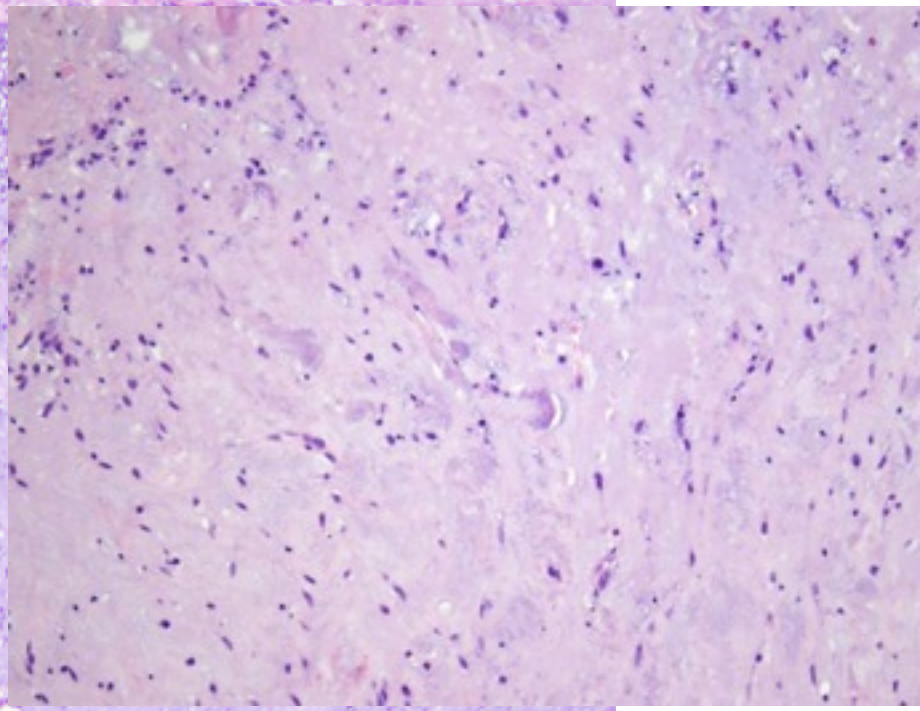


Post-Imatinib (8 weeks therapy)

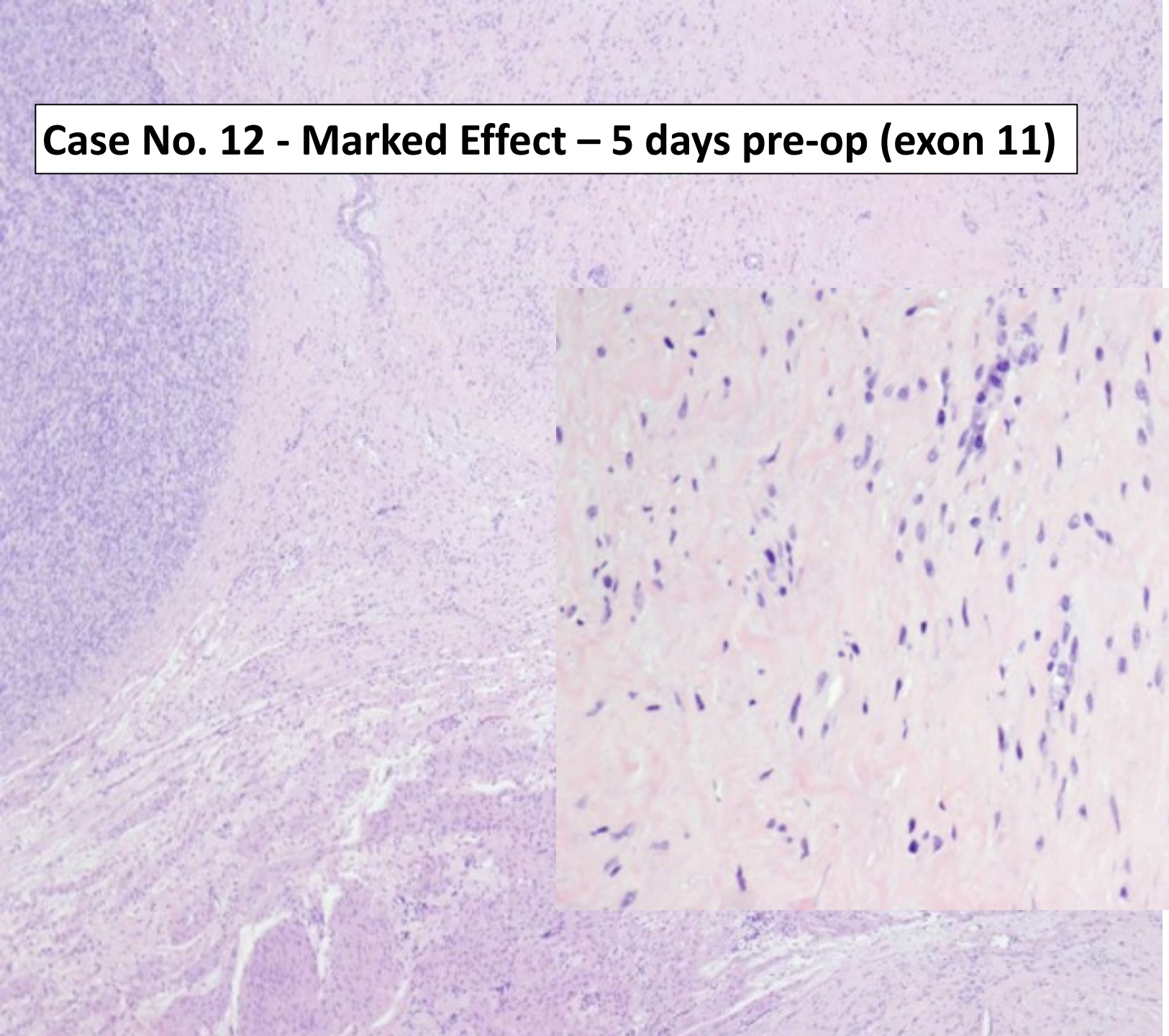




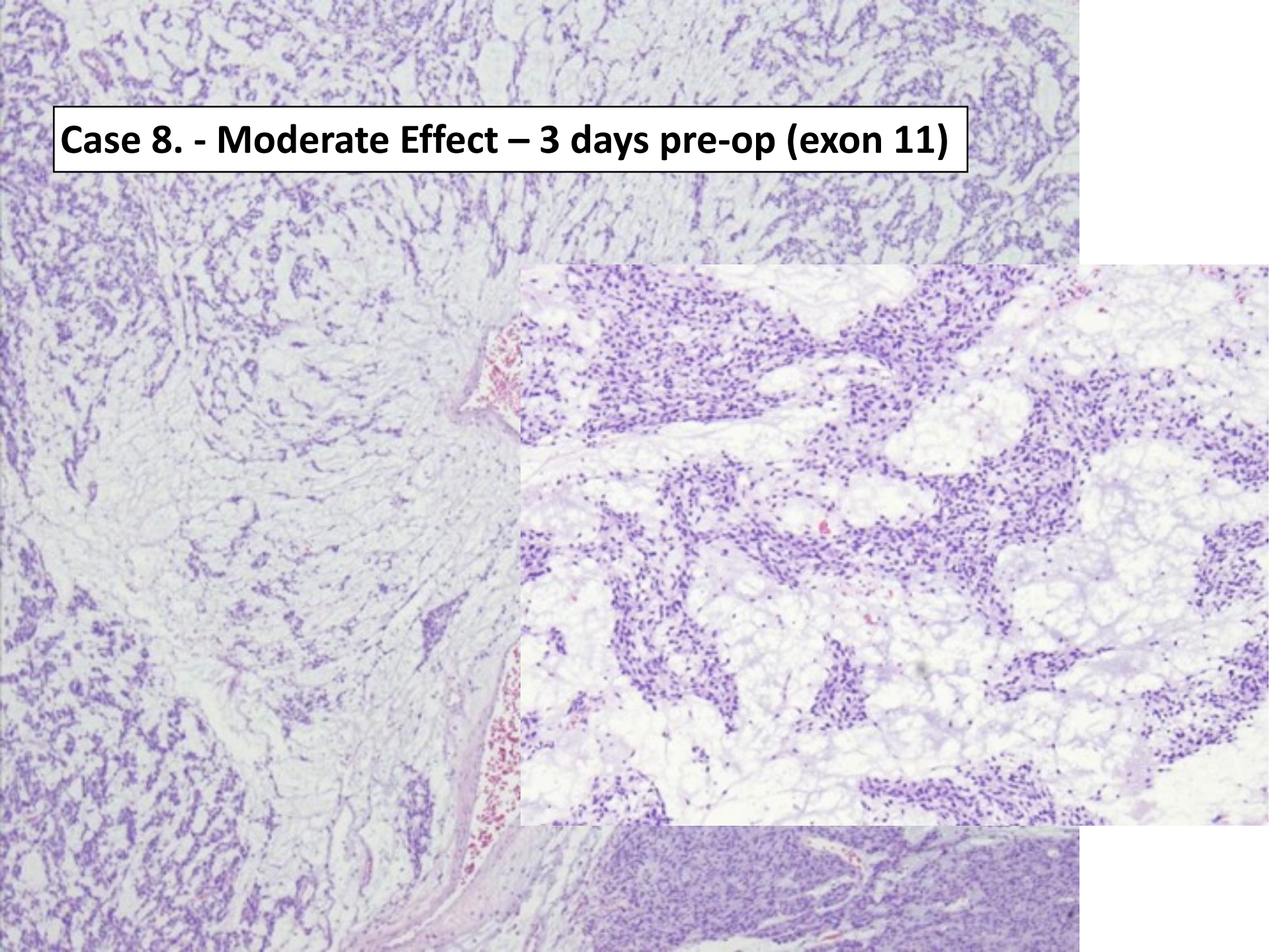
Case No. 22 - Marked Effect – 7 days pre-op (exon 11)

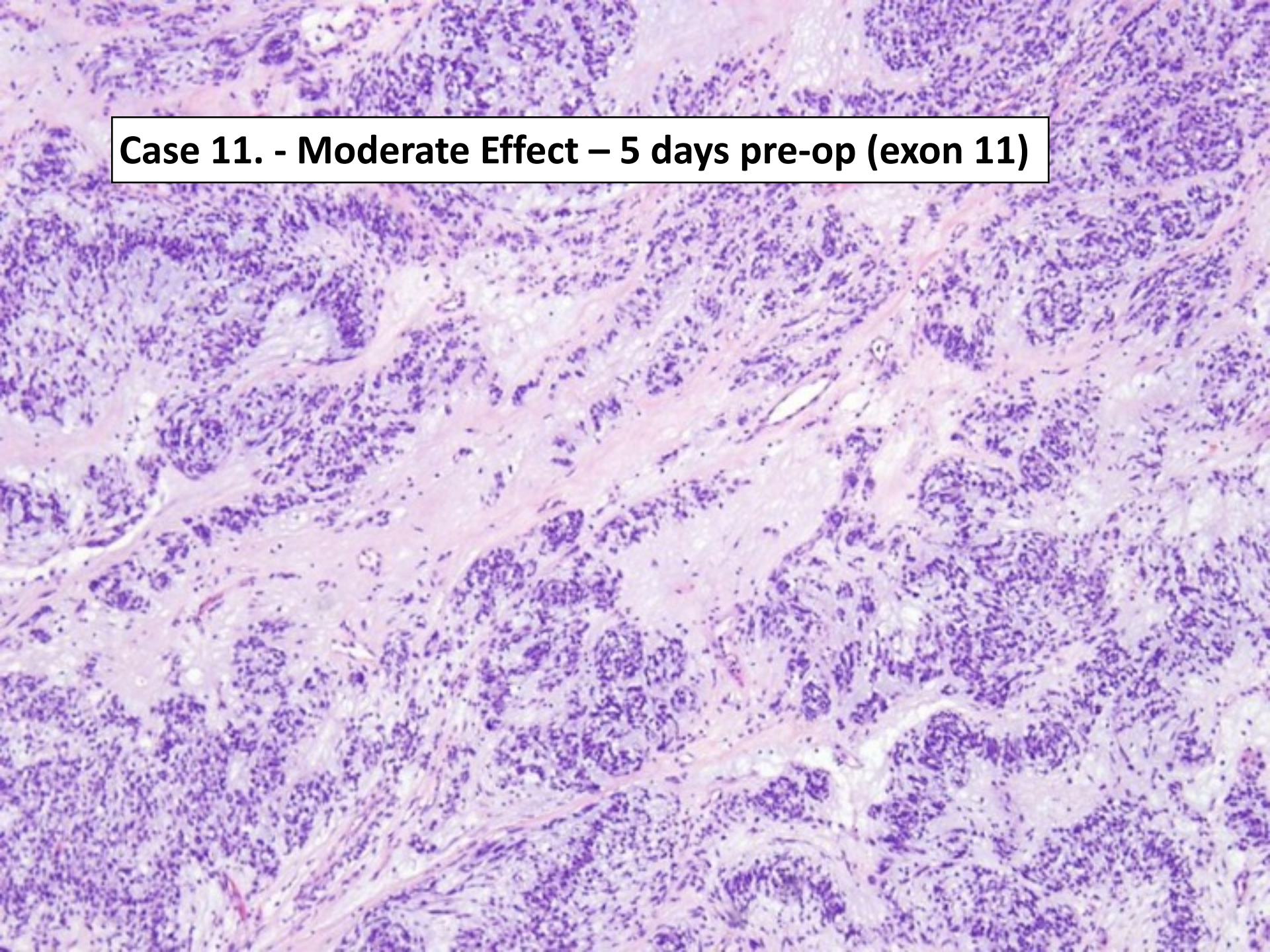


Case No. 12 - Marked Effect – 5 days pre-op (exon 11)

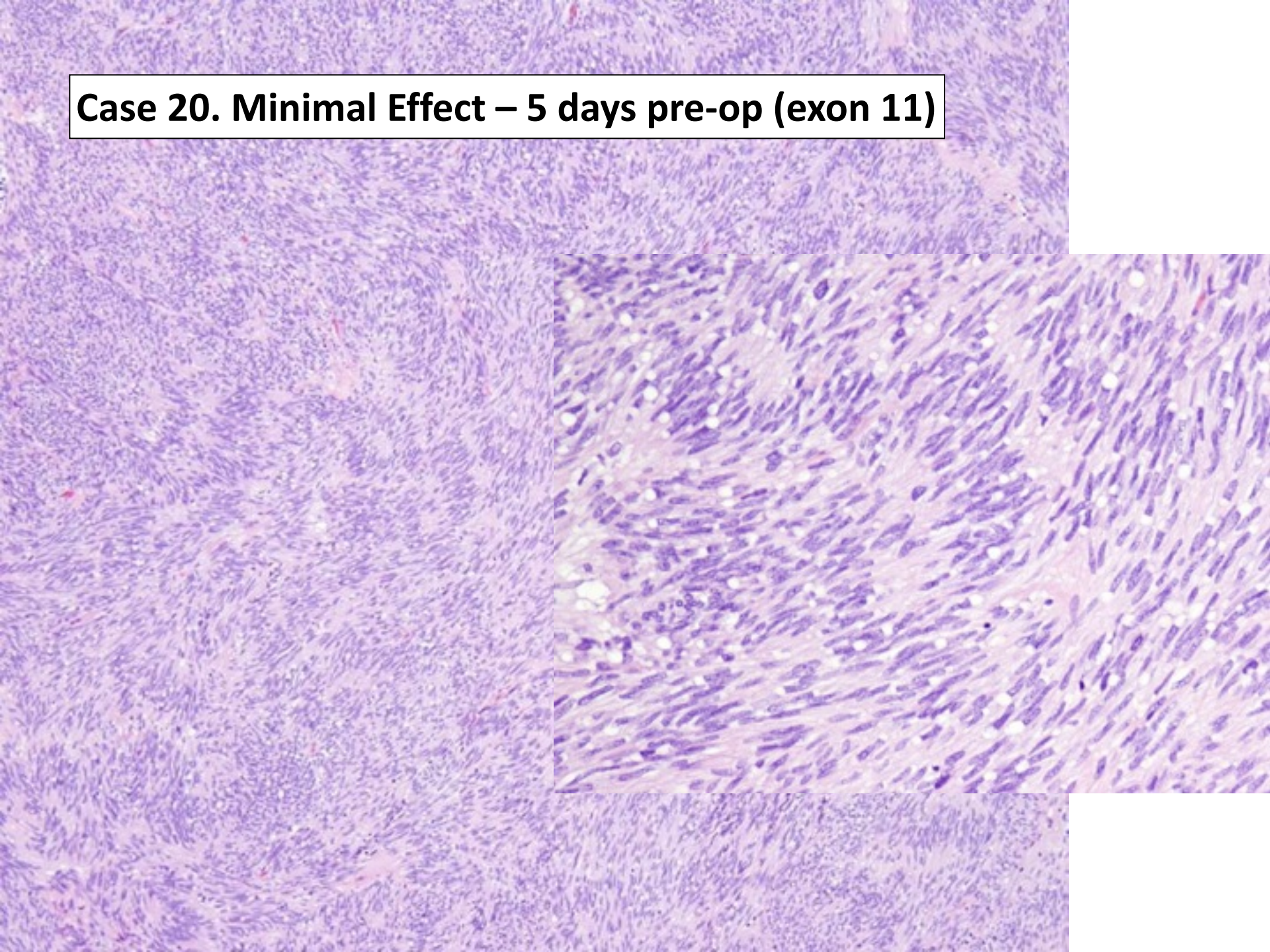


Case 8. - Moderate Effect – 3 days pre-op (exon 11)



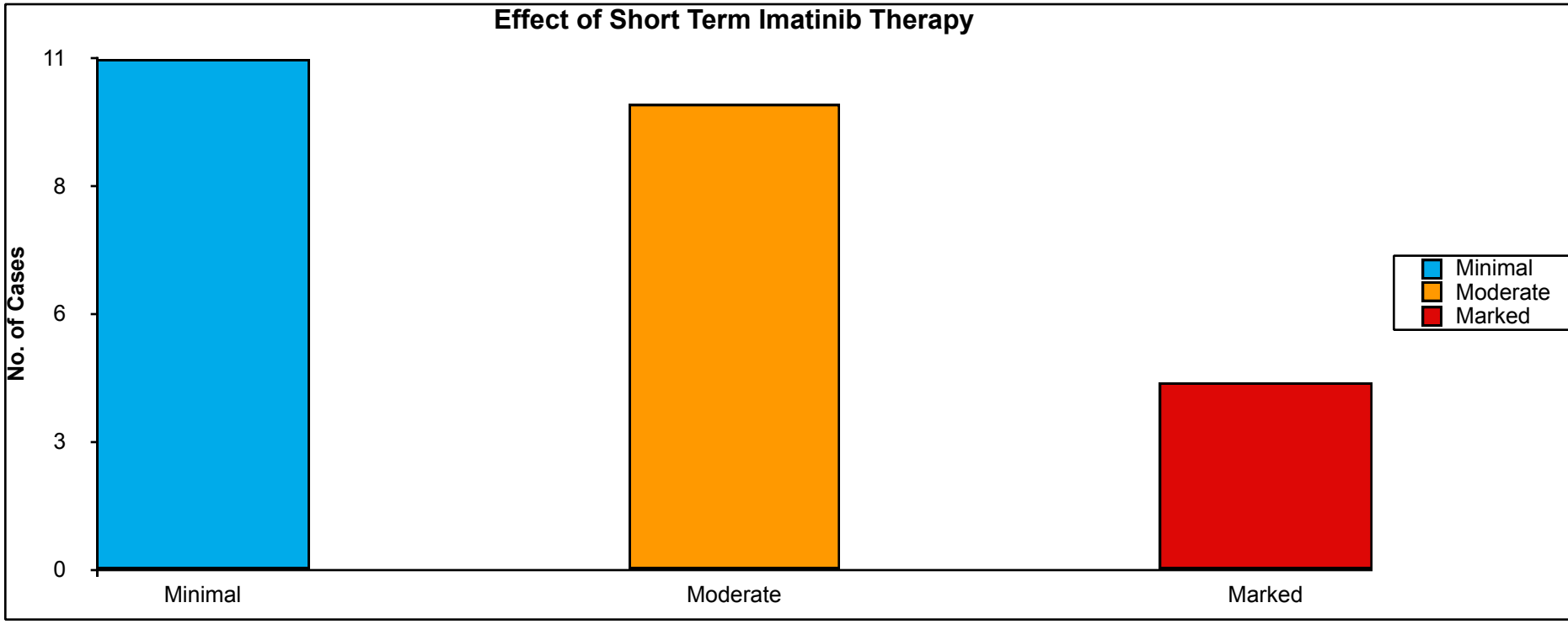

Case 11. - Moderate Effect – 5 days pre-op (exon 11)

Case 20. Minimal Effect – 5 days pre-op (exon 11)

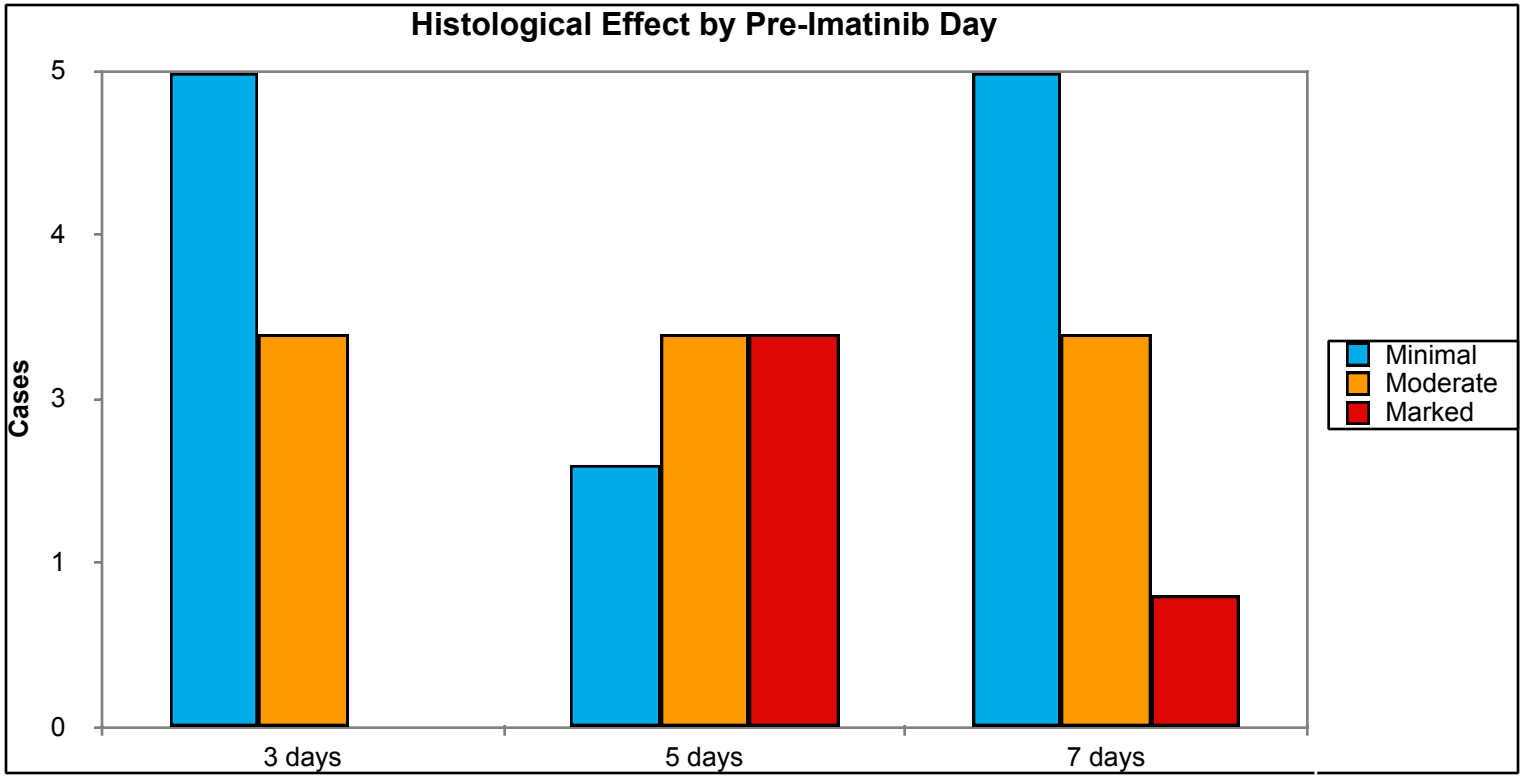


Results

- **Minimal effect: 11/25 (44%)**
- **Moderate effect: 10/25 (40%)**
- **Marked effect: 4/25 (16%)**

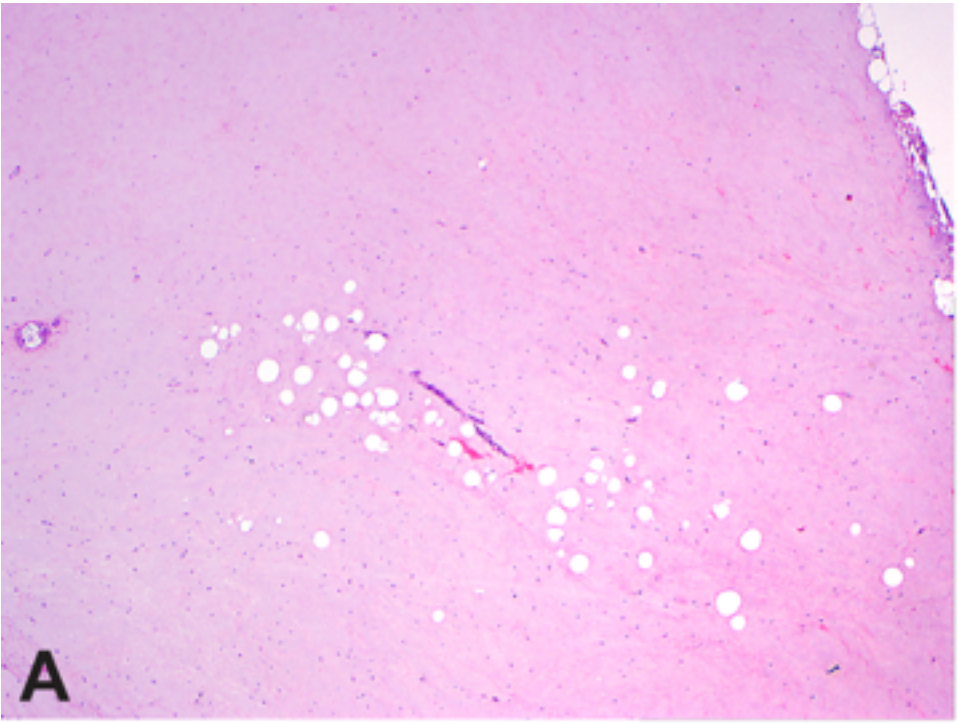


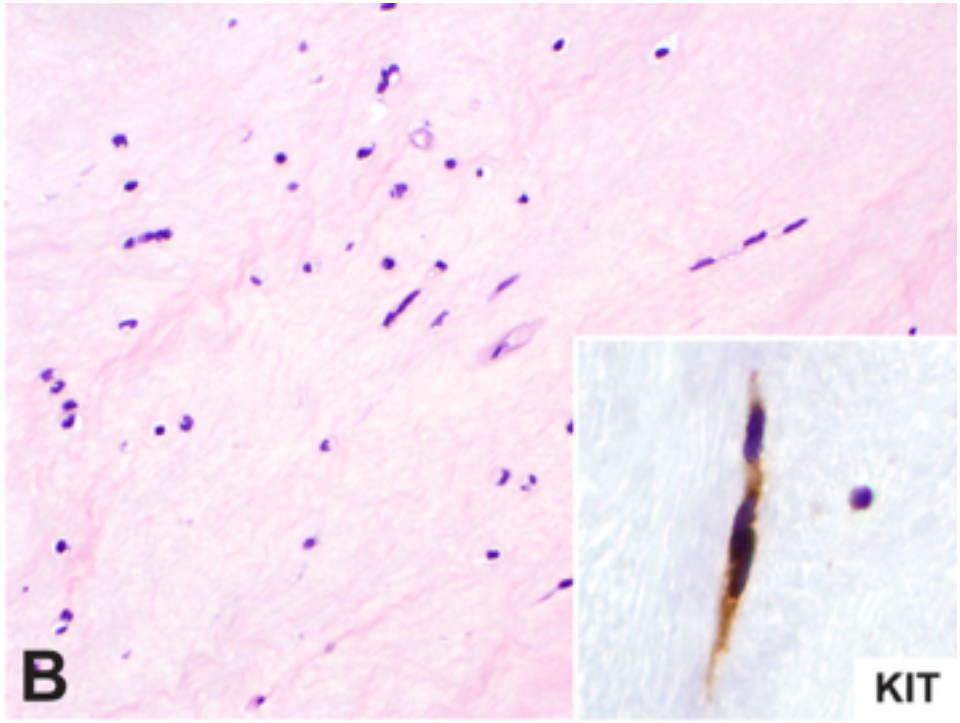
Early Histologic Effects of Imatinib Duration of Therapy



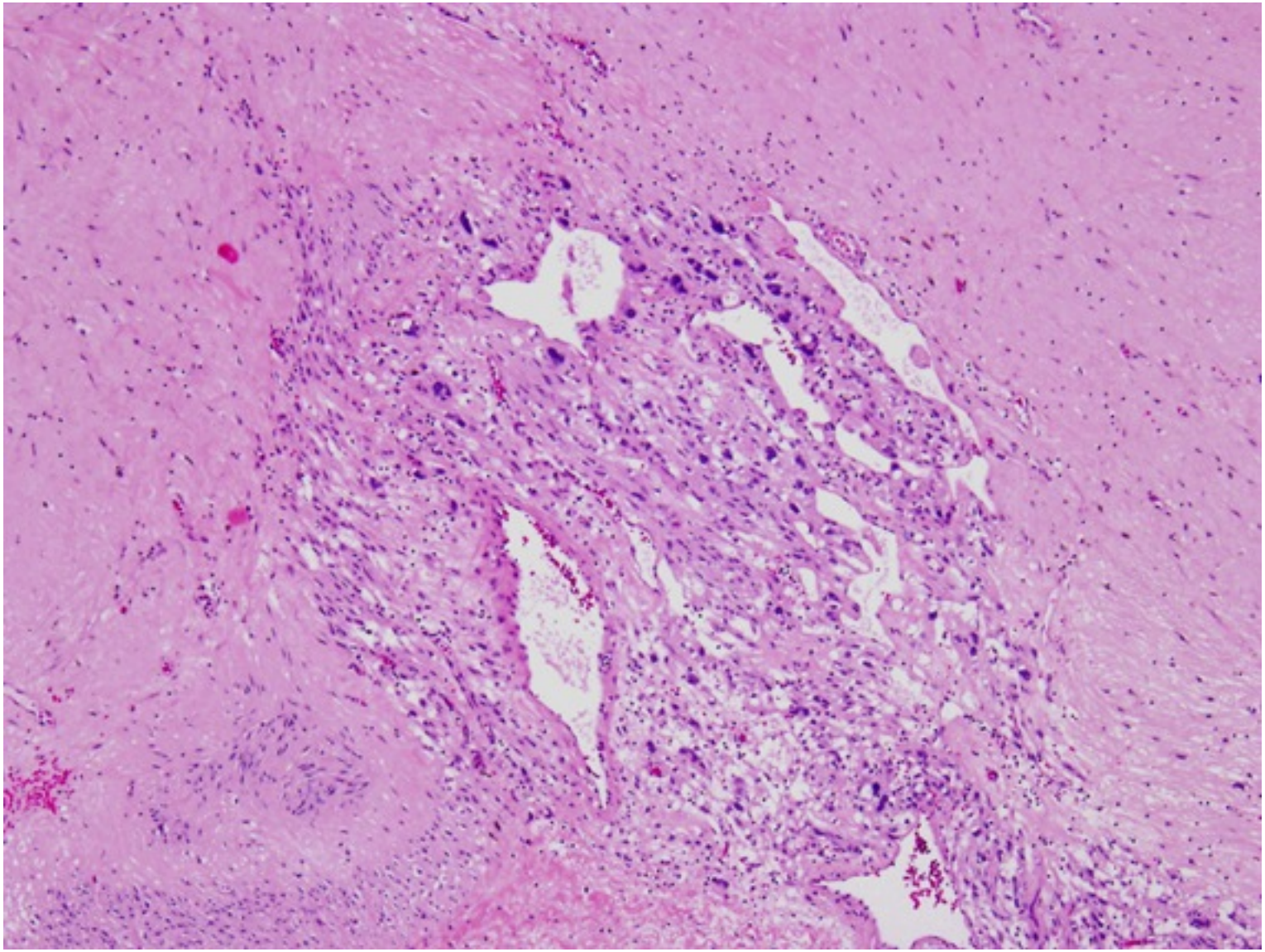
- Minimal and Moderate effects were seen across all durations of therapy
- Marked effect appeared to be a late finding peaking at 5 days

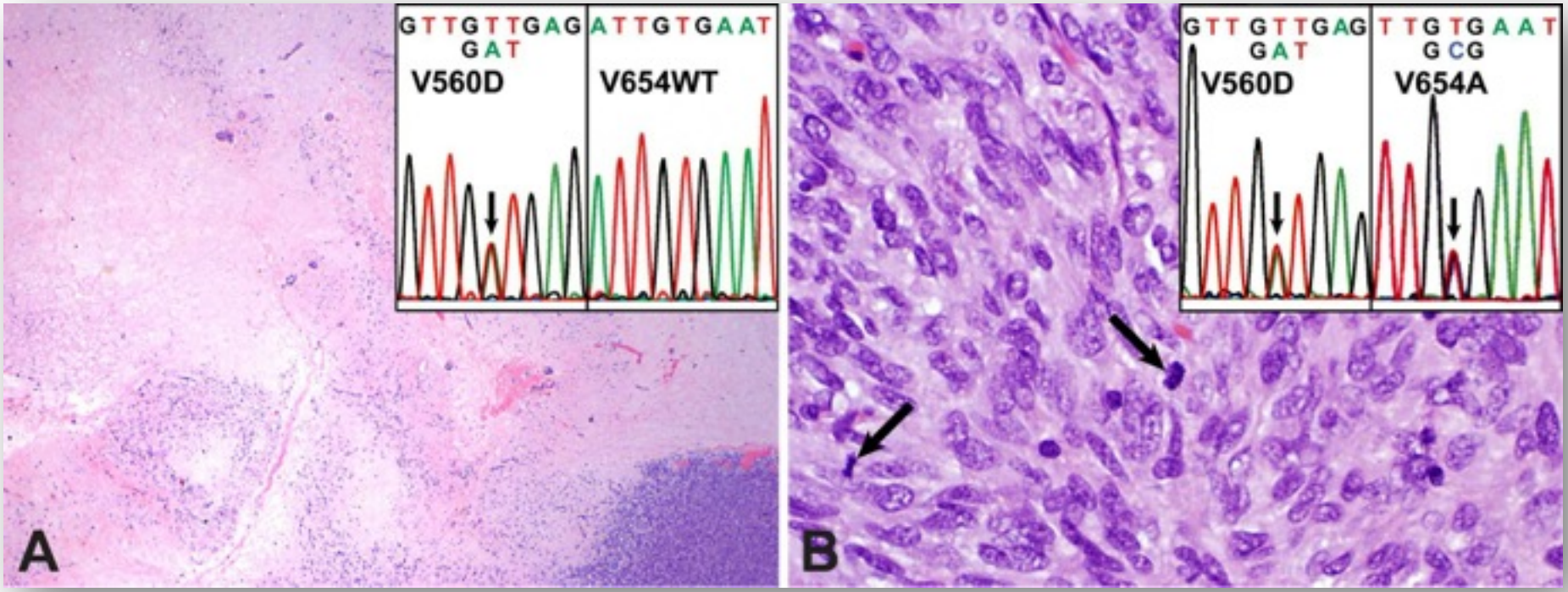
Long term Imatinib Tx





Long term Imatinib Tx




G T T G T T G A G
G A T
V560D
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G T T G T T G A G
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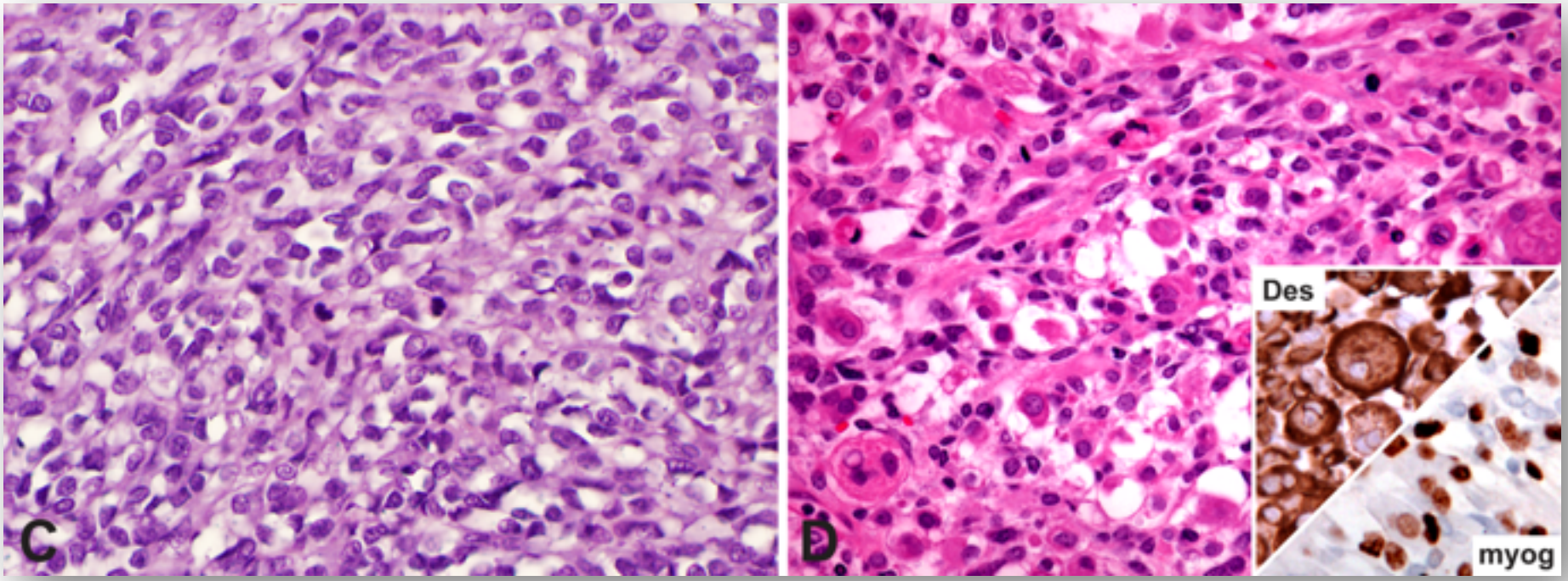
T T G T G A A T
G C G
V654A
B


C
D
Des
myog

Thanks!

Acknowledgements

- **Brian Rubin, Cleveland Clinic.**
- **Jason Hornick, Brigham & Women's Hospital/Harvard**
- **Jean-Michel Coindre & Frederic Chibon, Bordeaux, France (French Sarcoma Group)**
- **Michael Heinrich & Chris Corless, University of Oregon.**
- **Jon Trent, University of Miami.**
- **Many Fine Colleagues at UTMDACC.**