

# GIST 201: The Pathology of GIST: 9<sup>th</sup> Annual GIST Summit (GSI)

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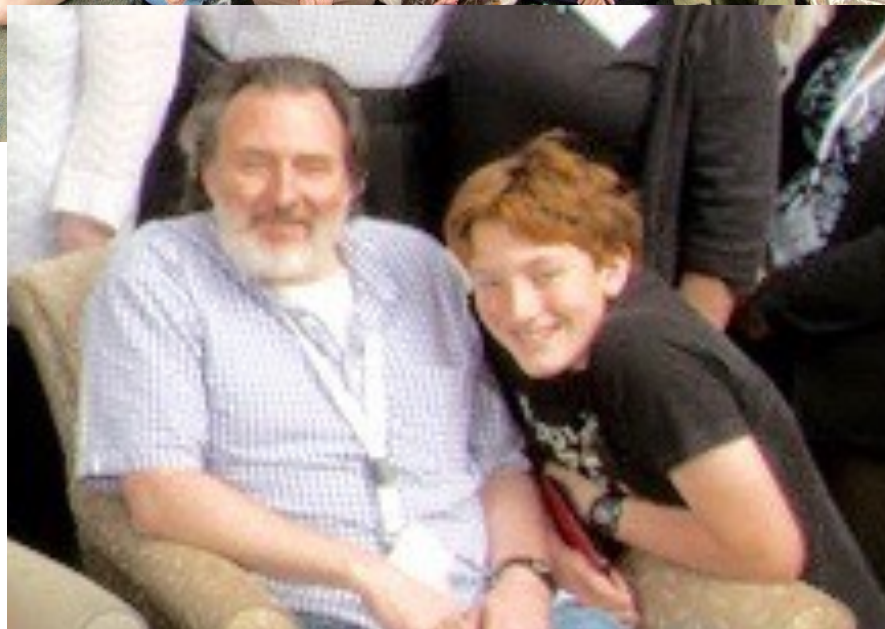
**Saturday 16 September 2017**



# Disclosures

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- **Research Support / Consulting**
  - **AstraZeneca / Medimmune**
  - **BMS**
  - **Novartis**
  - **Roche / Genentech**
  - **Merck**
  - **GlaxoSmithKline**
  - **Myriad**
  - **Oncothyreon**
  - **Life Tech**
  - **Illumina**
  - **GE Healthcare**
  - **Beta-Cat**
  - **ArcherDX**







THE UNIVERSITY OF TEXAS  
MD ANDERSON CANCER CENTER  
Houston, TX

















GROCERY LIST

- Paper plates
- Paper towels
- bread or buns
- milk
- toilet paper

that was easy.

Pampers

WATER  
MILK  
BREAD





# ***GIST Pathology: Lecture Overview***

- 1. What information should be in my pathology report?**
- 2. Why is this information there?**
- 3. 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.**





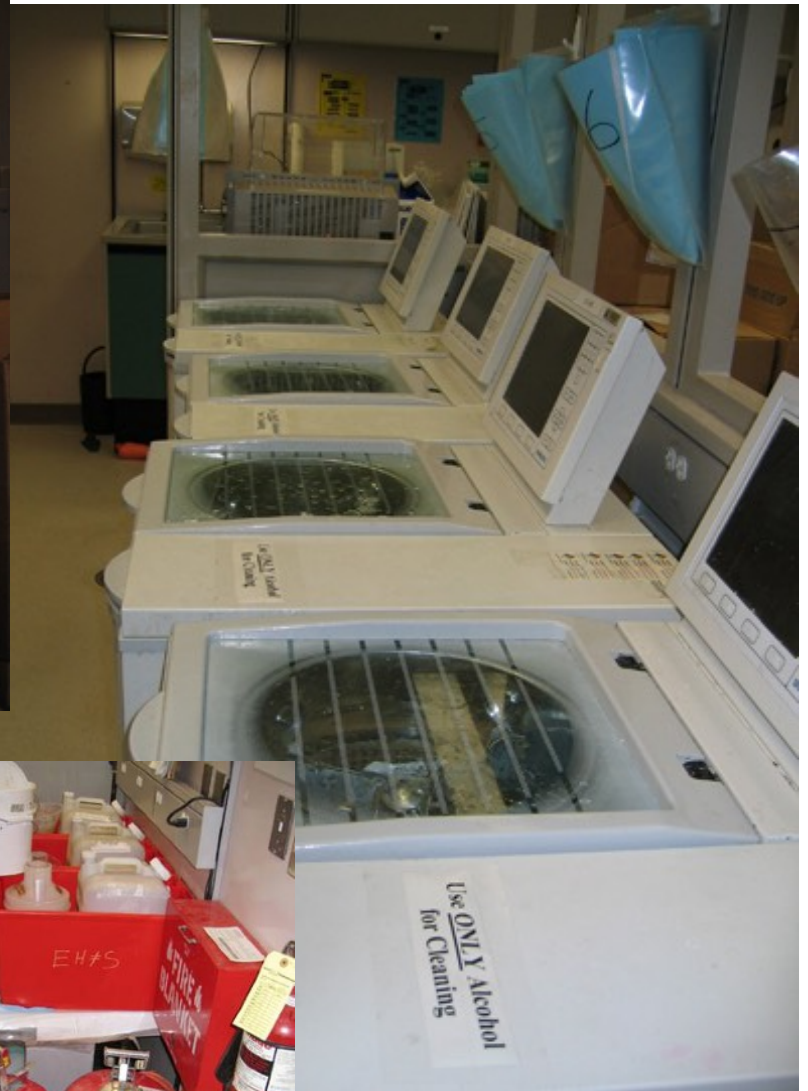


**Tumor is sampled and placed in plastic cassettes for further processing.**

**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.**



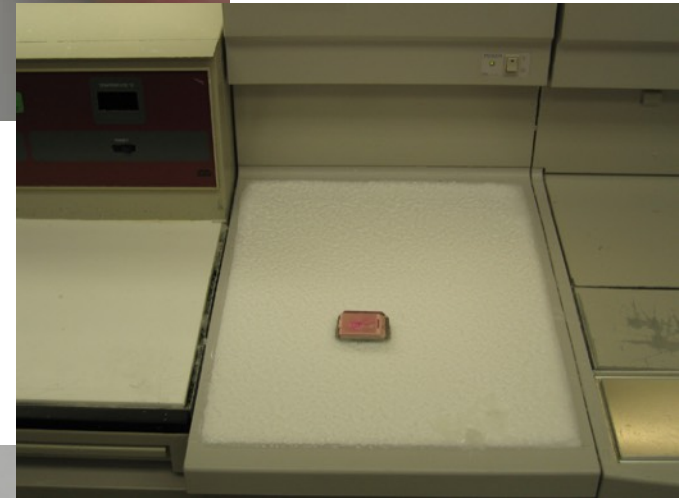
**Tissue processing is done overnight and utilizes graded treatments of formalin, ethanol, xylene and paraffin.**



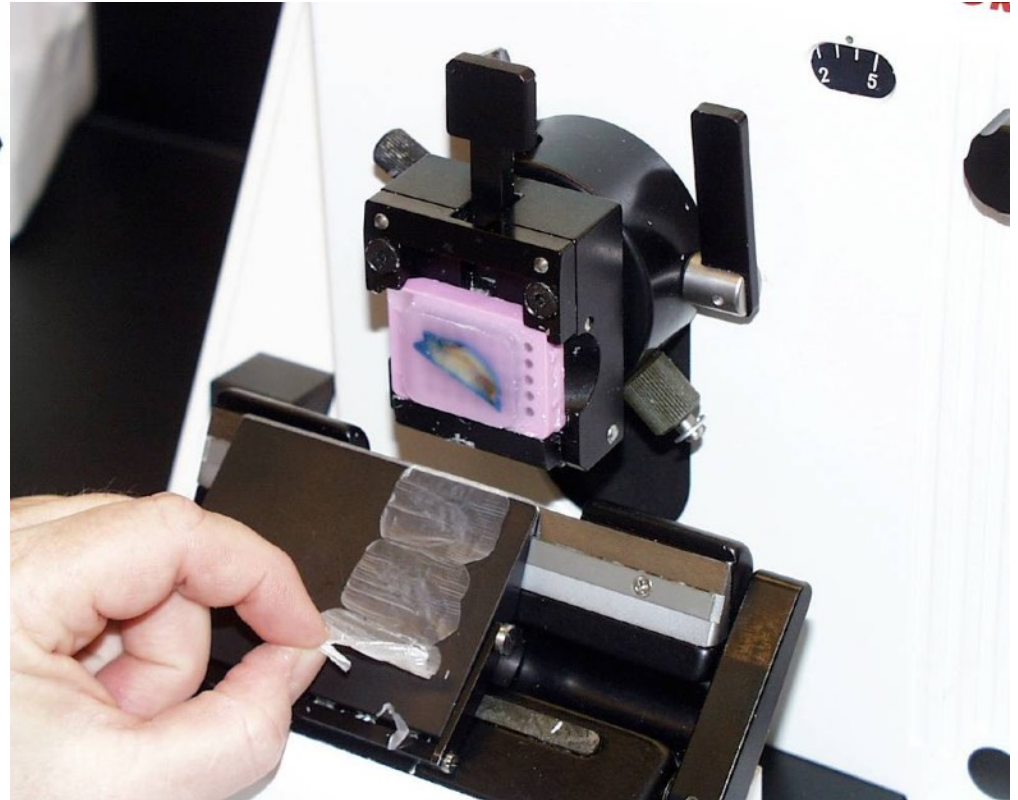
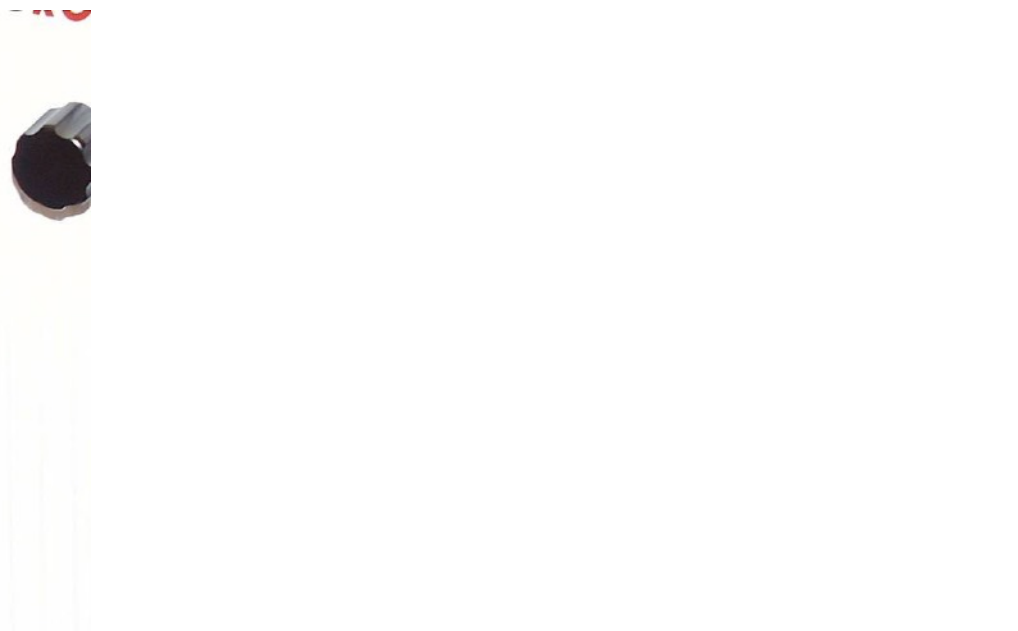
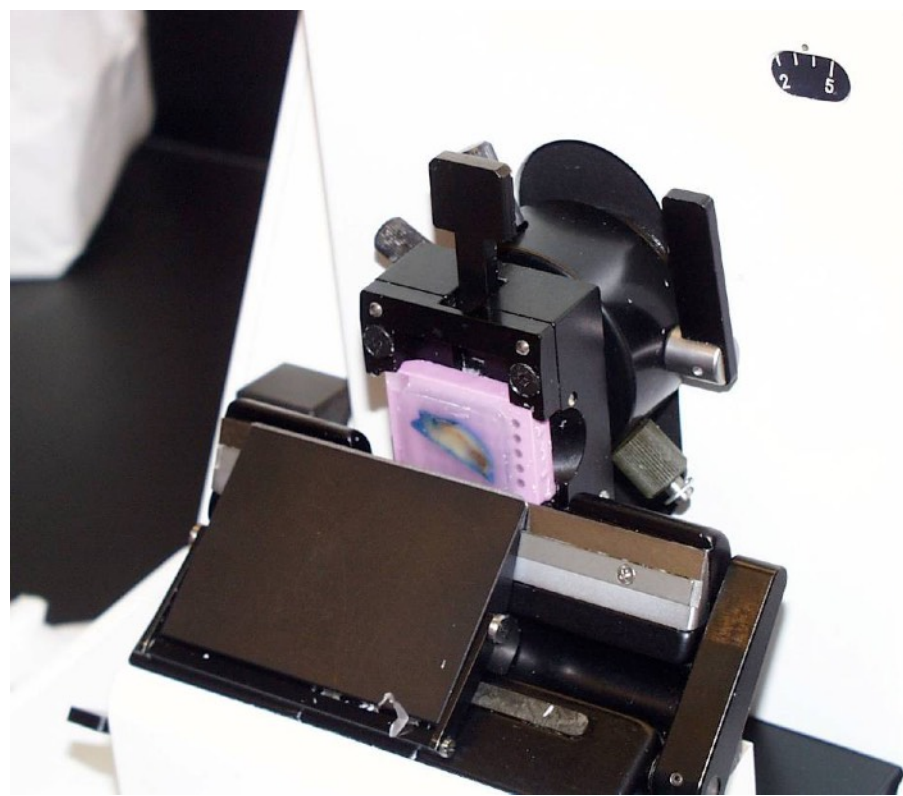


**Blocks are retrieved from the tissue processor.**

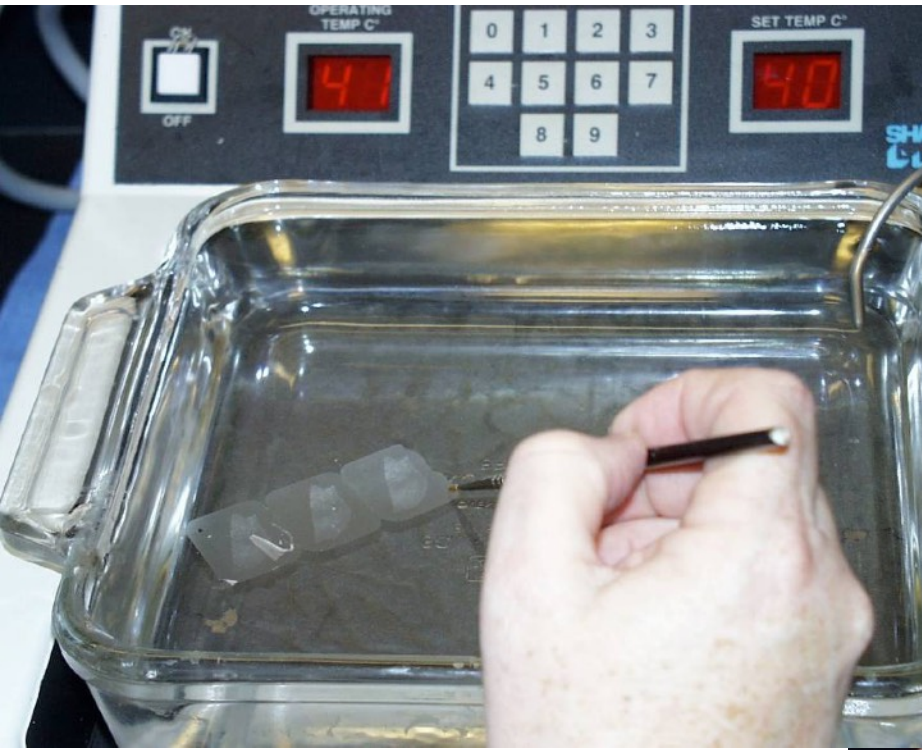




**The tissue fragments are embedded in a paraffin mold and cooled – resulting in a tissue block.**



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



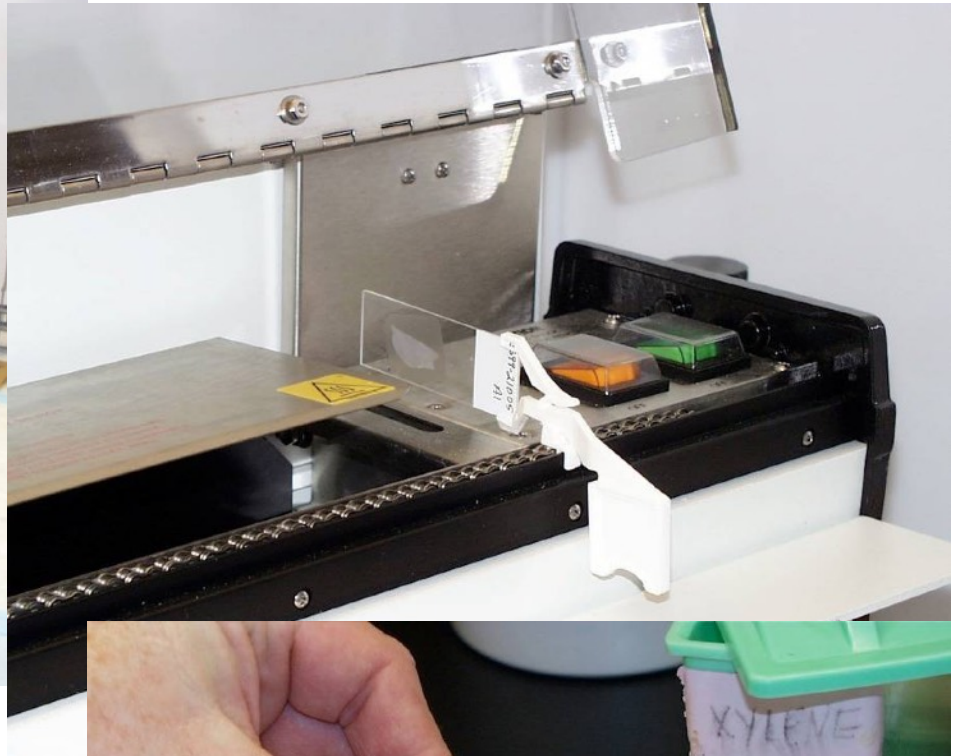
**Tissue paraffin ribbons are placed in a warm waterbath and then picked up on glass slides.**



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 should be in  
my pathology report?***



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

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Based on AJCC/UICC TNM, 7<sup>th</sup> edition

Protocol web posting date: June 2012

### Procedures

- Biopsy
- Resection

### Authors

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For the Members of the Cancer Committee, College of American Pathologists

\* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.

## Surgical Pathology Cancer Case Summary

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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 mm<sup>2</sup> on the glass slide section. With the use of older model microscopes, 50 HPF is equivalent to 5 mm<sup>2</sup>. Most modern microscopes with wider 40X lenses/fields require only 20 HPF to embrace 5 mm<sup>2</sup>. If necessary please measure field of view to accurately determine actual number of fields required to be counted on individual microscopes to count 5 mm<sup>2</sup>.*

**+ Necrosis**

+ \_\_\_ Not identified

+ \_\_\_ Present

+ Extent: \_\_\_%

+ \_\_\_ Cannot be determined

**Histologic Grade (Note B)**

- GX: Grade cannot be assessed
- G1: Low grade; mitotic rate  $\leq 5/50$  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

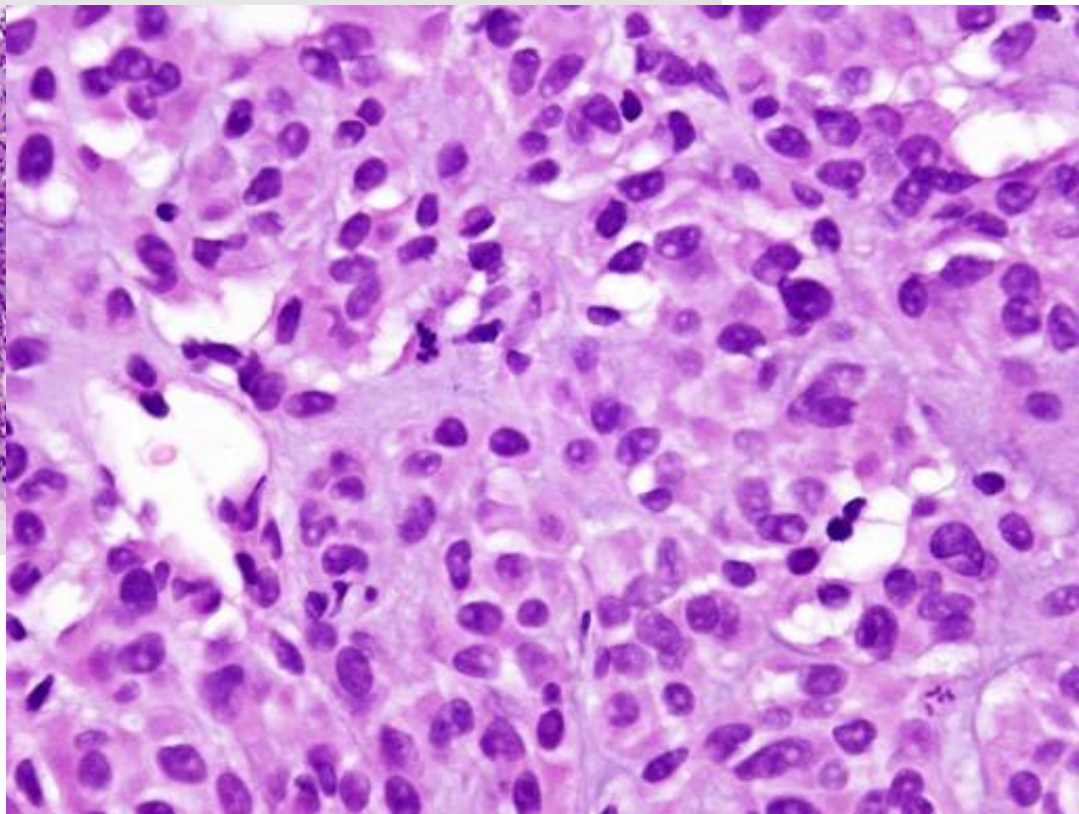
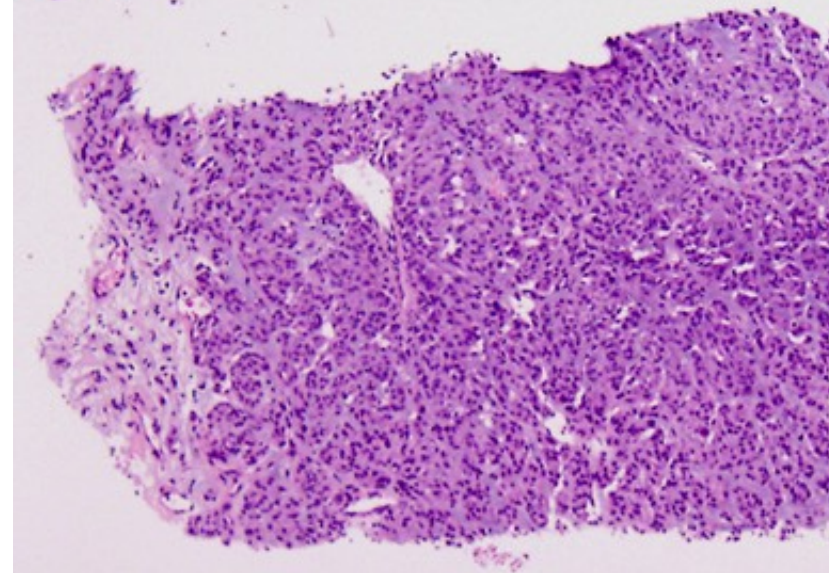
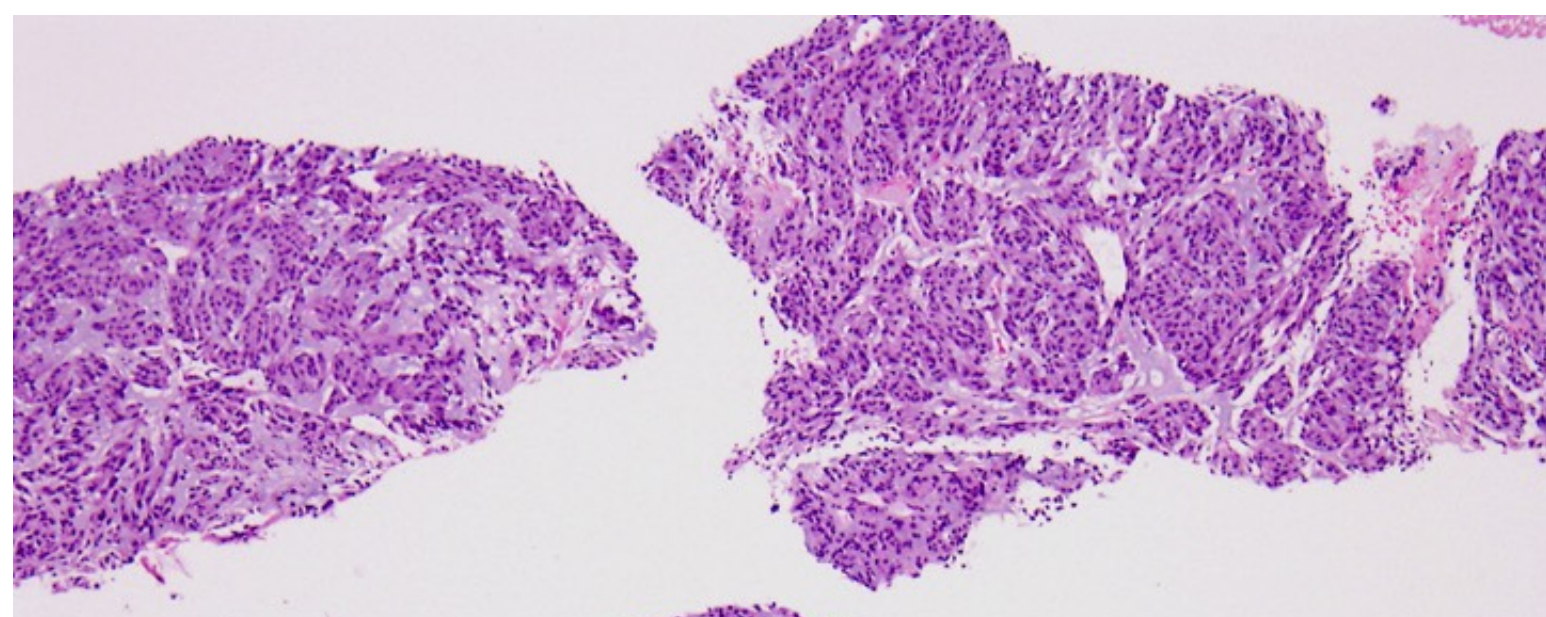
**+ Treatment Effect (Note F)**

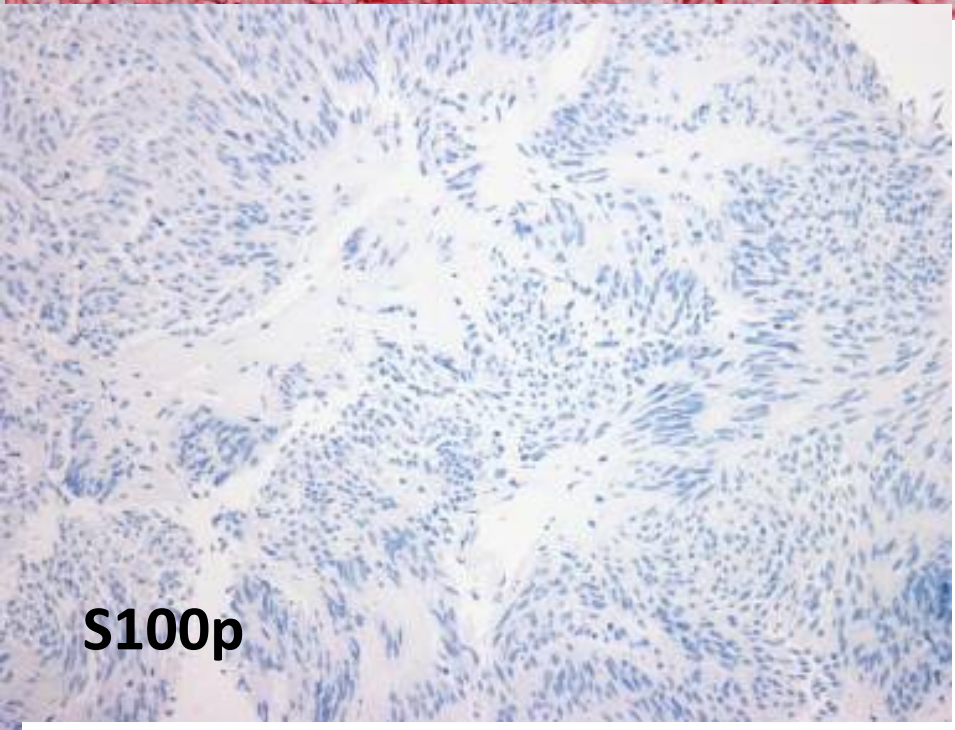
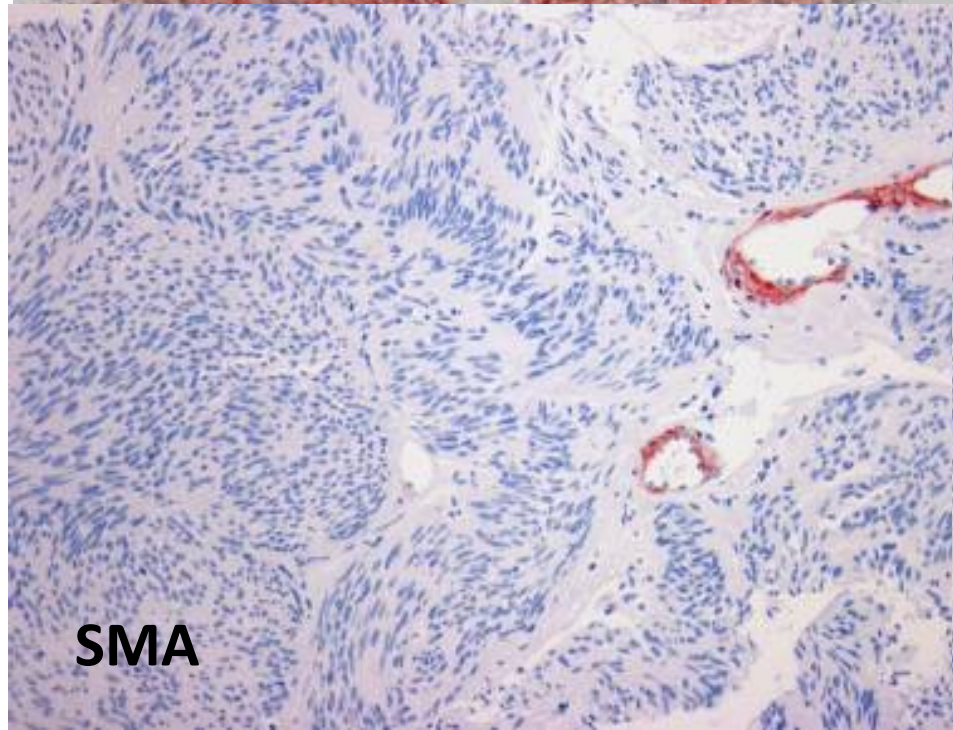
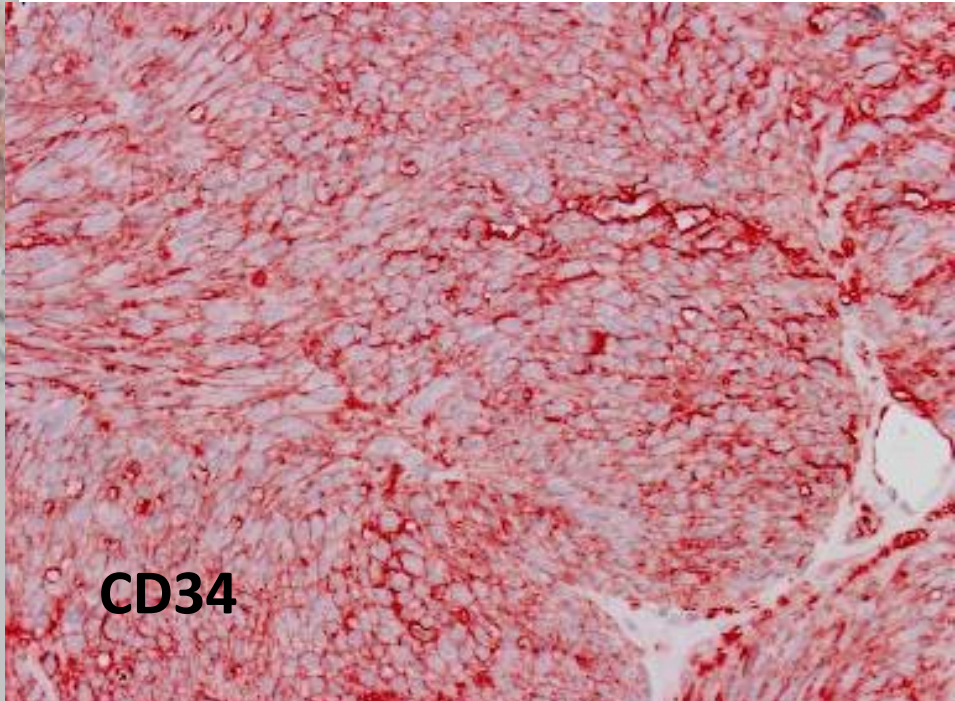
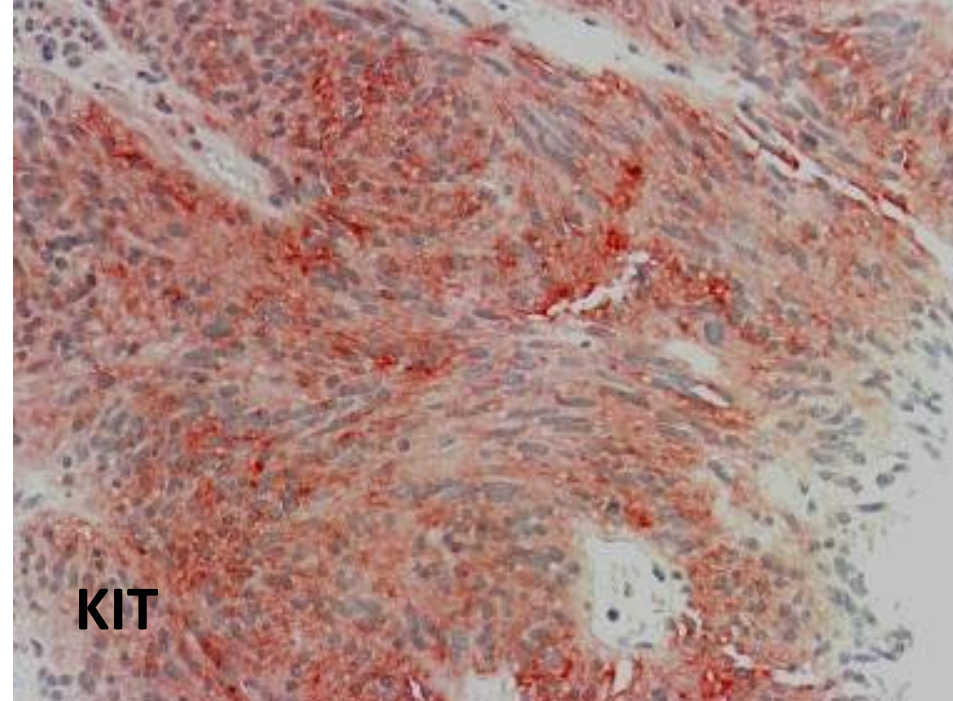
+ Specify percentage of viable tumor: \_\_\_%

**+ Comment(s)**

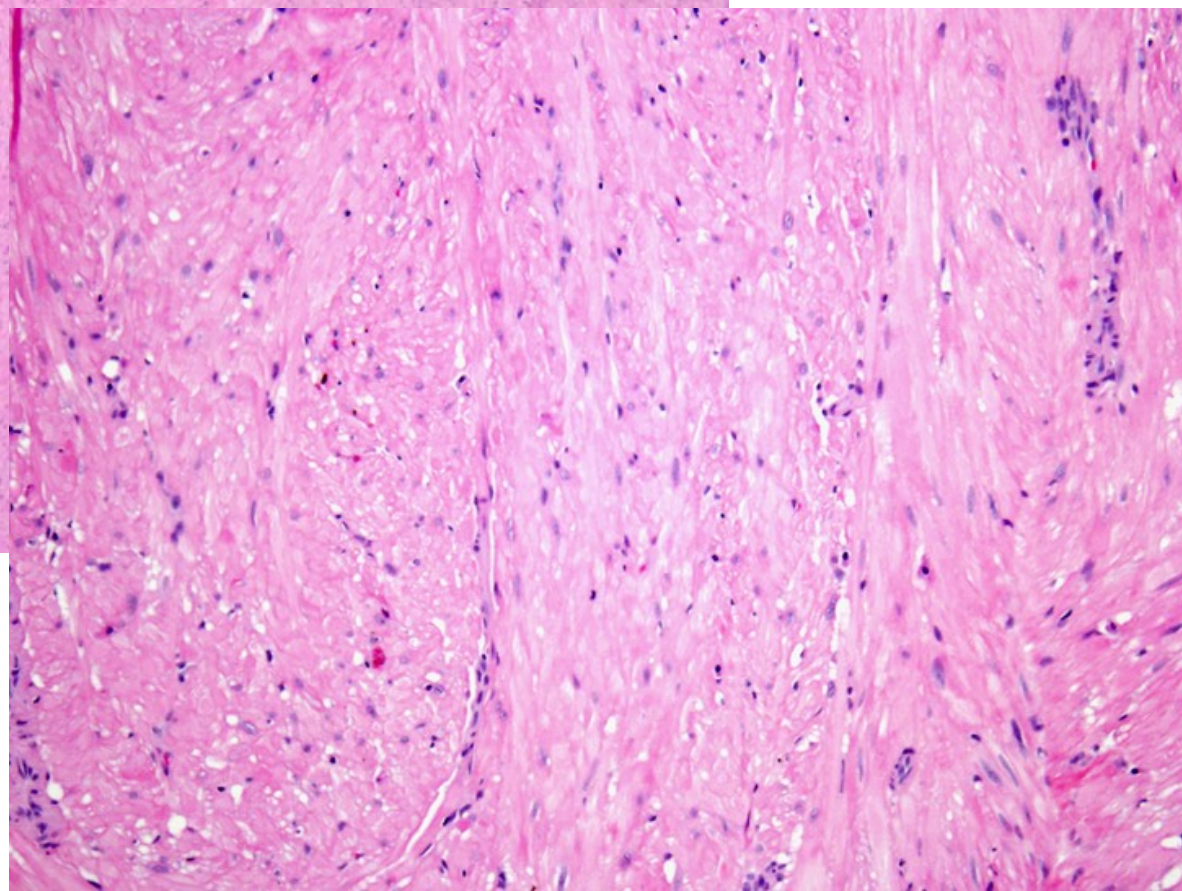
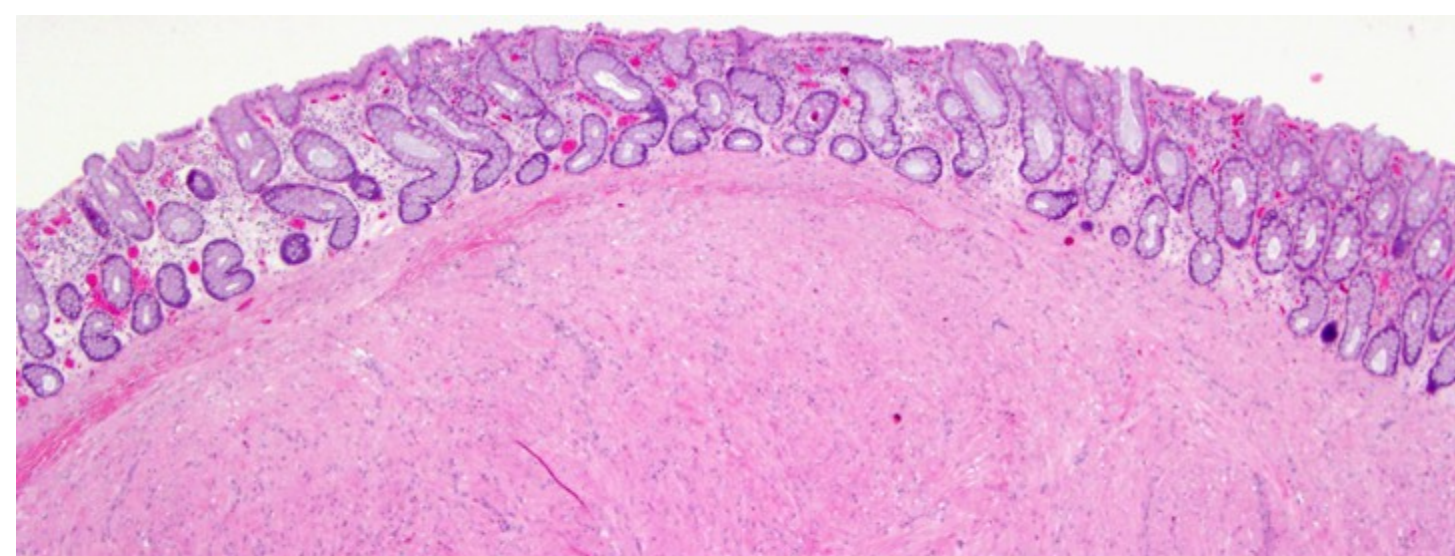
***Getting the diagnosis right***

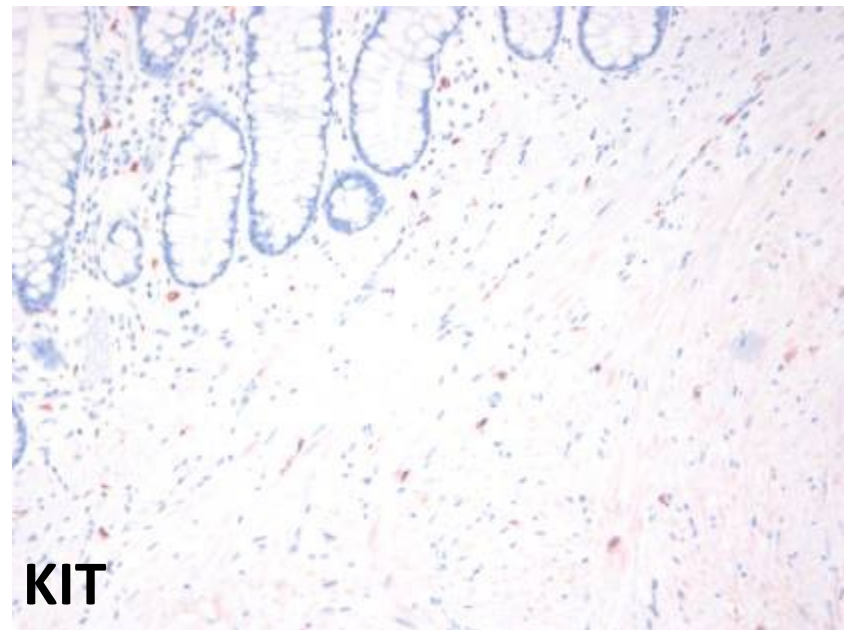
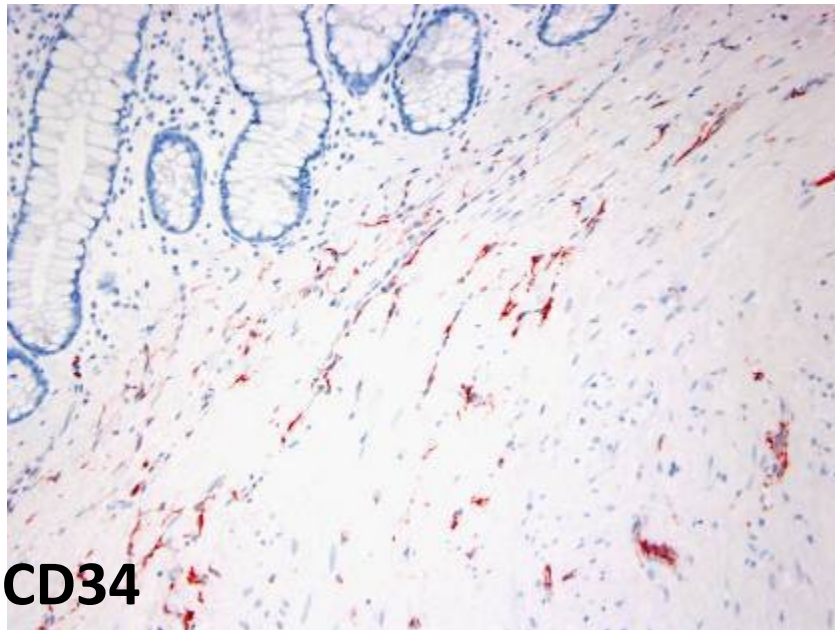
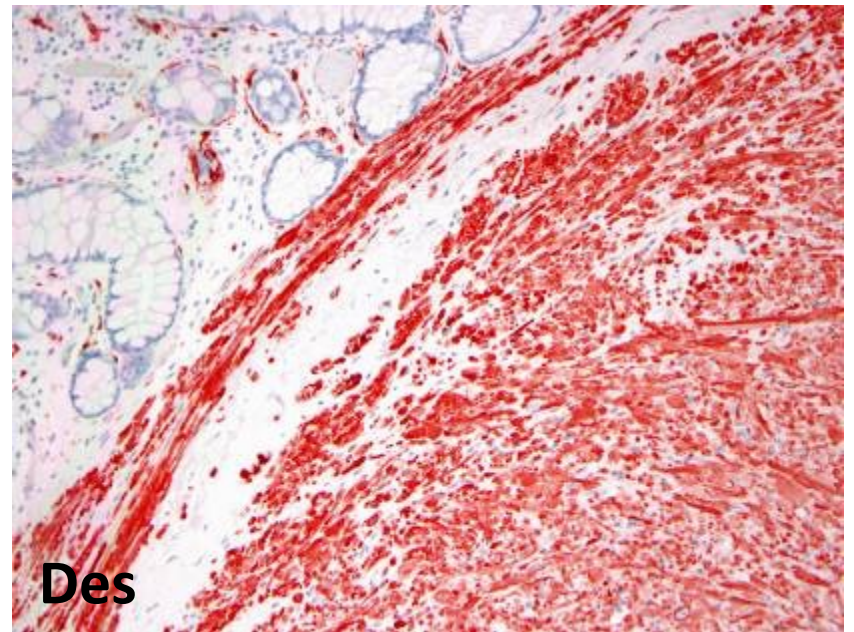
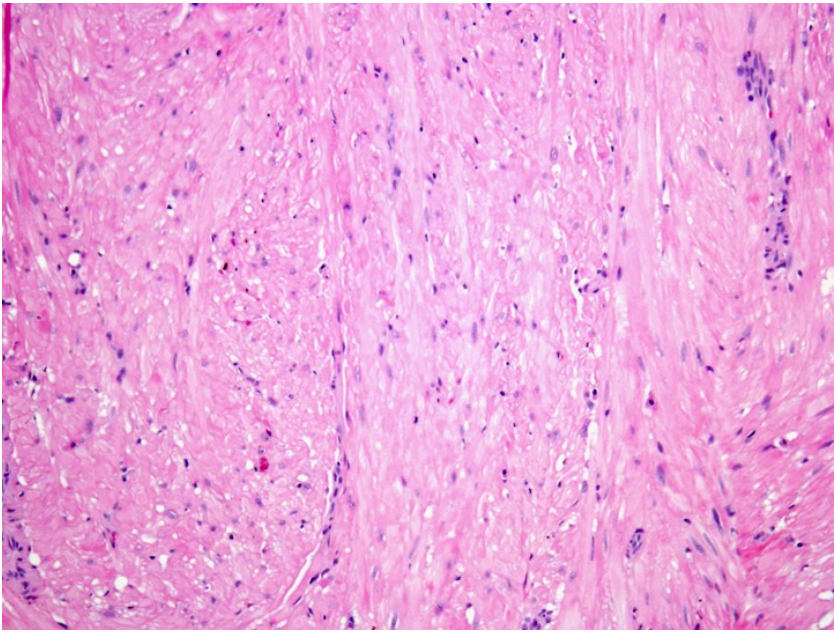
# ***Case 1***





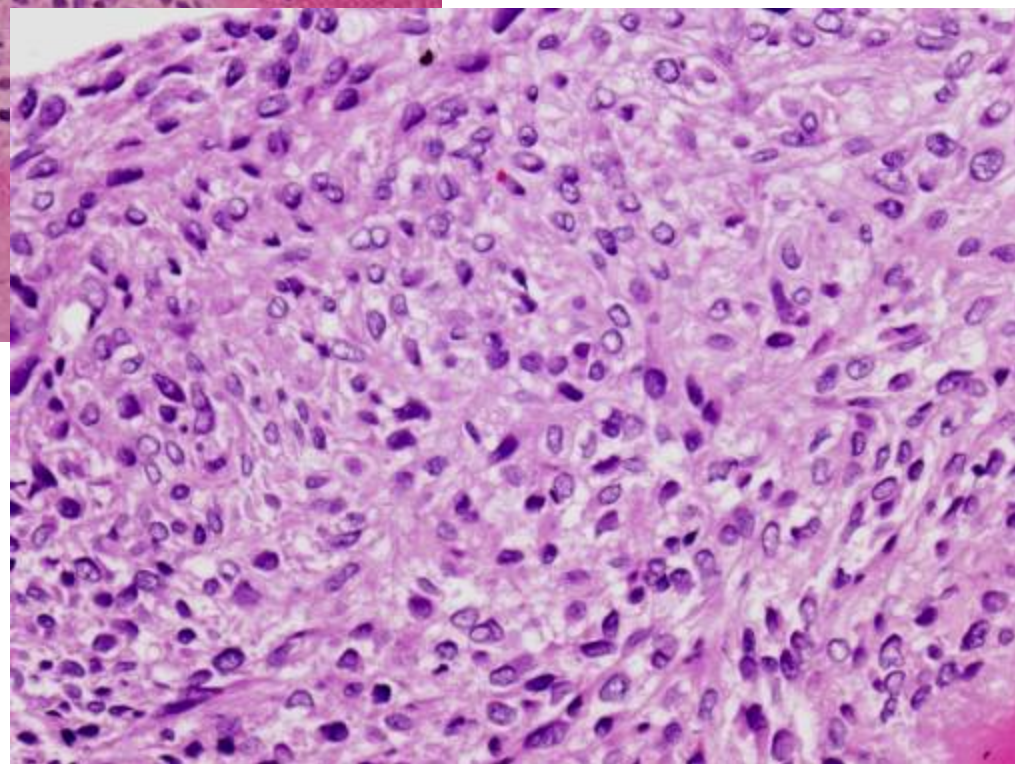
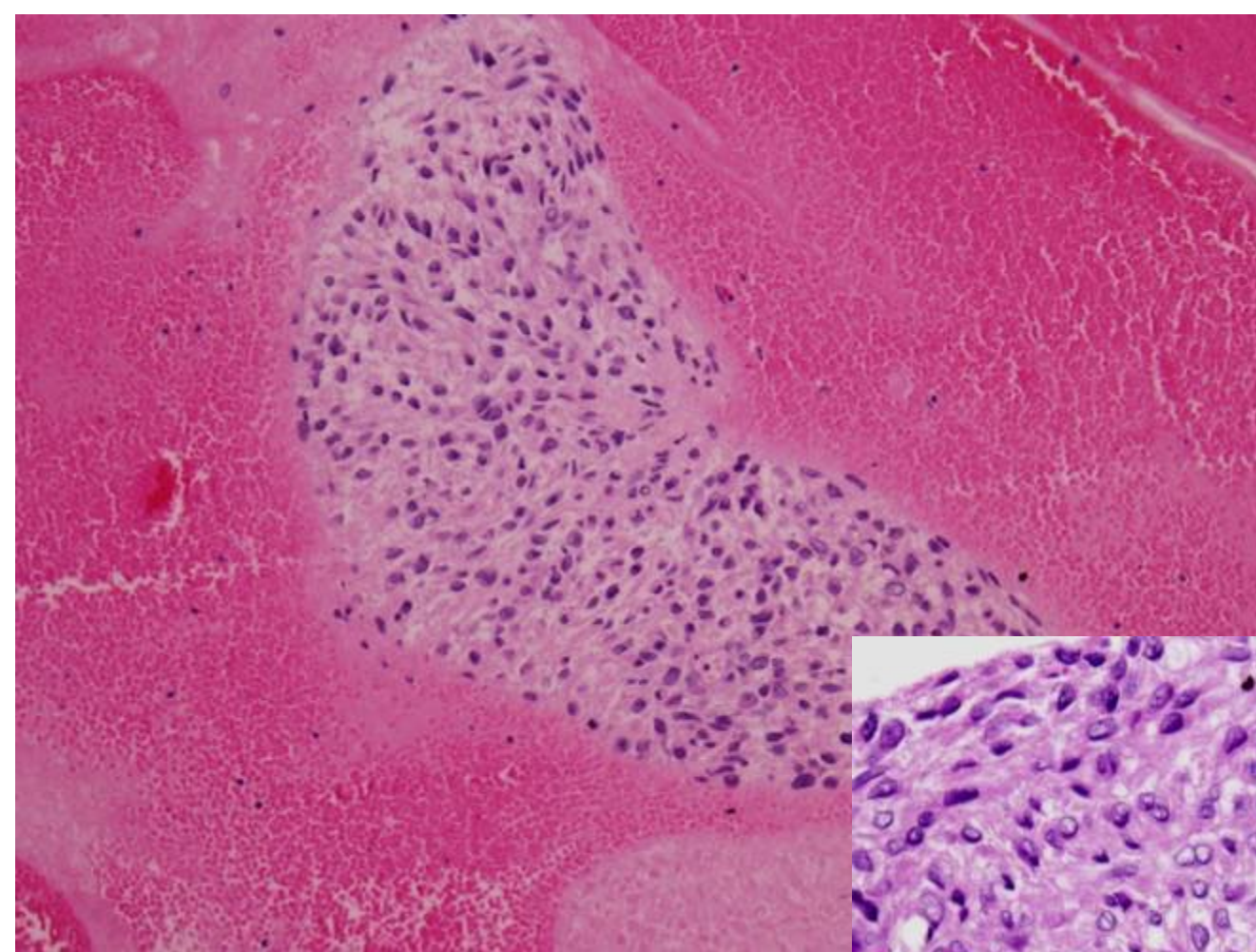
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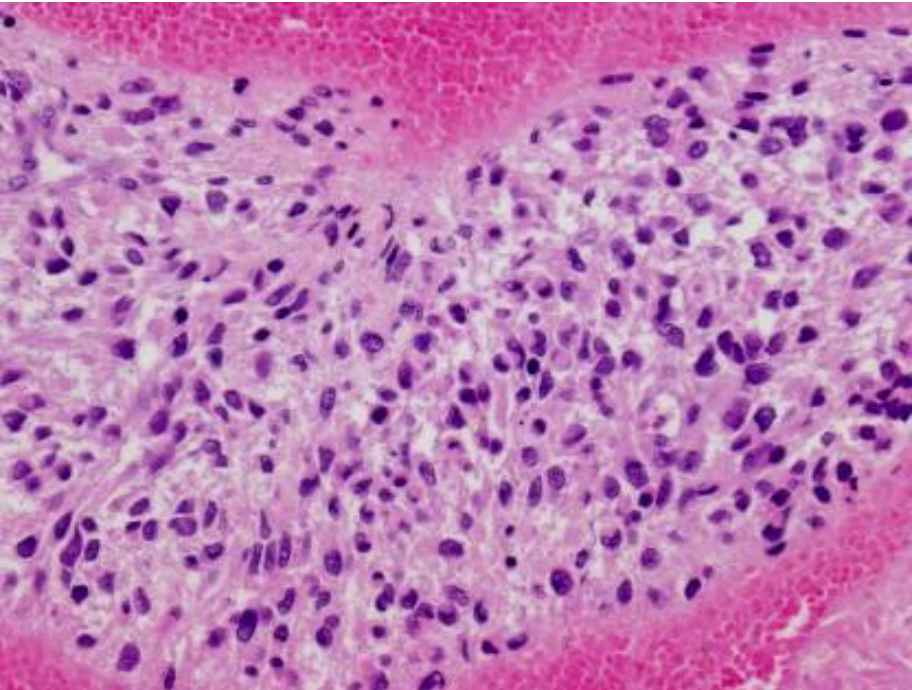




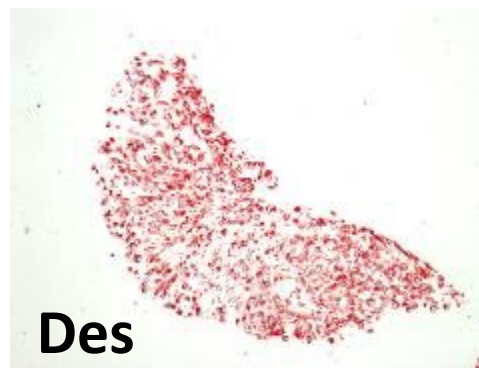


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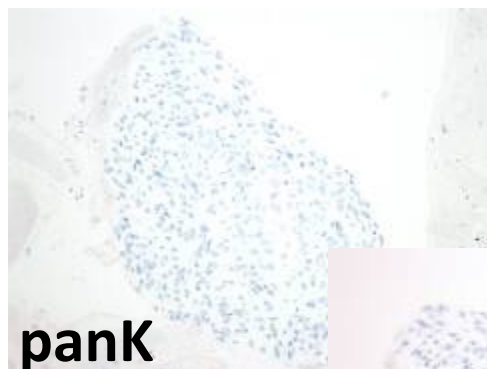




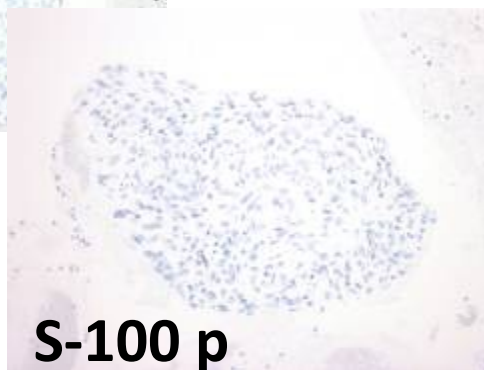
**SMA**



**Des**



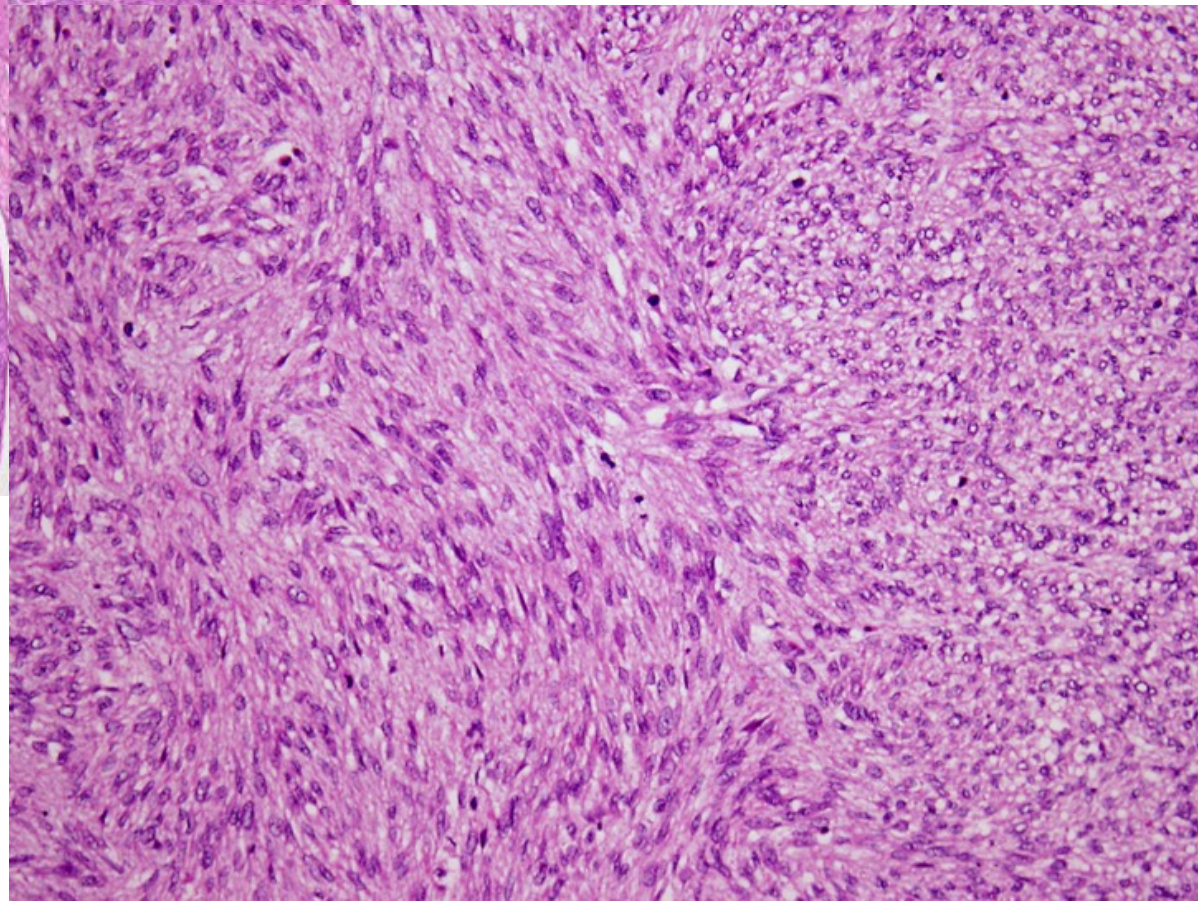
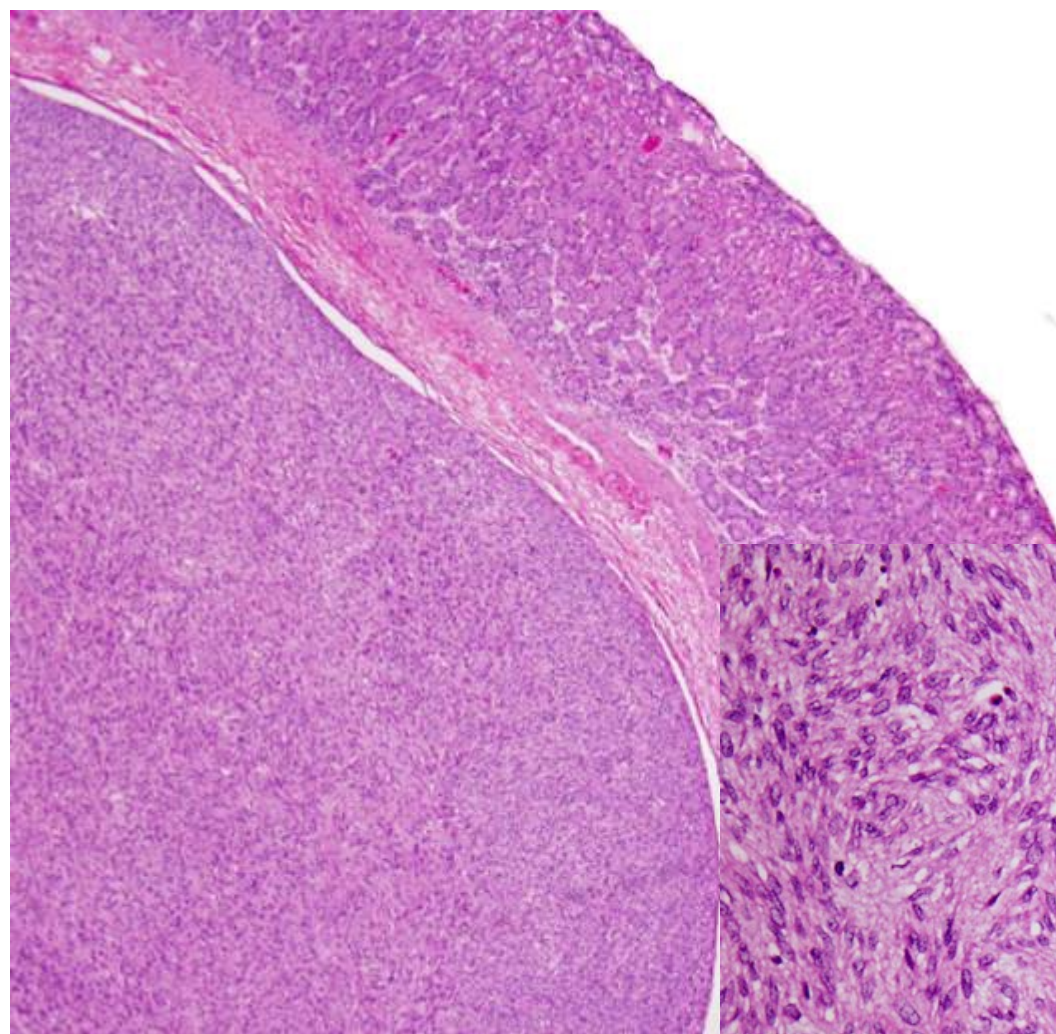
**panK**

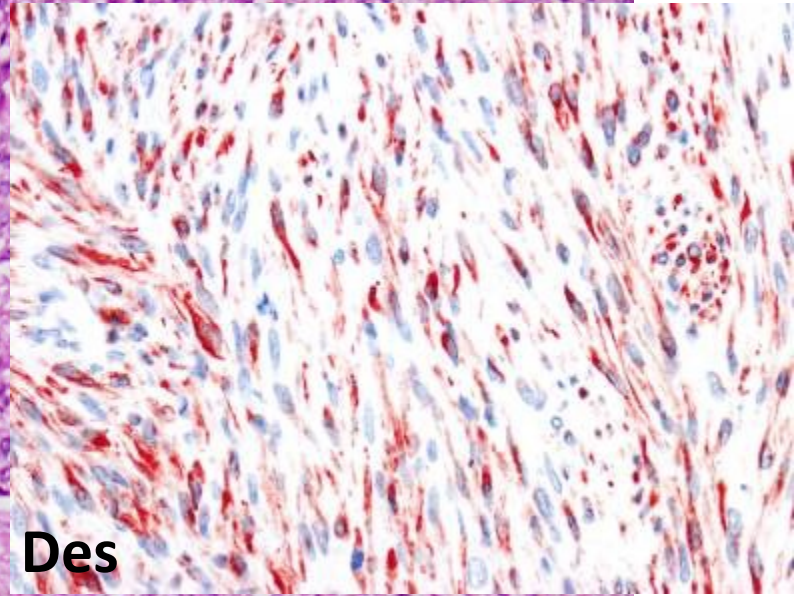
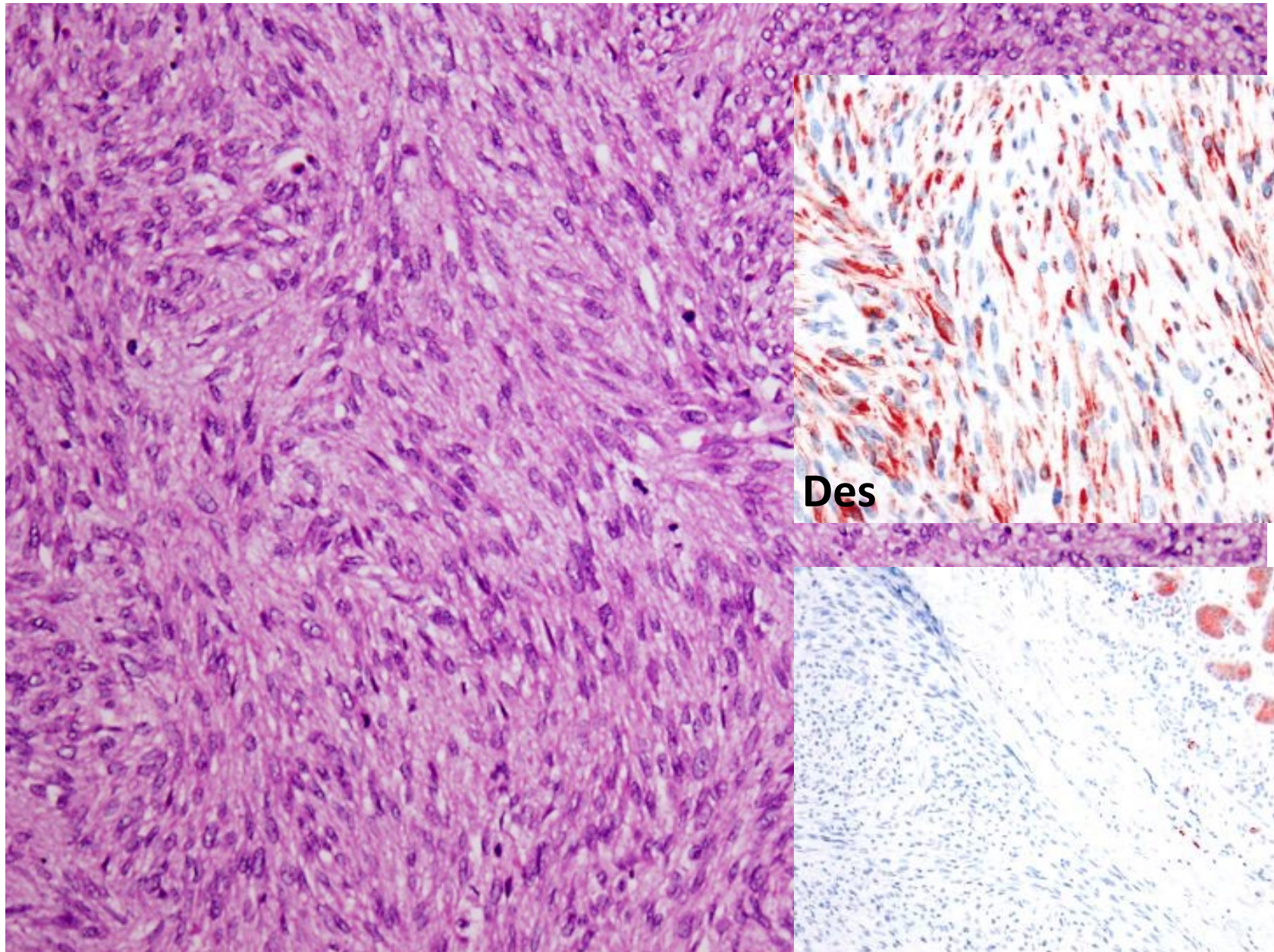


**S-100 p**

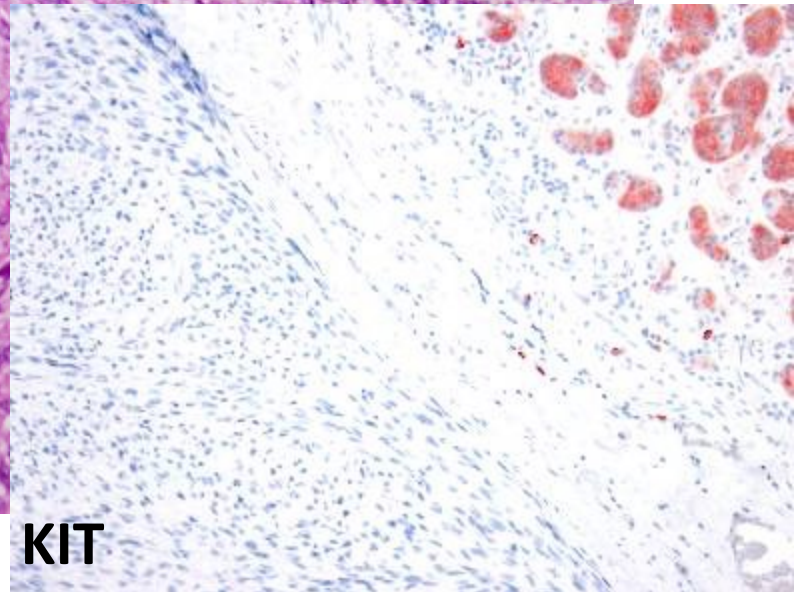


**KIT**

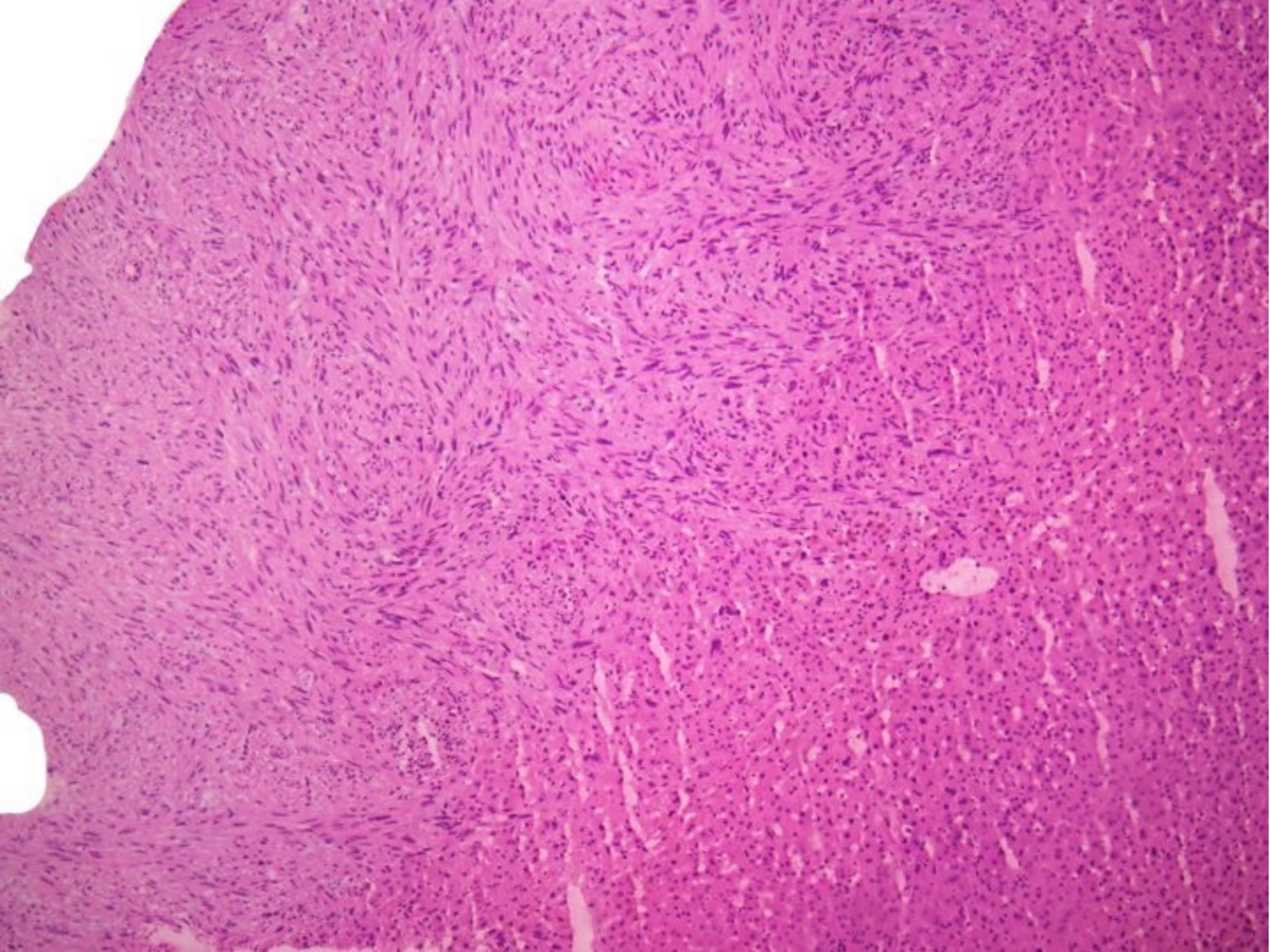




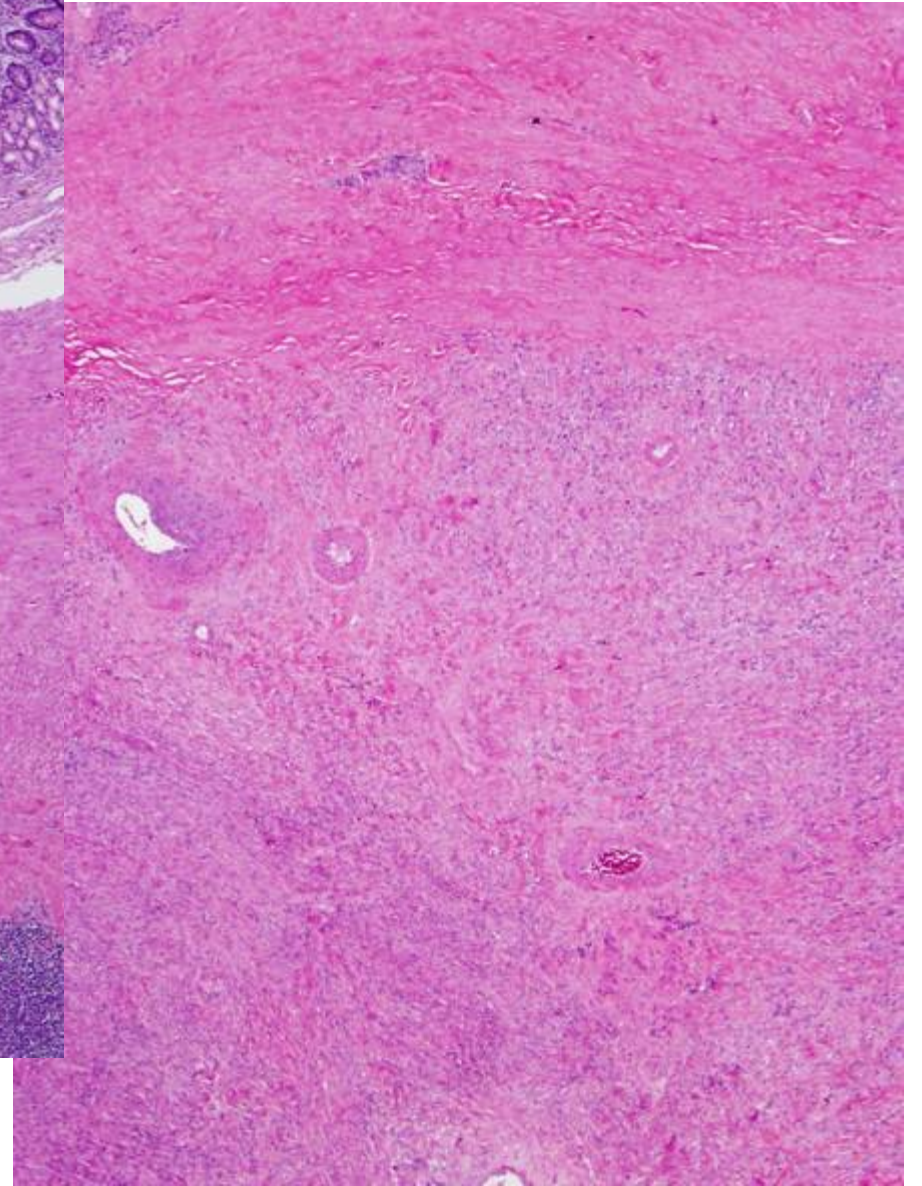
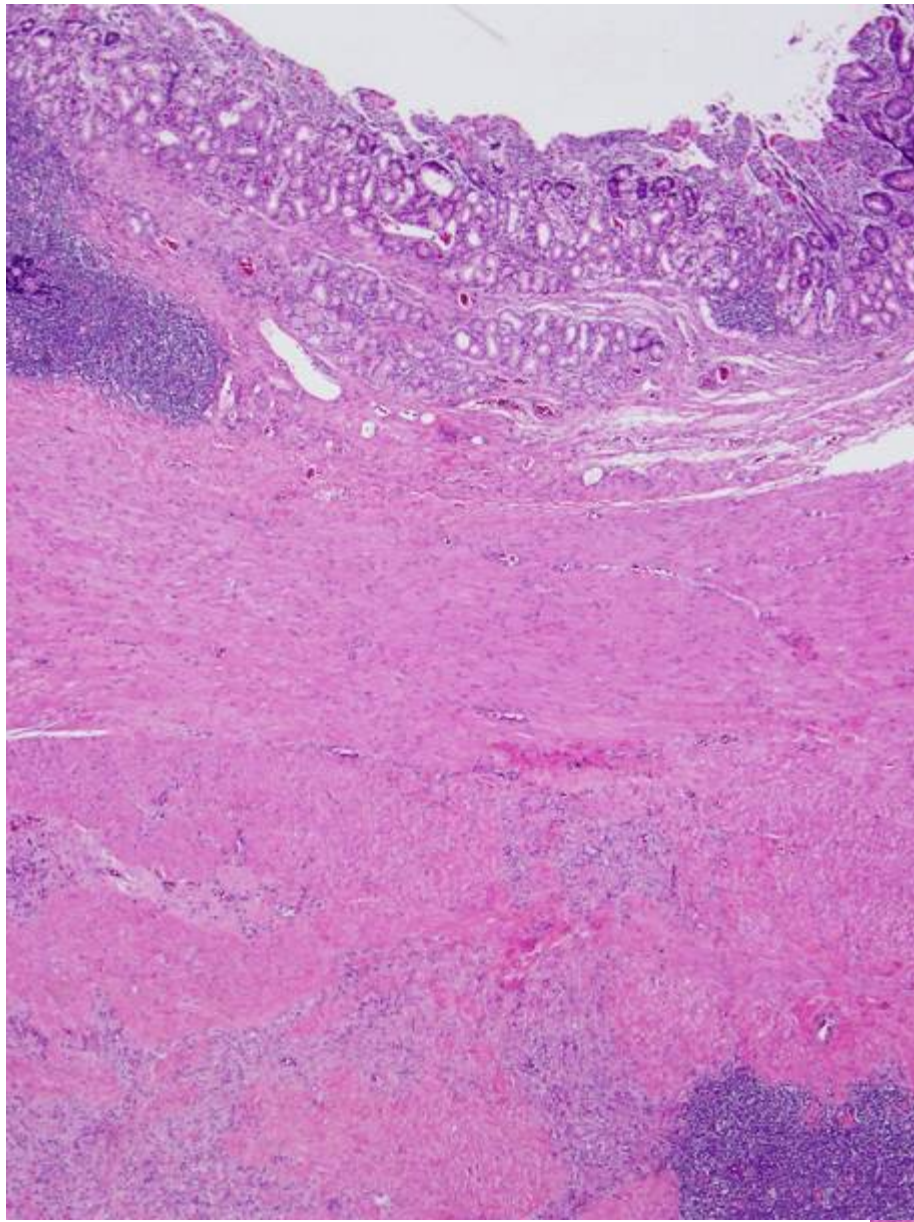
**Des**



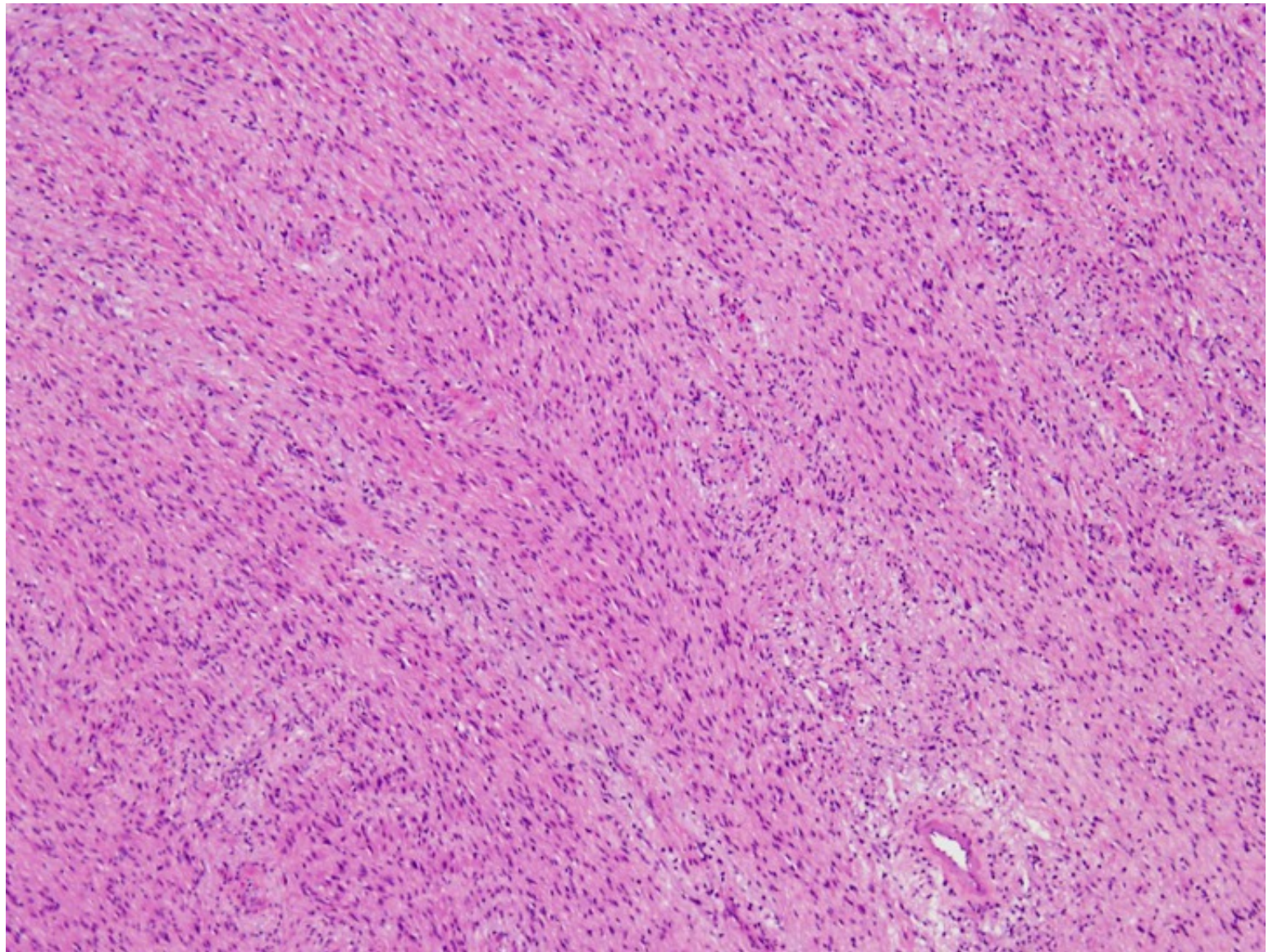
**KIT**

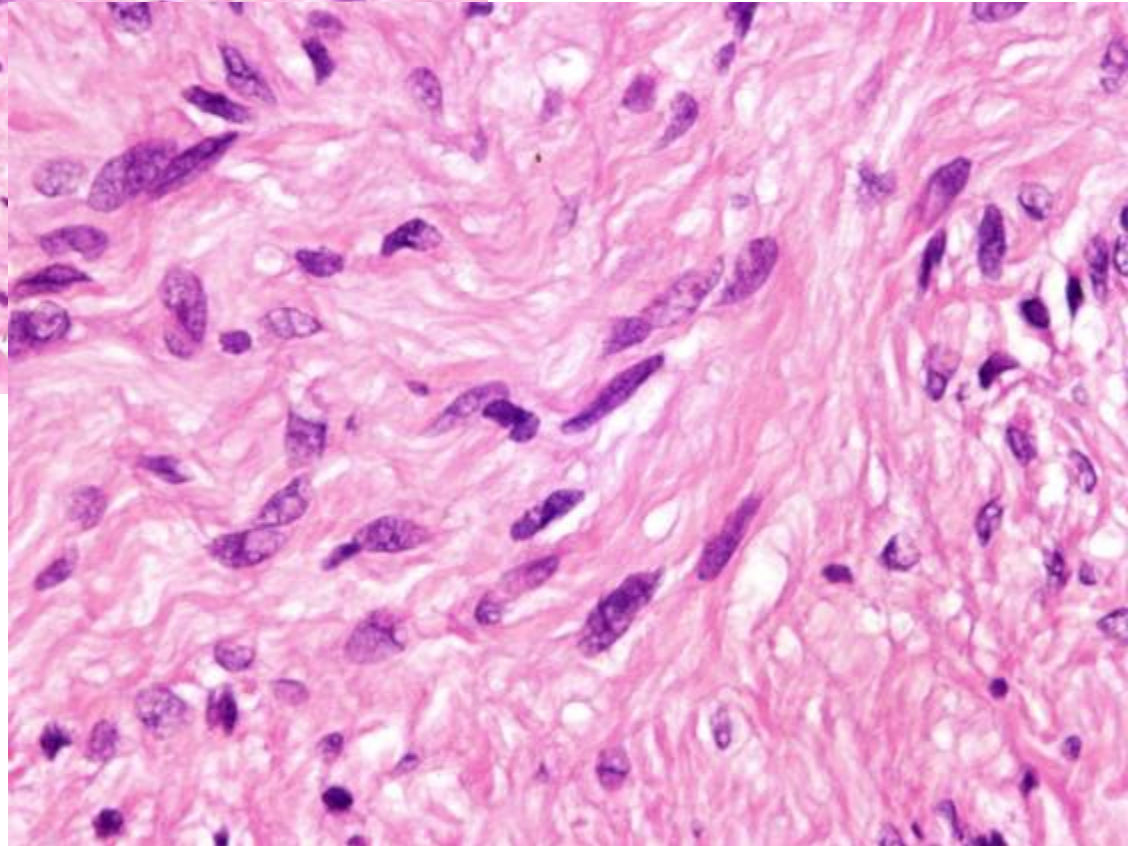
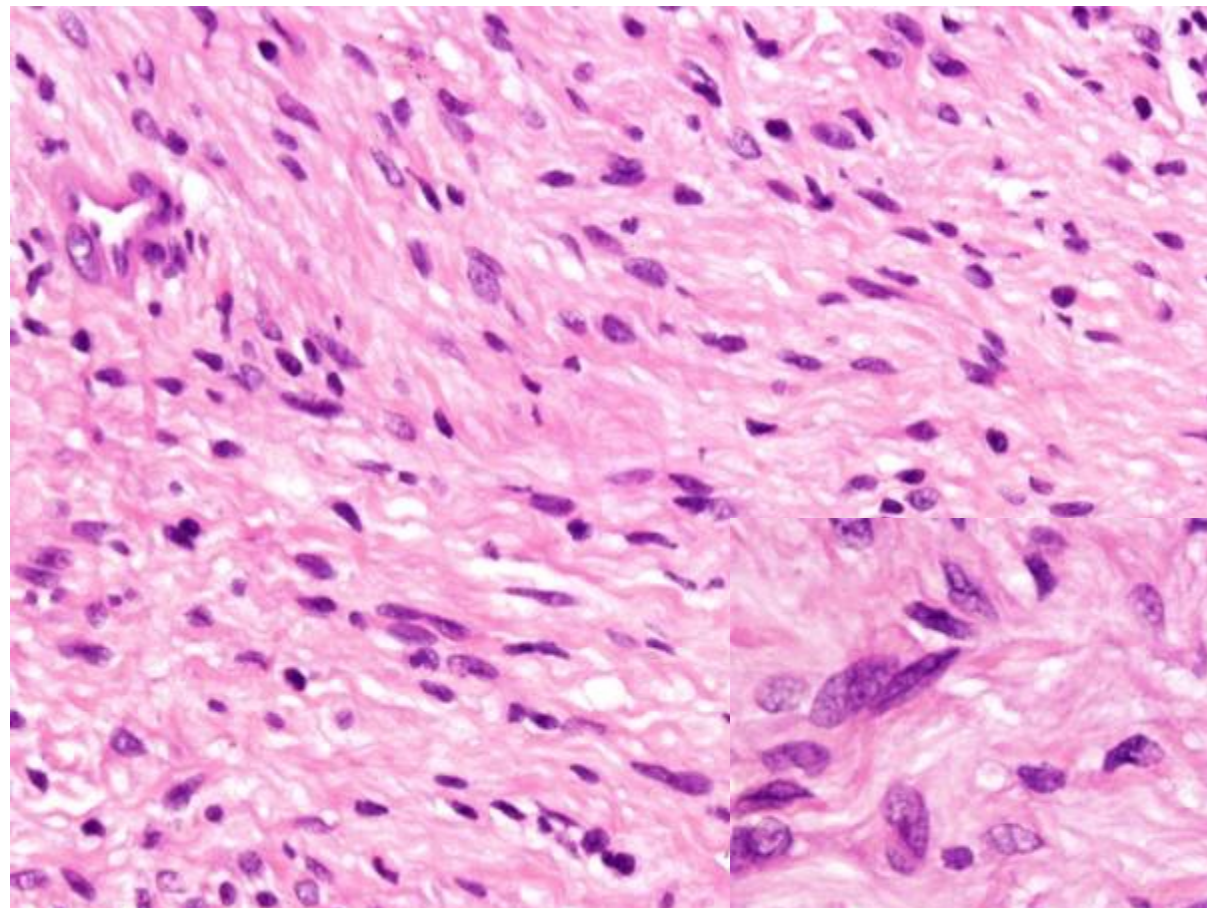


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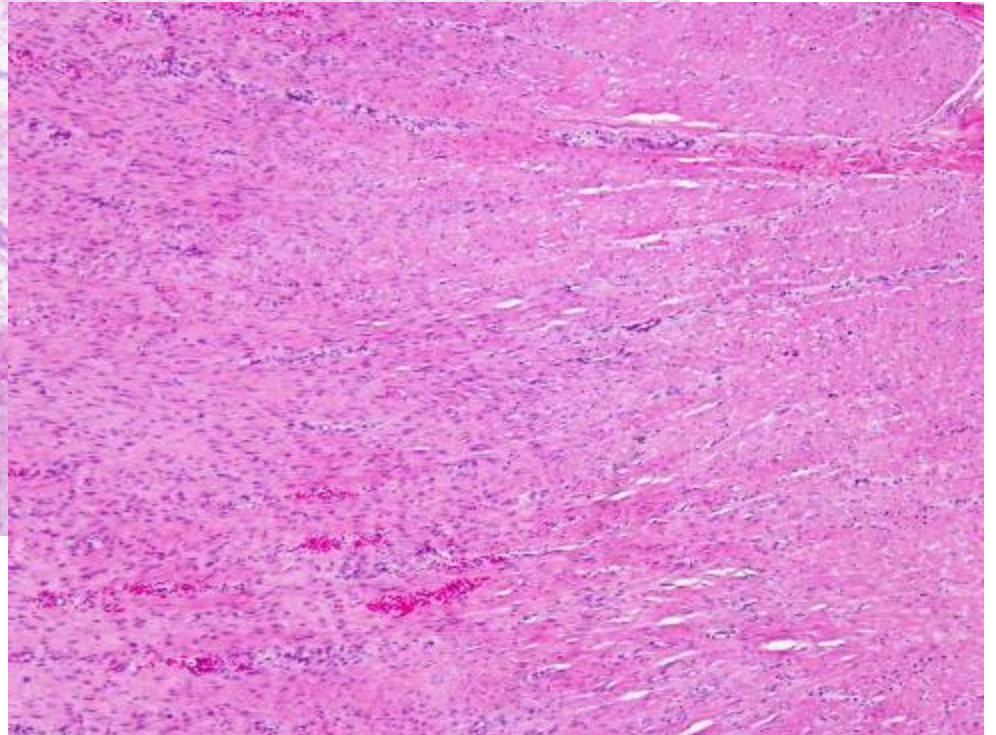
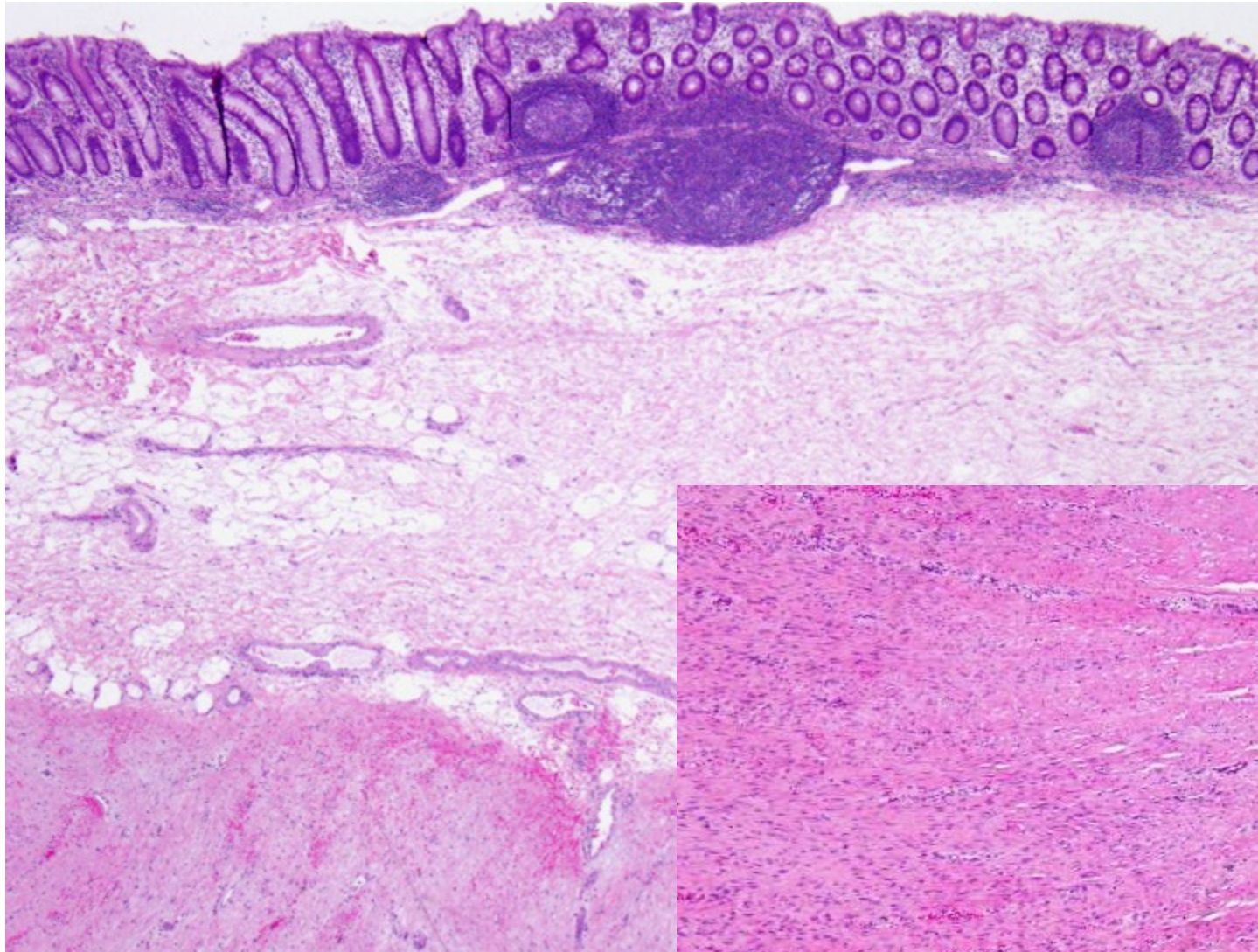


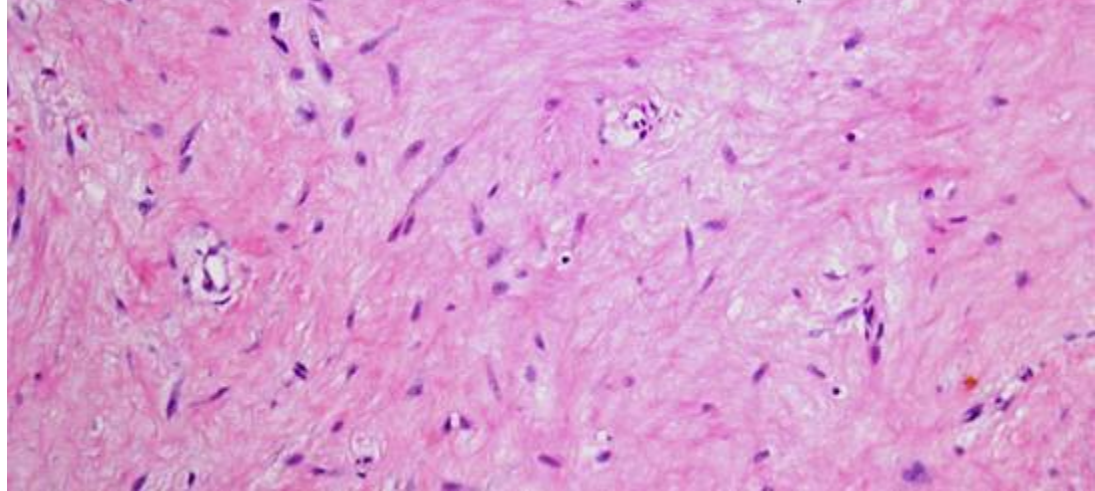
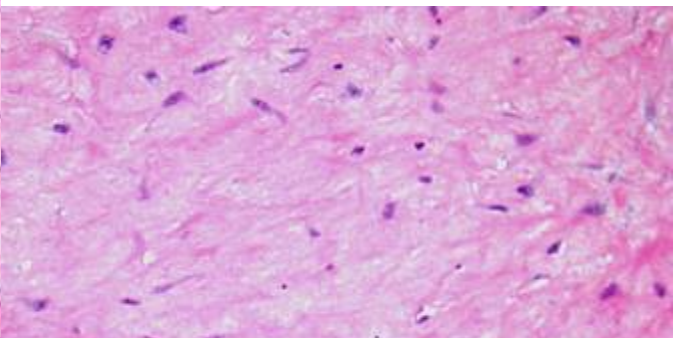
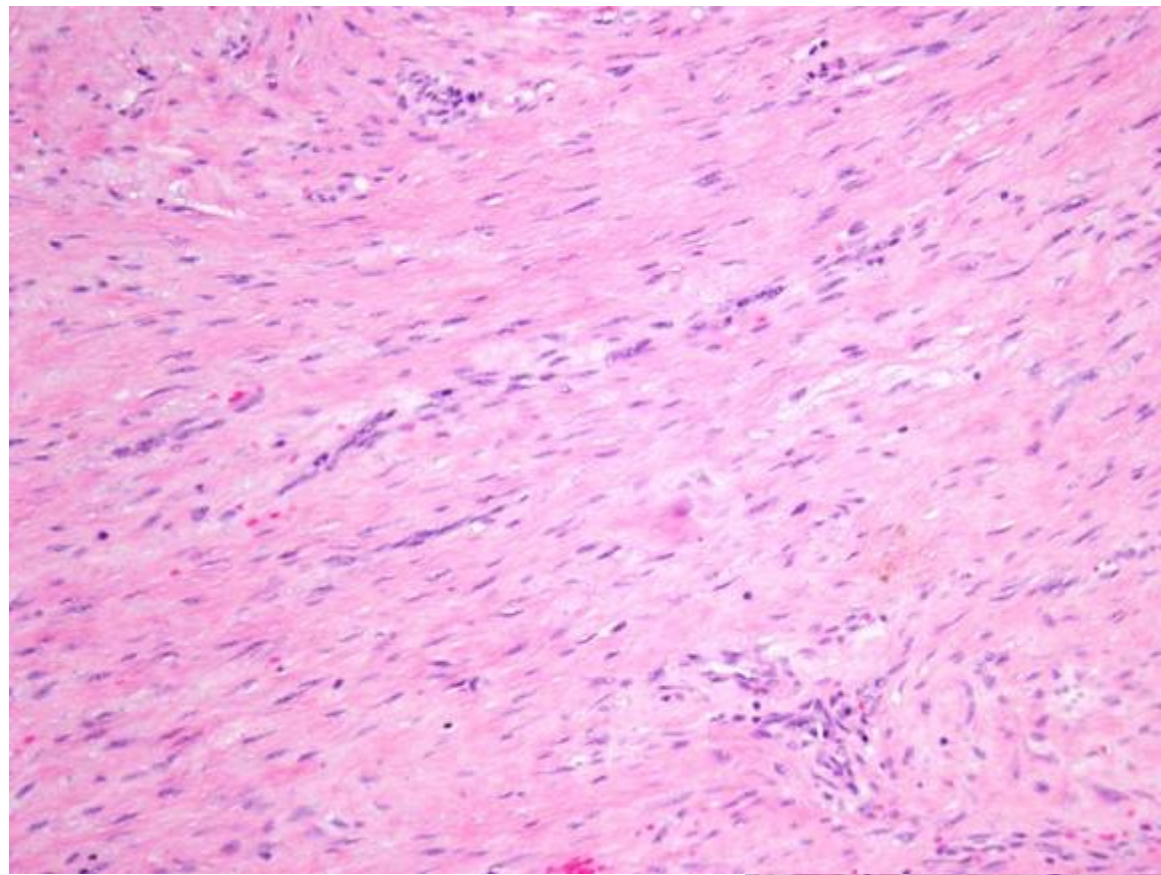


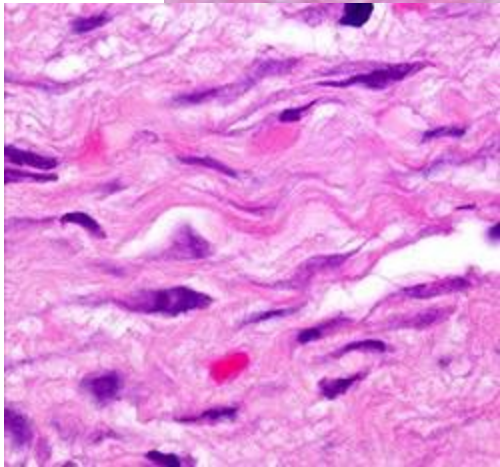
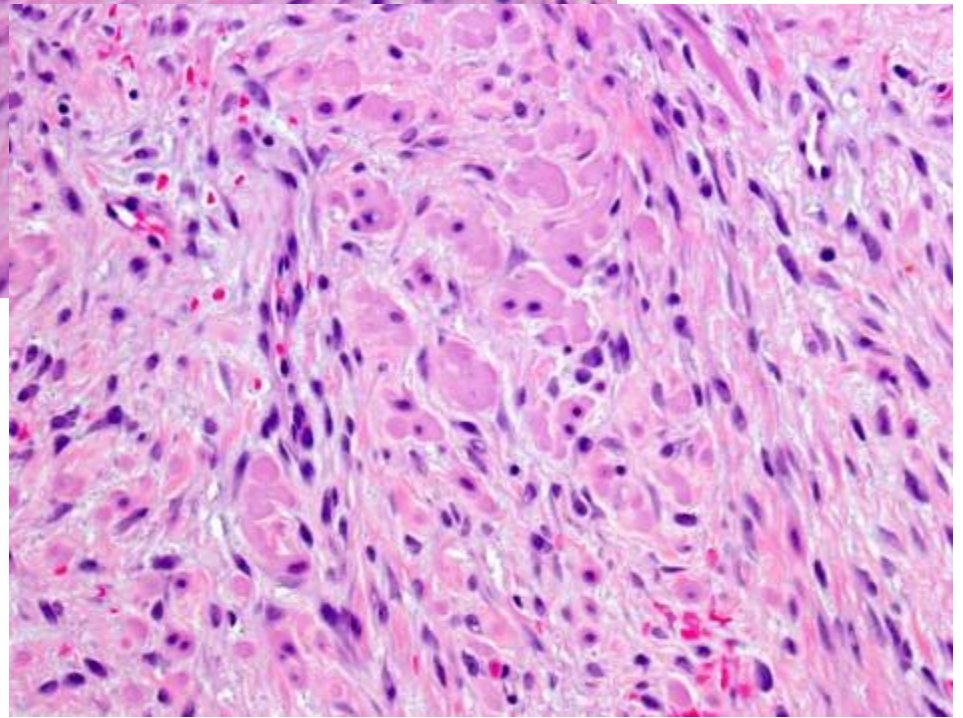
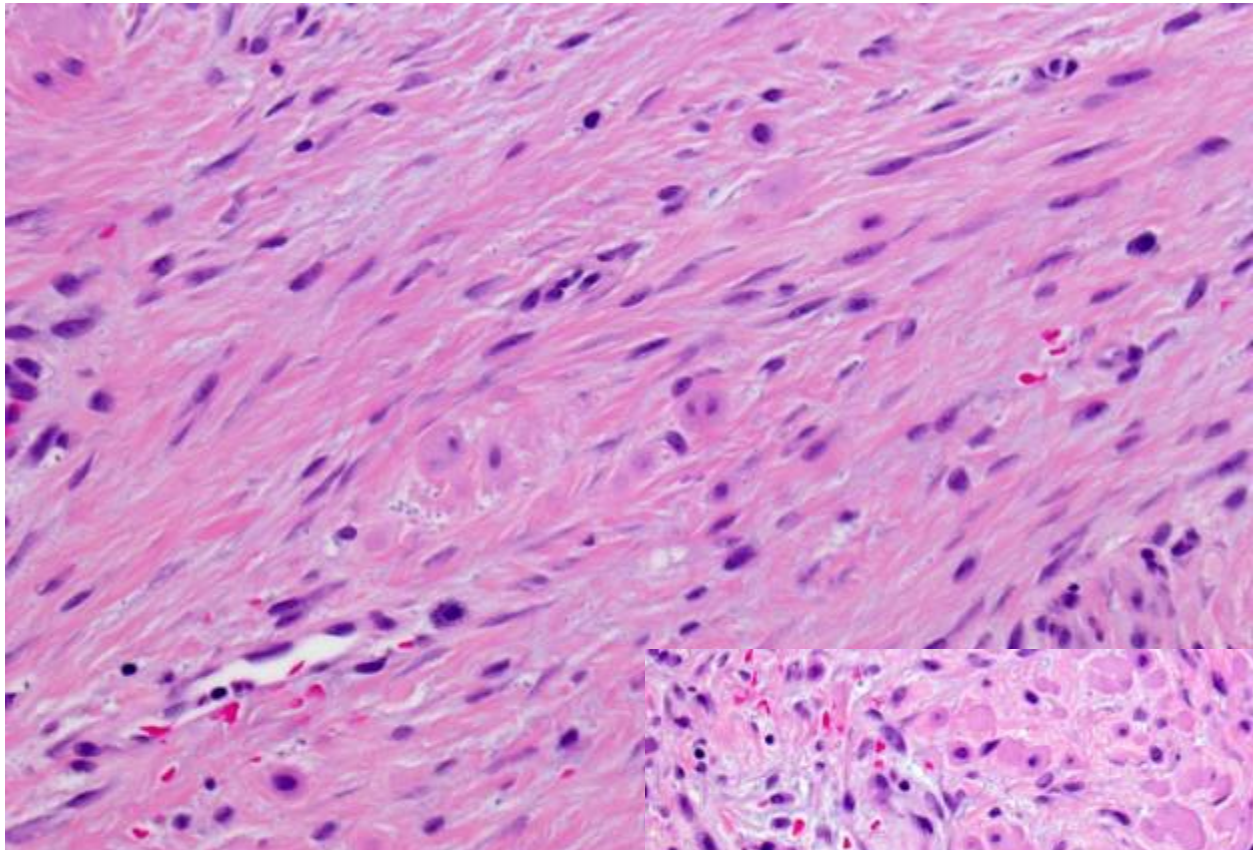


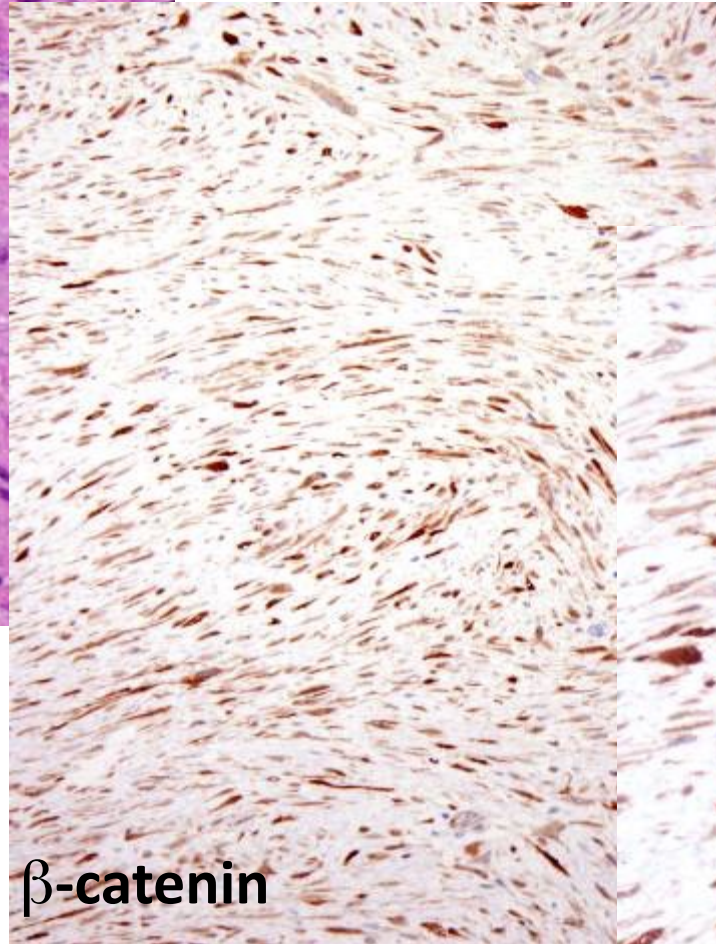
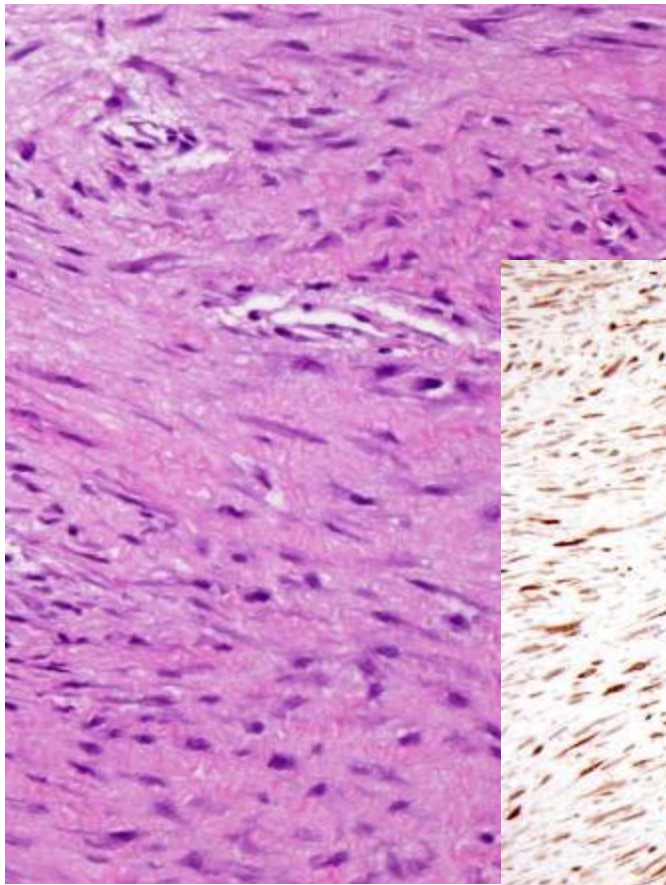


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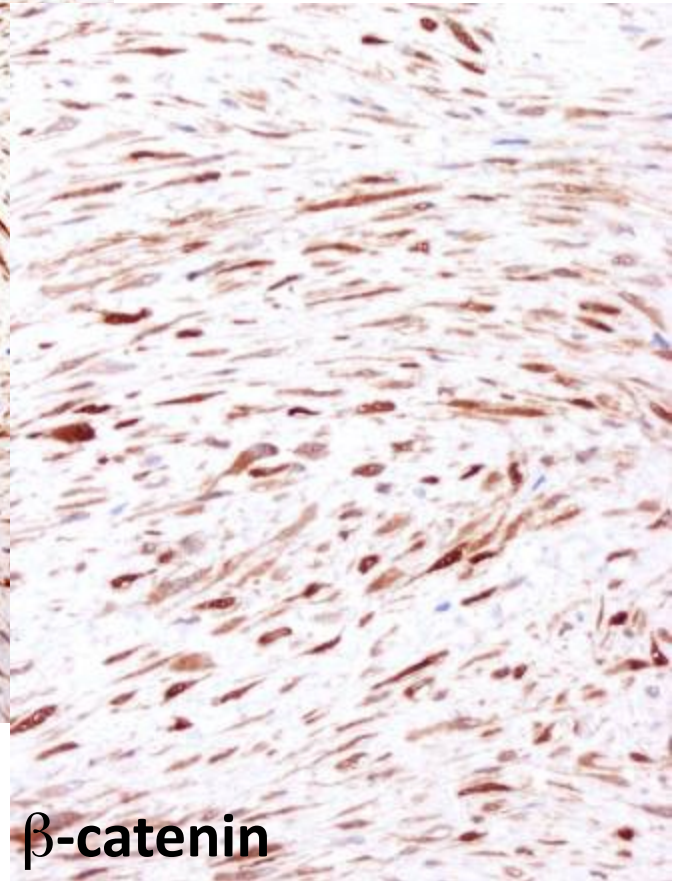




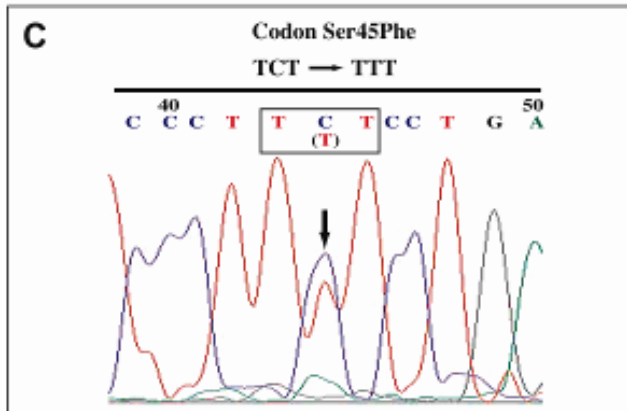
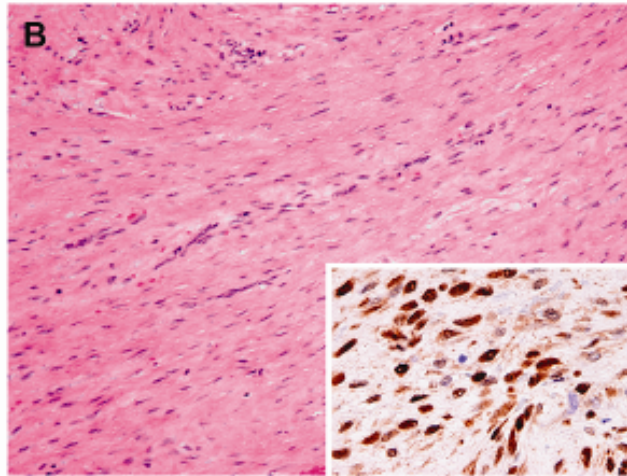
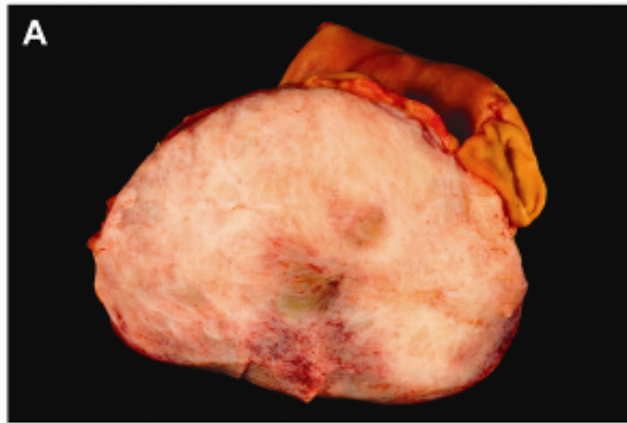




**$\beta$ -catenin**



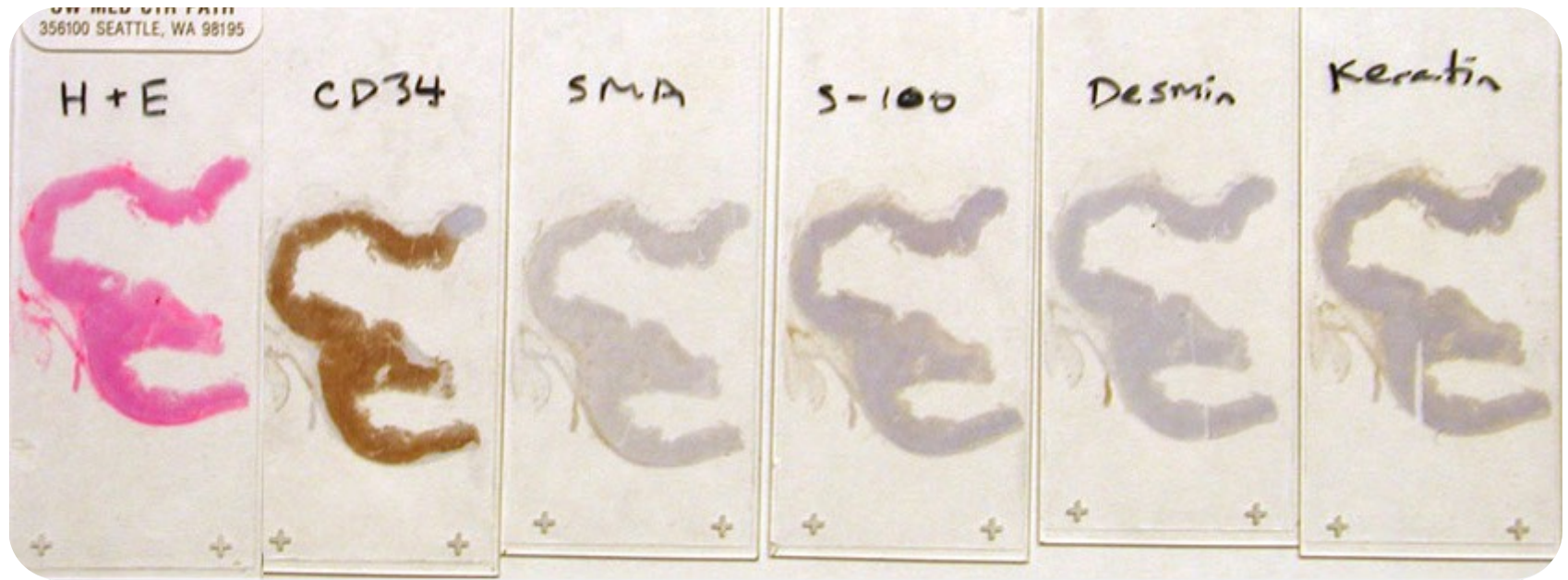
**$\beta$ -catenin**



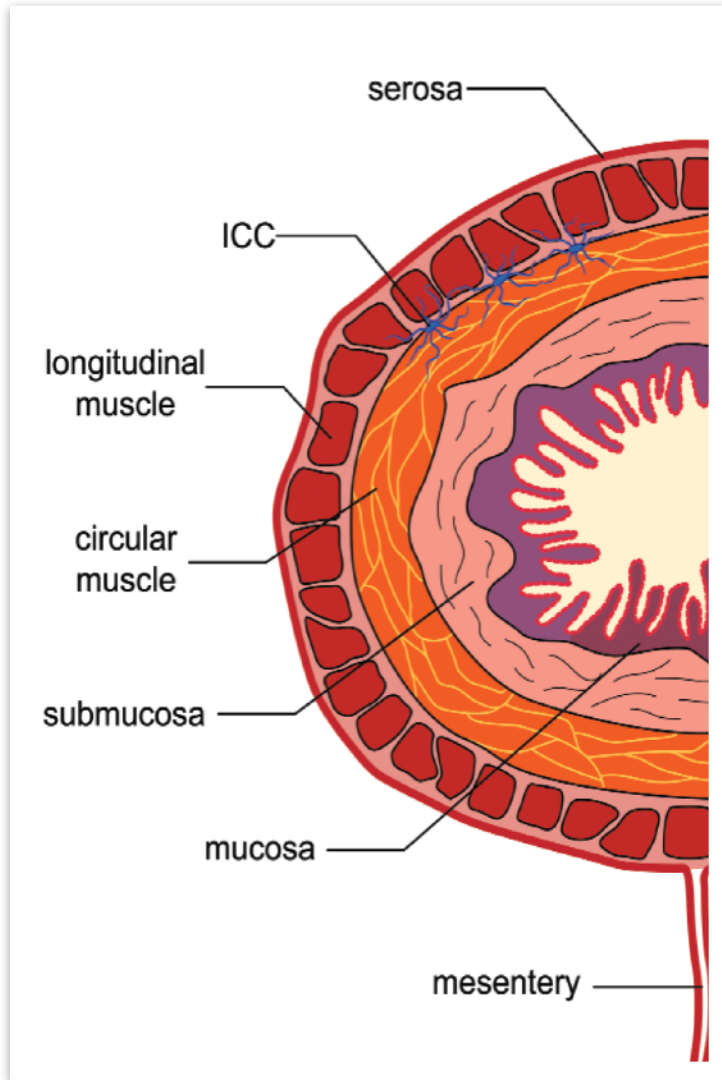




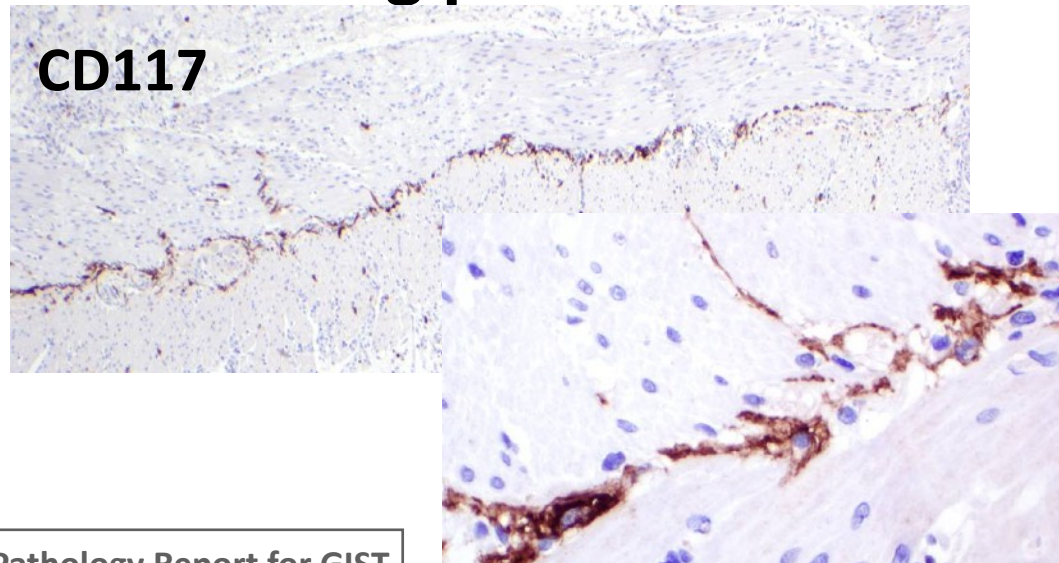
# ***Immunohistochemical Profile of GISTs (Circa 1997 and prior)***



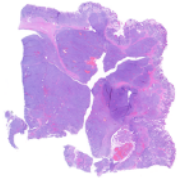
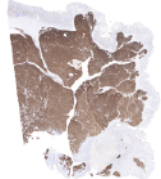
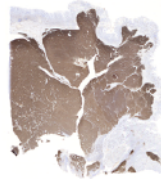
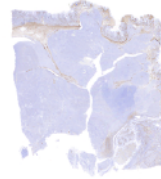
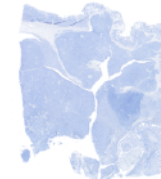
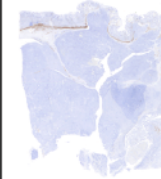
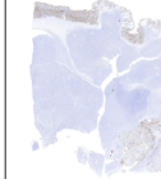
# ***Gastrointestinal Stromal Tumor***



- **Arise from the interstitial cells of Cajal (ICC)**
- **ICC have a “pacemaker” function and are important in coordinating peristalsis**



# *Immunohistochemical Profile of GIST*

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

**KIT (CD117) +ve (95%)**

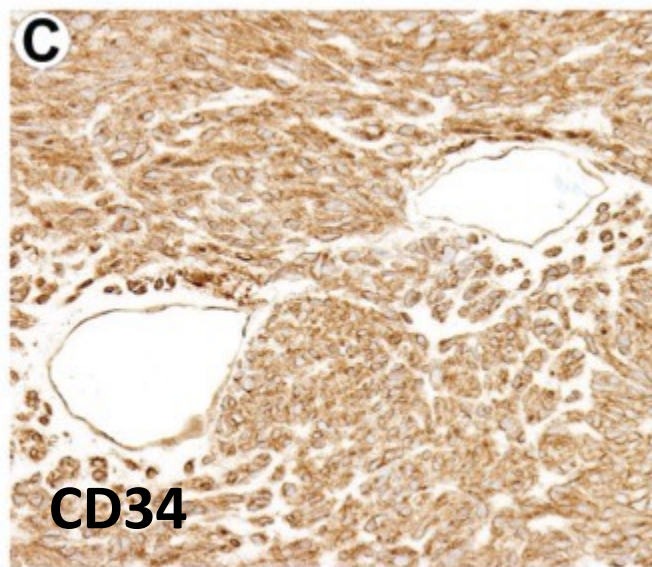
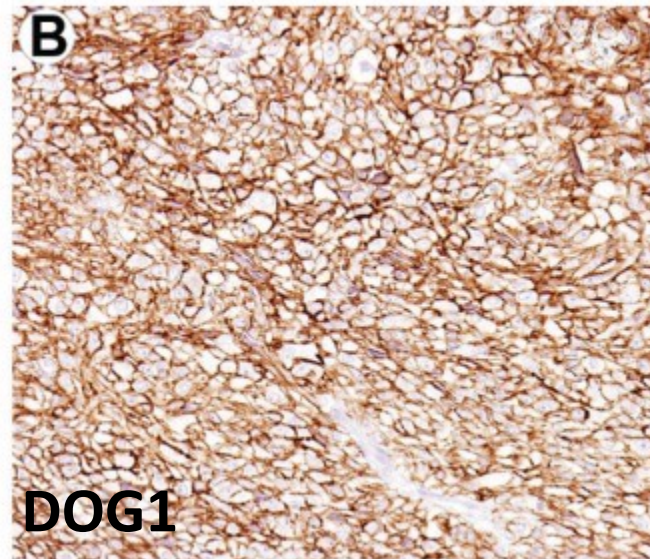
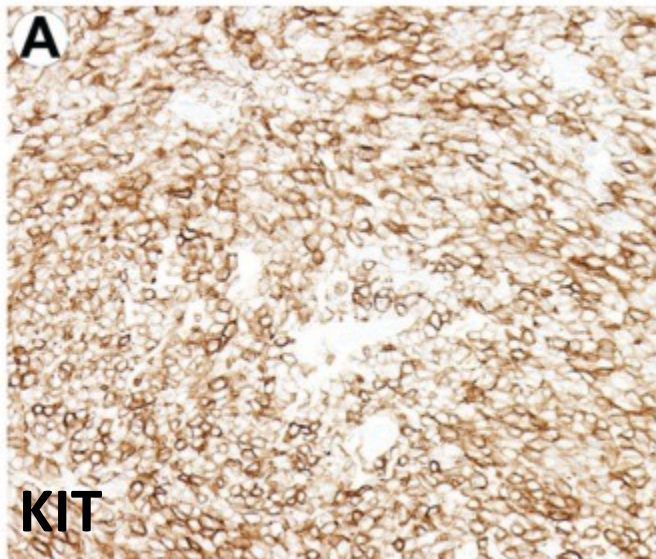
**CD34 +ve (70%)**

**SMA +ve (30-40%)**

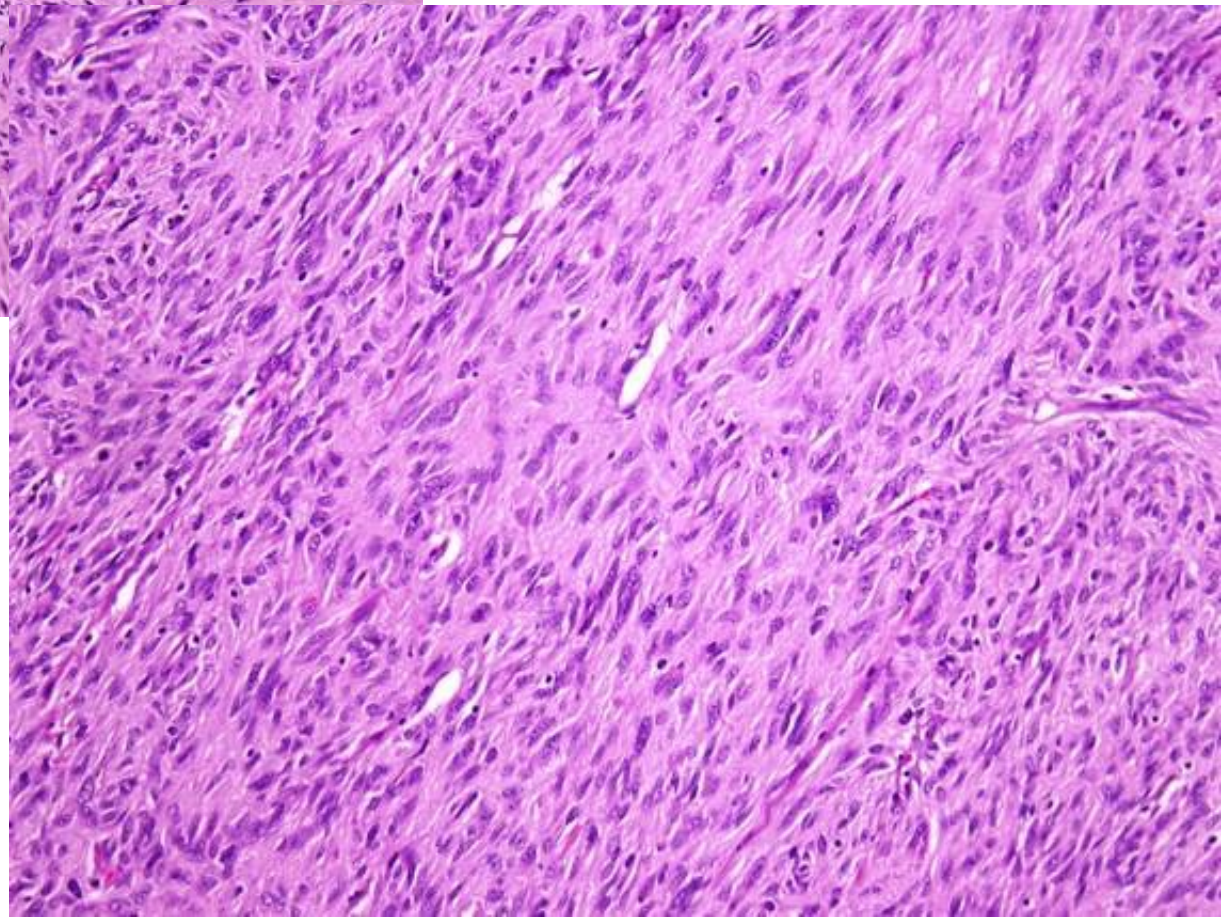
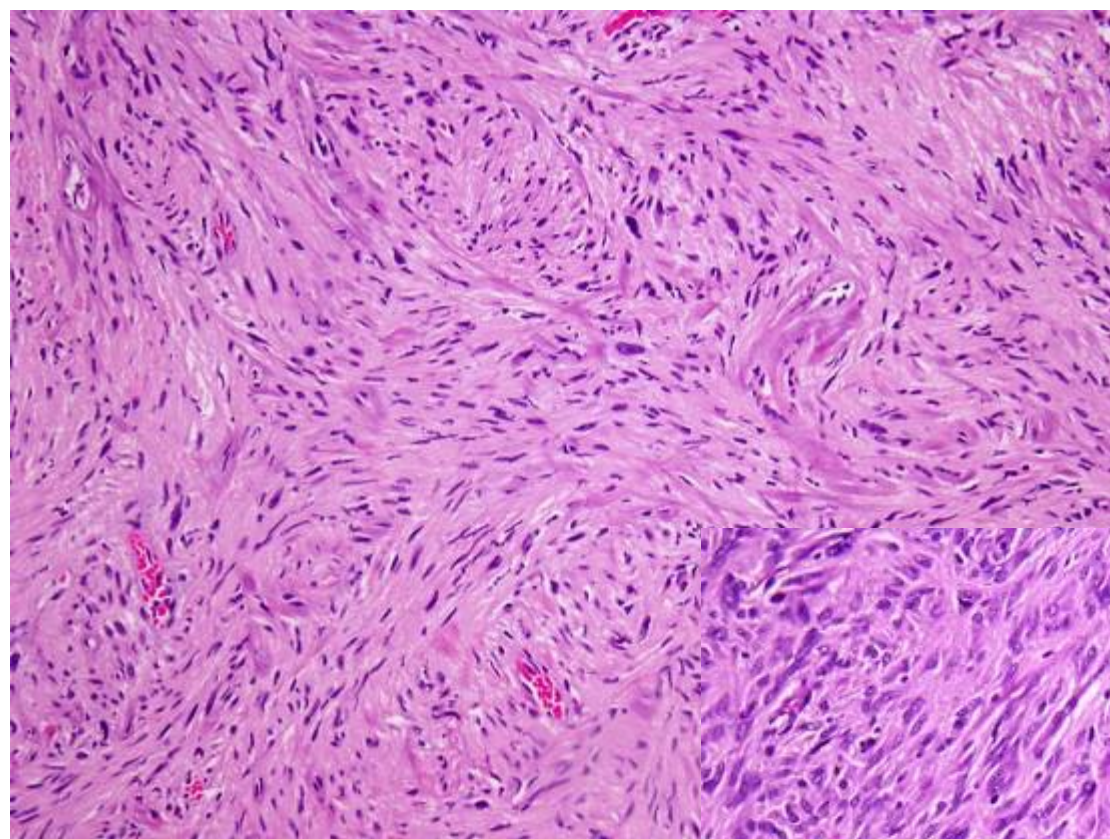
**Desmin -ve**

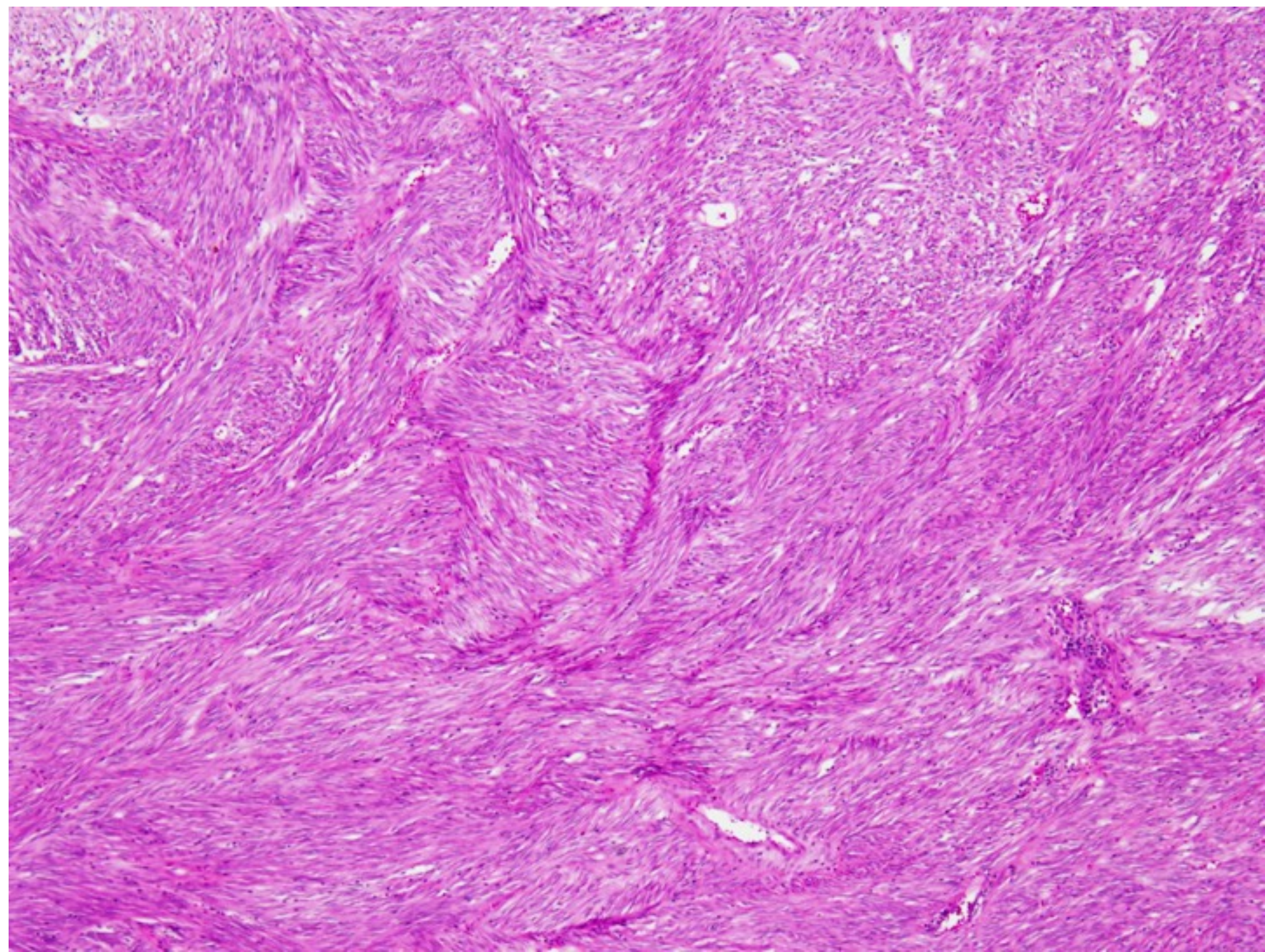
**S-100 protein -ve**

**Keratin -ve**

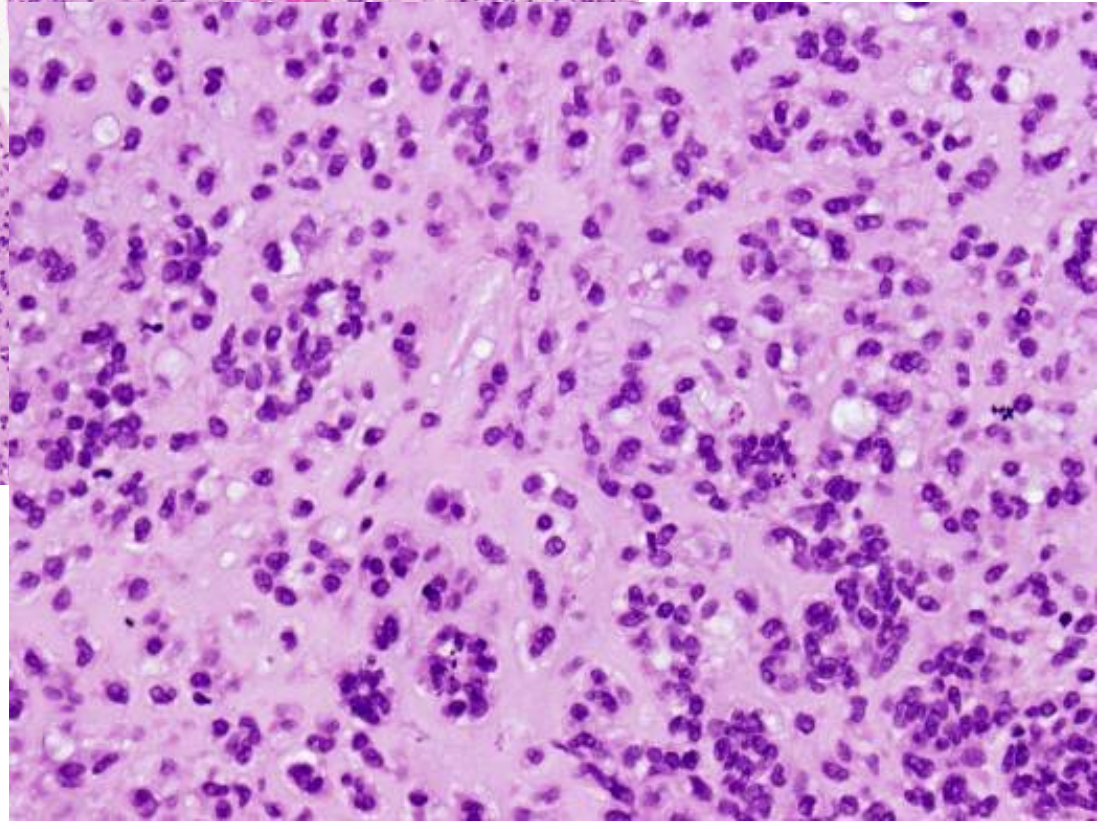
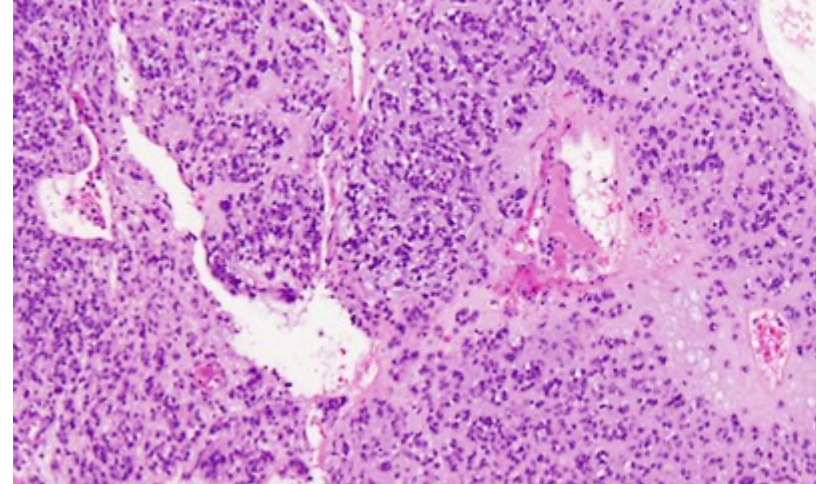
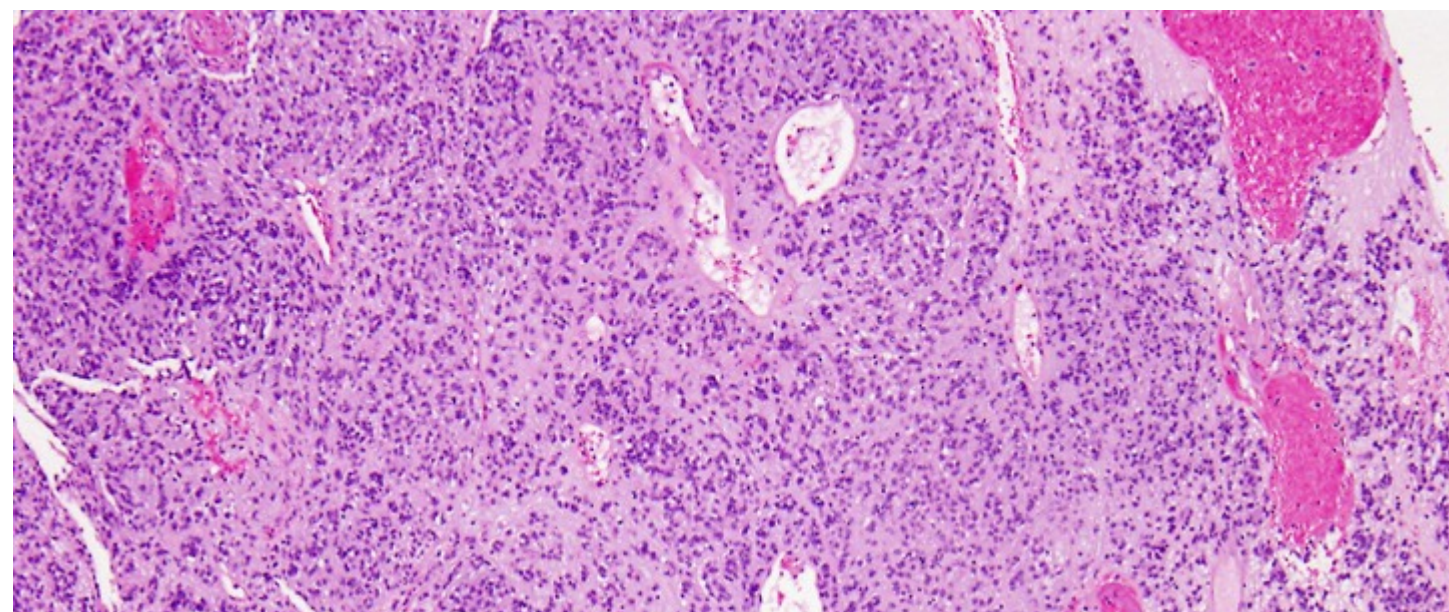


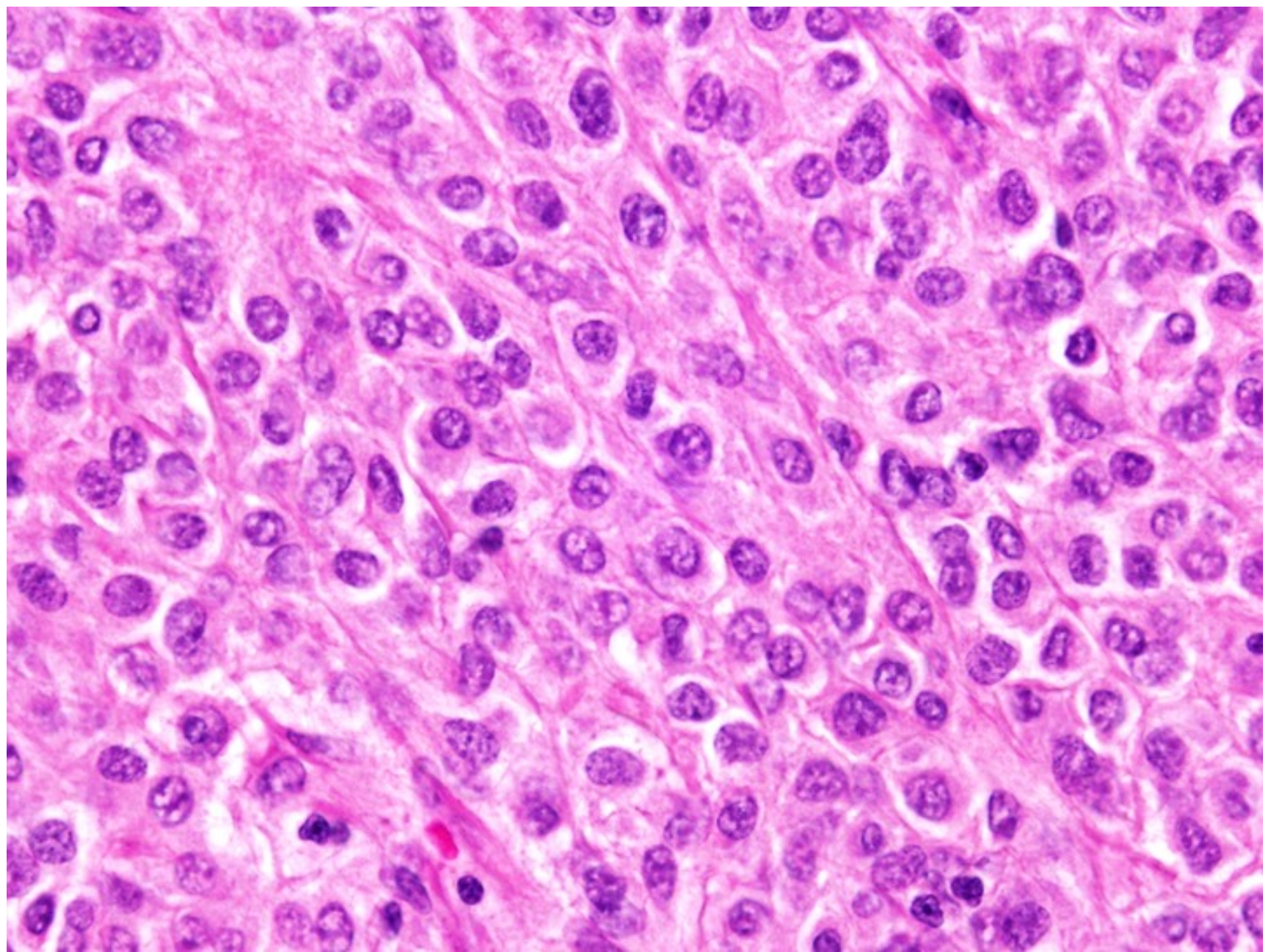
# ***The many faces of GIST***

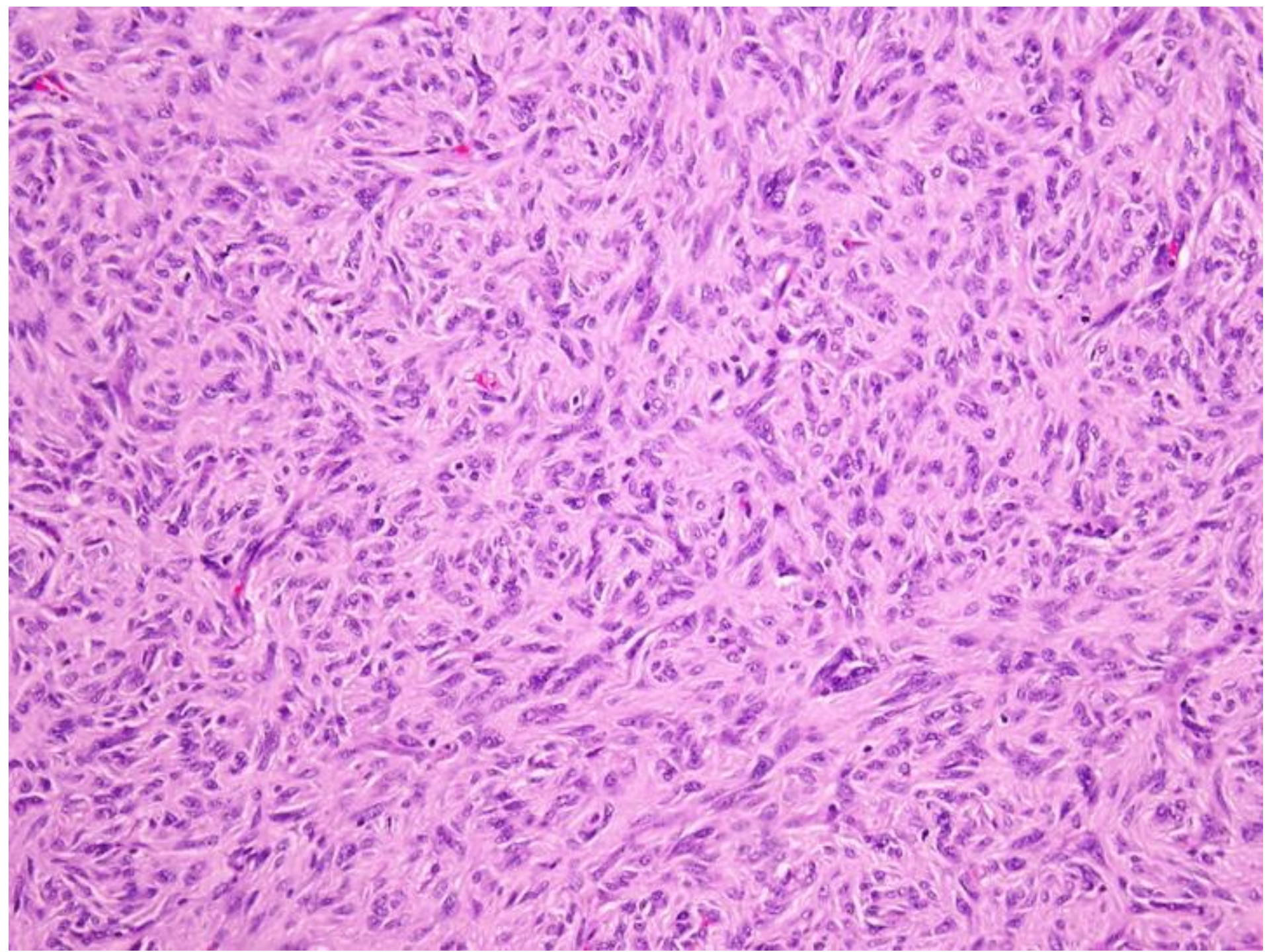


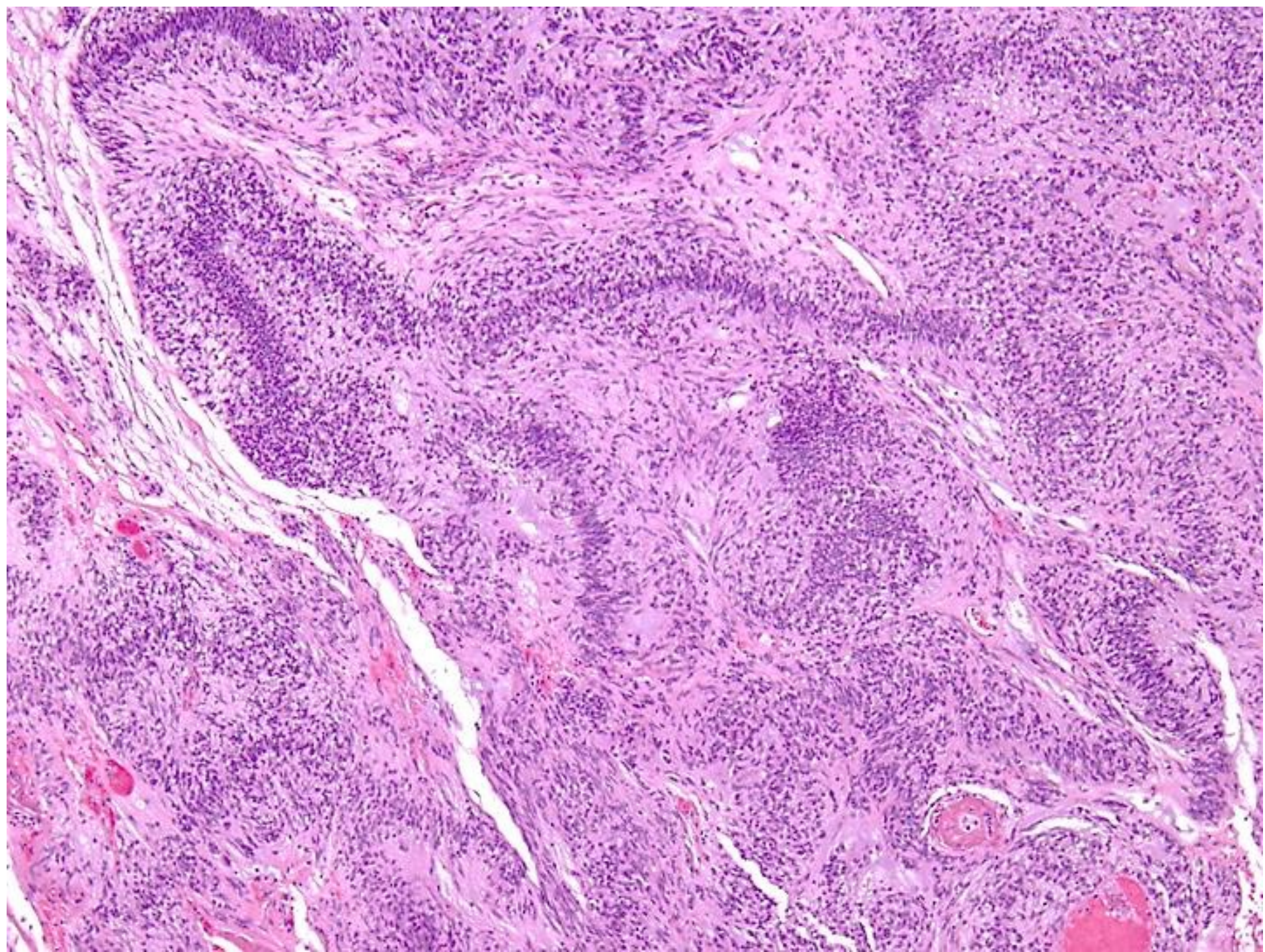


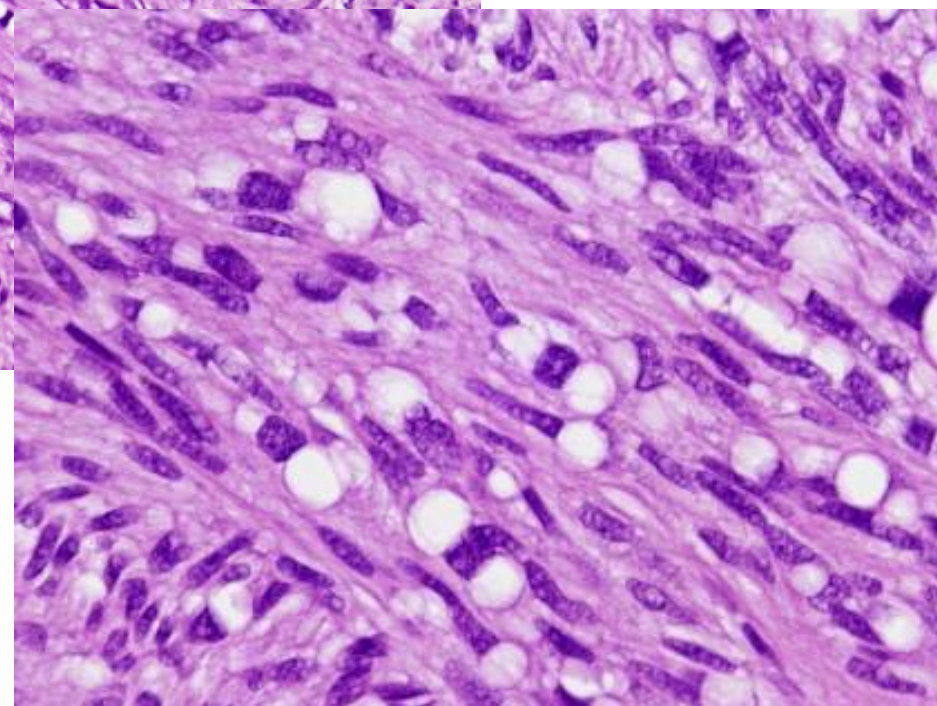
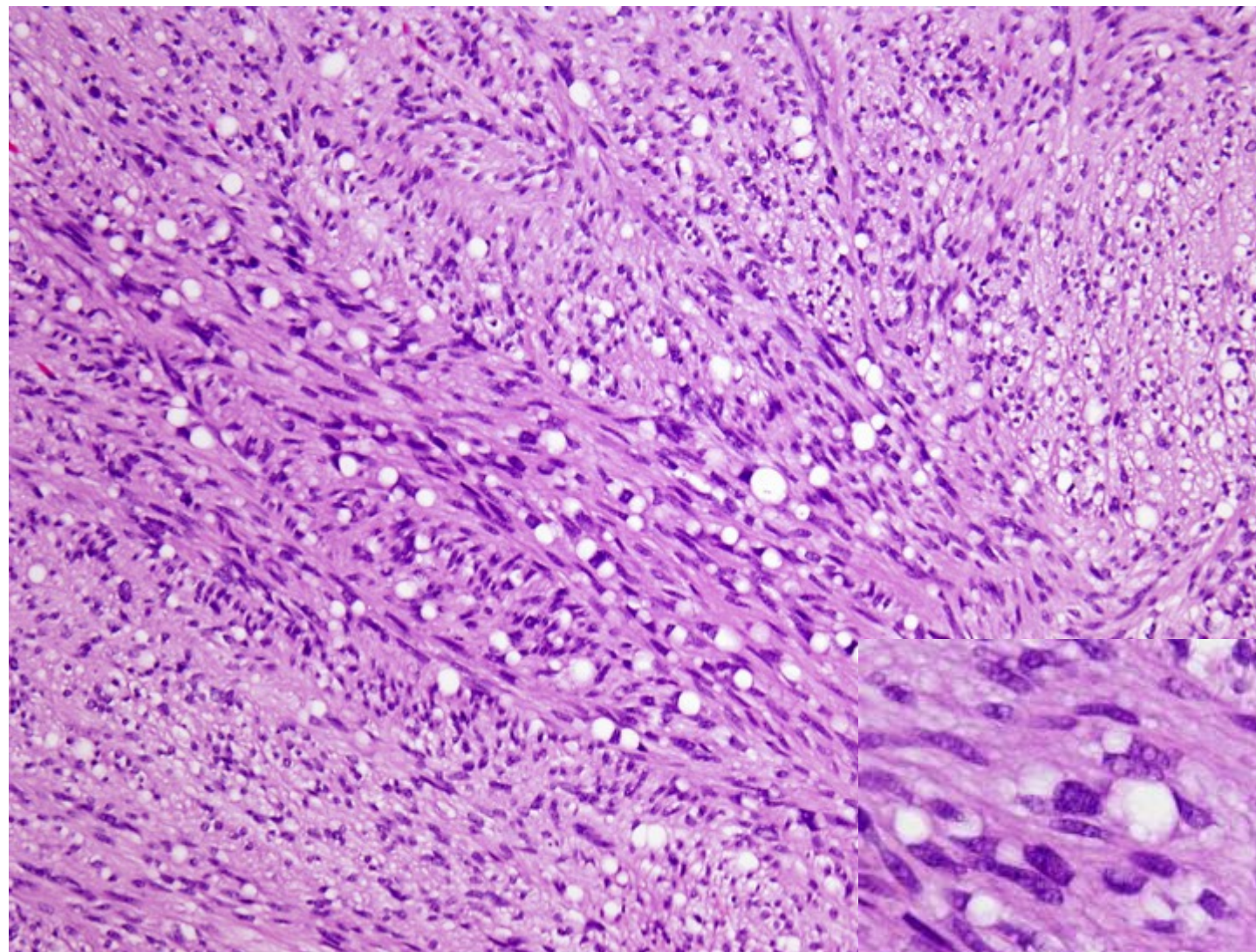


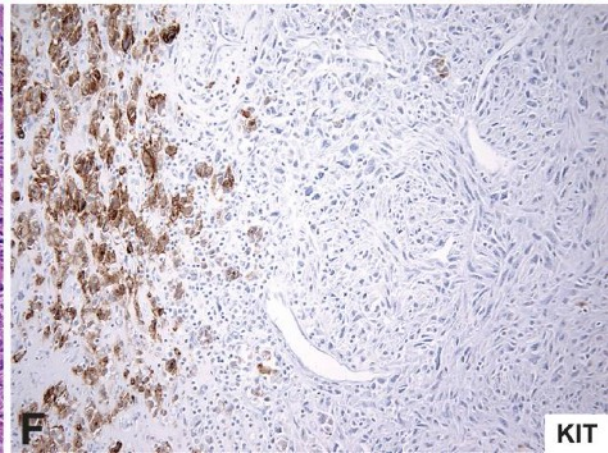
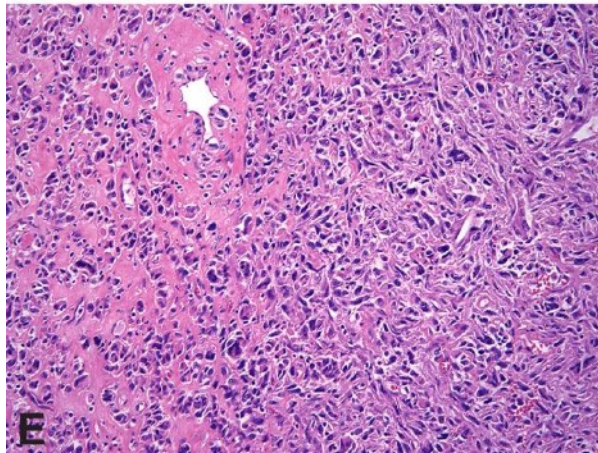
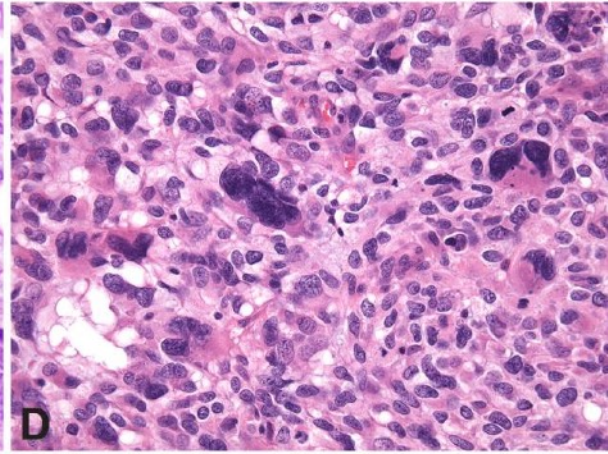
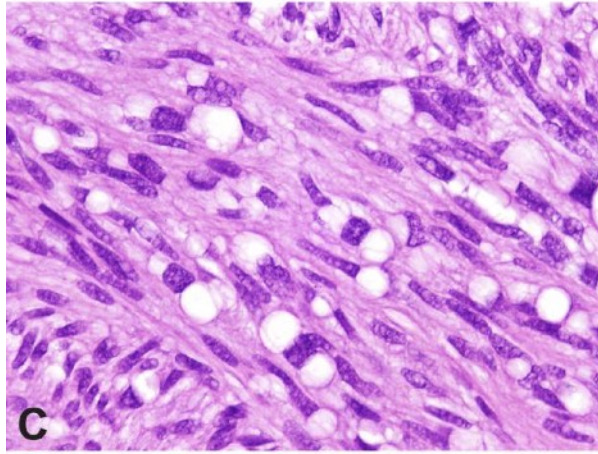
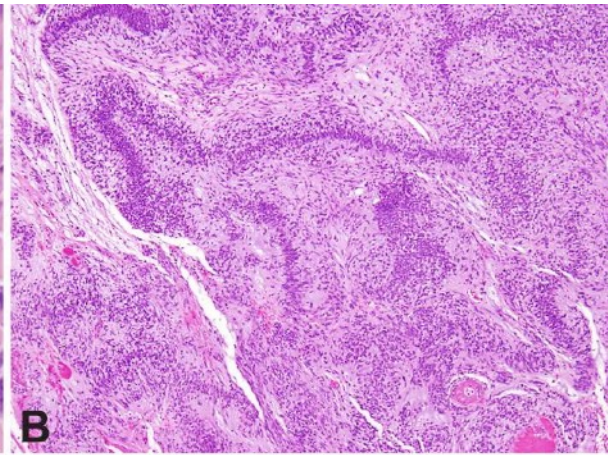
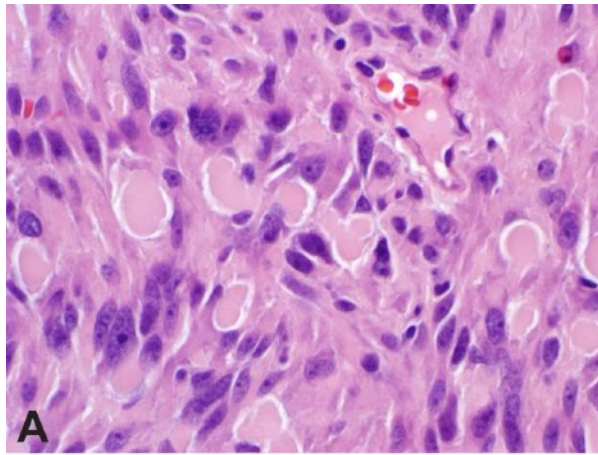


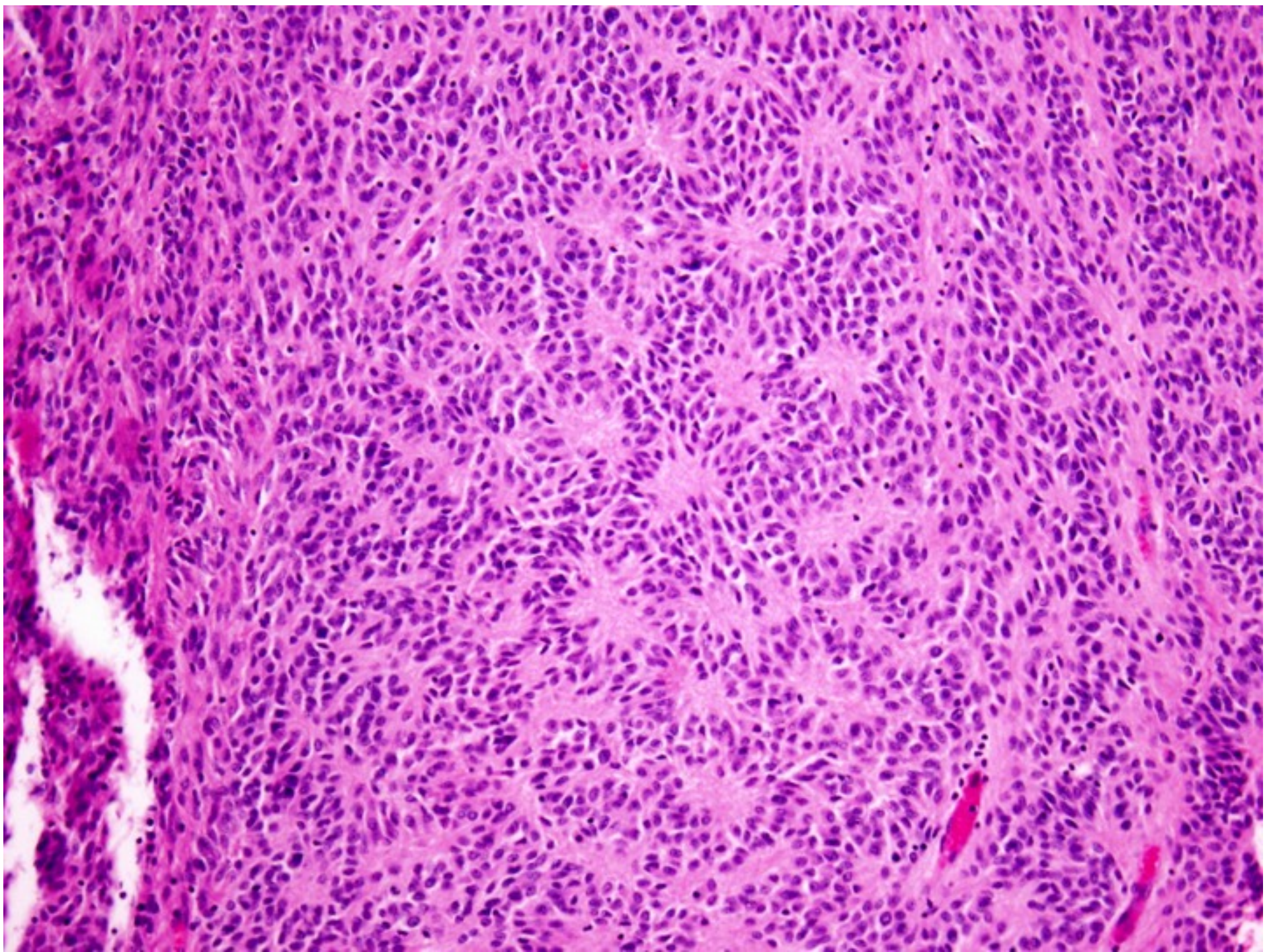












# *Clinical Characteristics of GIST*

**Wide age range – peak in 5<sup>th</sup>-7<sup>th</sup> decade**

**M = F**

**Small lesions = “incidentalomas”**

**Presenting symptoms include:**

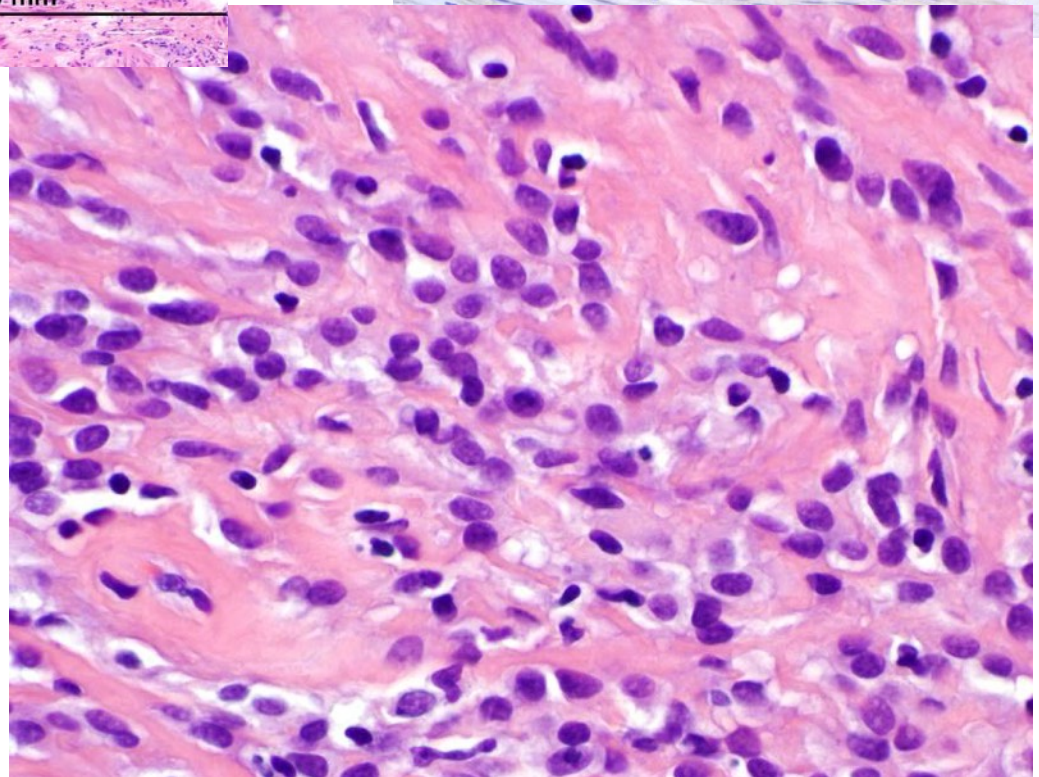
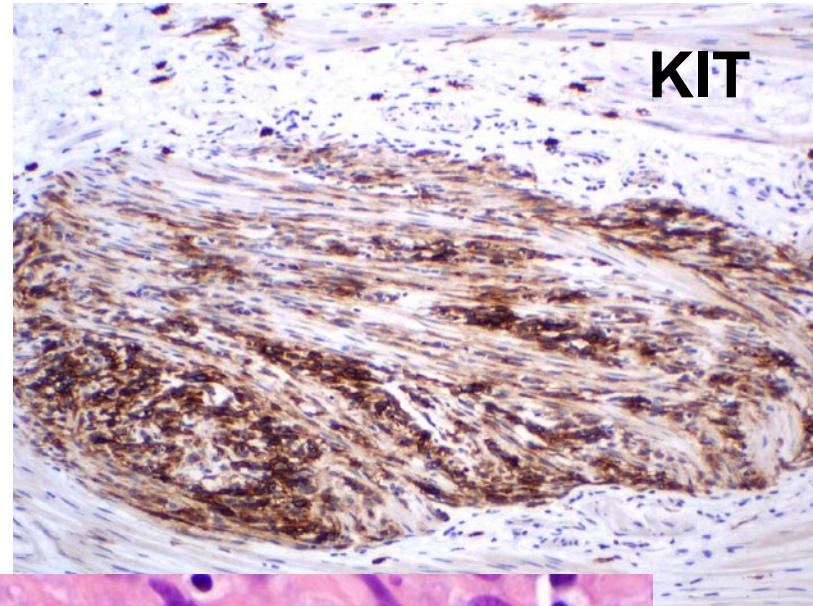
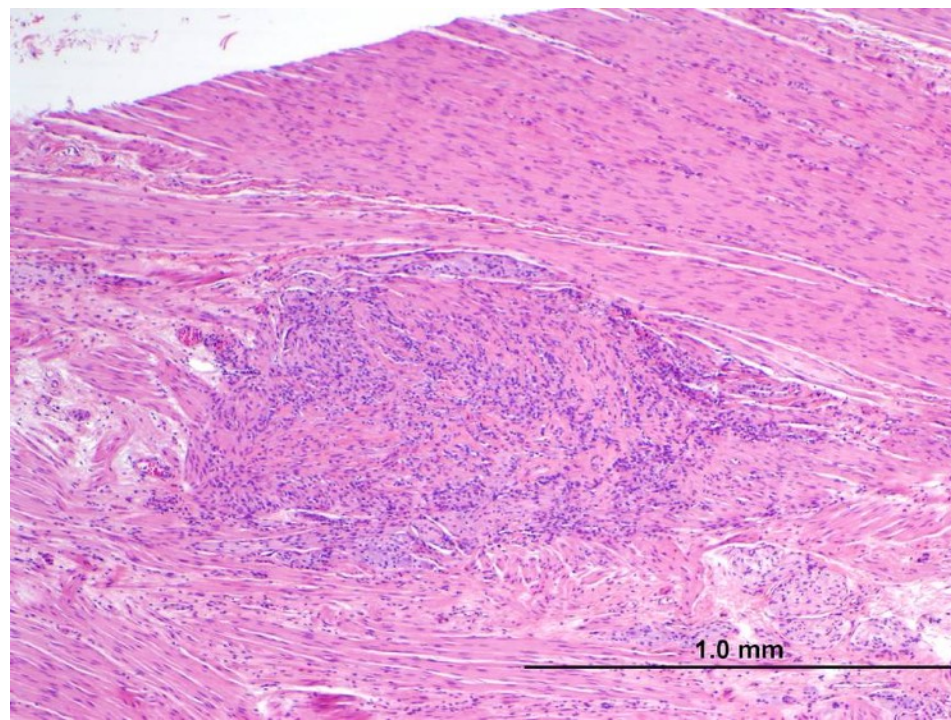
**abdominal pain,**

**gastrointestinal bleeding,**

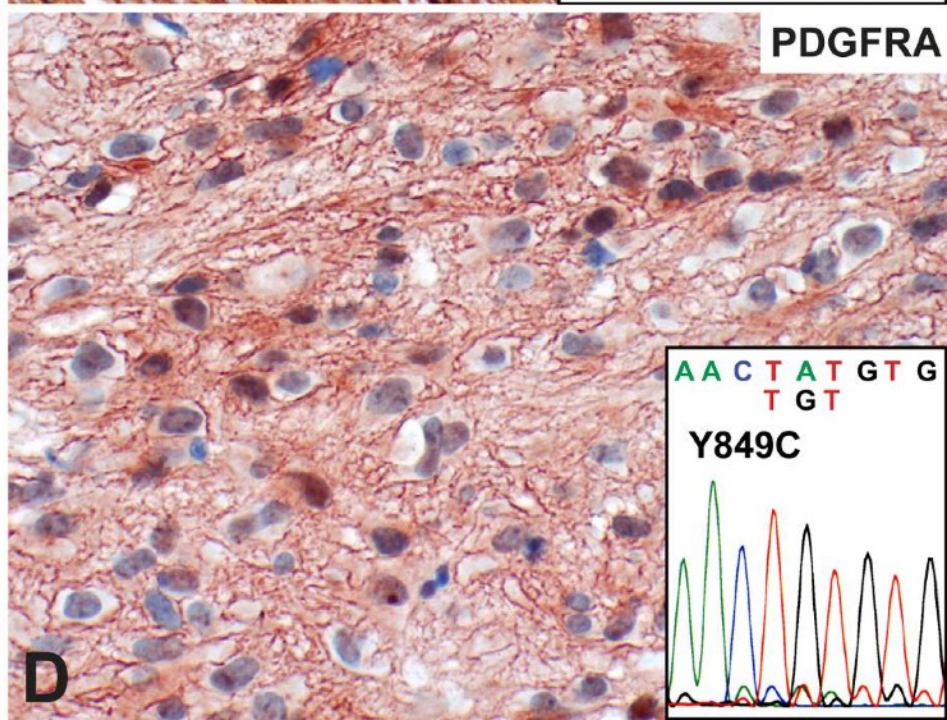
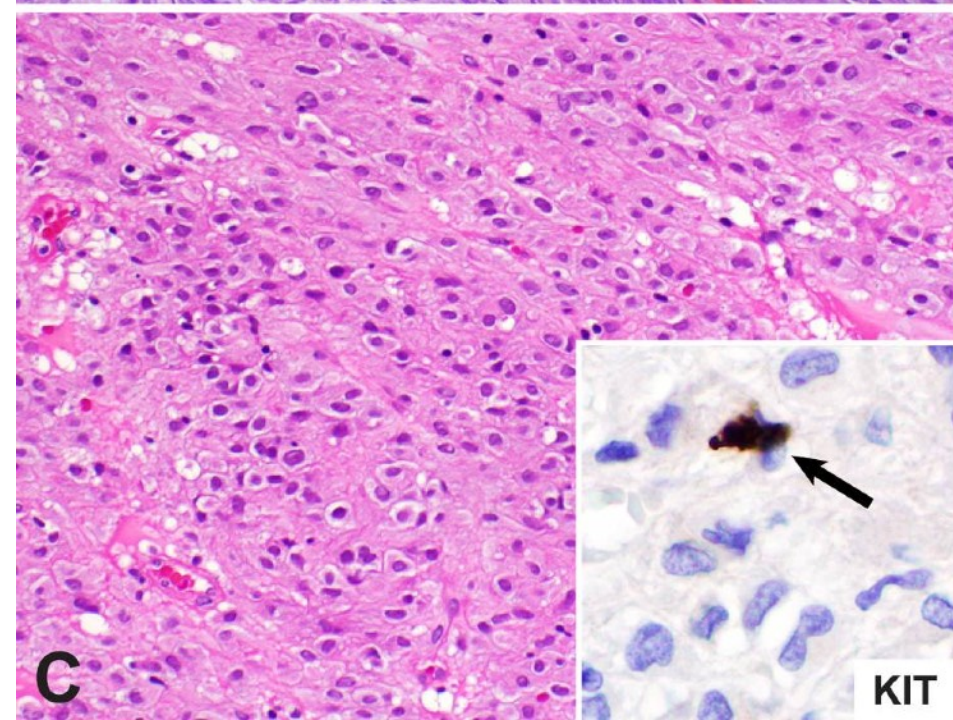
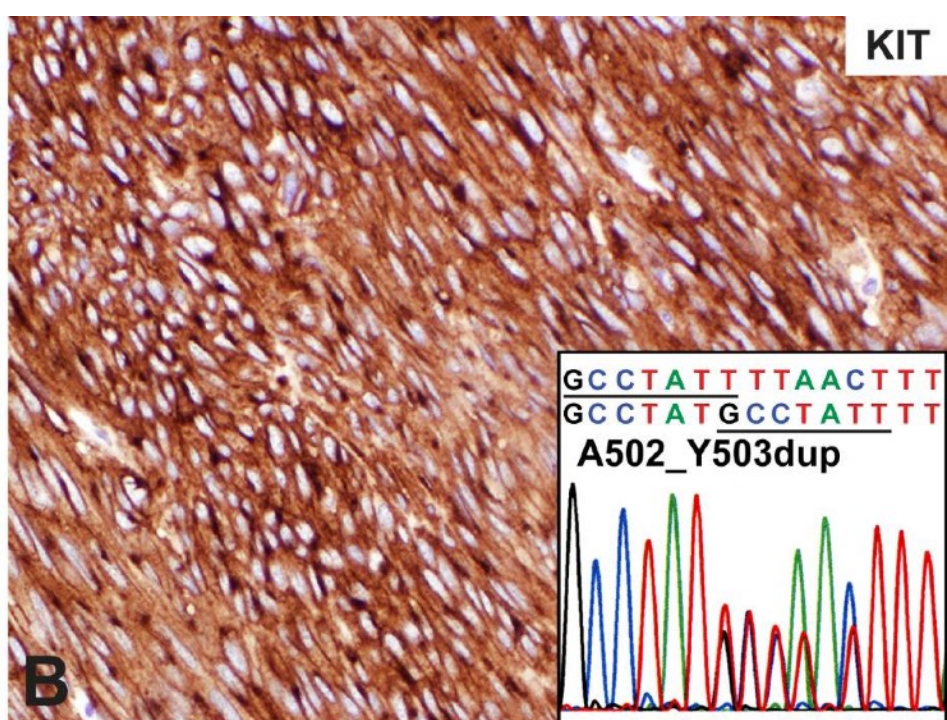
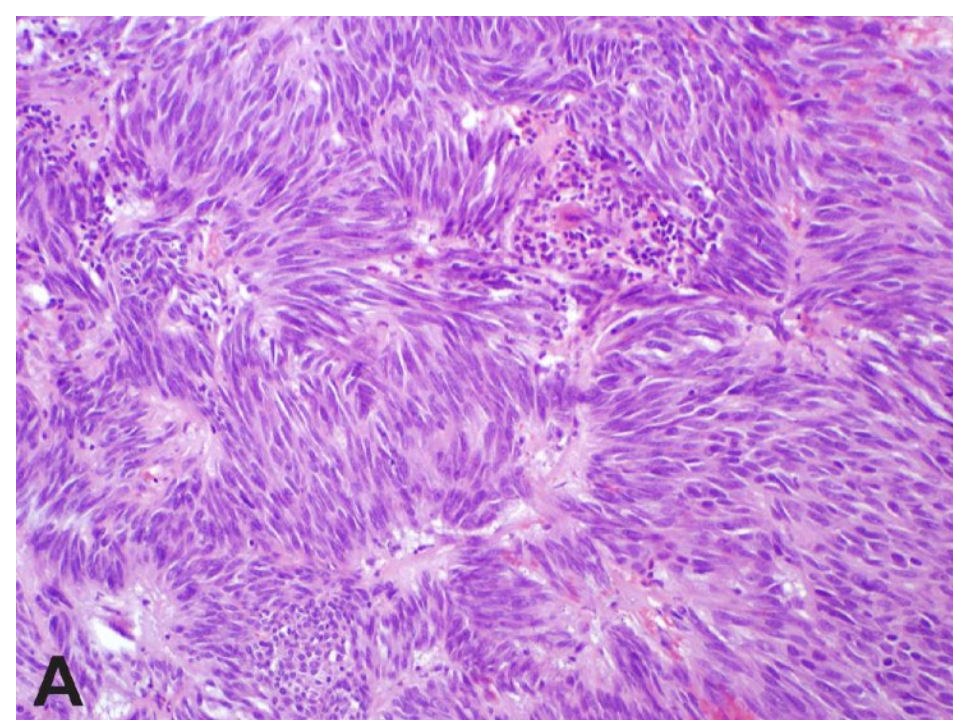
**early satiety,**

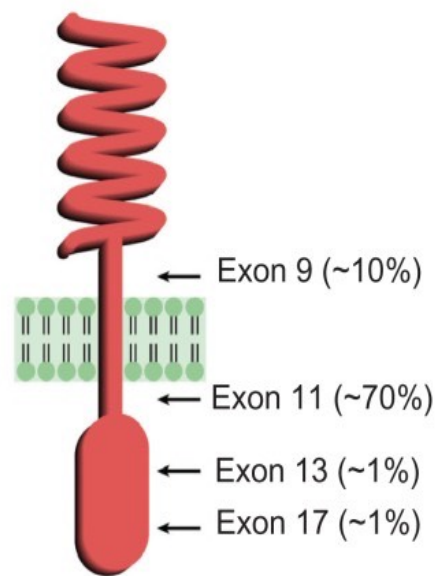
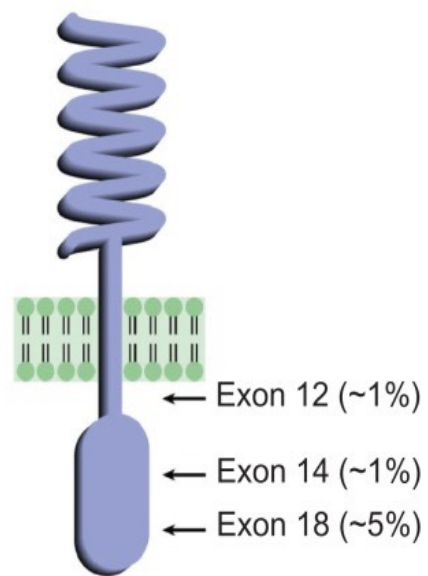
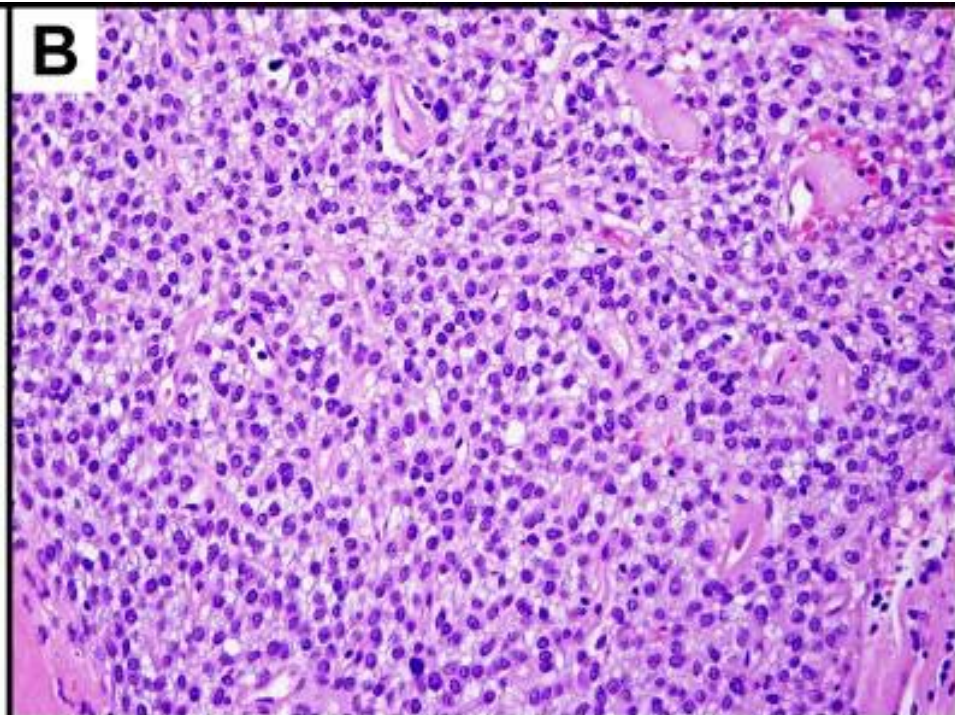
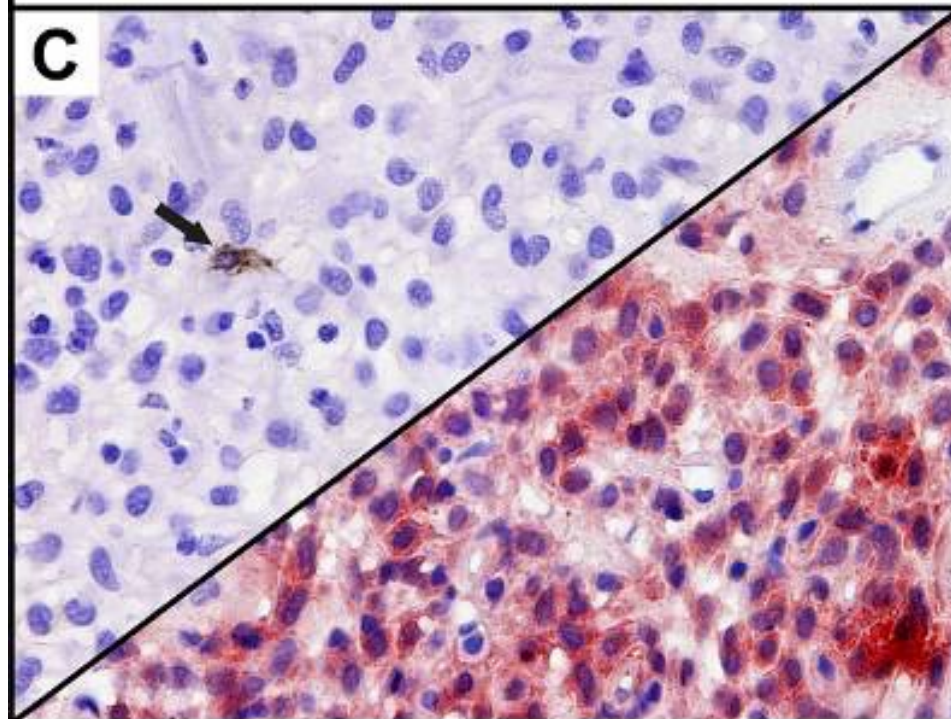
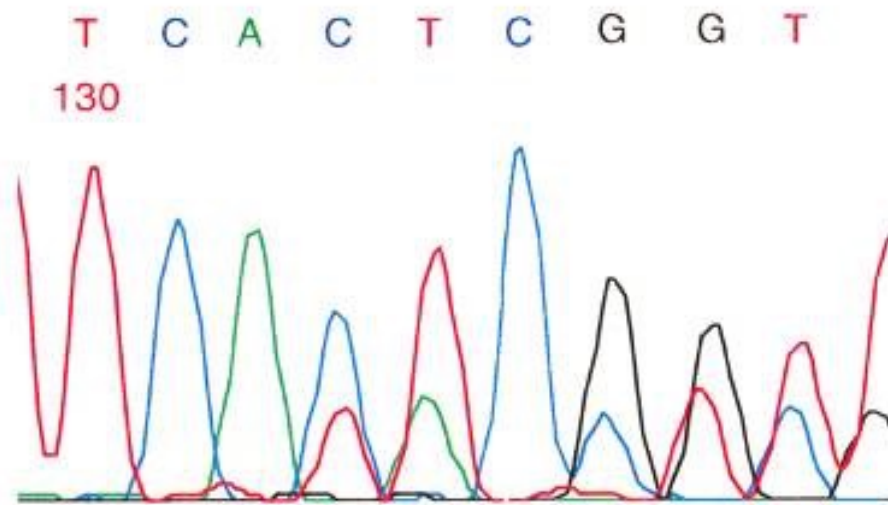
**symptoms referable to a mass**





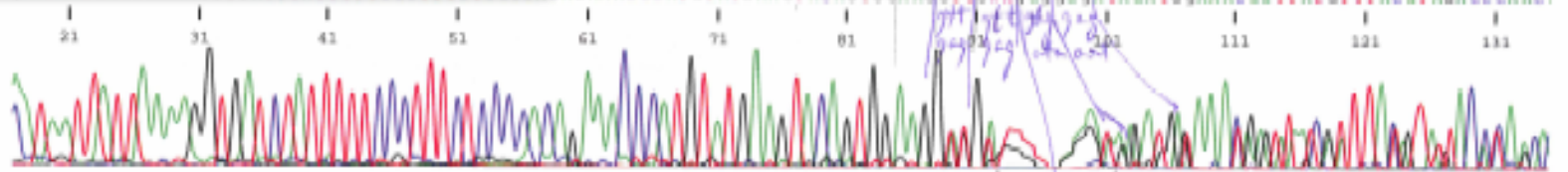
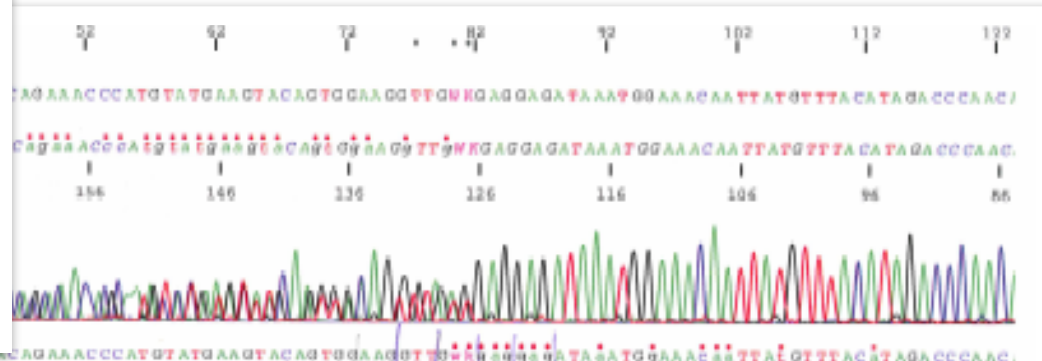
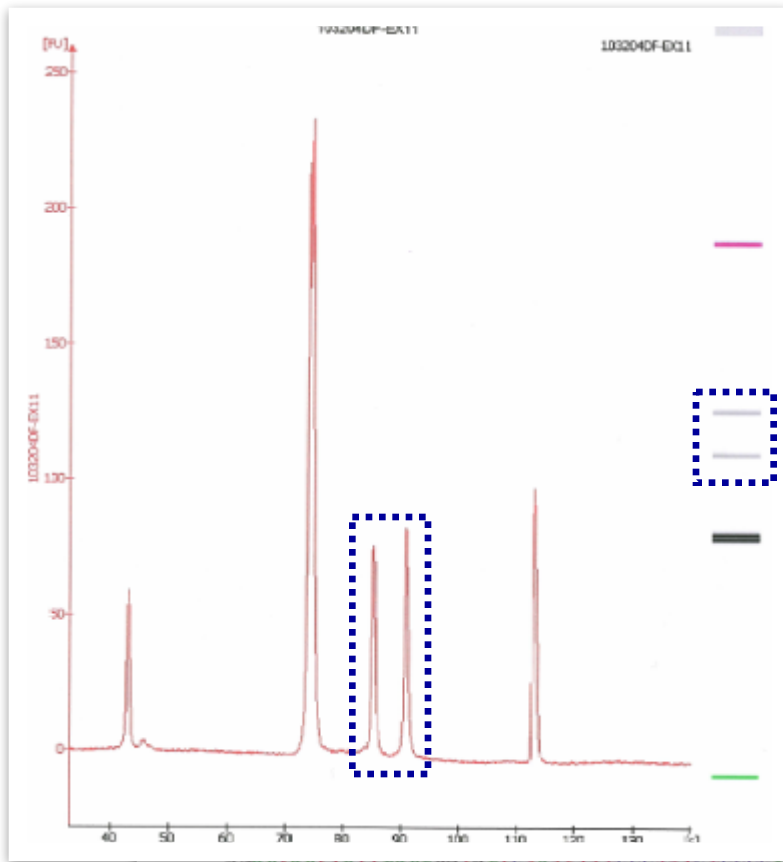
courtesy of Susan Abraham,  
UTMDACC, Houston, TX



**KIT****PDGFRA****B****C****D**

# Exon 11

## V559\_V560del



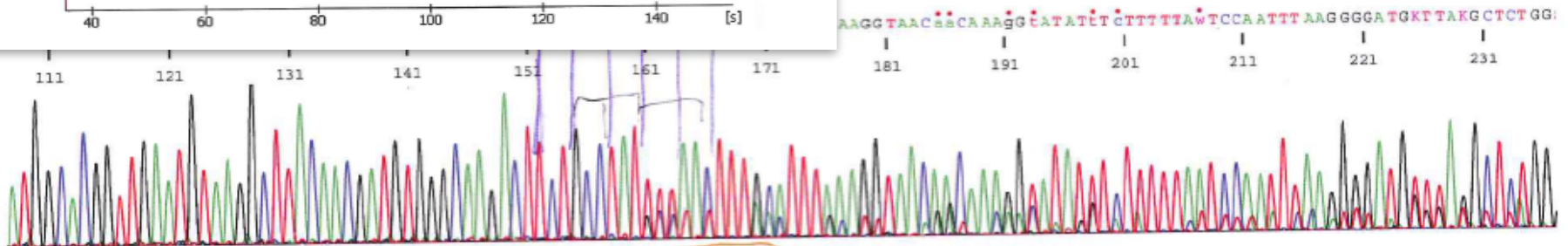
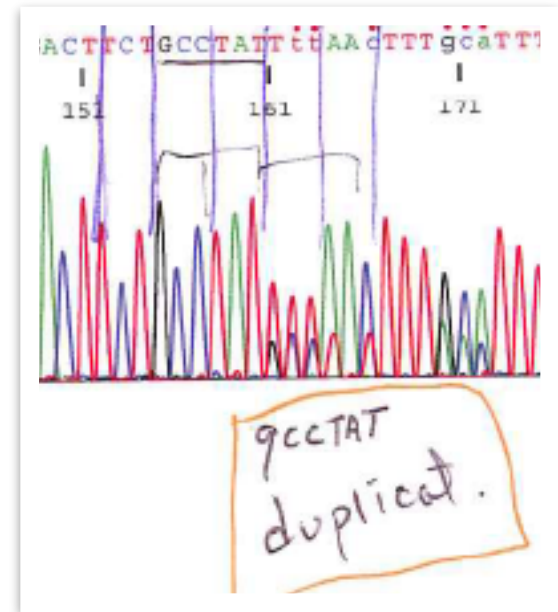
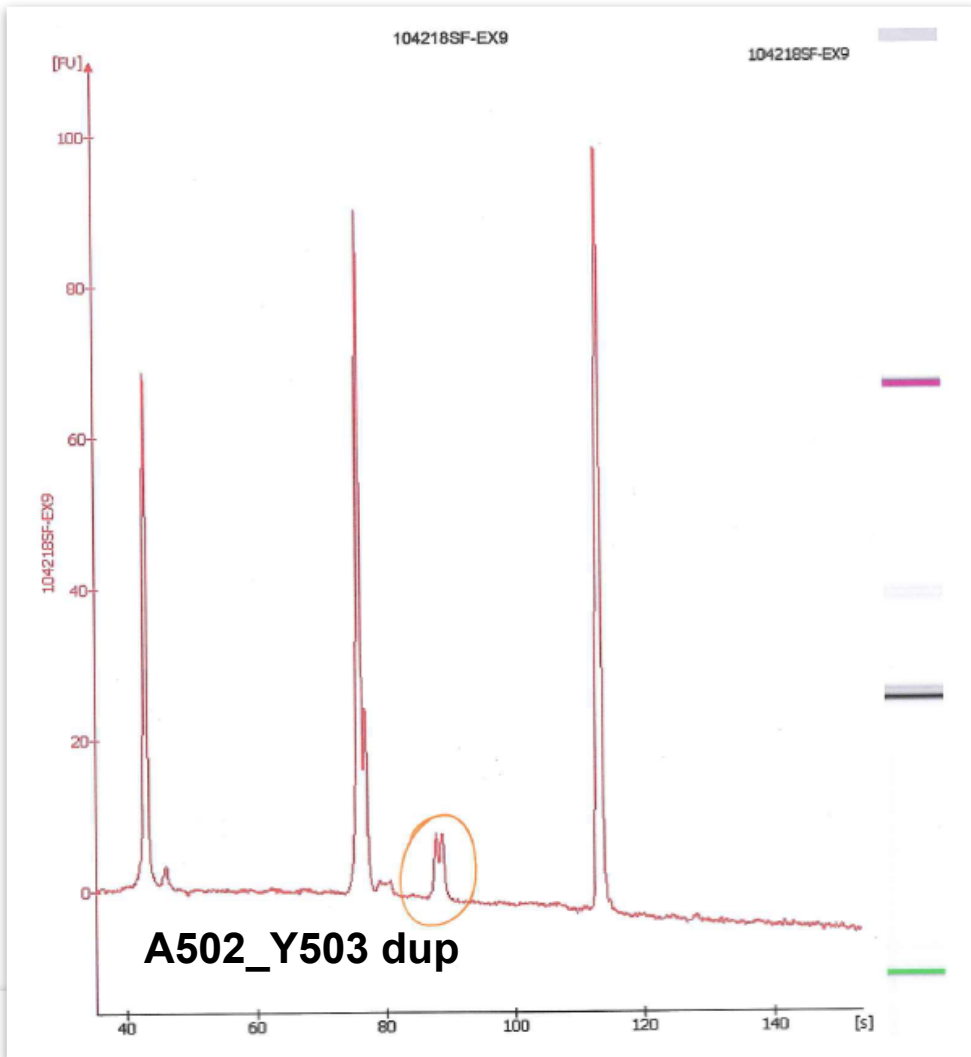
6 bp delct?

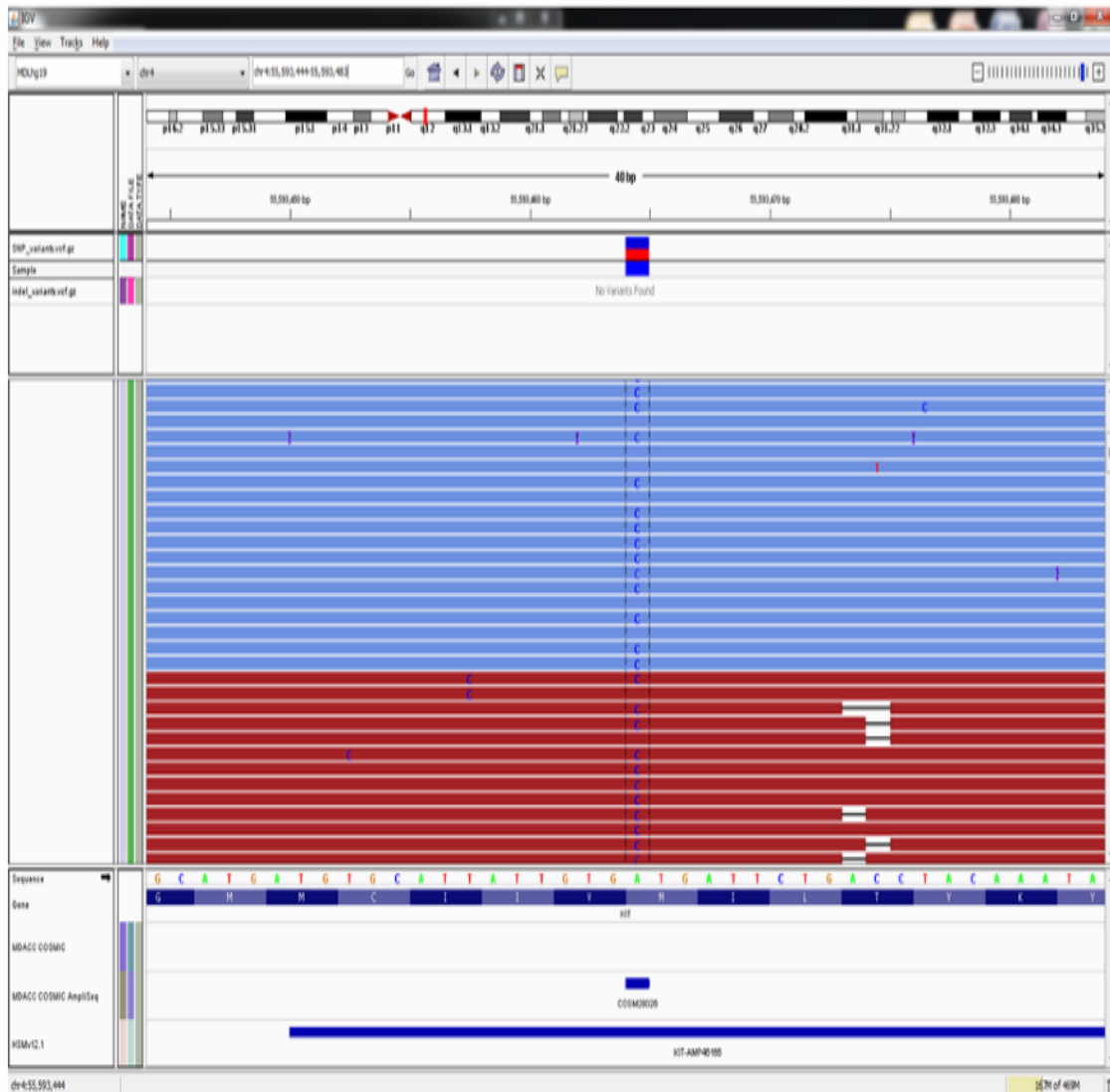
(V559-V560del)

TTGTTG  
gag gag ata aat

# Exon 9

## A502\_Y503dup





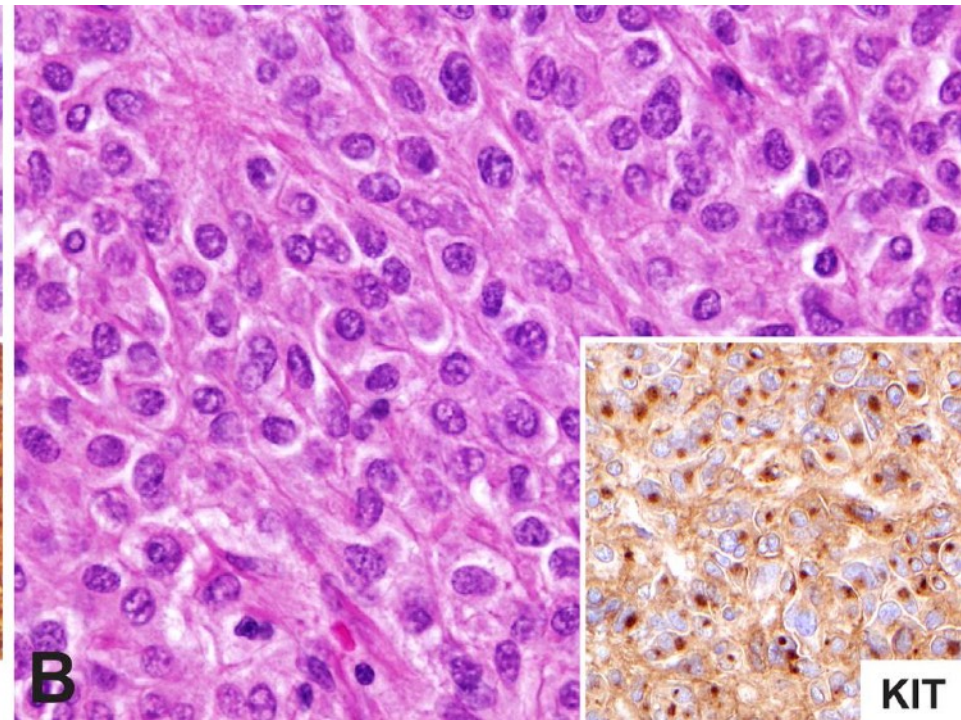
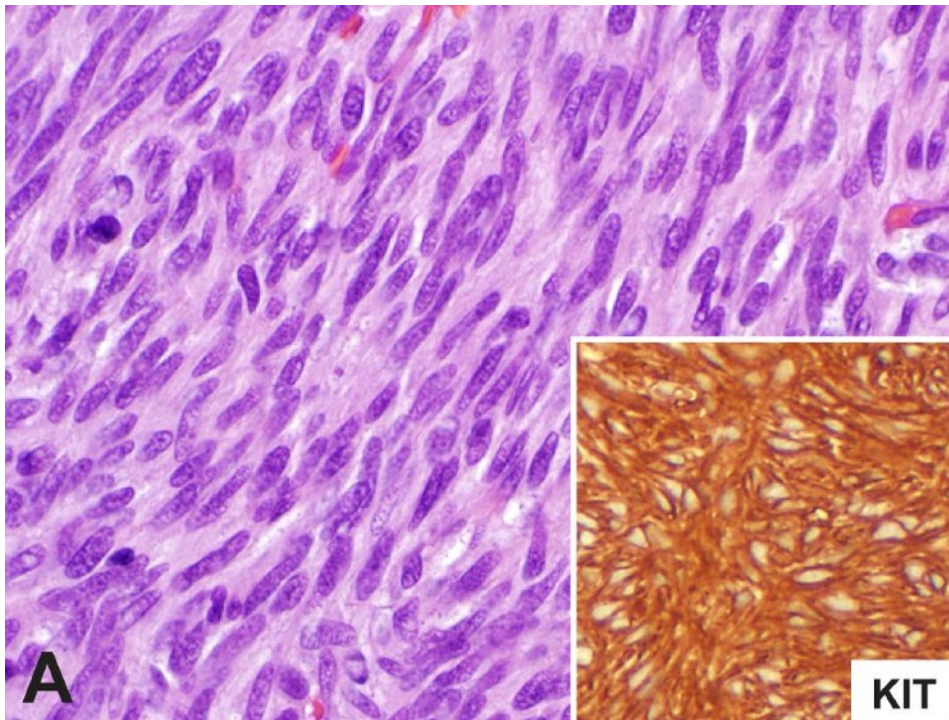
## Detection of SNV in KIT Exon 10,



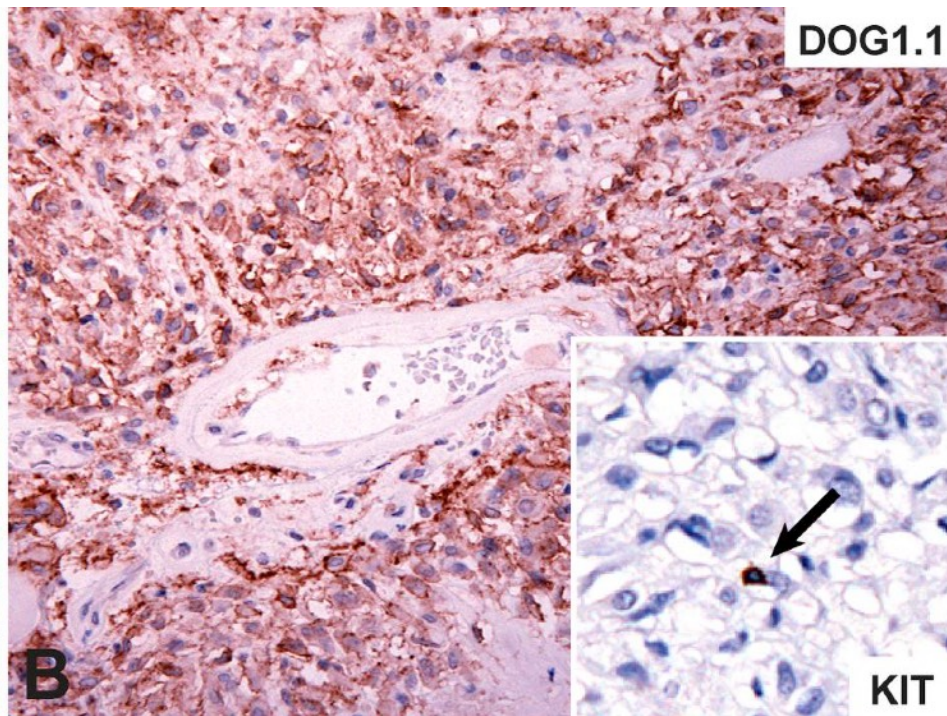
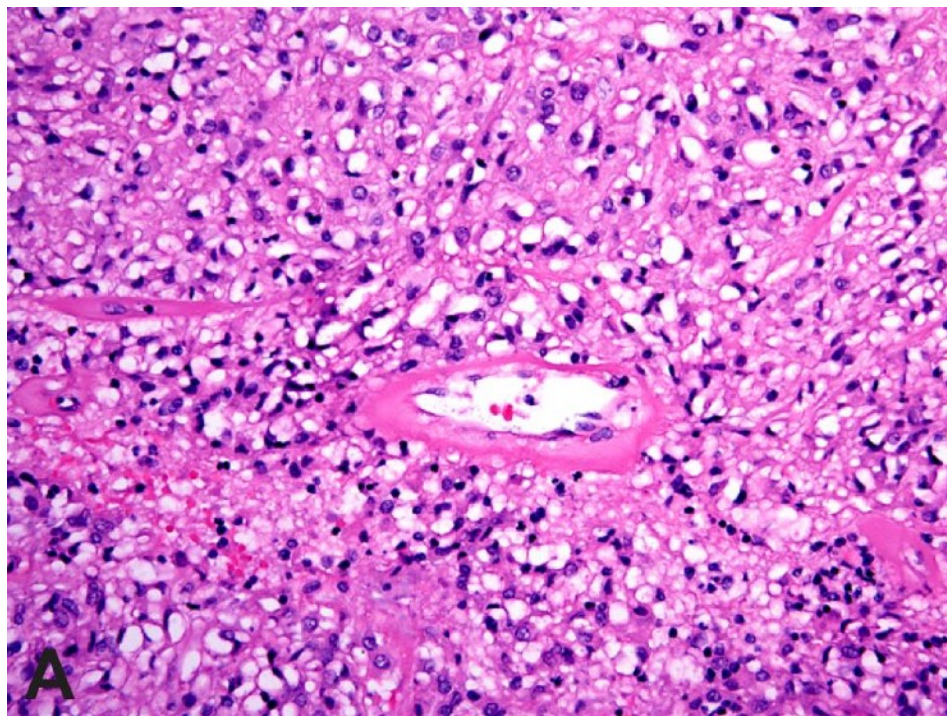
Patient Sample

3346						
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# ***KIT immunoreactivity in GIST***



# ***KIT-negative GIST***





# ***Gastric GISTs with Distinctive Histology (Multinodular/Plexiform)***

- **Pediatric GISTs**

**Female predominance (peak 2<sup>nd</sup> decade)**

**Indolent, but late metastases common**

**Molecular genetic basis unknown**

## **Carney Triad**

**Gastric GIST, pulmonary chondroma, paraganglioma**

**Molecular genetic basis unknown**

## **Carney-Stratakis Syndrome**

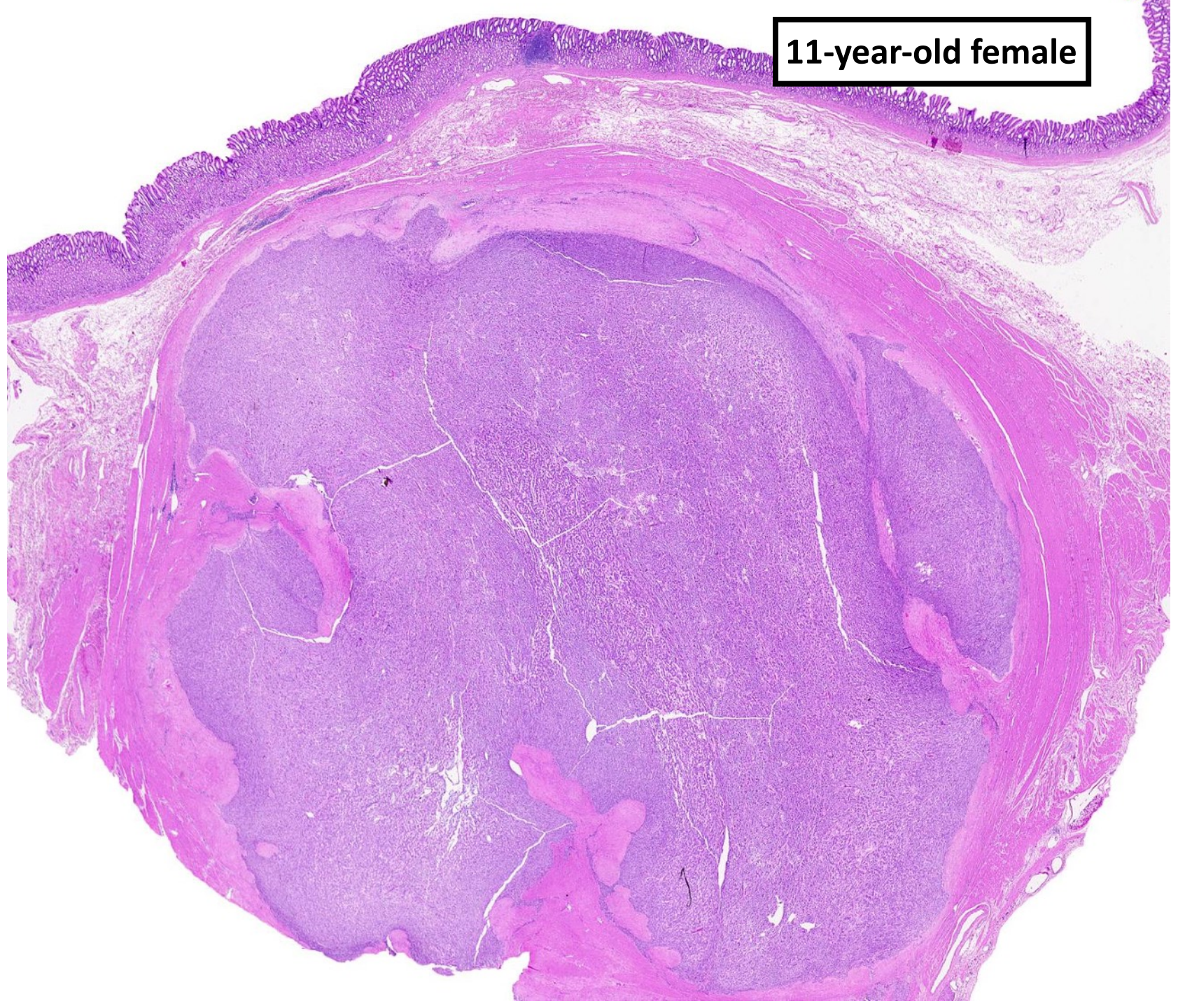
**Gastric GIST and paraganglioma**

**Germline mutations in succinate dehydrogenase subunit genes (*SDHA*, *SDHB*, *SDHC*, or *SDHD*)**

# ***GIST with Distinctive Histology***

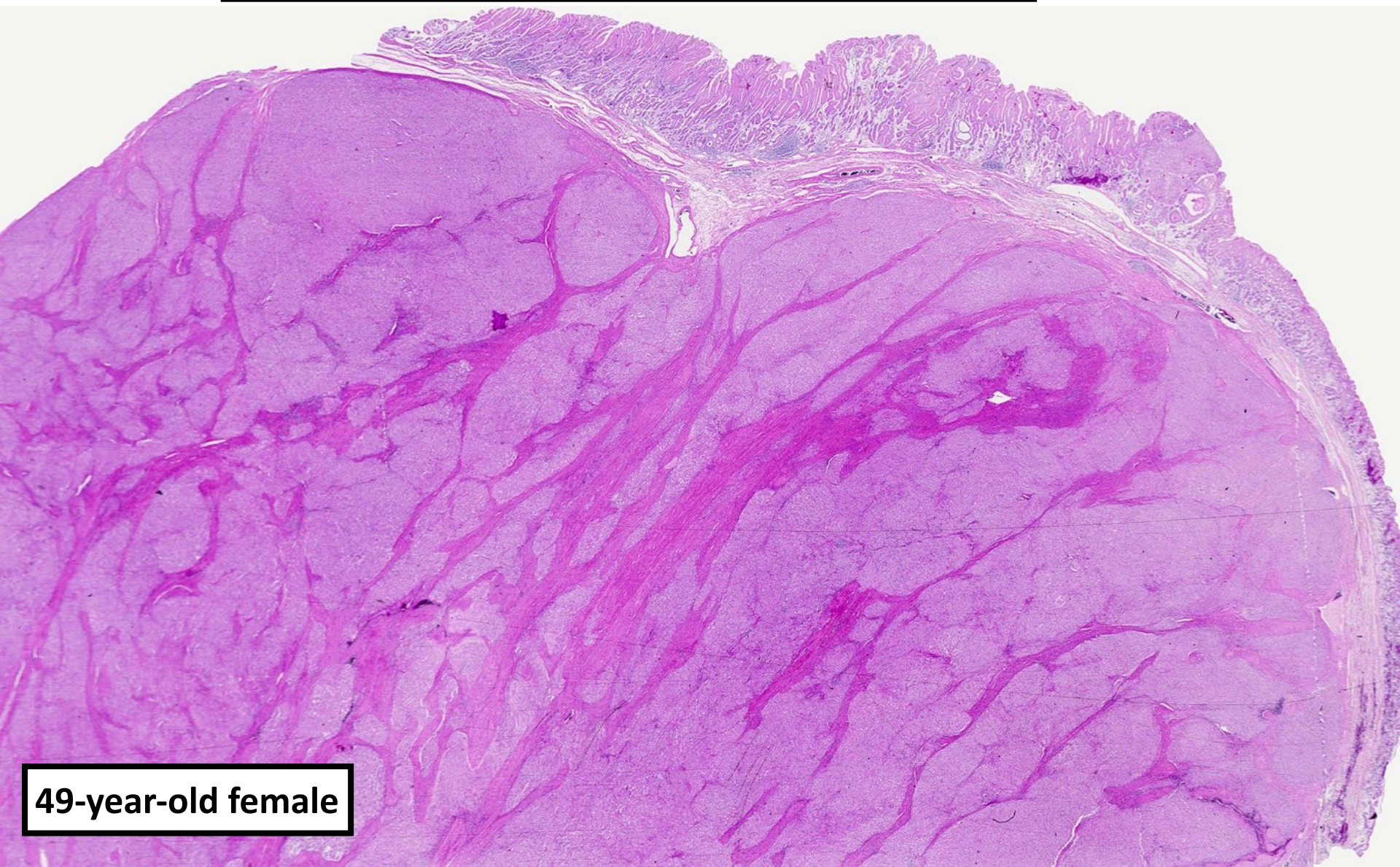
- **Multinodular/plexiform growth pattern**
- **Epithelioid or mixed morphology**
- **“Pediatric-type” or “type 2” GISTs**
- **Loss of SDHB staining by IHC**
- **Lymph node metastases common**
- **Distant metastases common – clinically indolent**
- **Current risk assessment criteria do not reliably predict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

**11-year-old female**



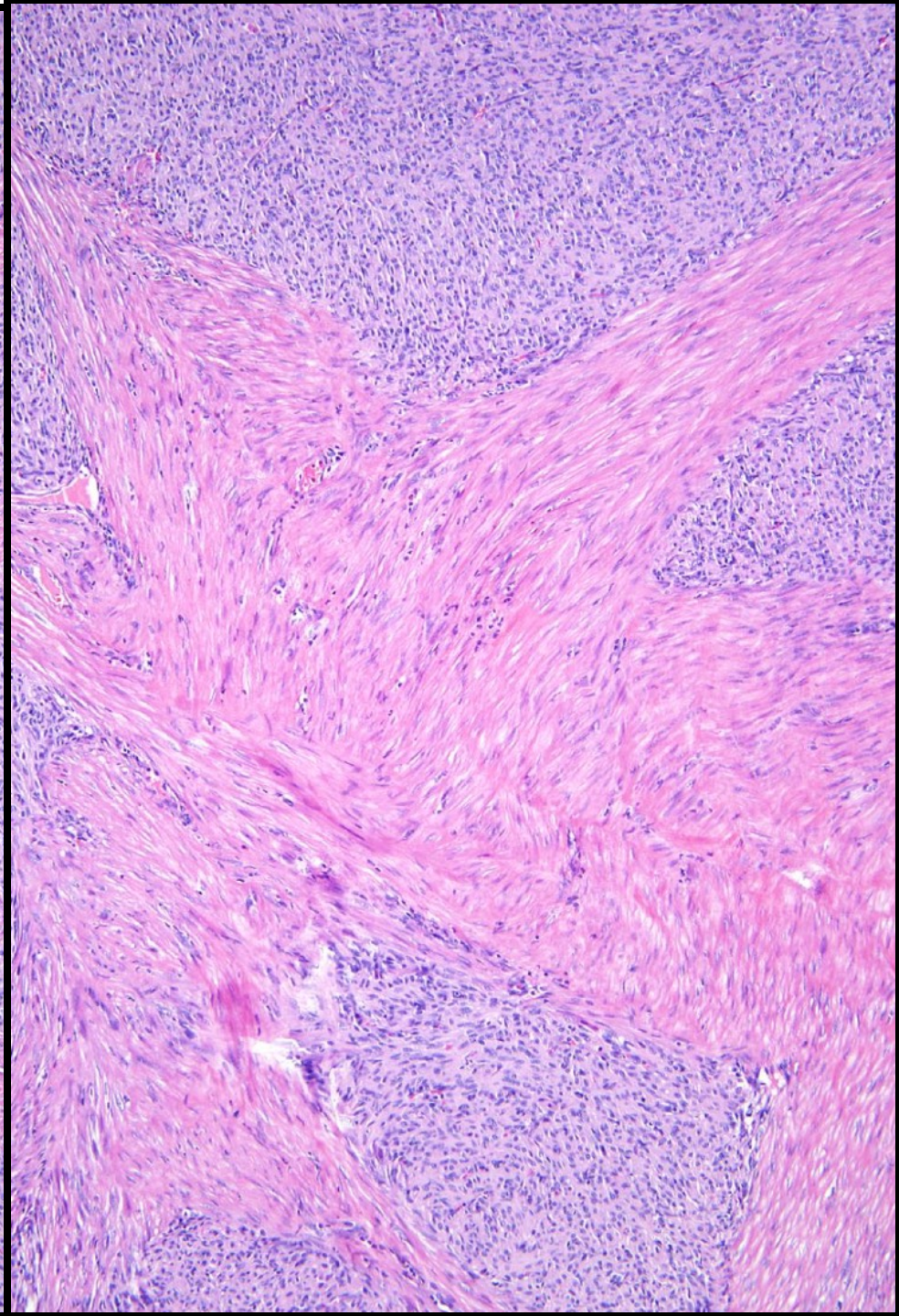
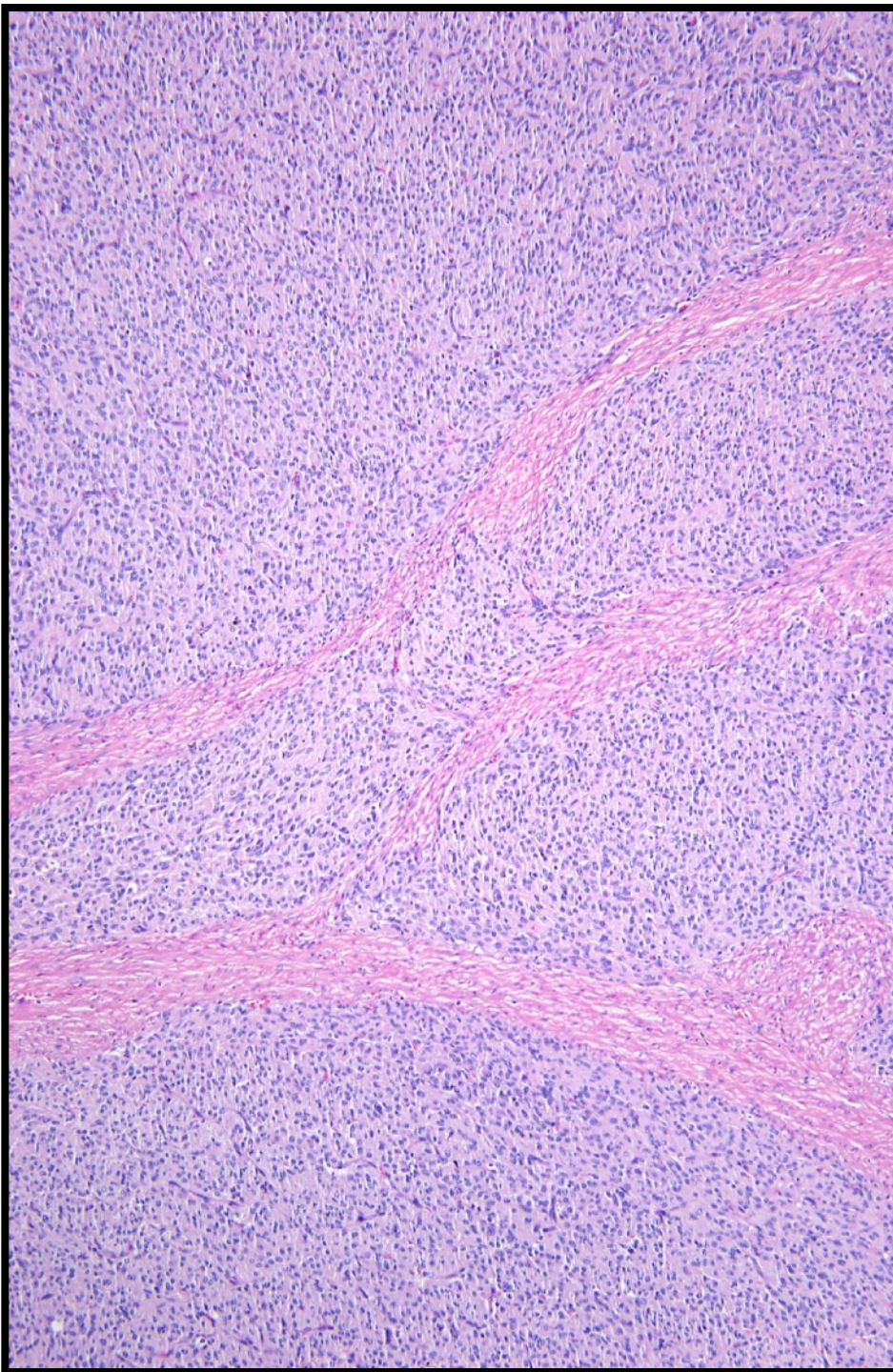
Courtesy of Jason Hornick, BWH/Harvard, Boston, MA

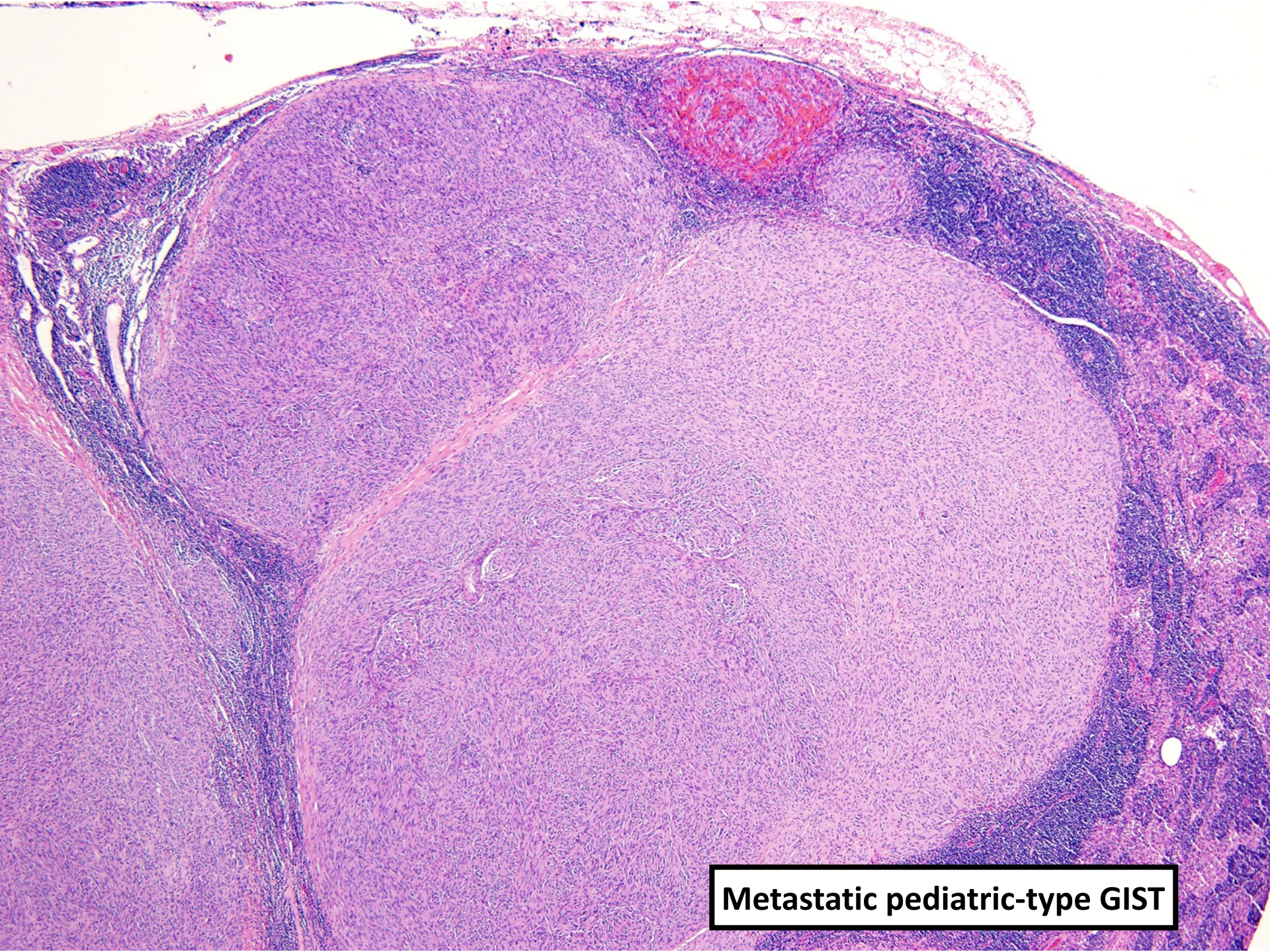
# Pediatric-type GIST in an Adult



49-year-old female

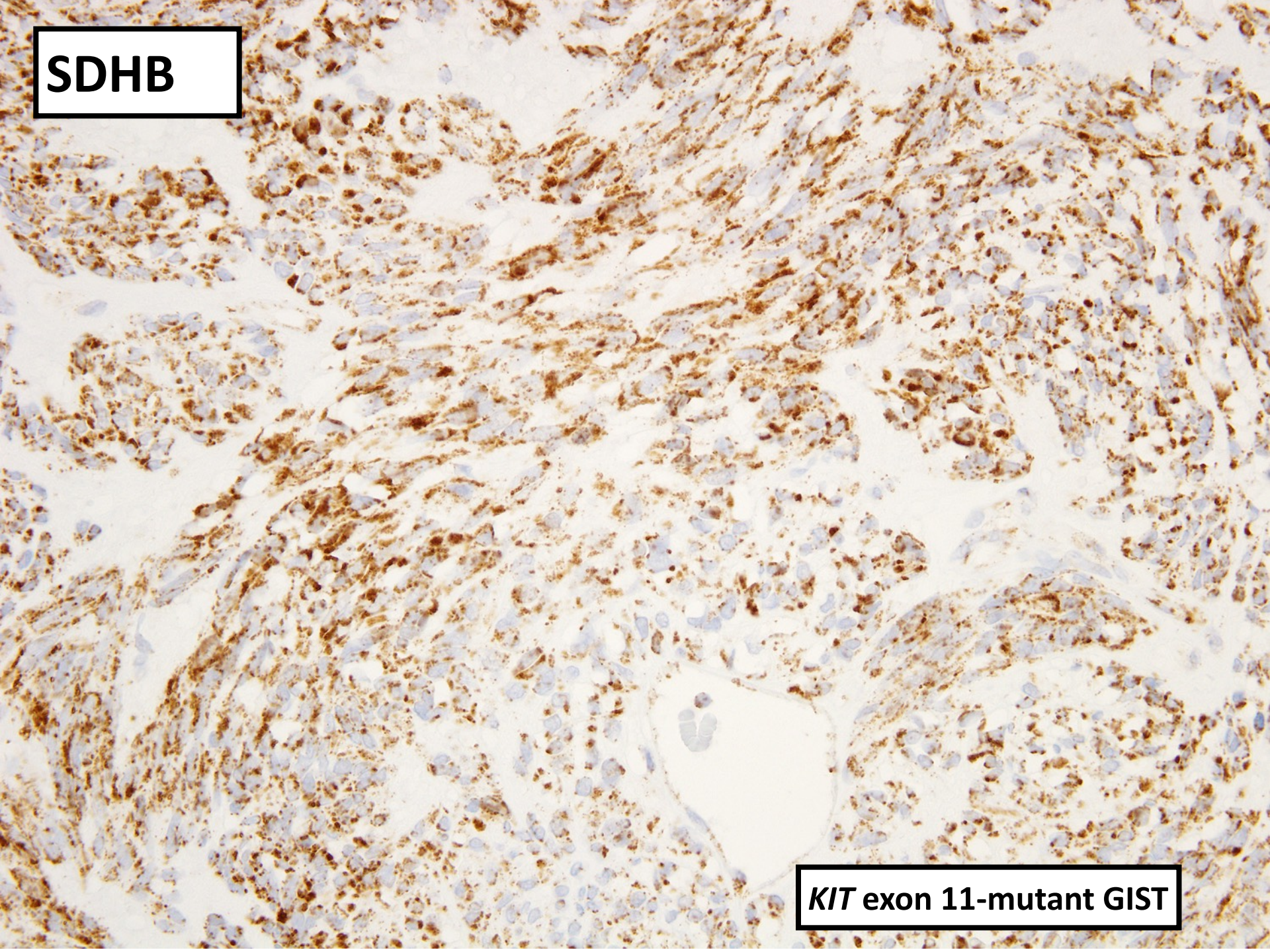
Courtesy of Jason Hornick, BWH/Harvard, Boston, MA





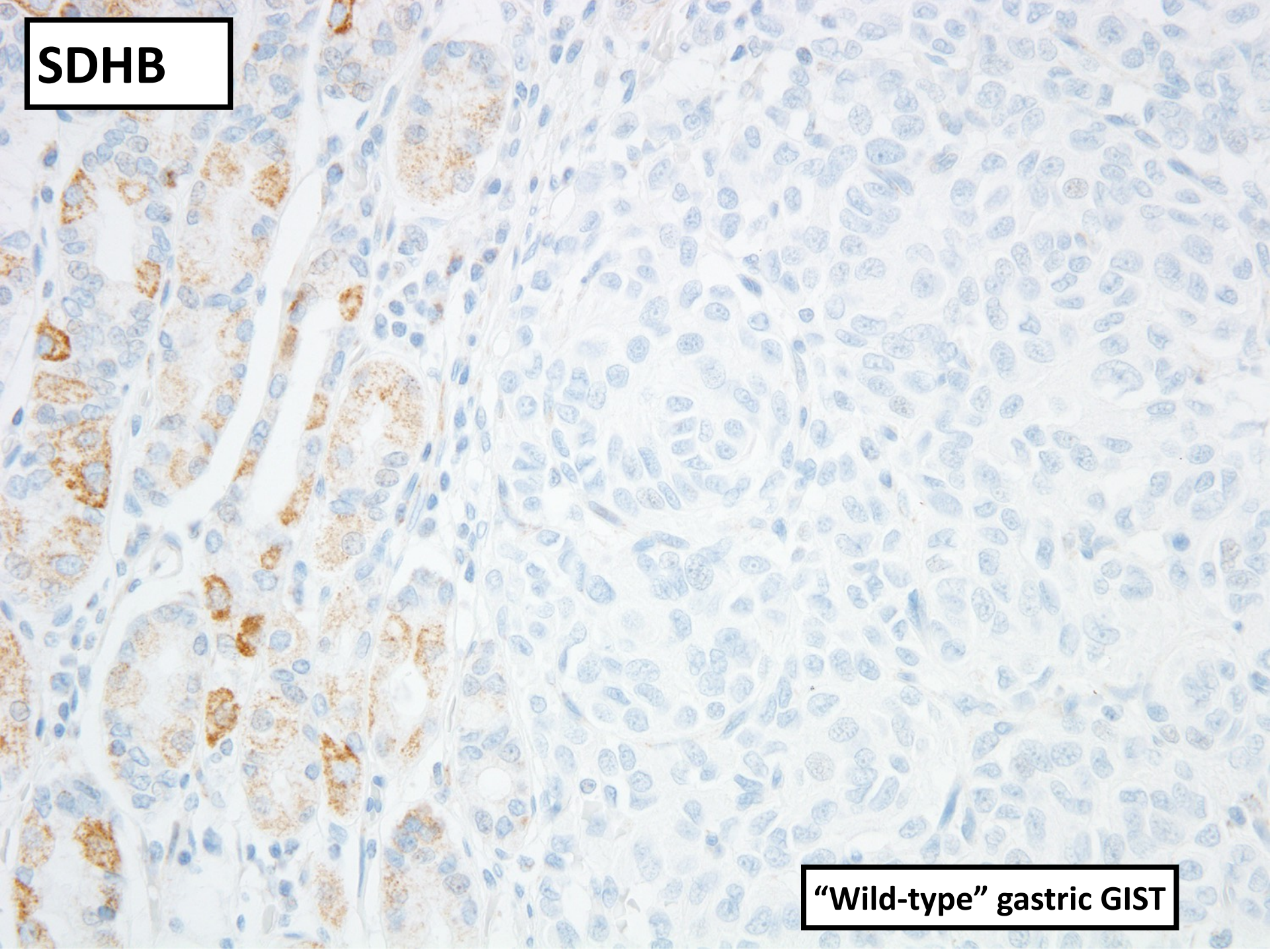
**Metastatic pediatric-type GIST**

**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**

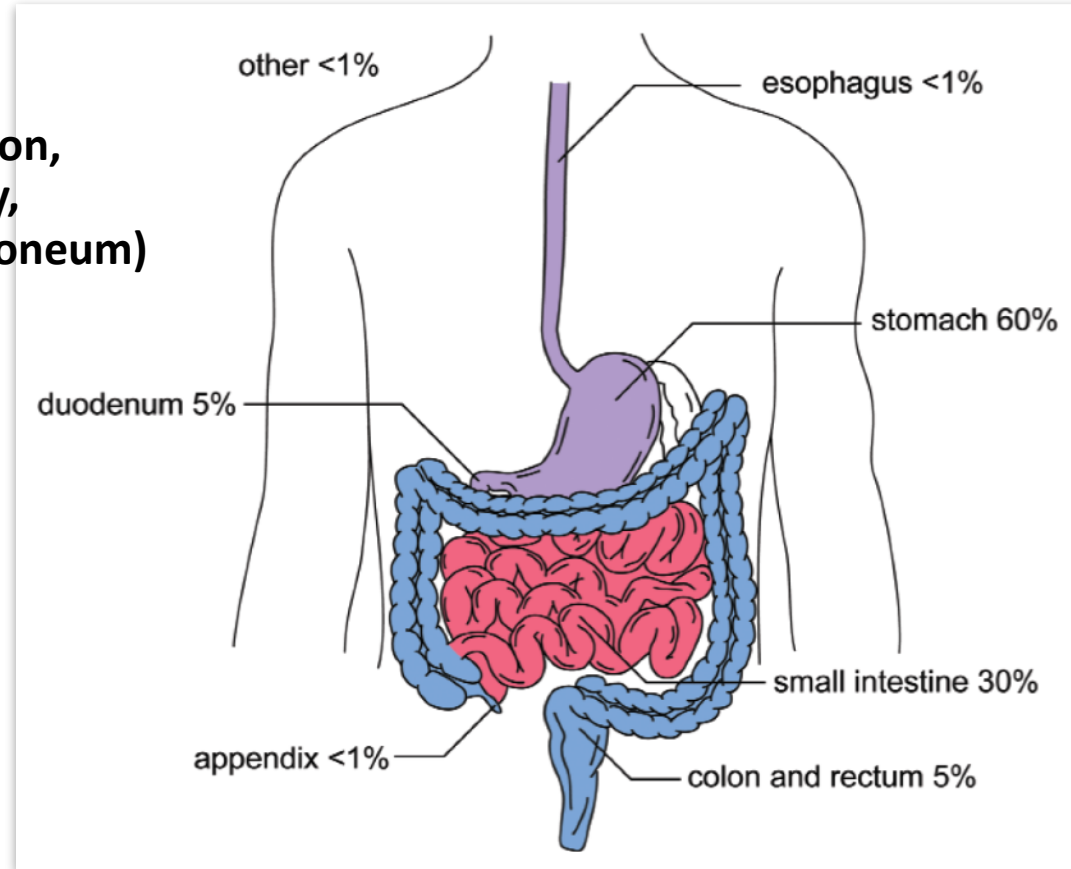
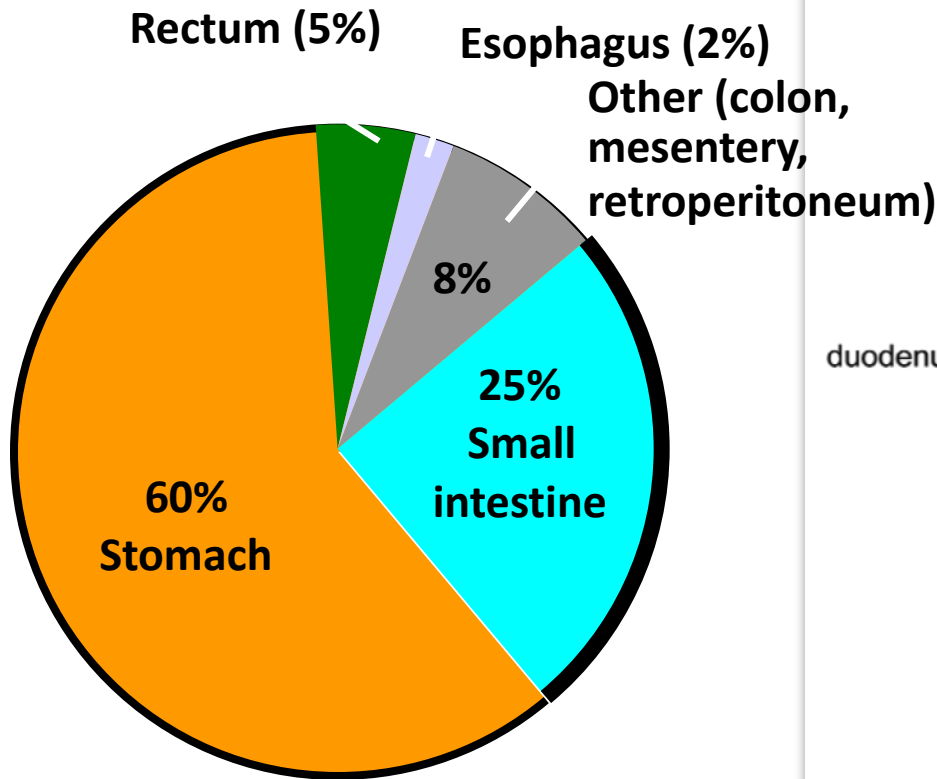
**Nuclear Organizer Regions**

**Problem – Small GISTs without mitoses  
can metastasize!**

# ***NIH Consensus Risk Assessment***

	<b>Size</b>	<b>Mitotic Count</b>
<b>Very Low Risk</b>	<b>&lt; 2 cm</b>	<b>&lt; 5/50 HPF</b>
<b>Low Risk</b>	<b>2-5 cm</b>	<b>&lt; 5/50 HPF</b>
<b>Intermediate Risk</b>	<b>&lt; 5 cm</b>	<b>6-10/50 HPF</b>
	<b>5-10 cm</b>	<b>&lt; 5/50 HPF</b>
<b>High Risk</b>	<b>&gt; 5 cm</b>	<b>&gt; 5/50 HPF</b>

# ***GIST: Sites of Involvement***



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

# 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%)

Miettinen et al. 2005 and 2006

\*\*\*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

# ***GIST - Gross Appearance***

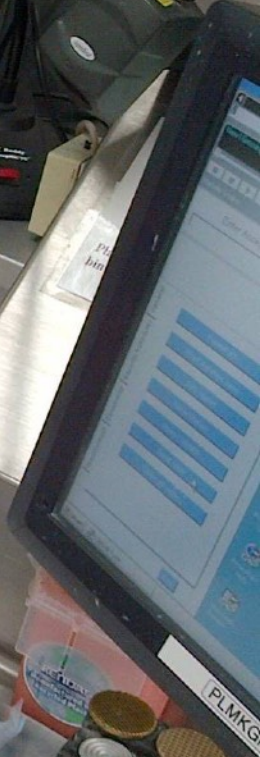


Courtesy of Brian Rubin, Cleveland Clinic



MILITARY ALPHABET

A - Alpha	N - November
B - Bravo	O - Oscar
C - Charlie	P - Papa
D - Delta	Q - Quebec
E - Echo	R - Romeo
F - Foxtrot	S - Sierra
G - Golf	T - Tango
H - Hotel	U - Uniform
I - India	V - Victor
J - Juliet	W - Whiskey
K - Kilo	X - X-ray
L - Lima	Y - Yankee
M - Mike	Z - Zulu

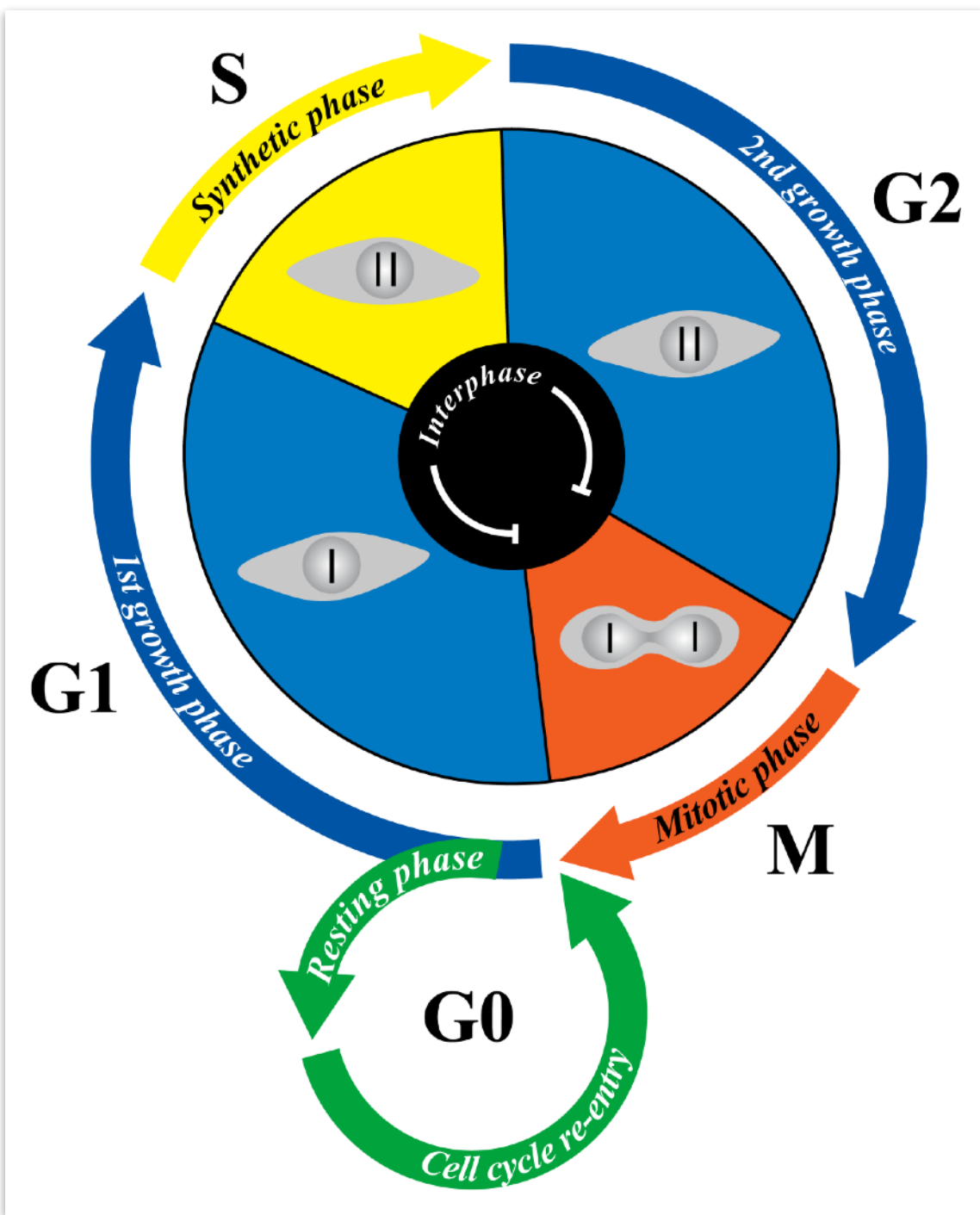


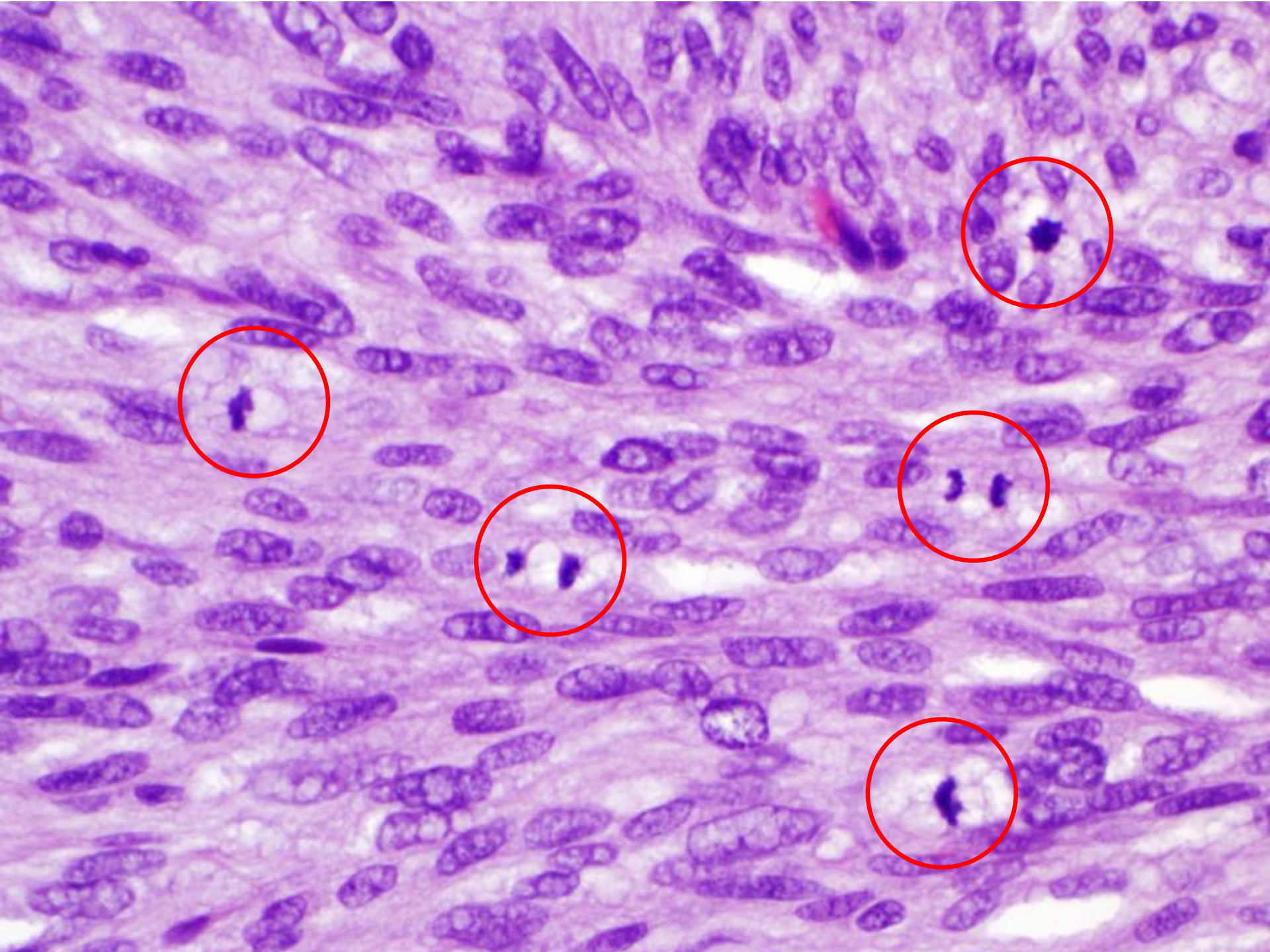




# 2007/2010/2014 NCCN GIST Risk Assessment Guidelines\*\*\*

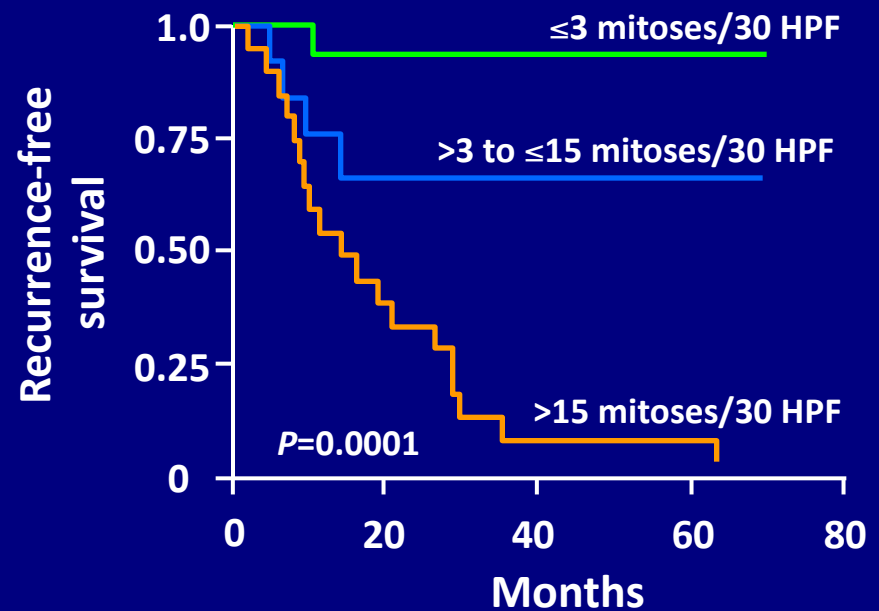
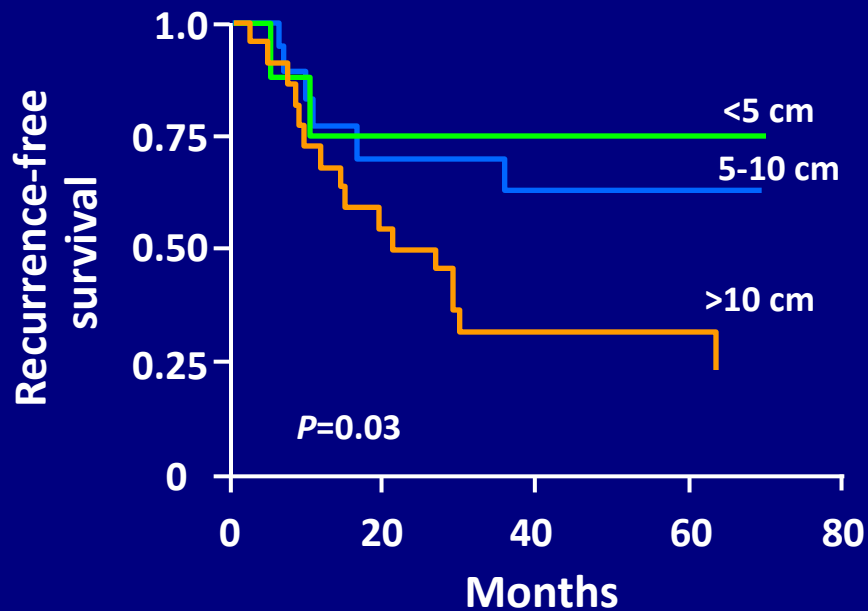
Tumor	Parameters	Risk of	Progressive	Disease# (%)	
	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
Mitotic	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
Index	> 2 ≤ 5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
≤ 5 per 50 hpf	> 5 ≤ 10 cm	Low (3.6%)	(Insuff. data)	Moderate (24%)	(Insuff. data)
	> 10 cm	Moderate (16%)	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%)
*** Modified from Miettinen & Lasota, <i>Semin Diagn Pathol</i> , 2006 by Dr. Chris Corless, OHSU					
Database based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST					
	> 5 ≤ 10 cm	High (55%)	(Insuff. data)	High (85%)	(Insuff. data)
	> 10 cm	High (86%)	High (86%)	High (90%)	High (71%)





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

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



# 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<sup>2</sup>) using a 40x objective.

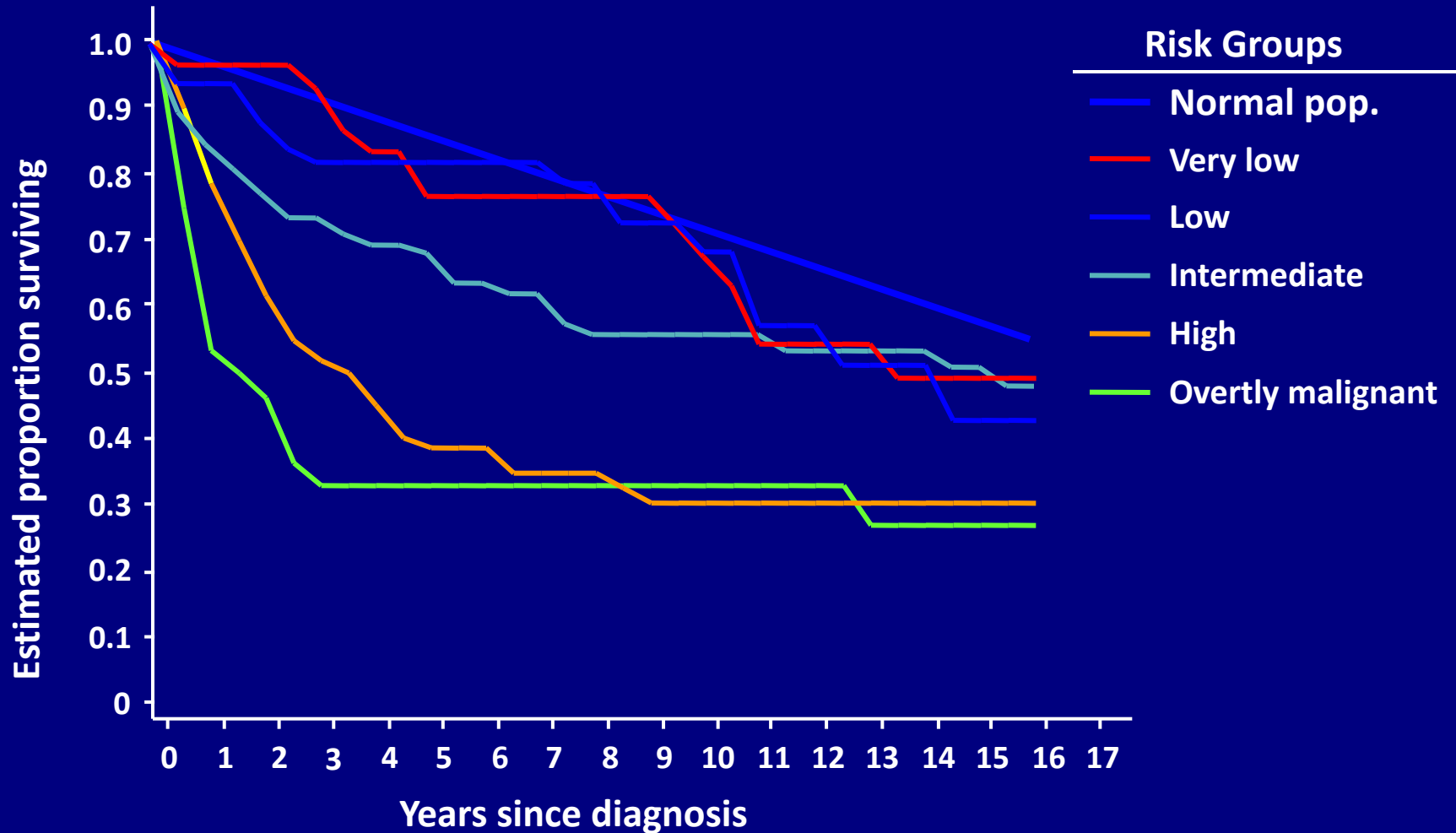
1. 0-9 mitoses per 10 HPFs
2. 10-19 mitoses per 10 HPFs
3. >20 mitoses per 10 HPFs

- 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

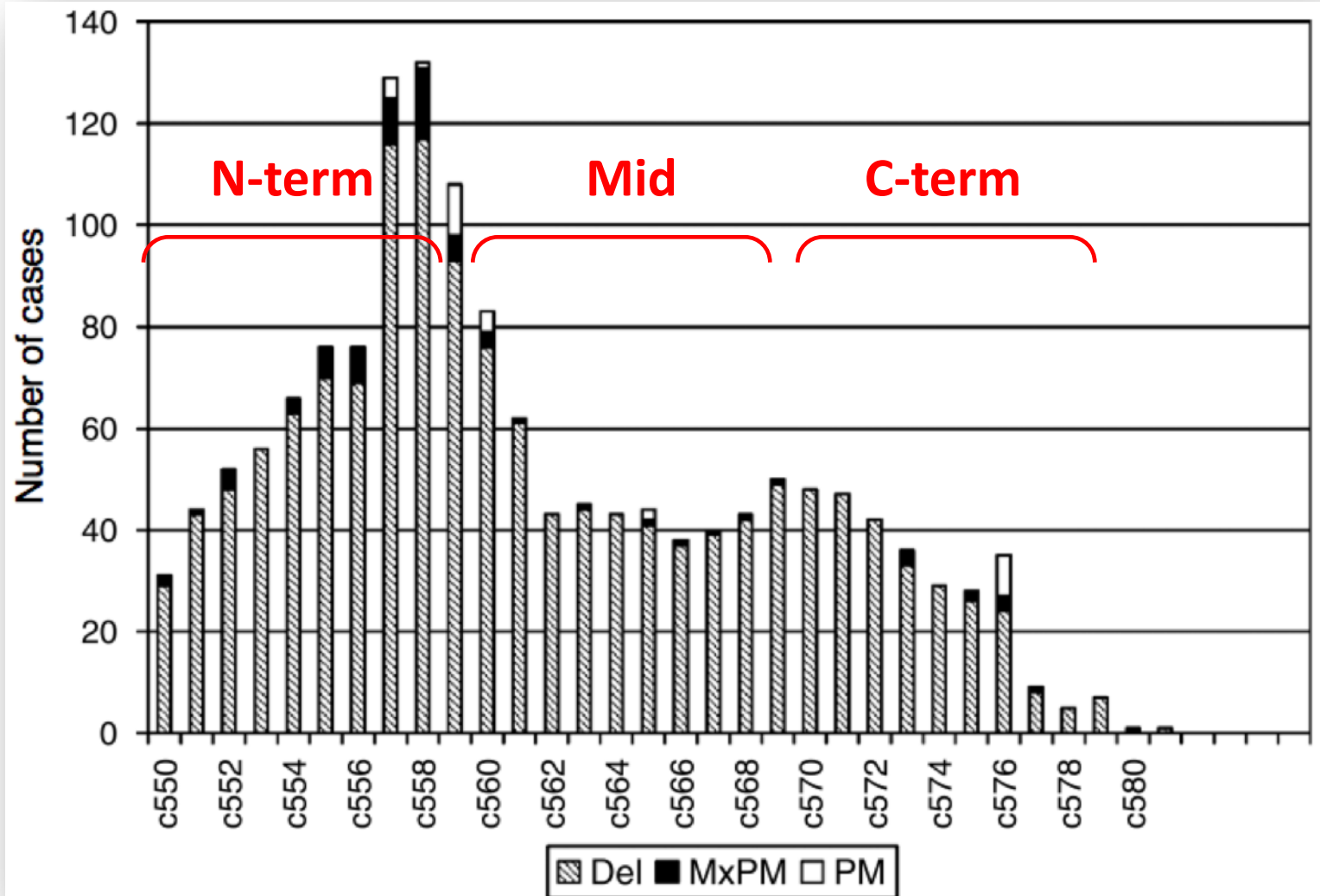


# *Genomic complexity and prognosis*

## *Possible approaches*

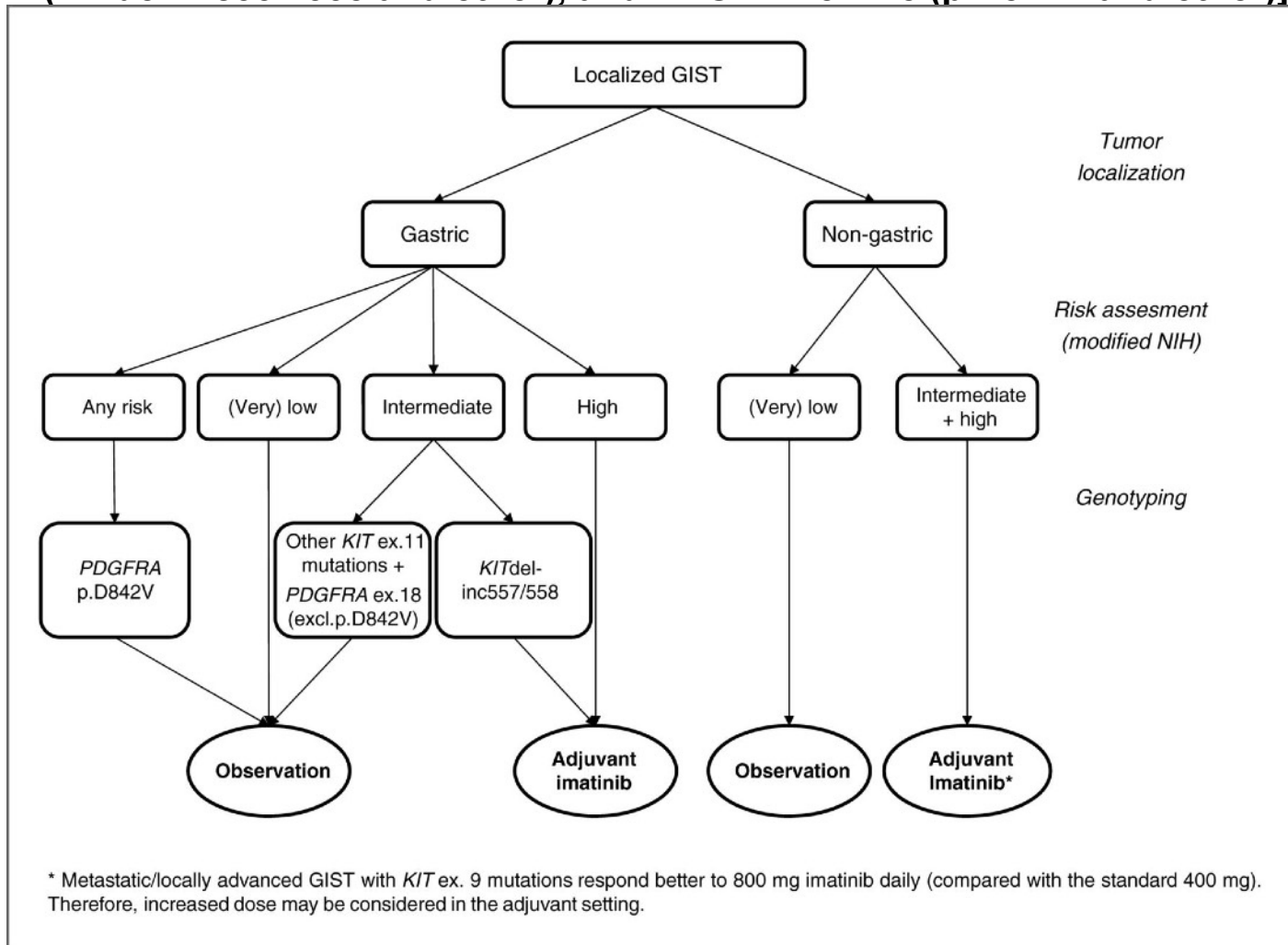
- **(Histological grading)**
- **Risk assessment +:**
  - **Array-CGH**
  - **Carter signature**
  - **Next generation Sequencing**

# Spectrum of KIT Exon 11 Mutations



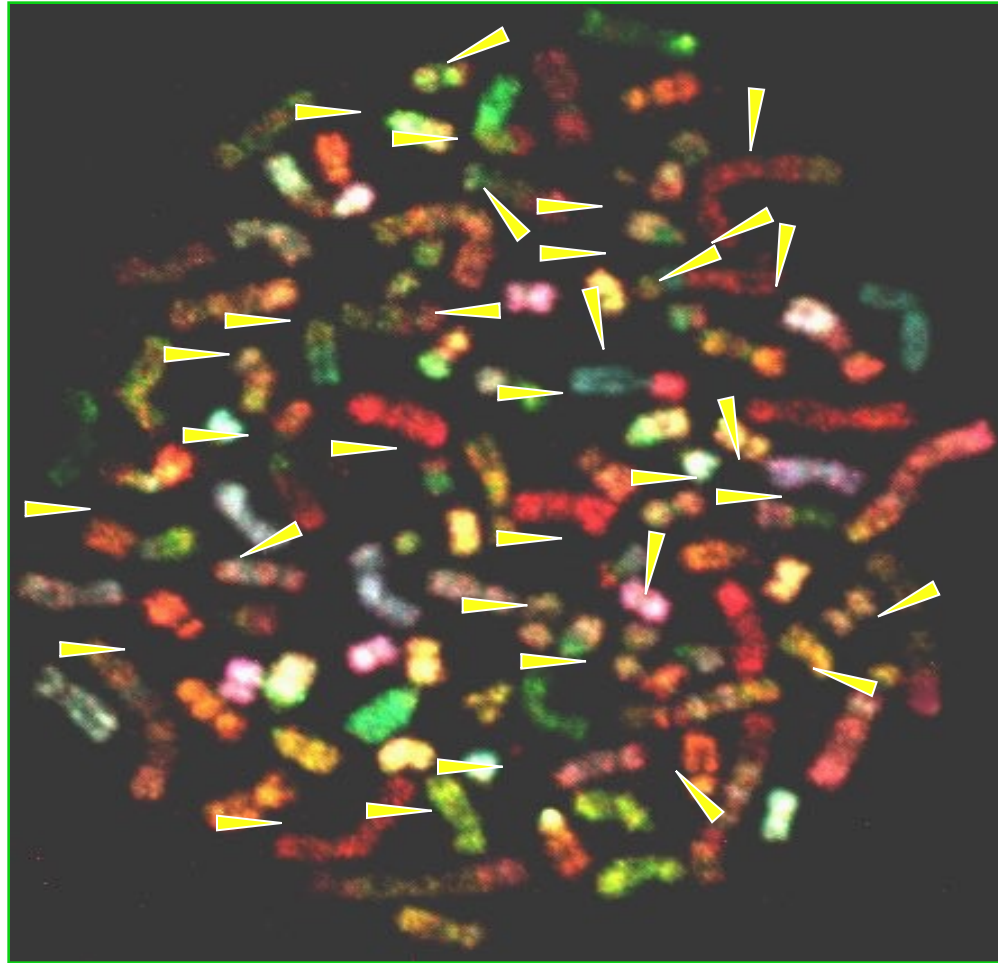


The recommendations for adjuvant imatinib therapy by integration of the risk assessment (based on modified NIH classification) and tumor genotype [KIT ex. 9 p.A502\_Y503dup, KIT ex. 11 (KITdel-inc557/558 and other), and PDGFRA ex. 18 (p.D842V and other)] in ...



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

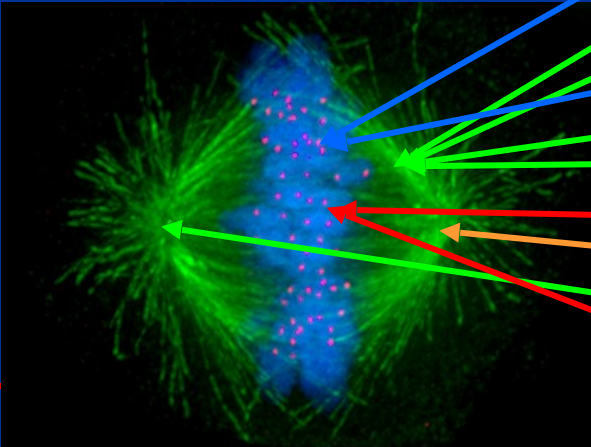
# Chromosomal complexity and prognosis



97 chromosomes and more than 50 translocations

# 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	<u>chromosome, pericentric region</u>
GO:0005819				27,03	<u>spindle</u>
GO:0005876				25,02	<u>spindle microtubule</u>
GO:0005694				12,73	<u>chromosome</u>
GO:0005875				11,42	<u>microtubule associated complex</u>
GO:0005874				7,88	<u>microtubule</u>
GO:0000776				12,42	<u>kinetochore</u>
GO:0005871				10,67	<u>kinesin complex</u>
GO:0005813	4	48	0,0001	7,96	<u>centrosome</u>
GO:0000940					<u>some</u>
GO:0030496					
GO:0005657					
GO:0005814	2	9	0,0012	9,52	<u>centriole</u>
GO:0015630	2	13	0,0022	7,84	<u>microtubule cytoskeleton</u>
GO:0000922	2	16	0,0032	7,02	<u>spindle pole</u>
GO:0000785	3	75	0,0059	4,47	<u>chromatin</u>
GO:0000786	2	32	0,0111	4,77	<u>nucleosome</u>
GO:0001939	1	3	0,0187	8,30	<u>female pronucleus</u>
GO:0005816	1	3	0,0187	8,30	<u>spindle pole body</u>



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

# 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 ?**

# ***Chromosomal instability signature***

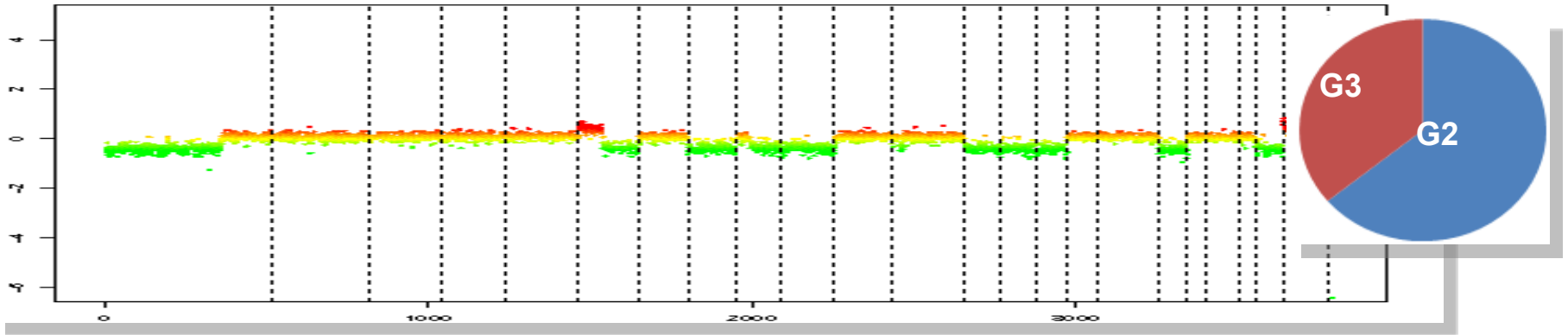
Carter et al Nat Genet 2002

- **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 French series of sarcomas**

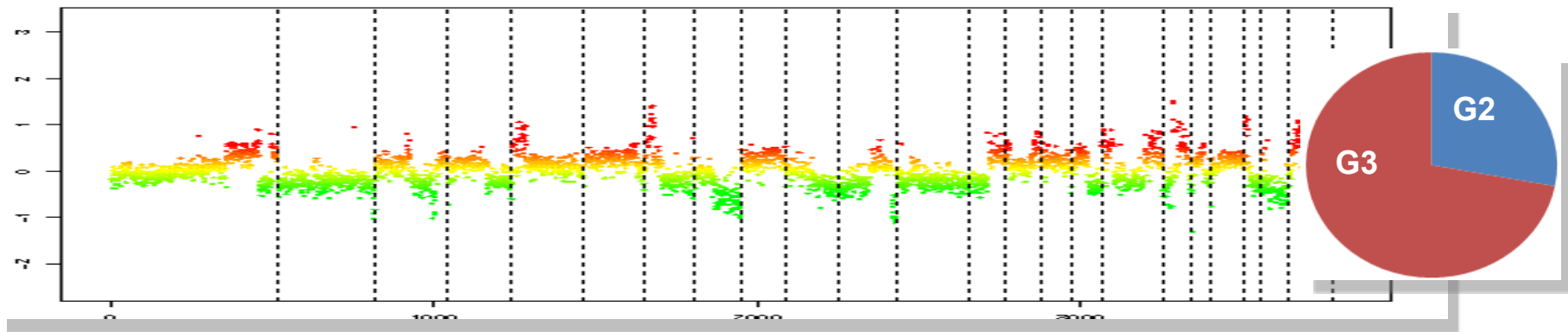
Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)

# CINSARC : arrayCGH analysis and correlation with FNCLCC grading

## « Arm » Profile



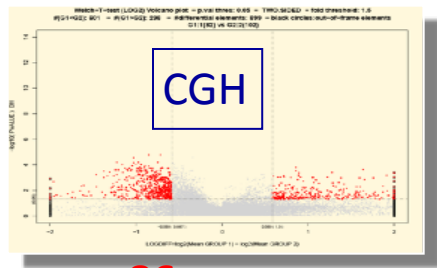
## « Rearranged » Profile



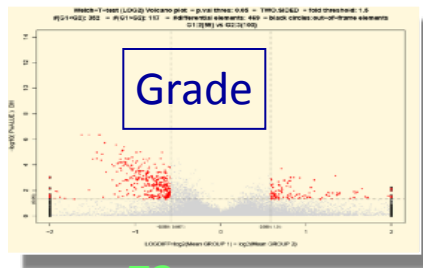
Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)

# Molecular grading in sarcomas

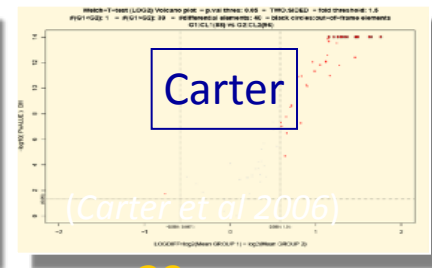
3 tests to compare the expression profiles of tumors classified according to:



86 genes



73 genes



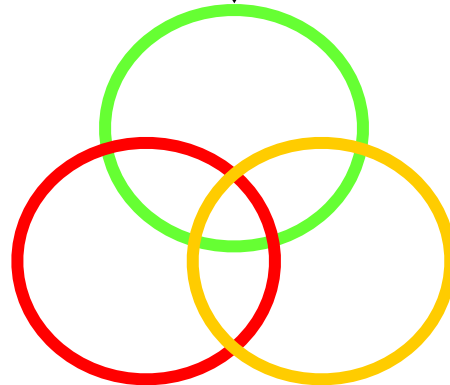
39 genes

**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

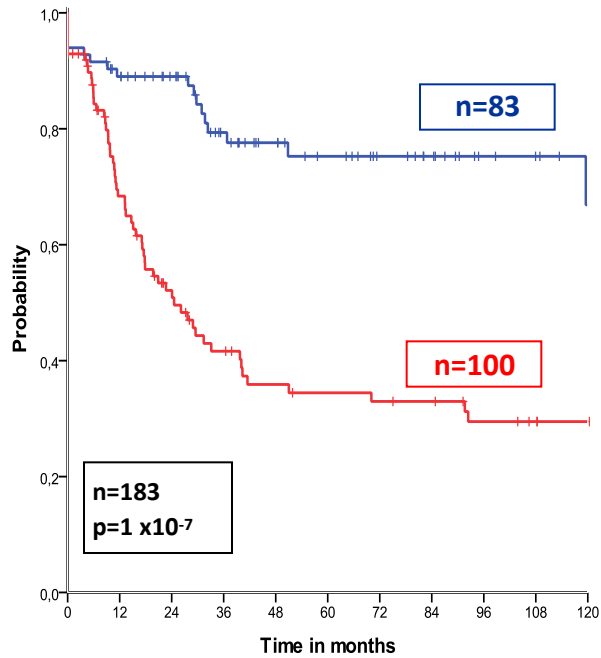


Complexity INdex  
In SARComas  
CINSARC

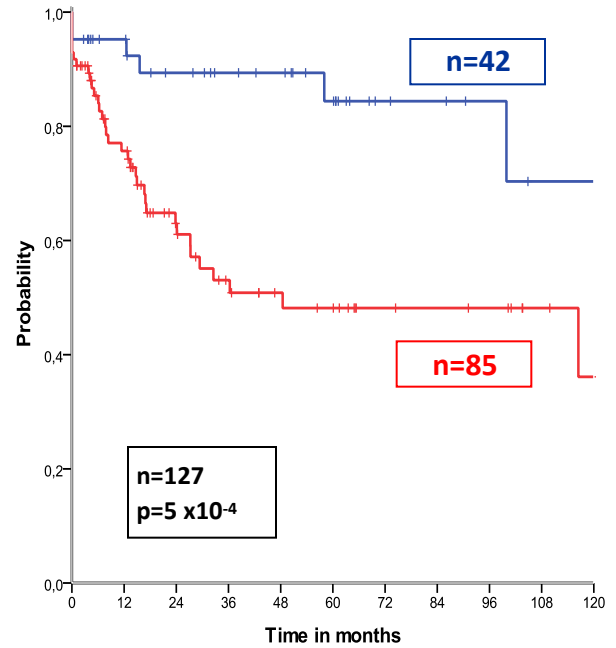
Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)

## Prognostic value of CINSARC: Metastasis free survival

### Cohort 1



### Cohort 2



## Multivariate analysis

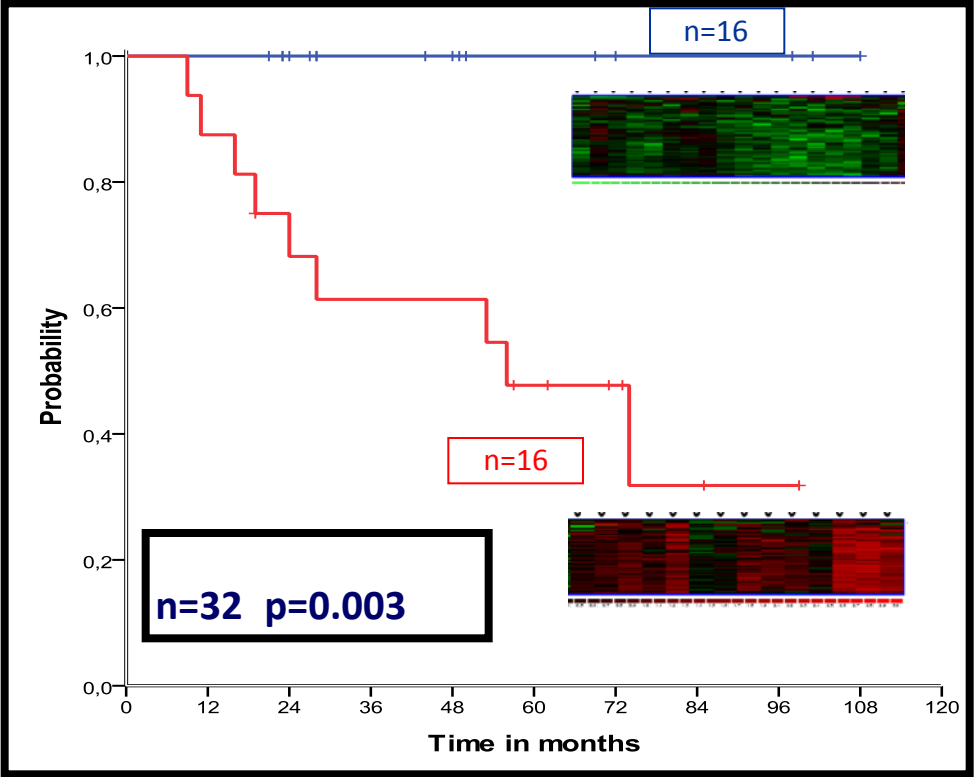
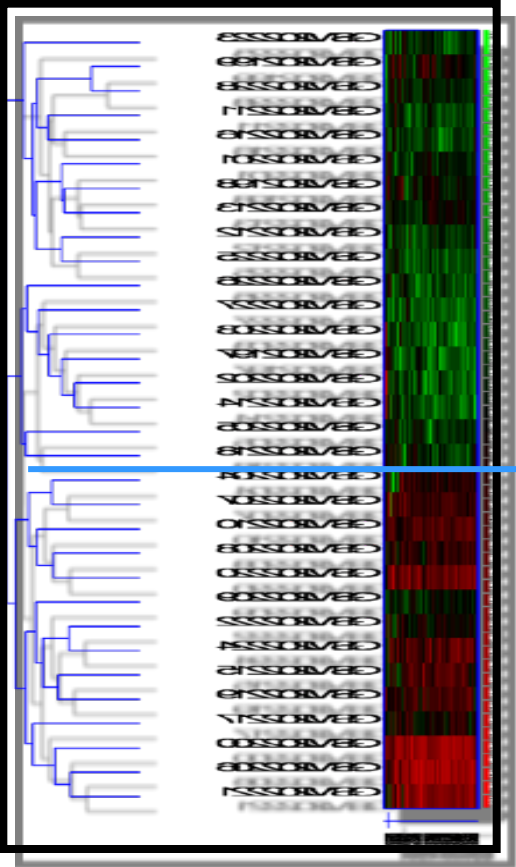
CINSARC is an independent prognostic factor



# CINSARC and GIST

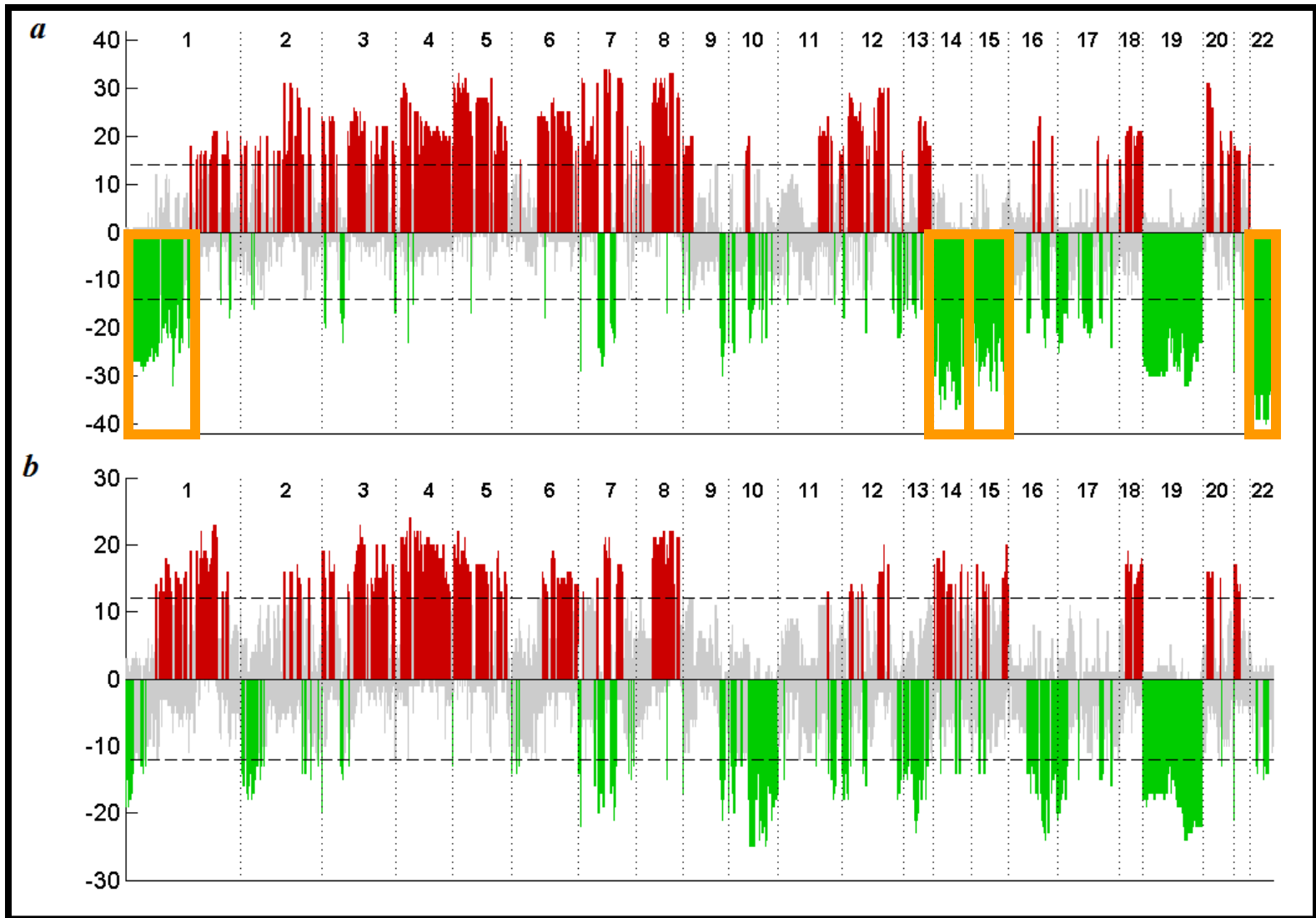
## In-silico study of 32 GISTs

(Yamaguchi *et al* 2008)

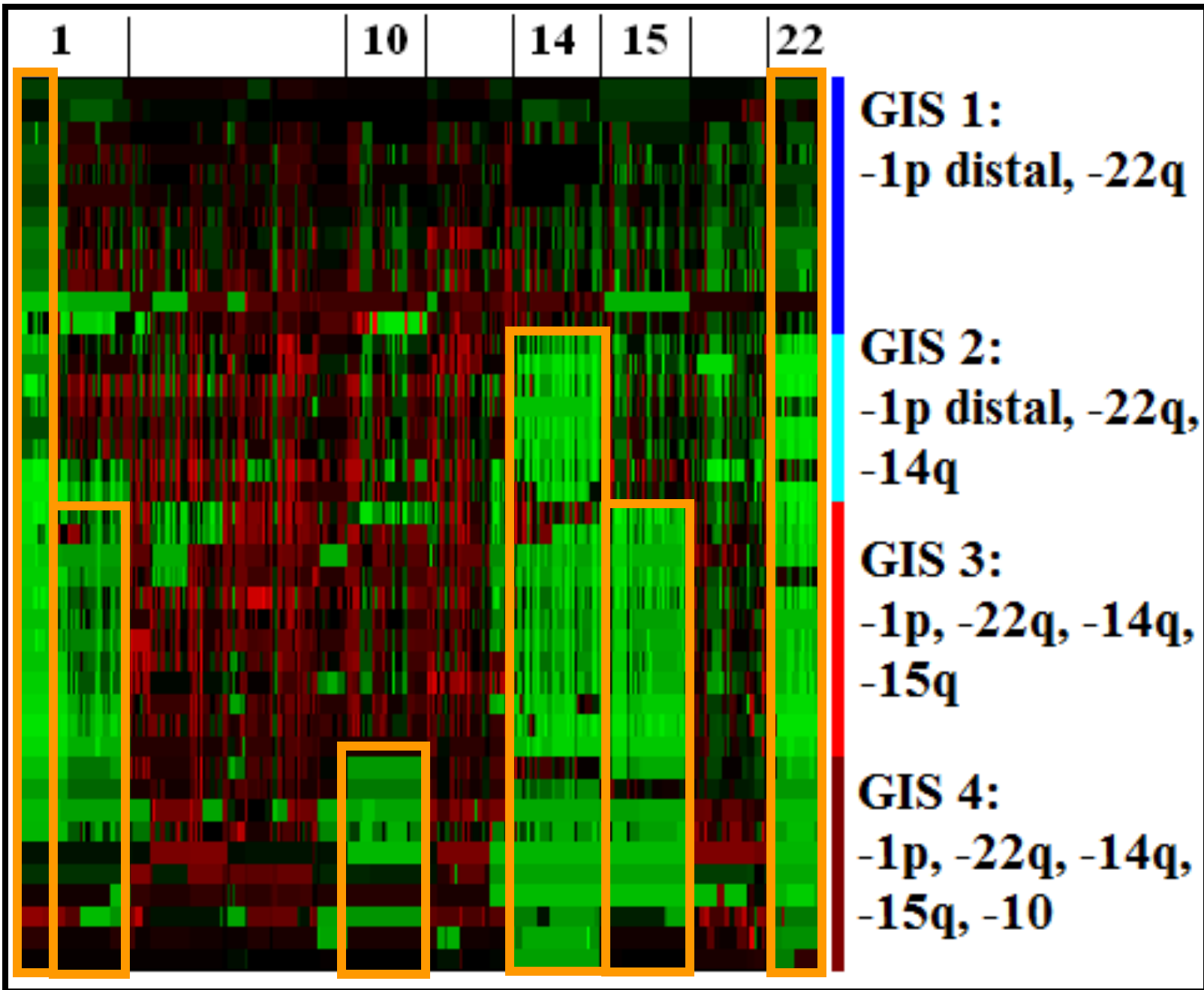


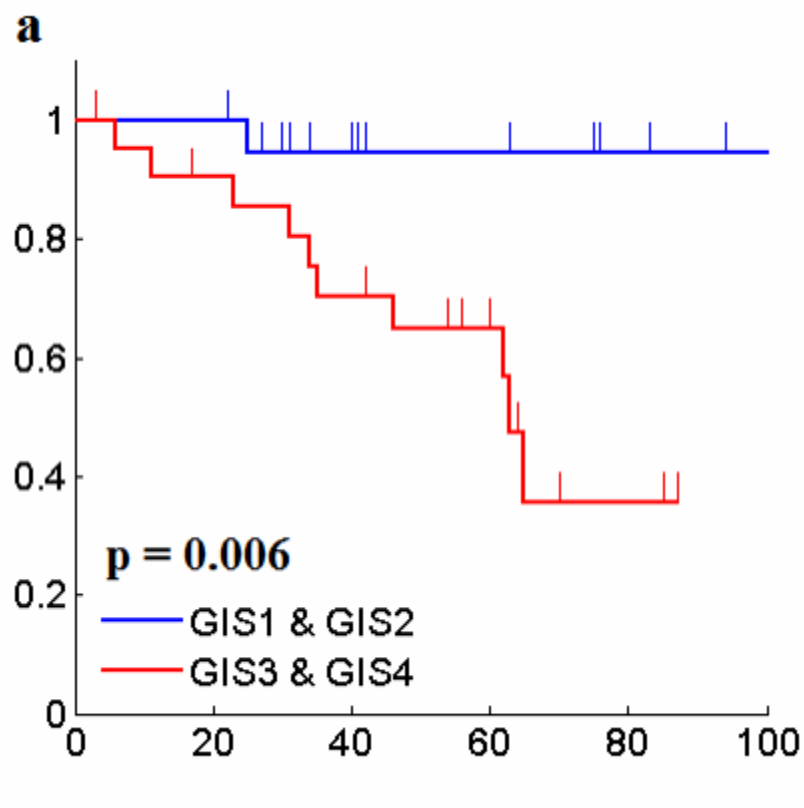
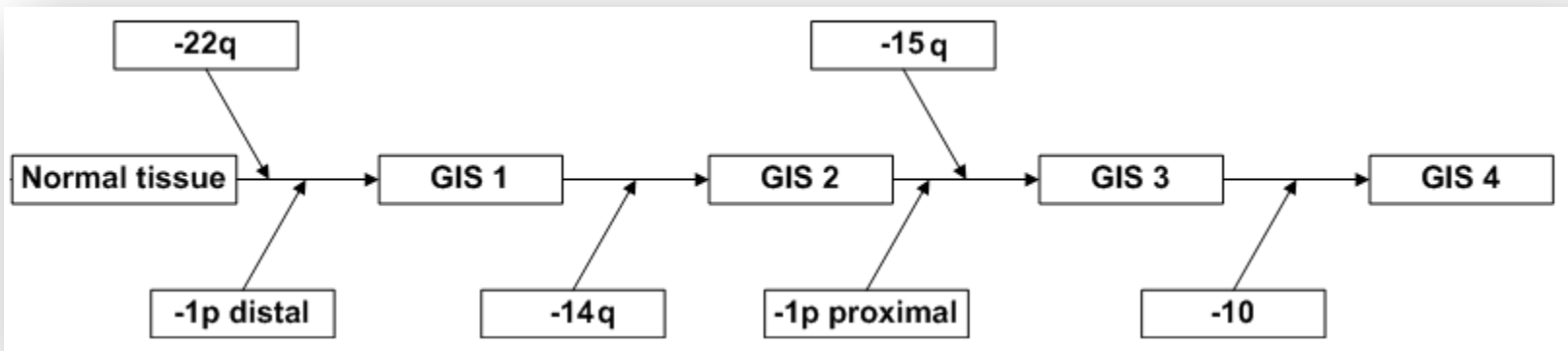
Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)

# GIST (n=42)



# LMS (n=30)

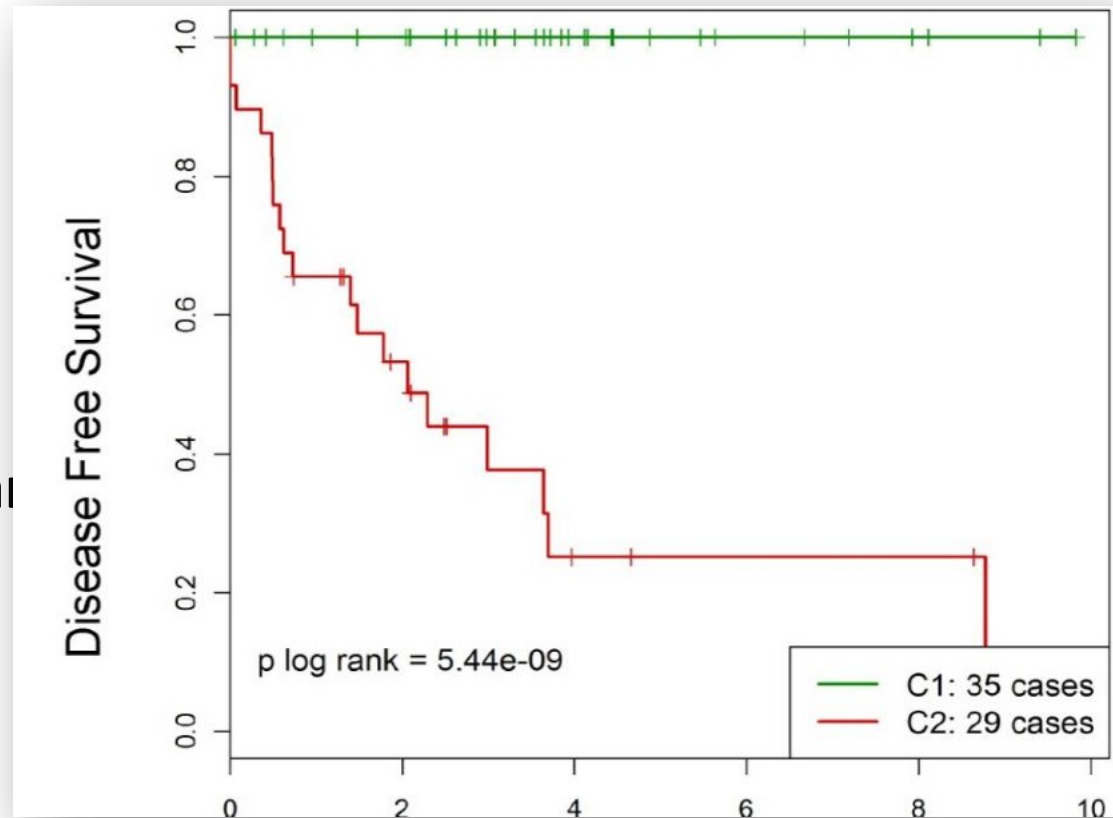




# *GIST and molecular signature*

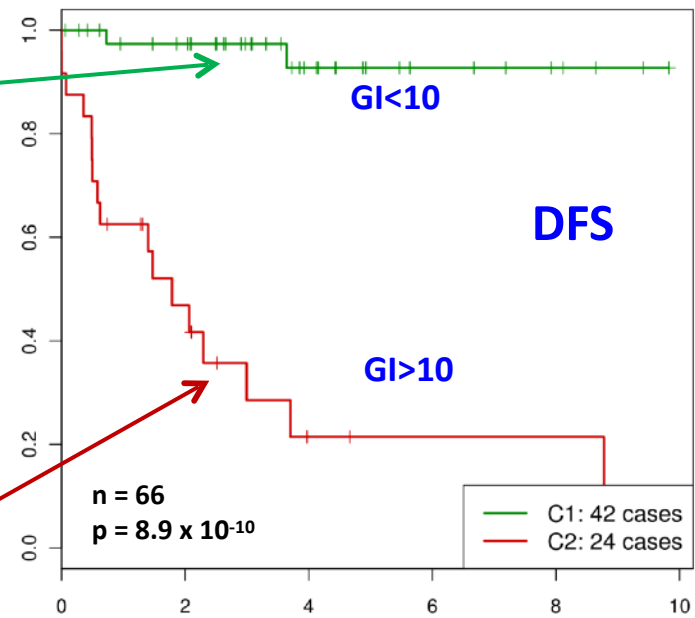
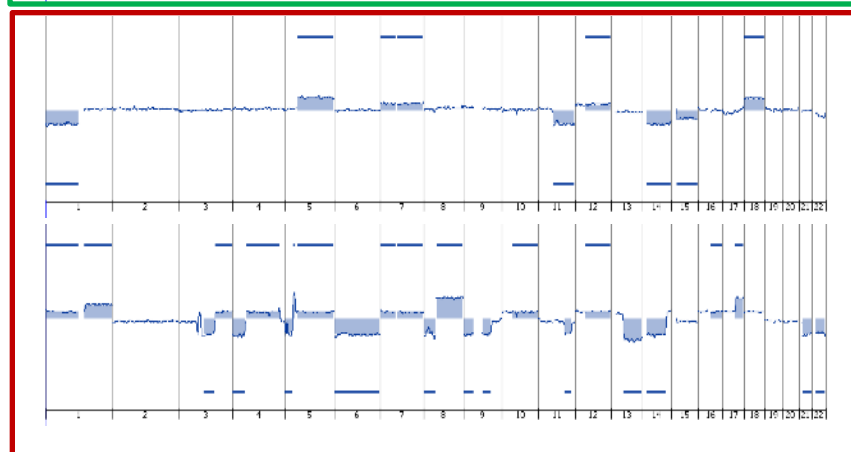
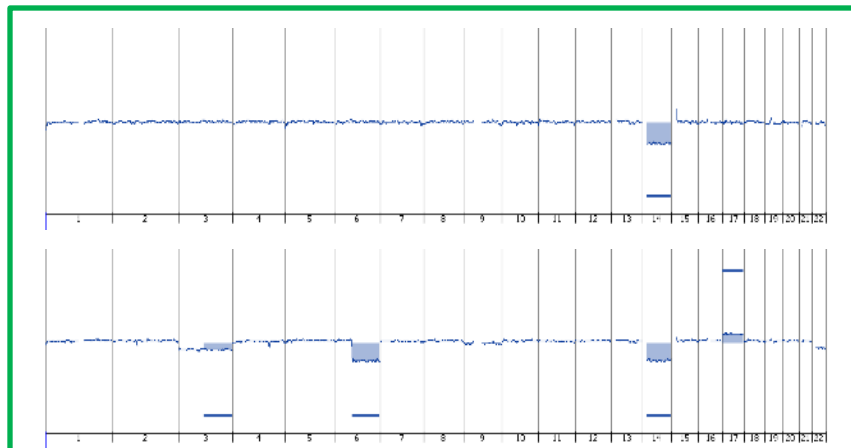
(Lagarde et al. Clin Cancer Res 2012;18: 826-838)

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



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

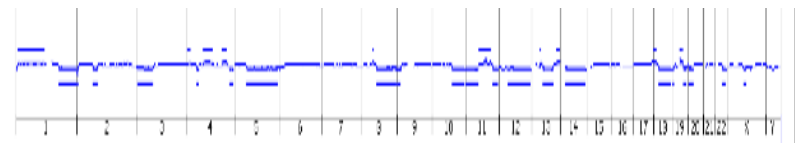
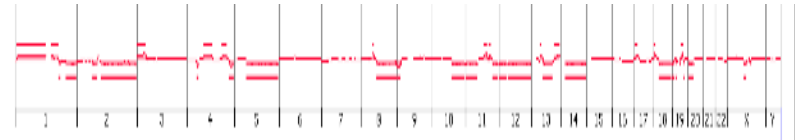
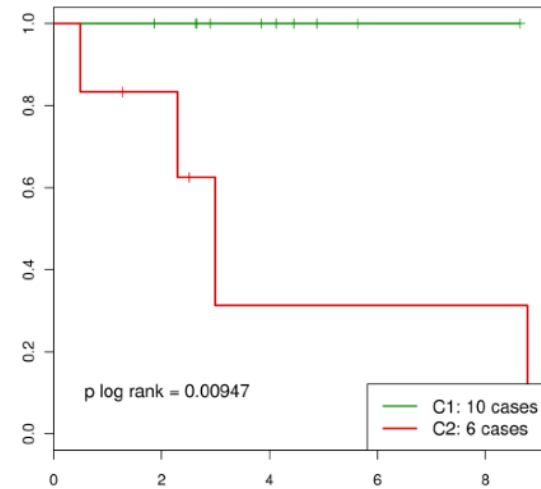
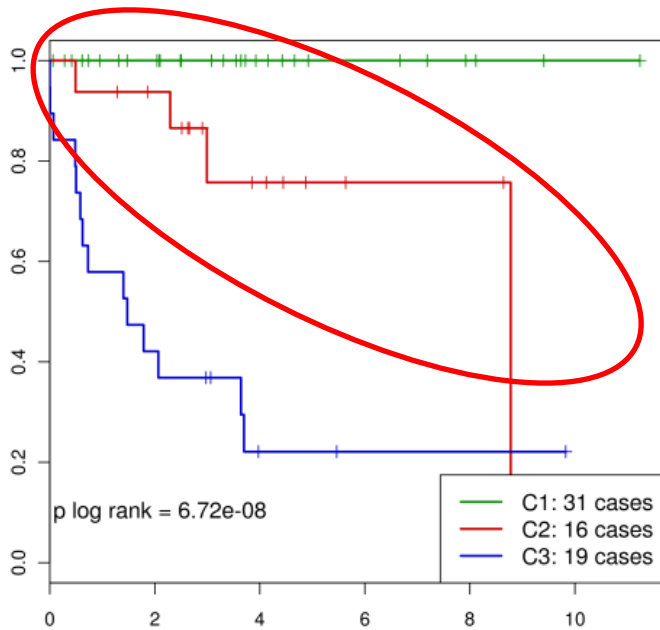
# Genomic Index (GI) is a prognostic factor in GIST...



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)

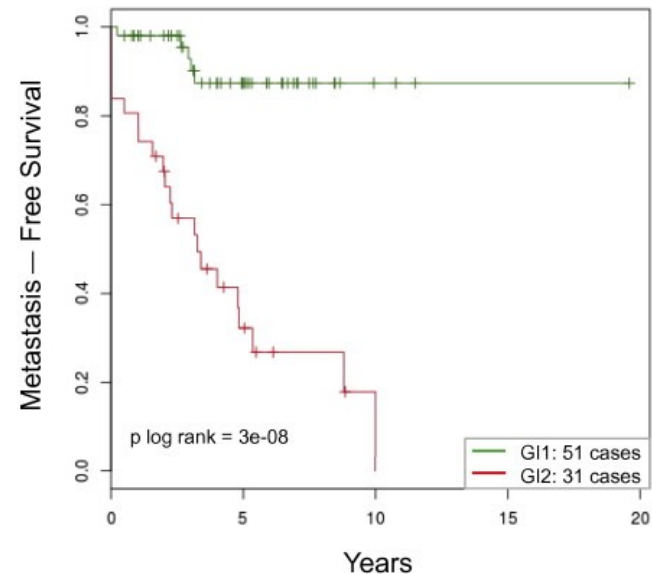
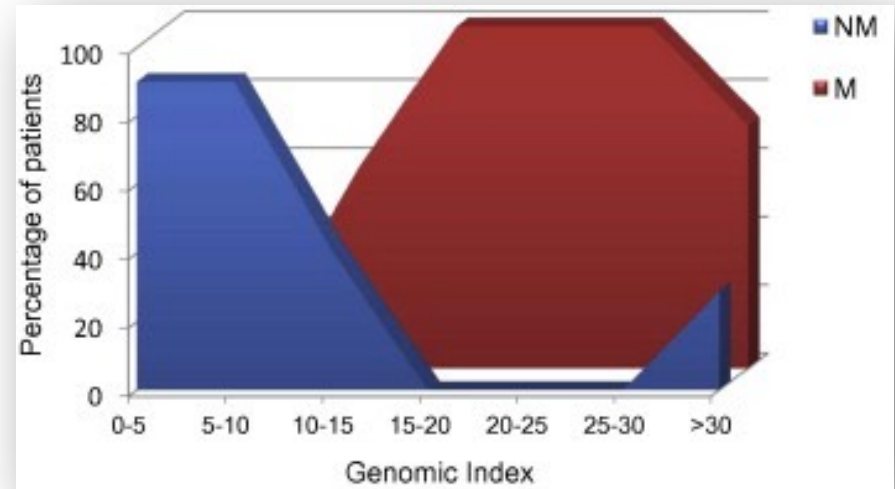


Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)

# 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

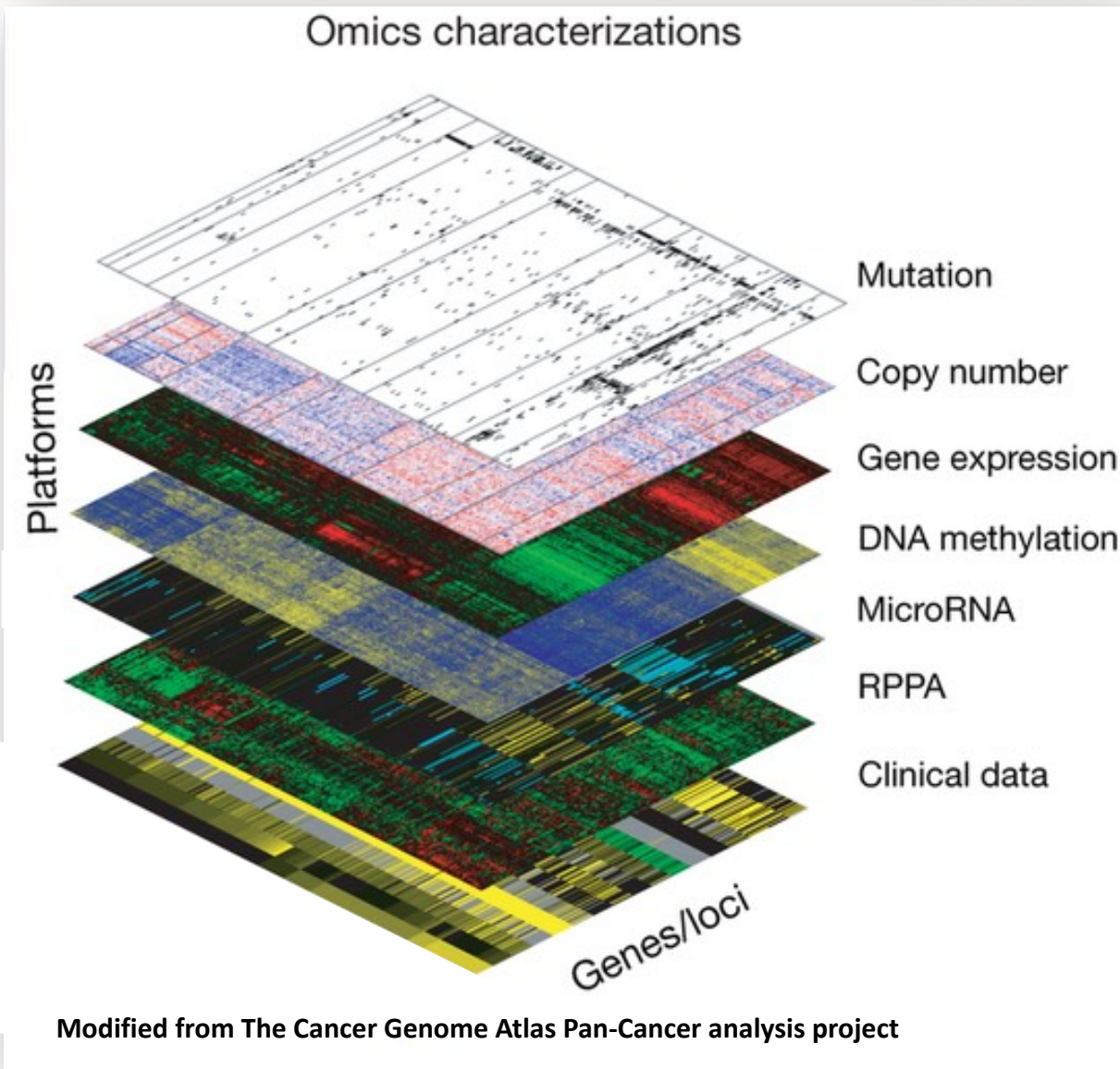


		0	1 y	2 y	3 y	4 y	5 y
GI1	Patients at risk	51	47	43	35	29	22
	Cumulated events	0	1	1	3	5	5
	Metastasis FS	1	0.98	0.98	0.93	0.87	0.87
GI2	Patients at risk	31	25	20	15	11	7
	Cumulated events	5	6	10	13	16	19
	Metastasis FS	0.84	0.81	0.68	0.57	0.45	0.32

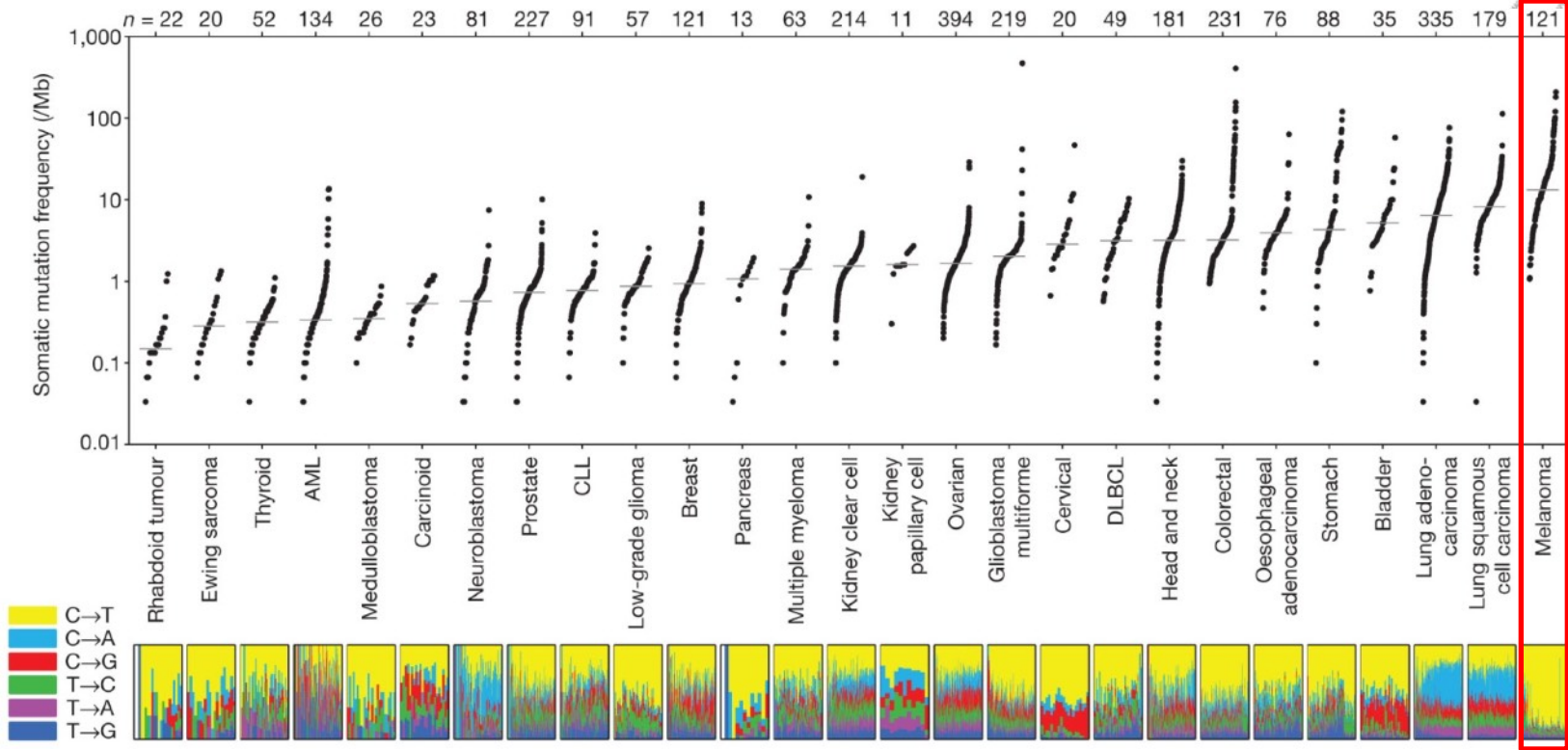
Chibon & Colleagues. Eur J Cancer 2014;  
51(1):75-83.



# Sarcoma TCGA Integrative Analysis



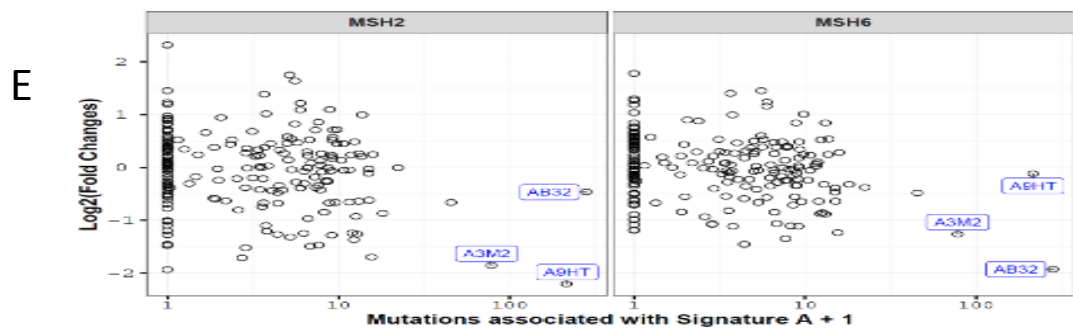
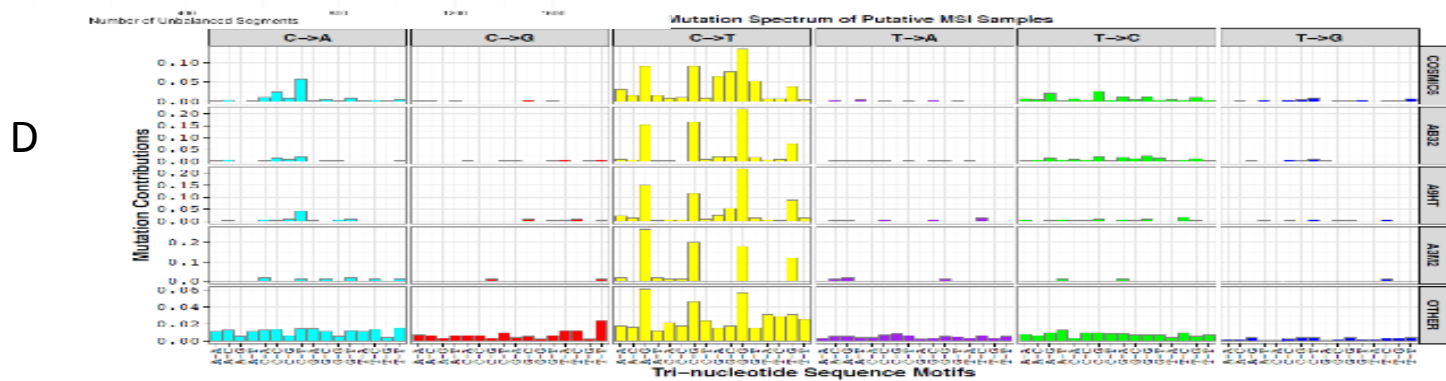
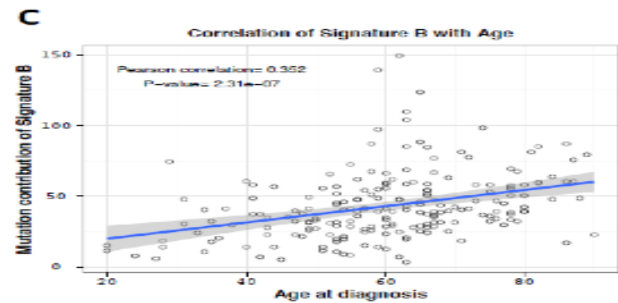
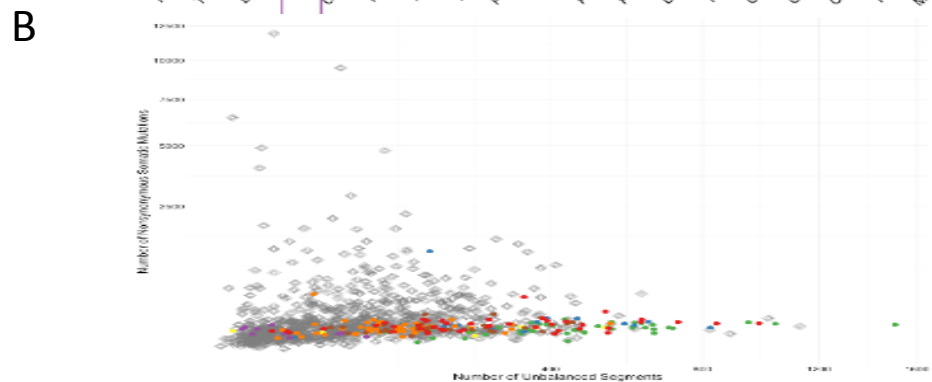
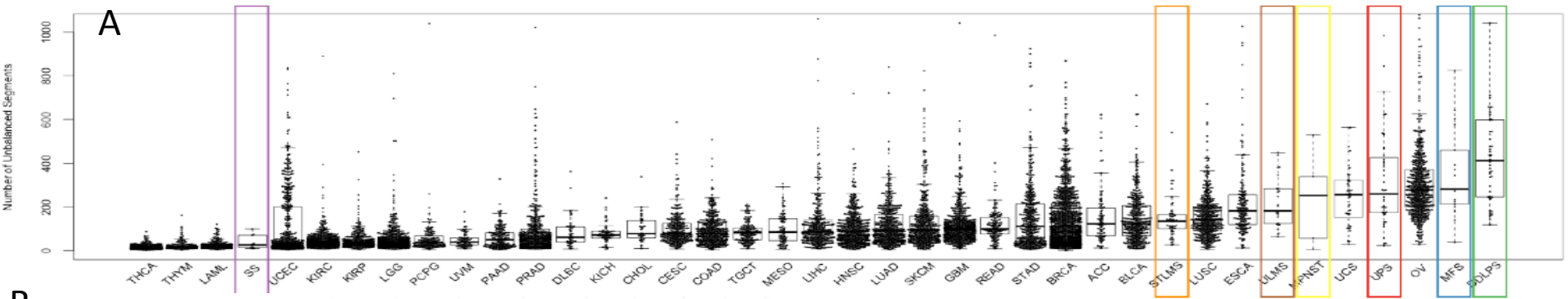
# Whole Exome Sequencing (WES): Melanoma has the Highest Mutation Rate of Cancers Sequenced to Date



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

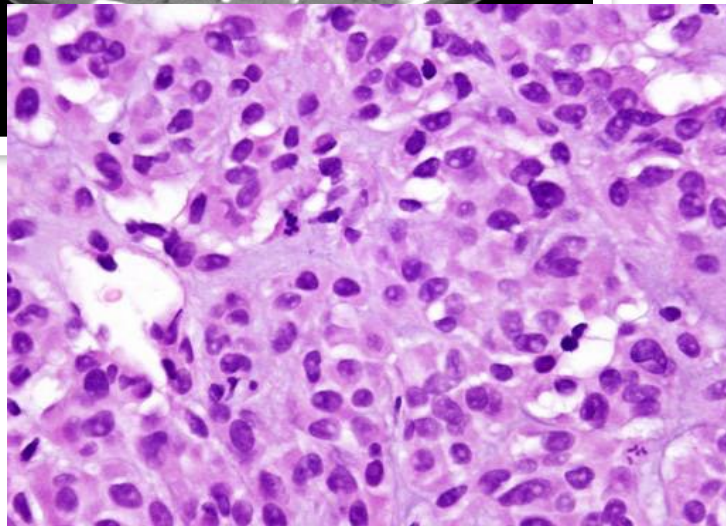
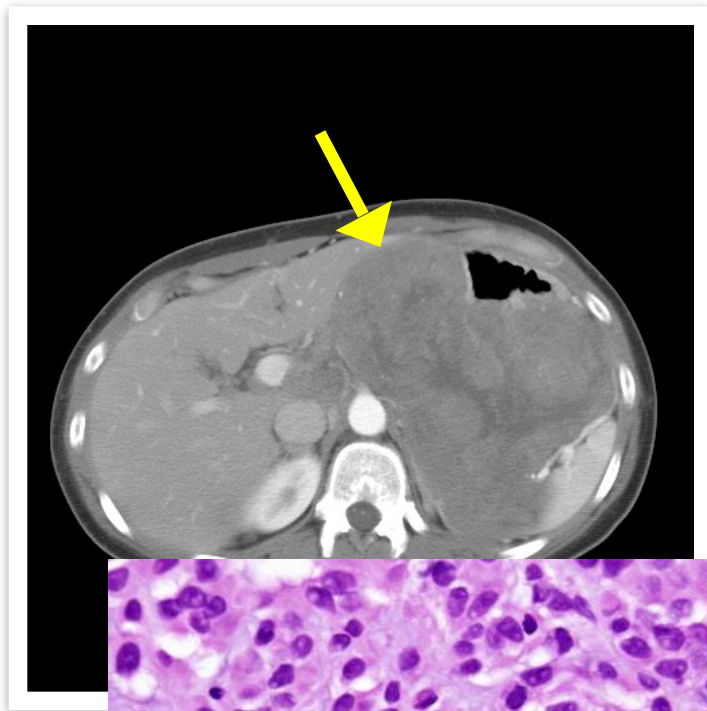
**Broad Institute**  
Mike Lawrence  
Gad Getz  
*Nature*, 2013



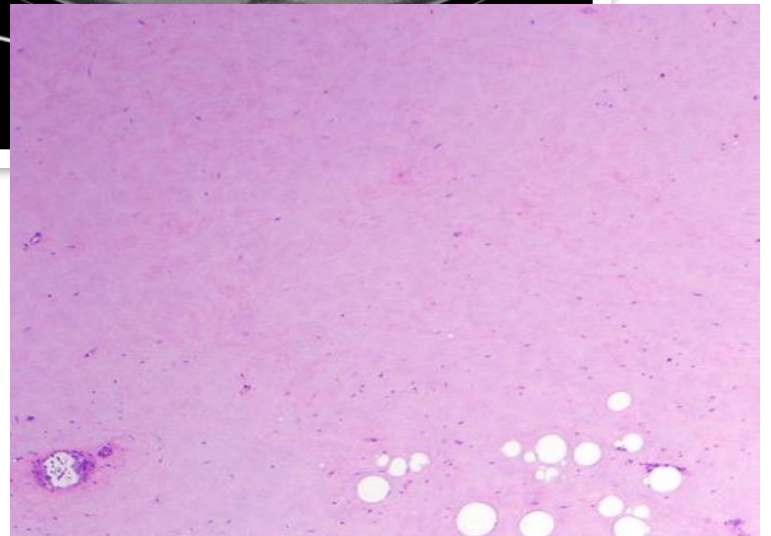
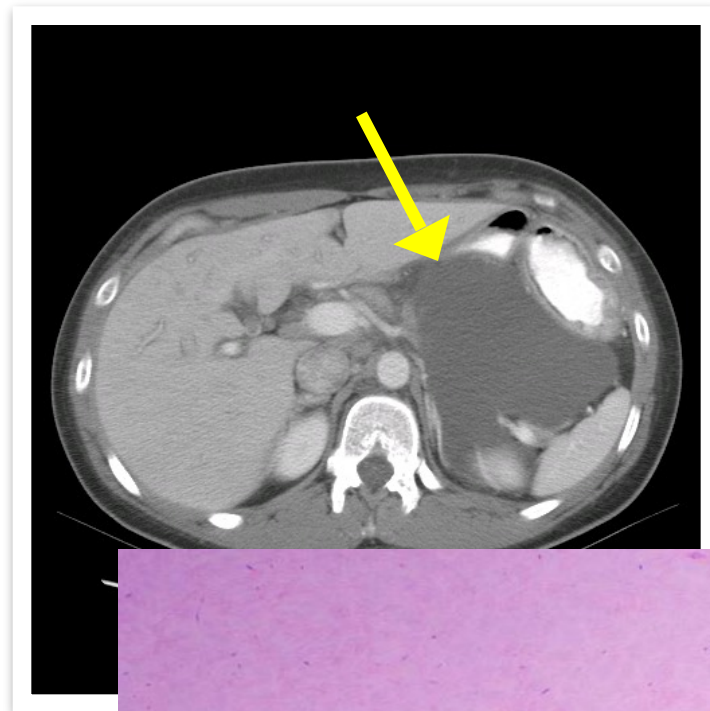


***Treatment can cause big changes.***

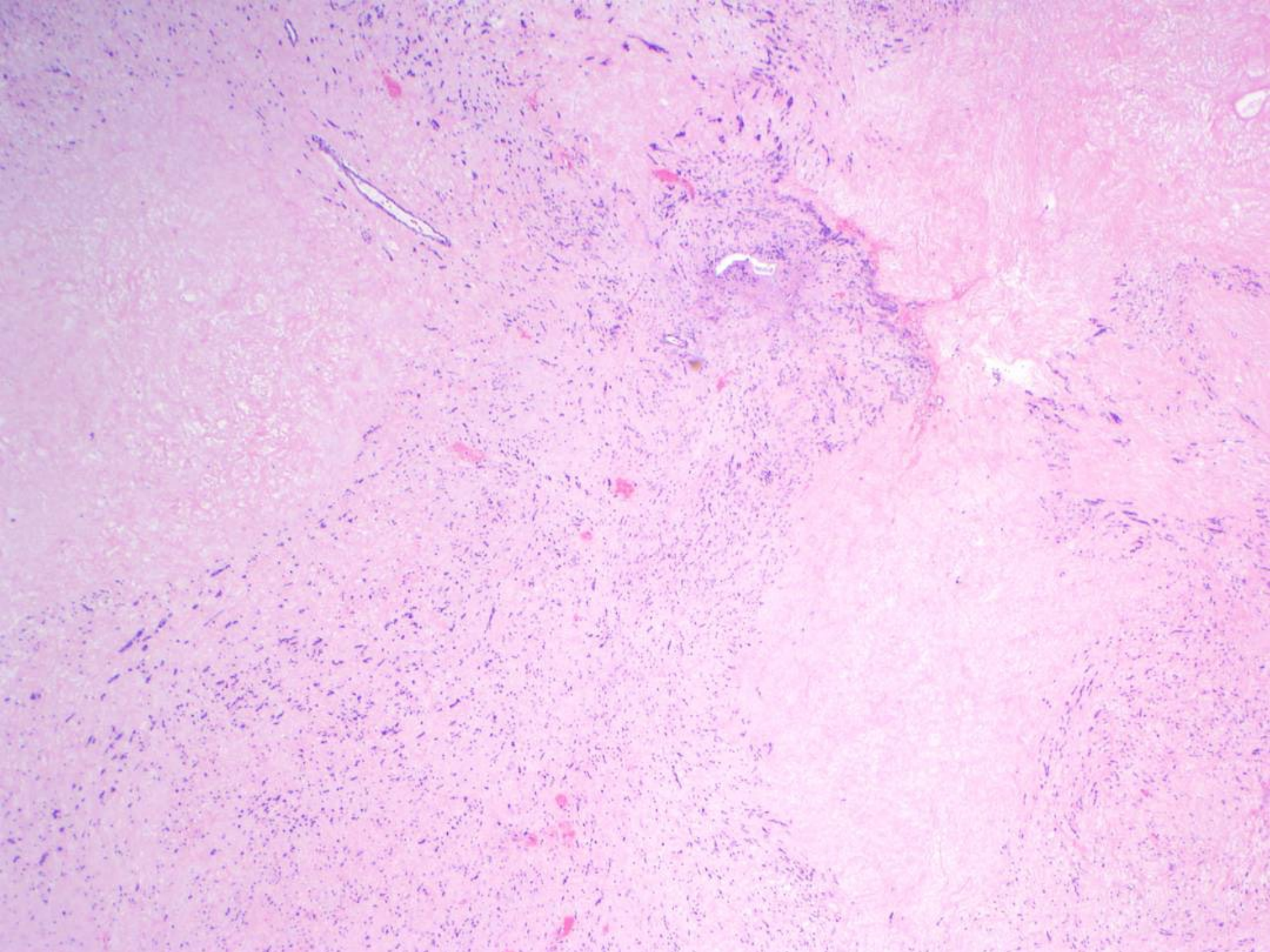
# *Treatment effect*

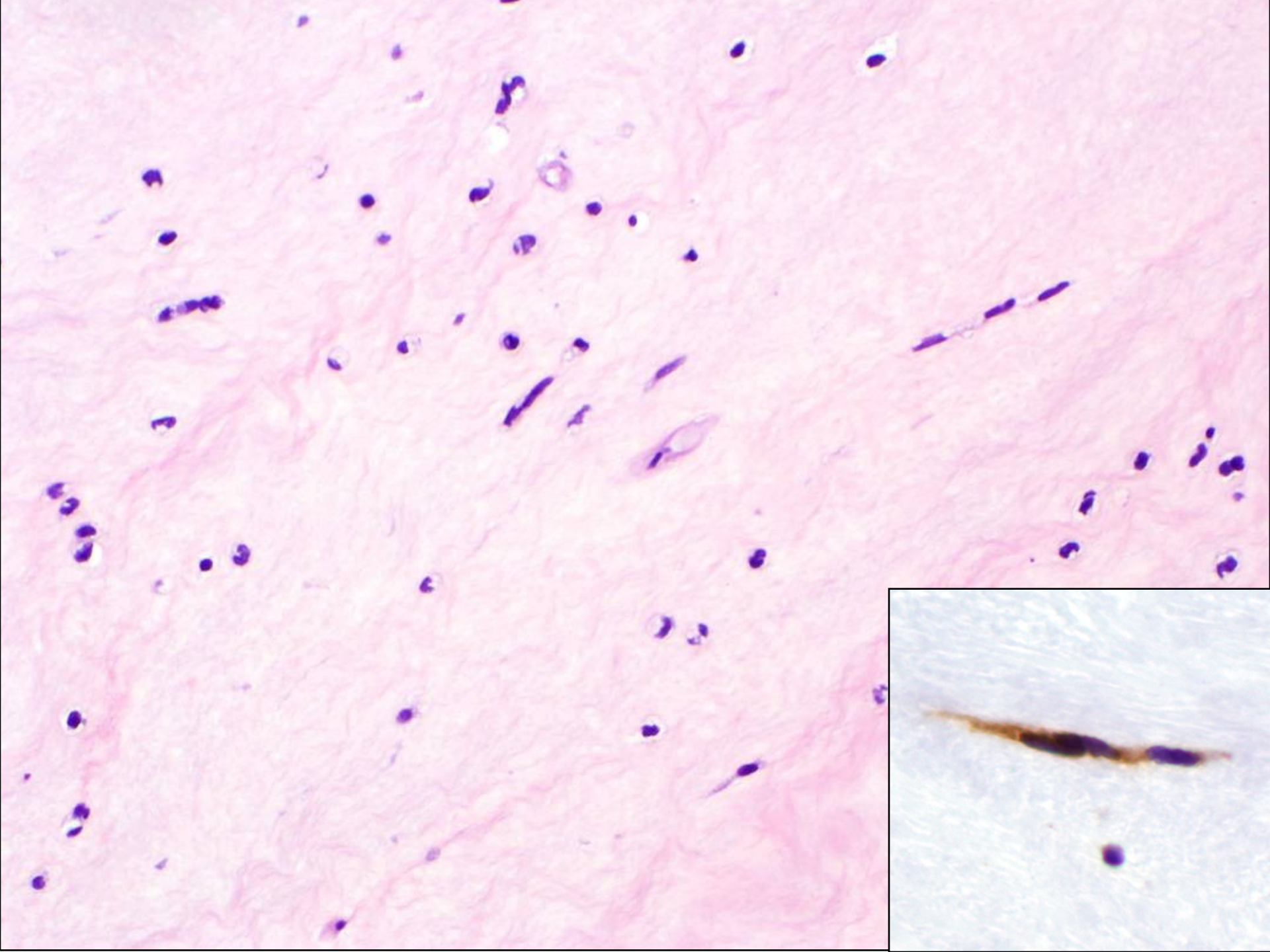


**Pre-Imatinib**



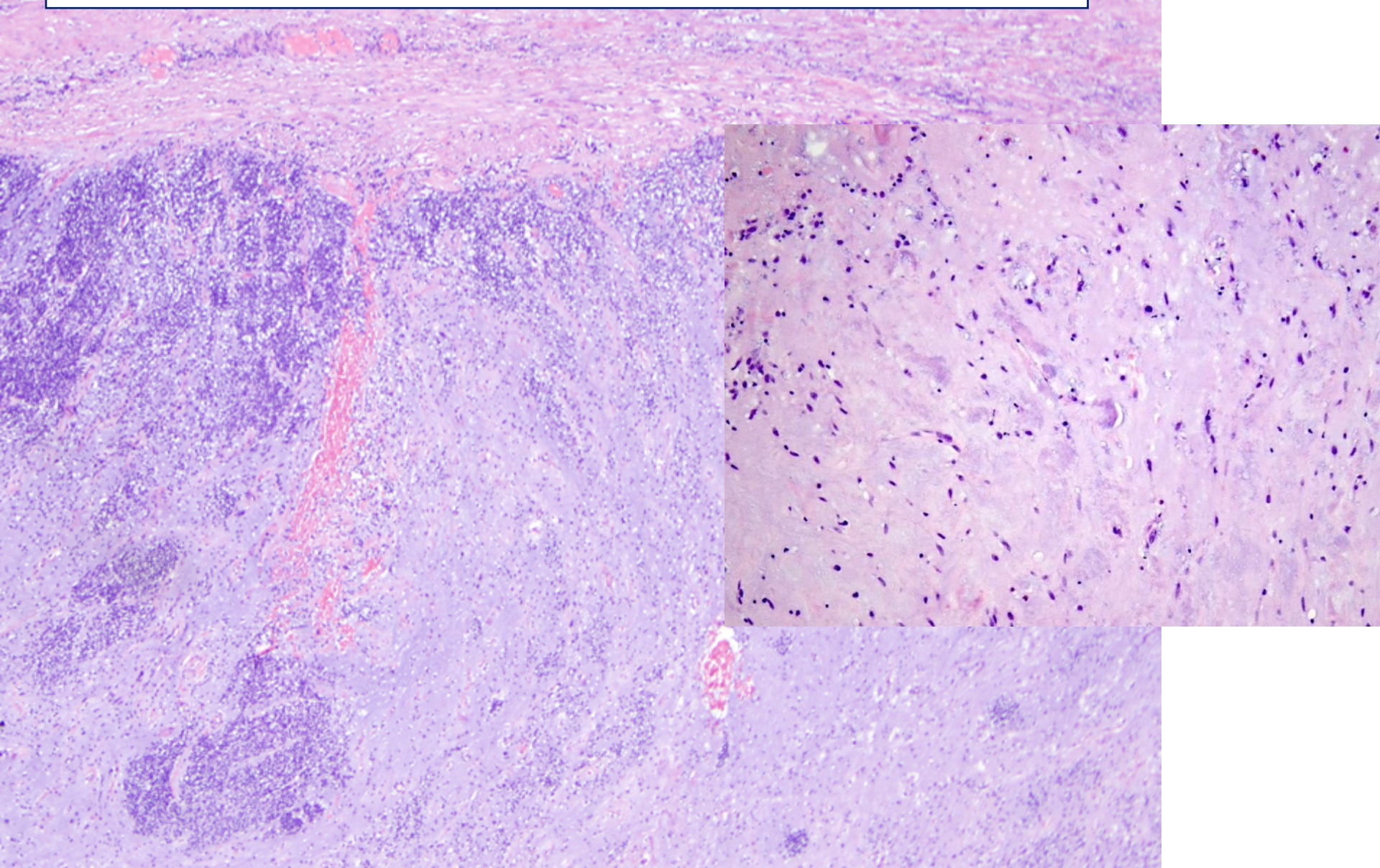
**Post-Imatinib (8 weeks therapy)**



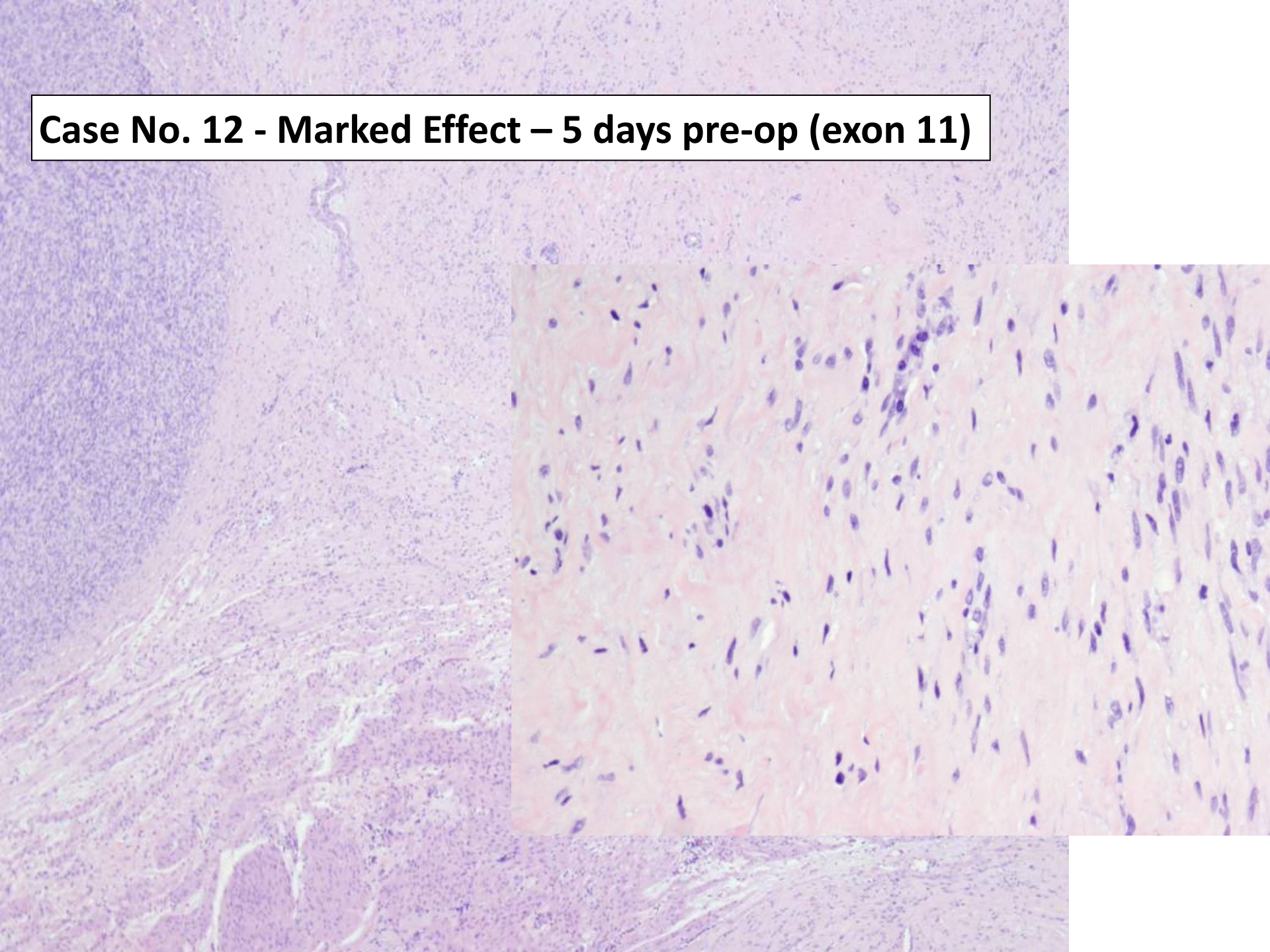




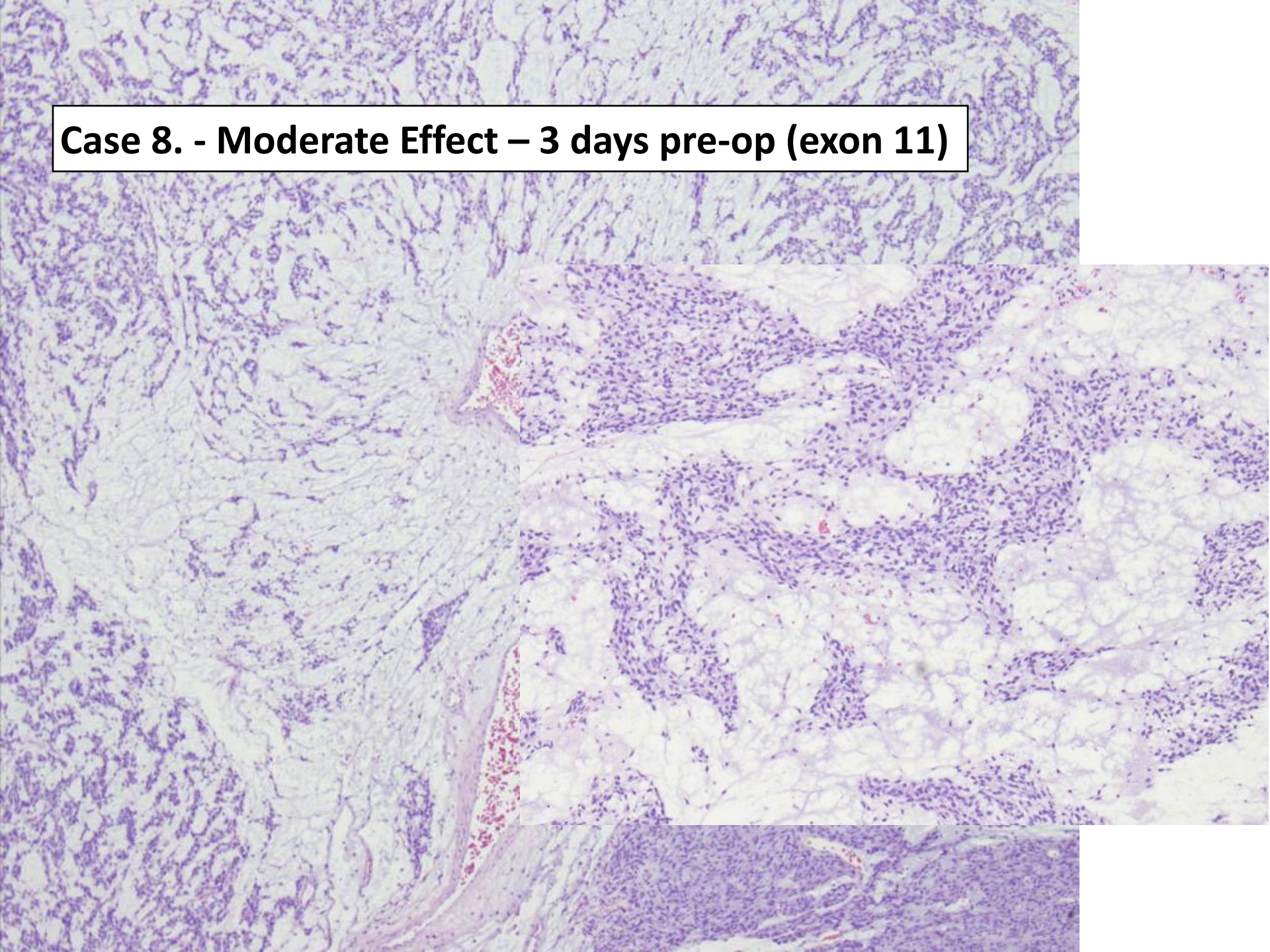
**Case No. 22 - Marked Effect – 7 days pre-op (exon 11)**



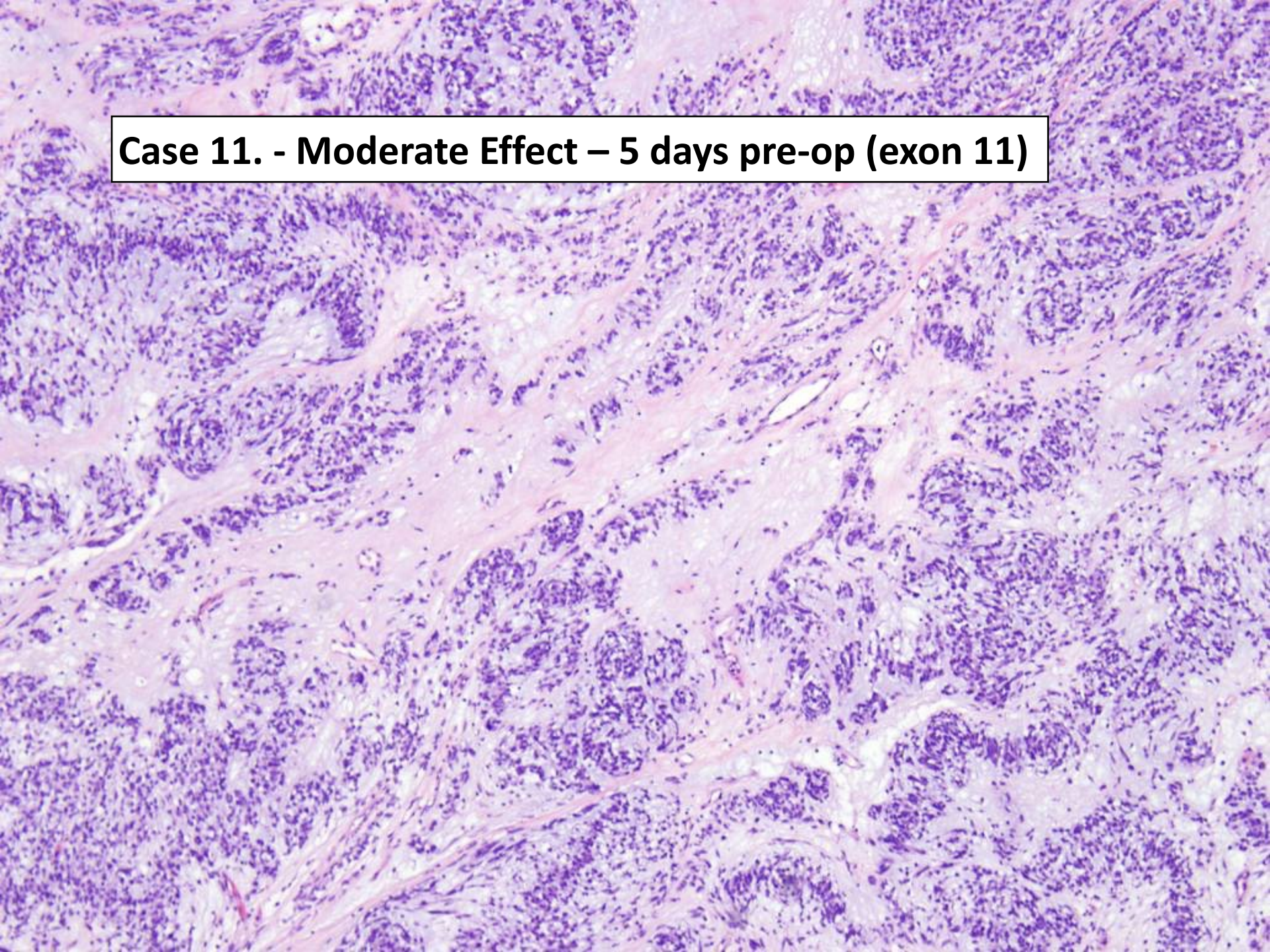
**Case No. 12 - Marked Effect – 5 days pre-op (exon 11)**



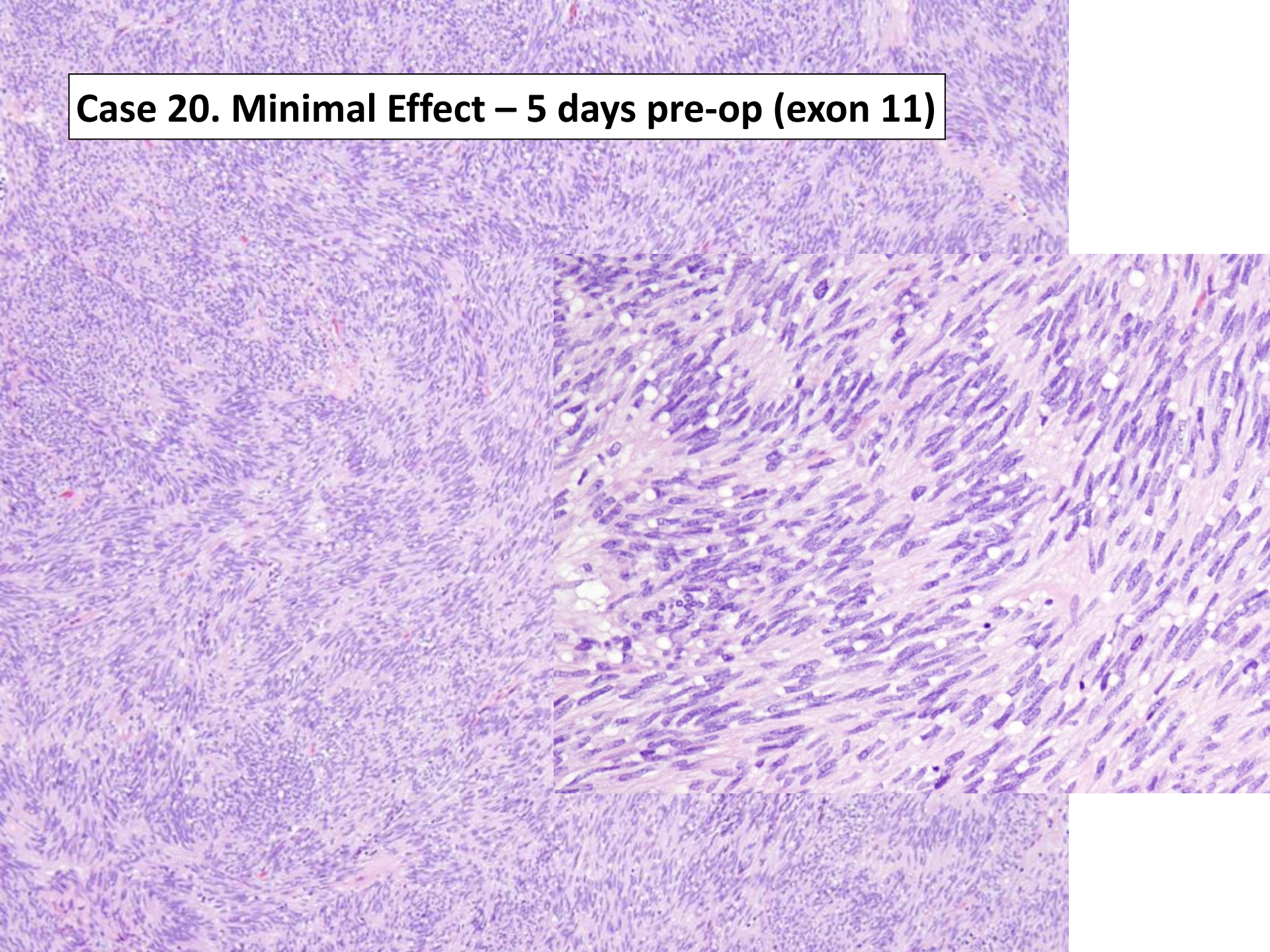
**Case 8. - Moderate Effect – 3 days pre-op (exon 11)**



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

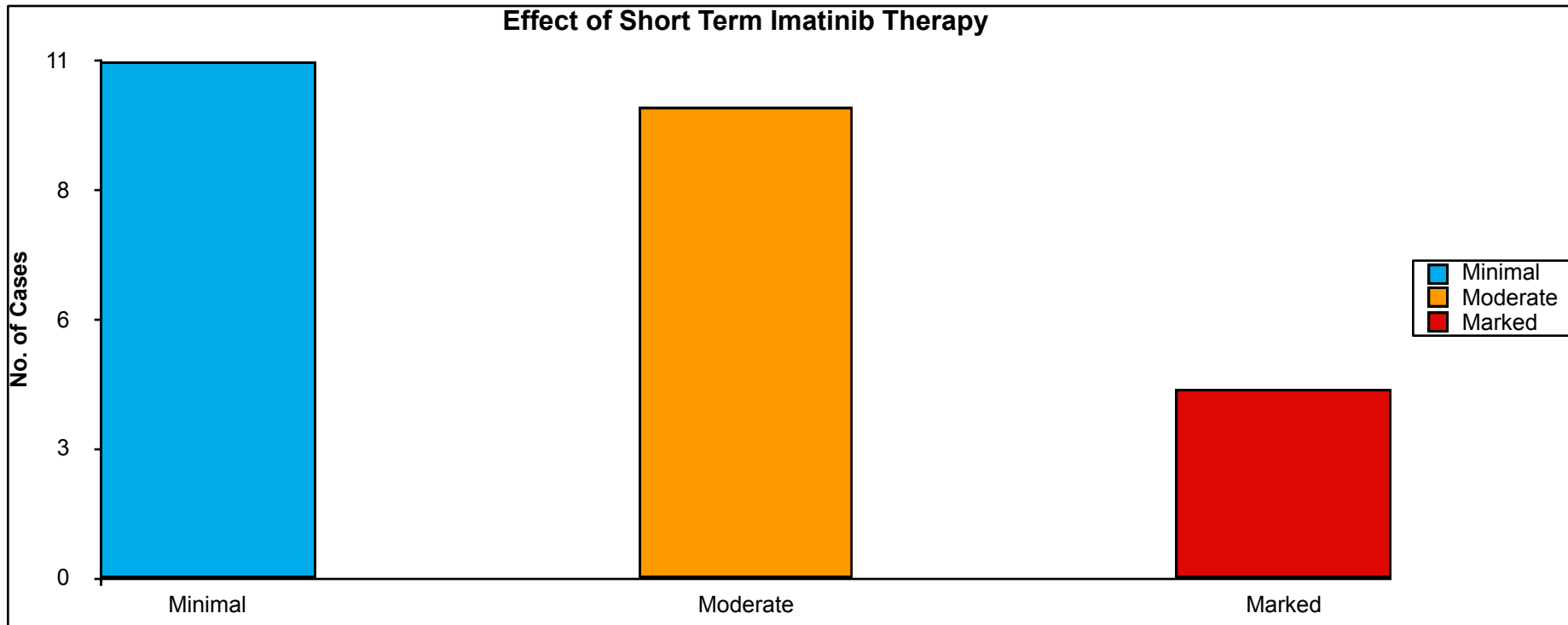


**Case 20. Minimal Effect – 5 days pre-op (exon 11)**



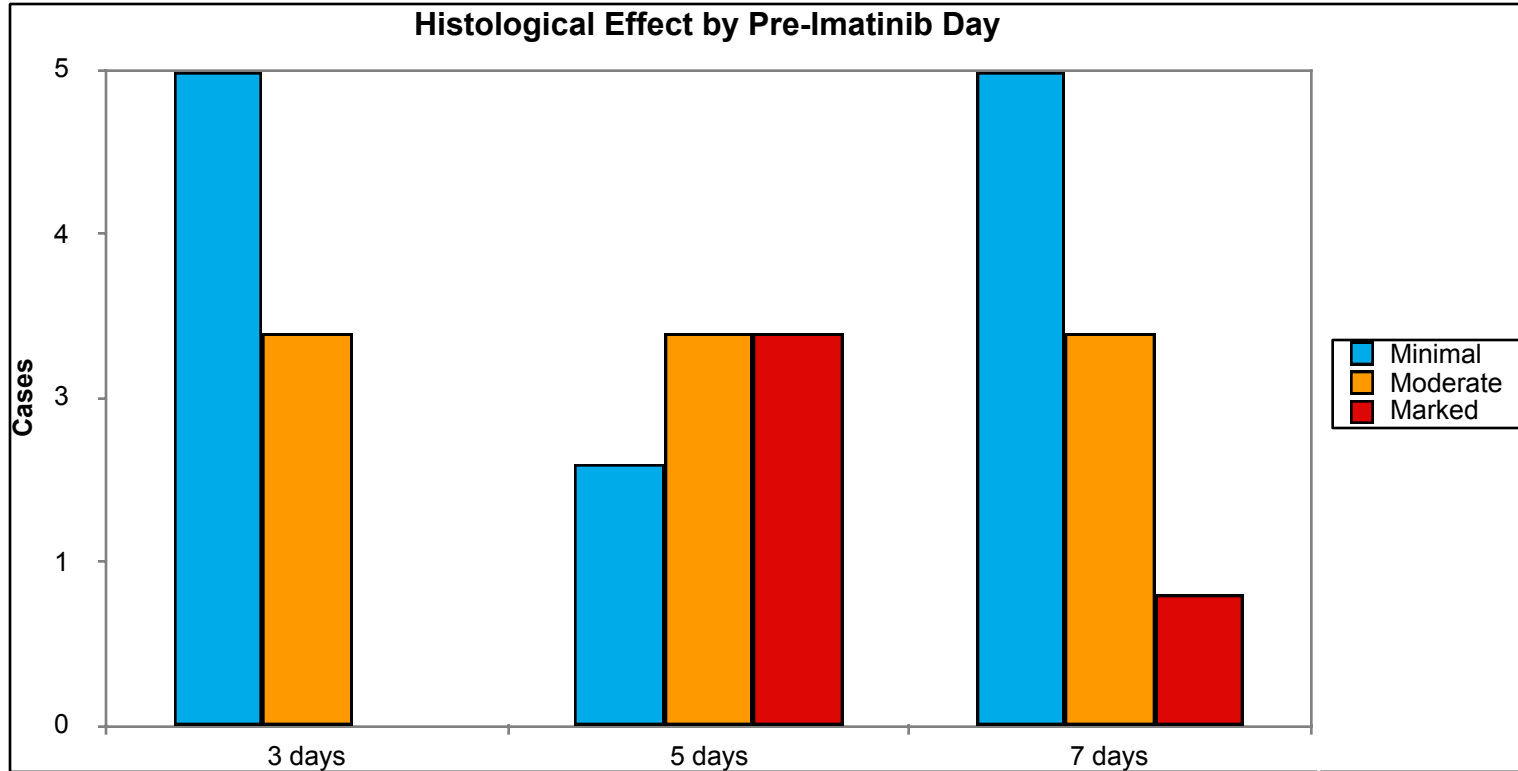
# Results

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



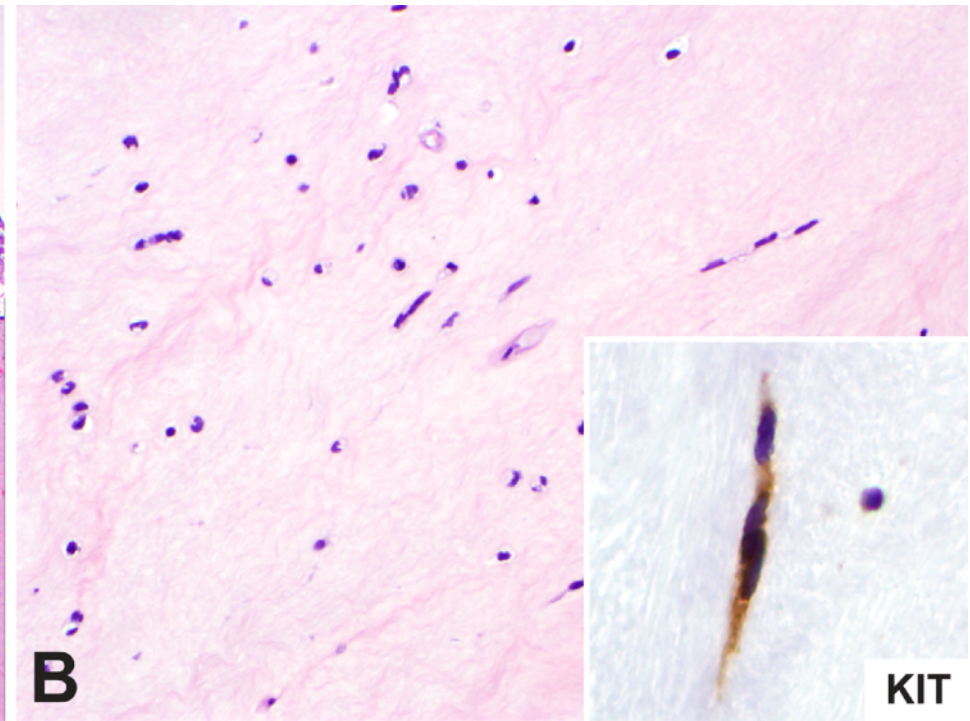
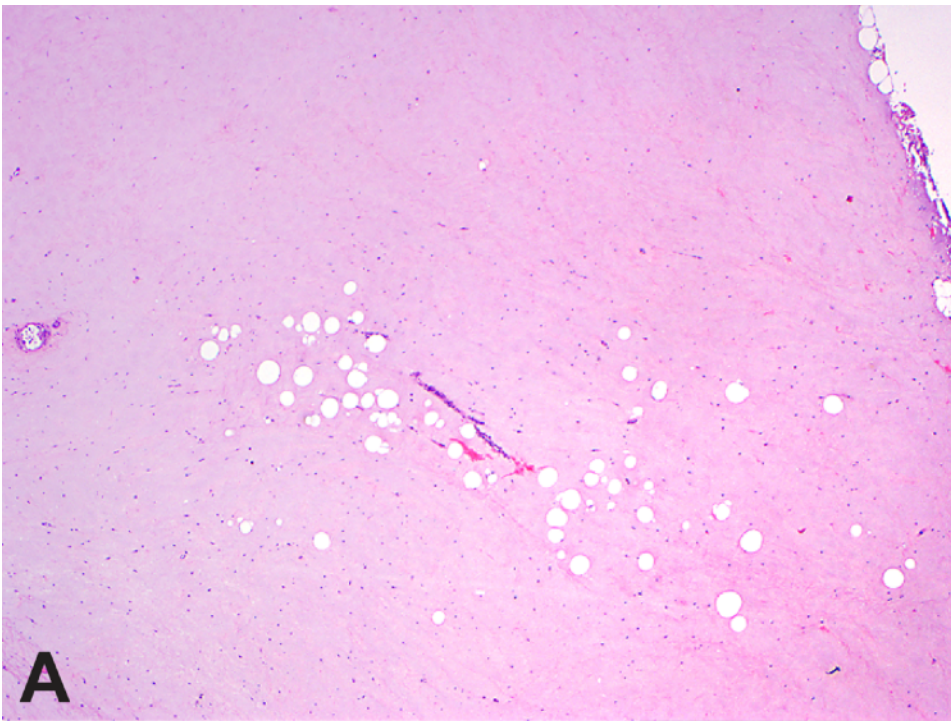
# *Early Histologic Effects of Imatinib*

## *Duration of Therapy*



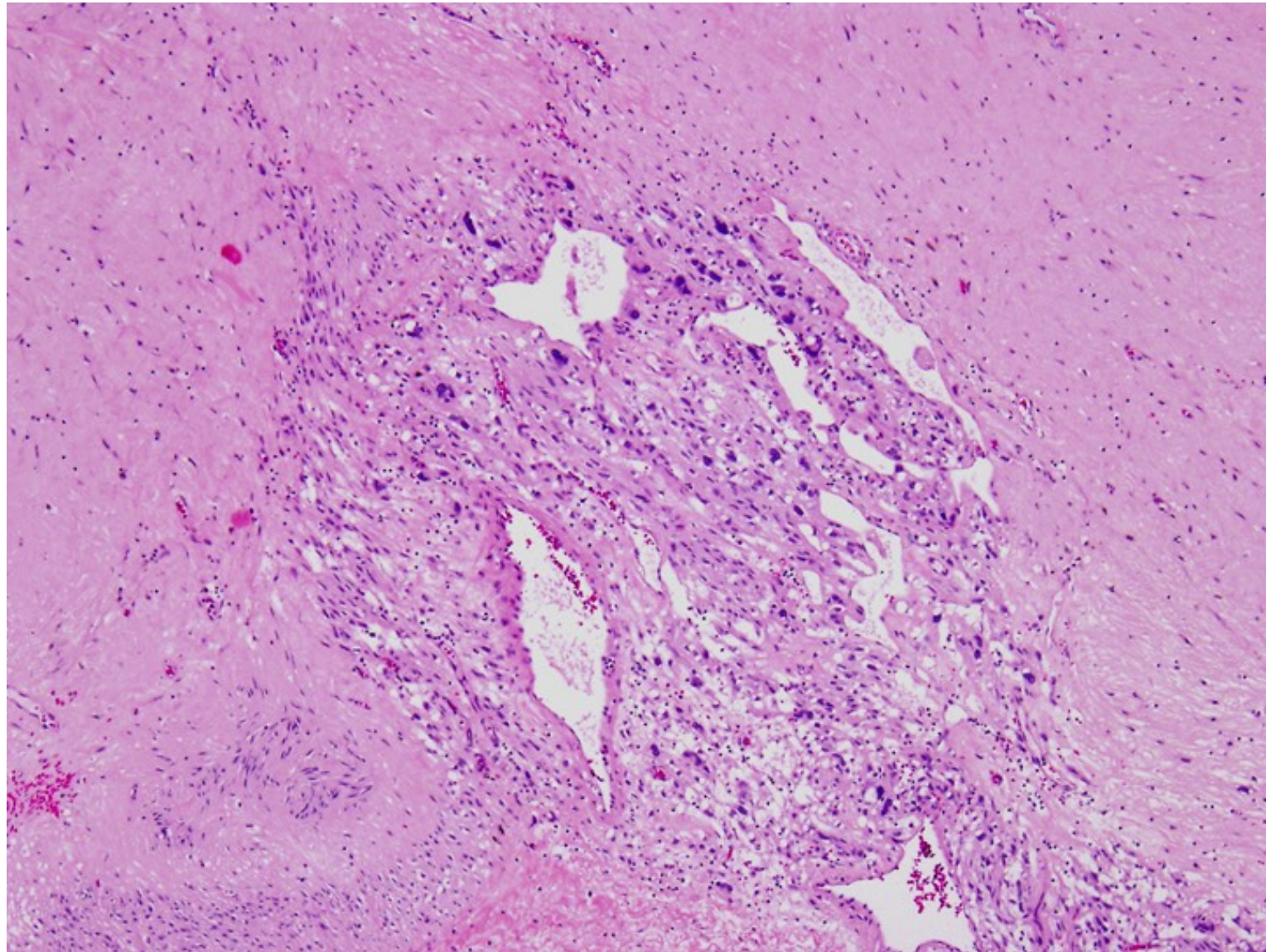
- Minimal and Moderate effects were seen across all durations of therapy
- Marked effect appeared to be a late finding peaking at 5 days

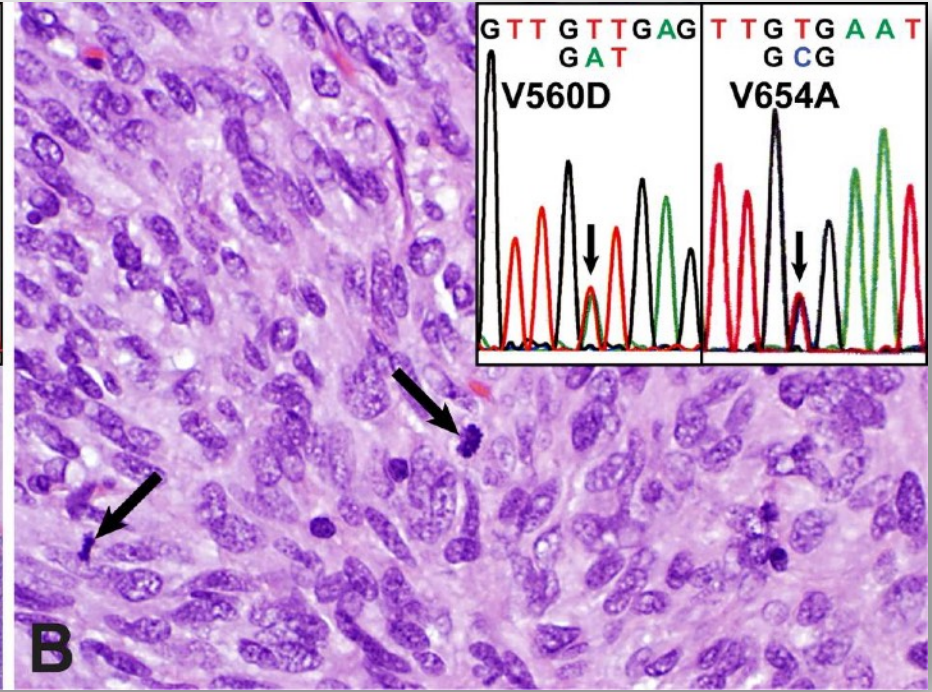
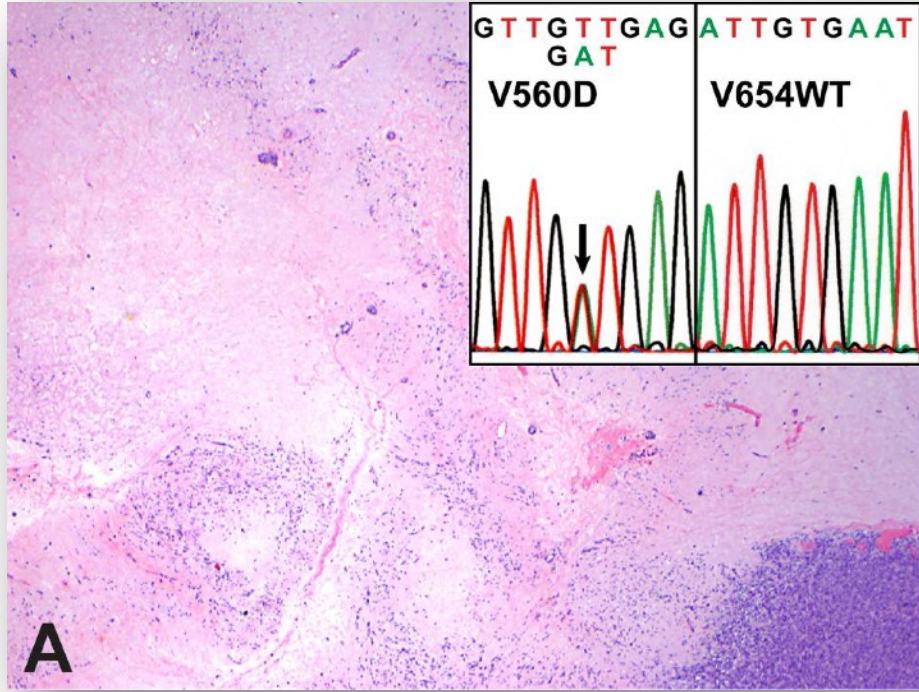
# *Long term Imatinib Tx*

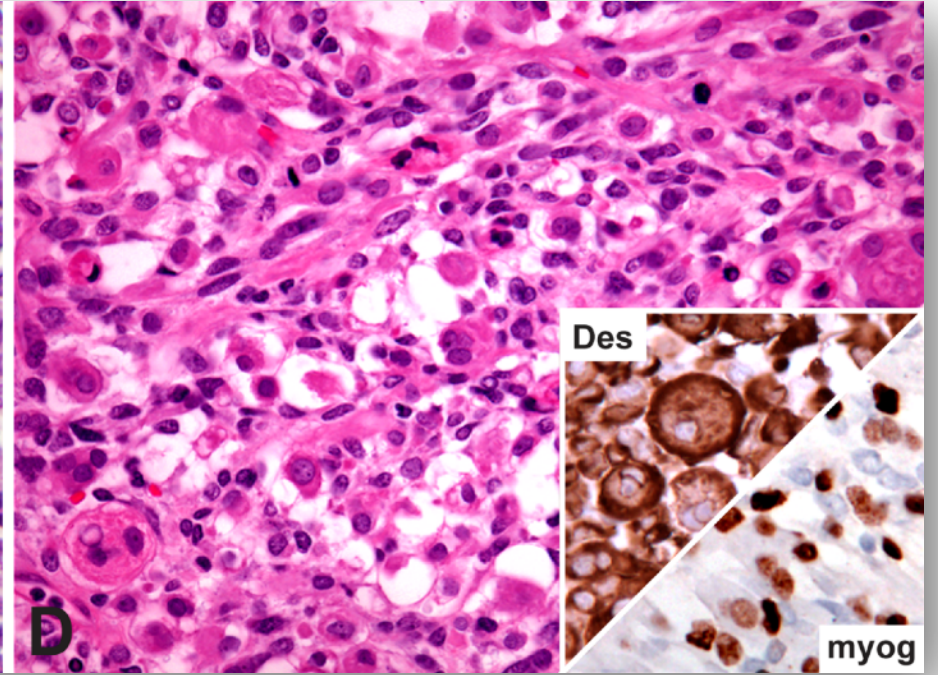
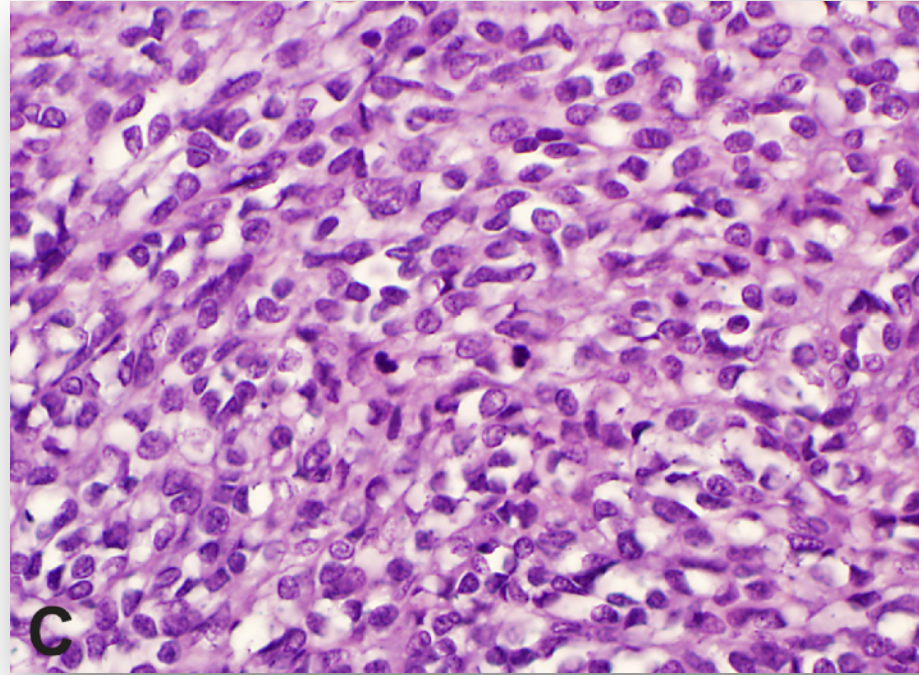




# ***Long term Imatinib Tx***







**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.**