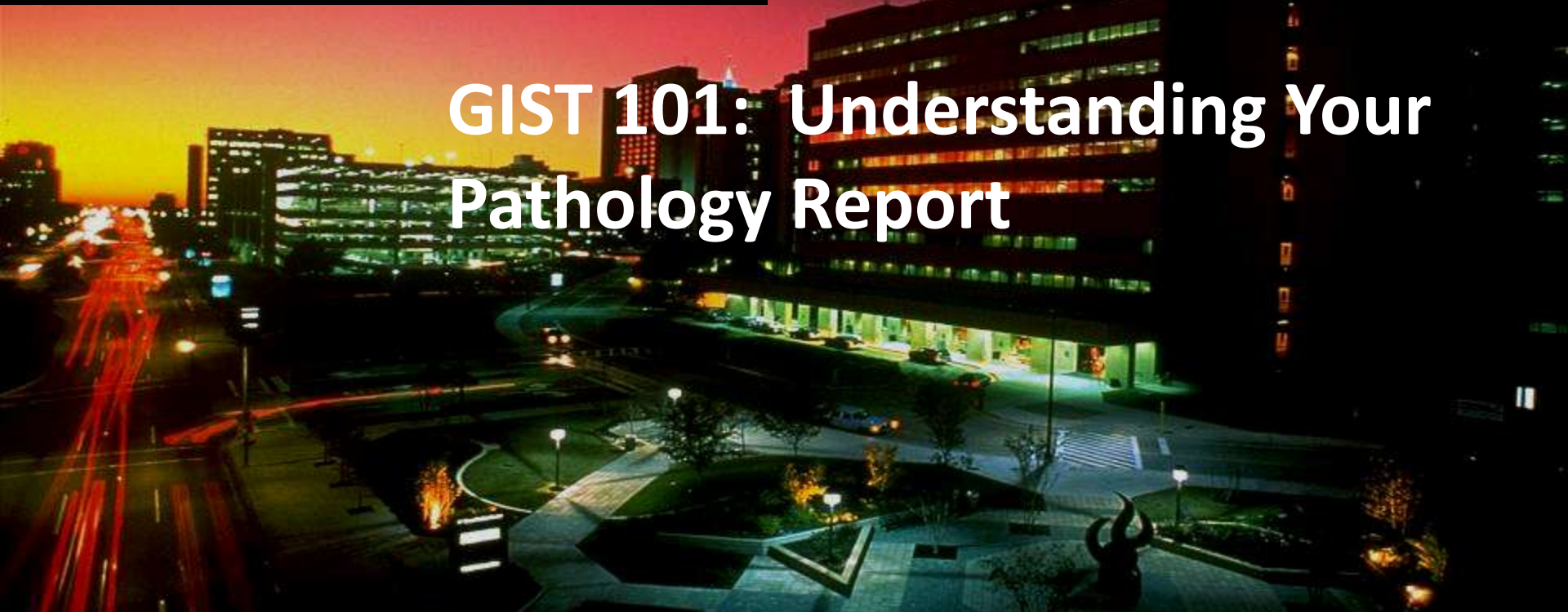


# GIST 101: Understanding Your Pathology Report



**GSI Patient Summit Saturday 22 September 2012**

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**Section of Soft Tissue/Sarcoma Pathology**

**Faculty, Sarcoma Research Center**



# ***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?**
- 5. What is new and exciting in GIST pathology?**

*What happens to my tumor in  
pathology?*



**Tumor is examined by a pathologist.**

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





**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.**



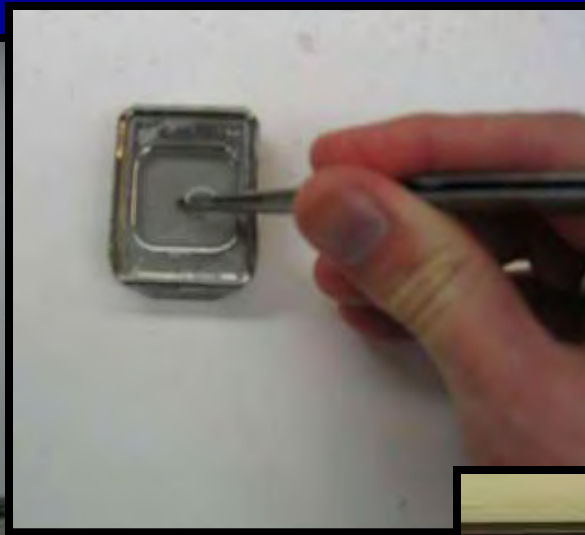
Tissue processing is done overnight and utilizes graded treatments of formalin, ethanol, xylene and paraffin.



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







**The tissue fragments are embedded in a paraffin mold and cooled – the result being a tissue block.**





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





**Tissue paraffin ribbons are placed in a warm waterbath and the 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 (hemotoxin & 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?***



cap

## 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

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

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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 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: \_\_\_%

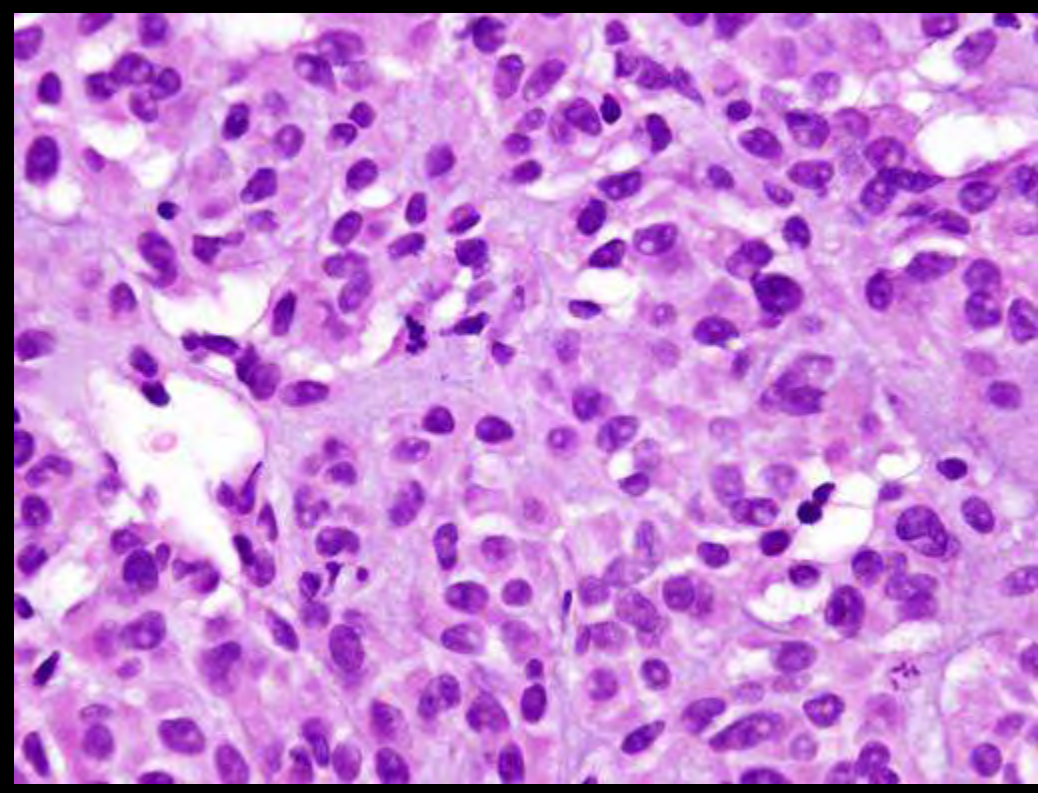
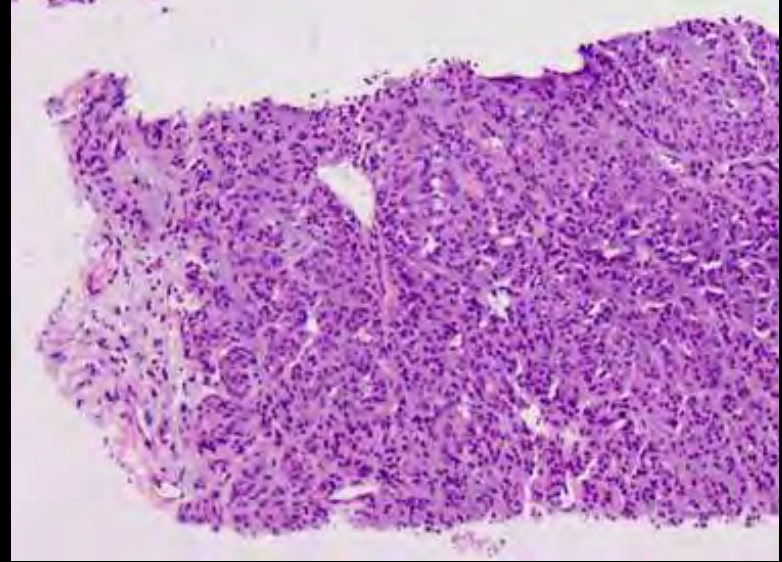
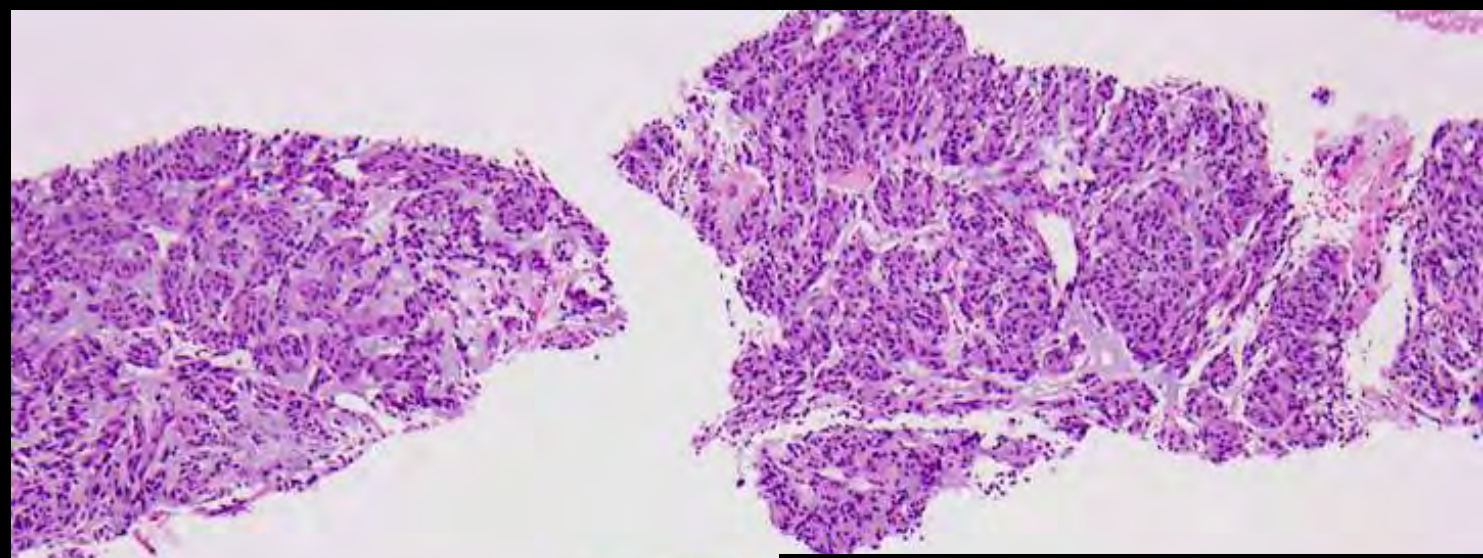
**+ Comment(s)**

***Getting the diagnosis right.***

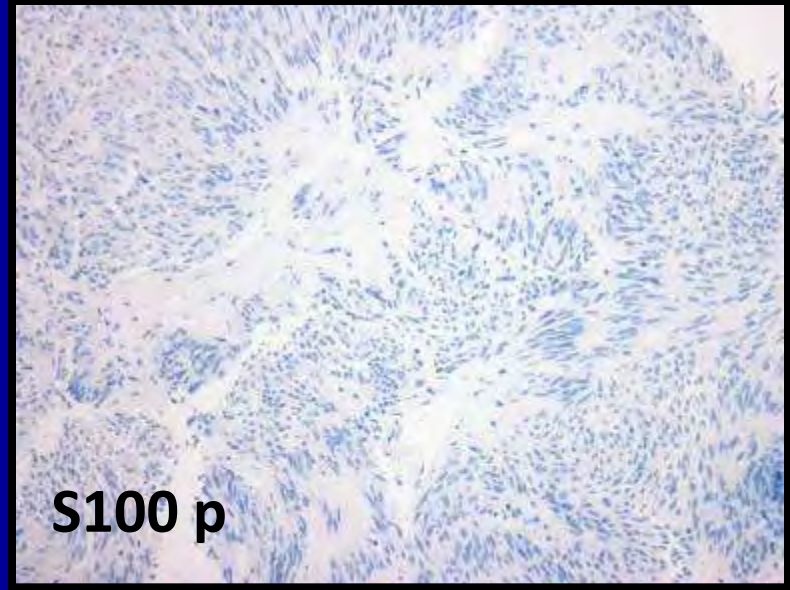
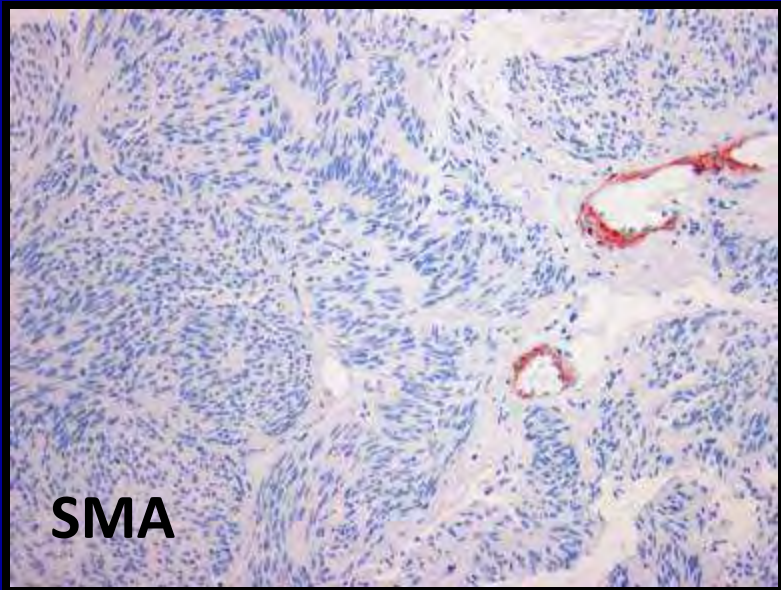
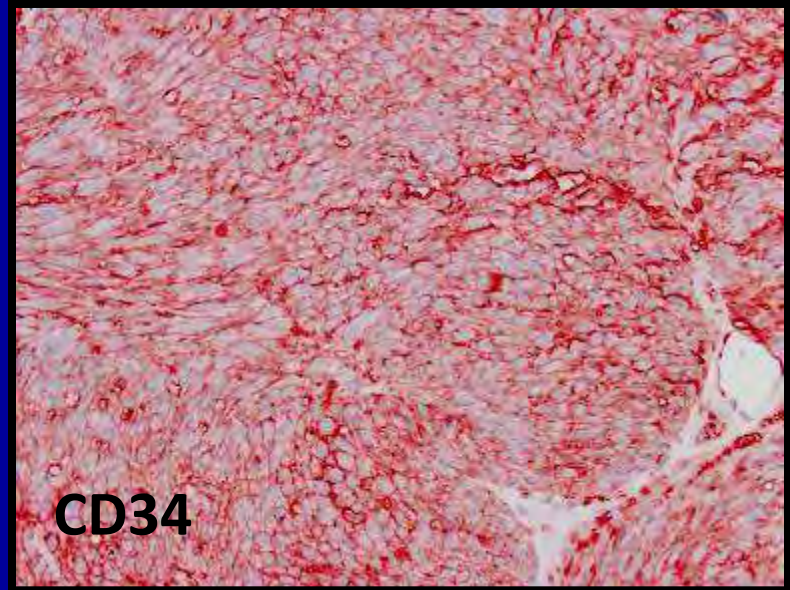
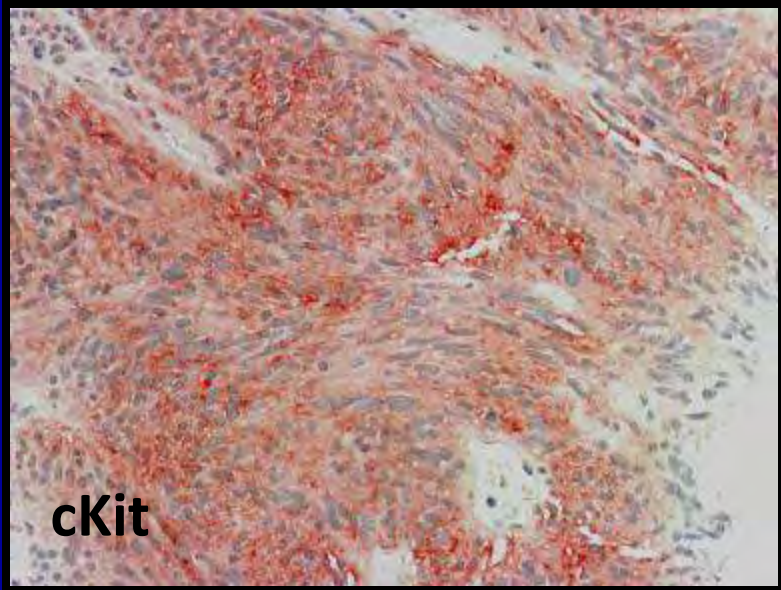
## *Case 1*

**Female, aged 40, with 25 cm mass  
involving the small bowel.**





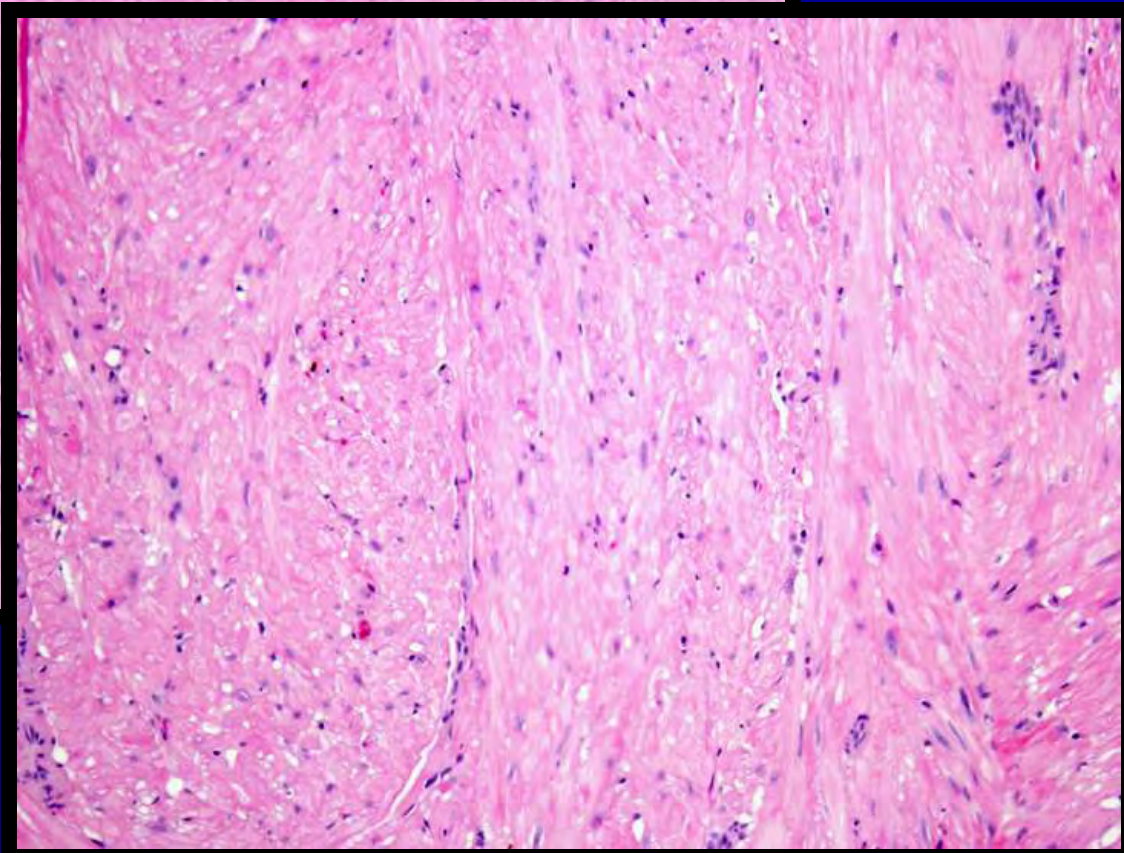
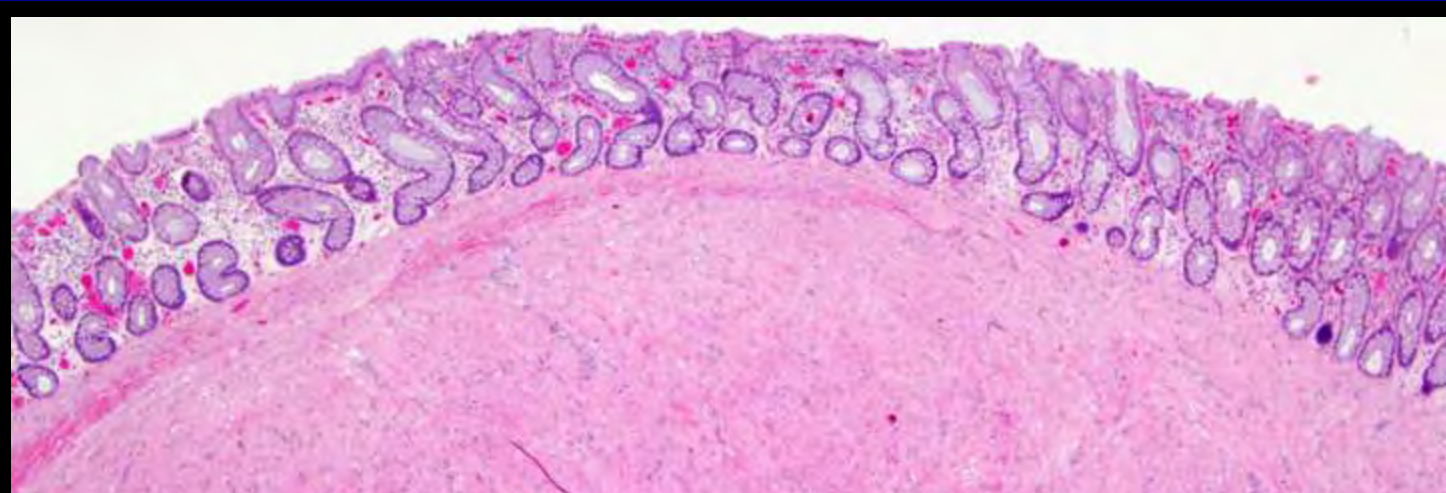




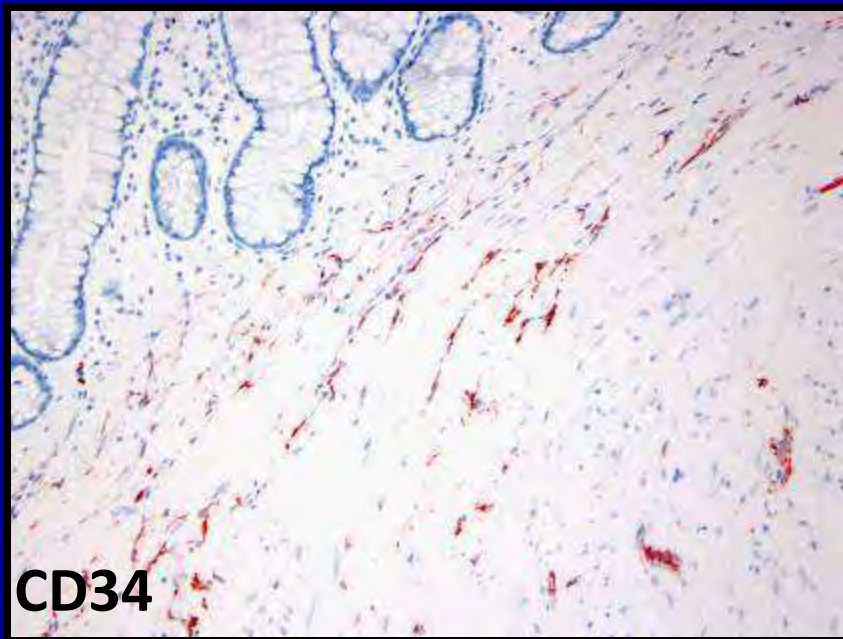
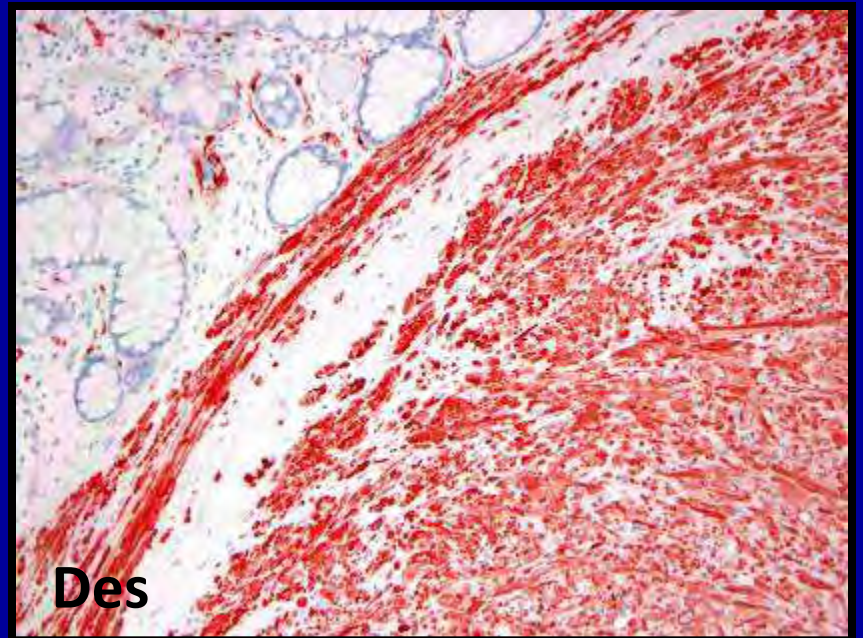
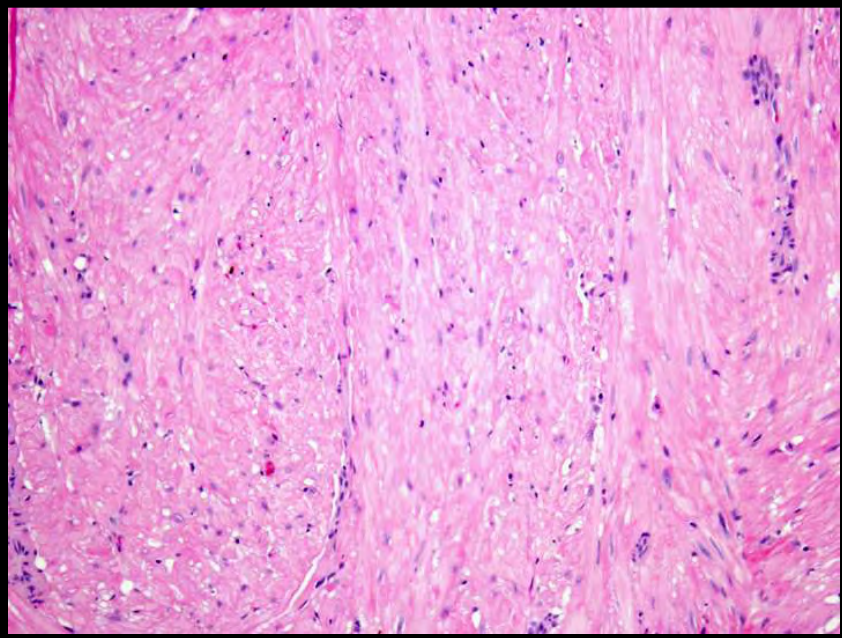
## **Case 2**

***Male, aged 38, with 10 mm polyp at 10 cm in rectum.***





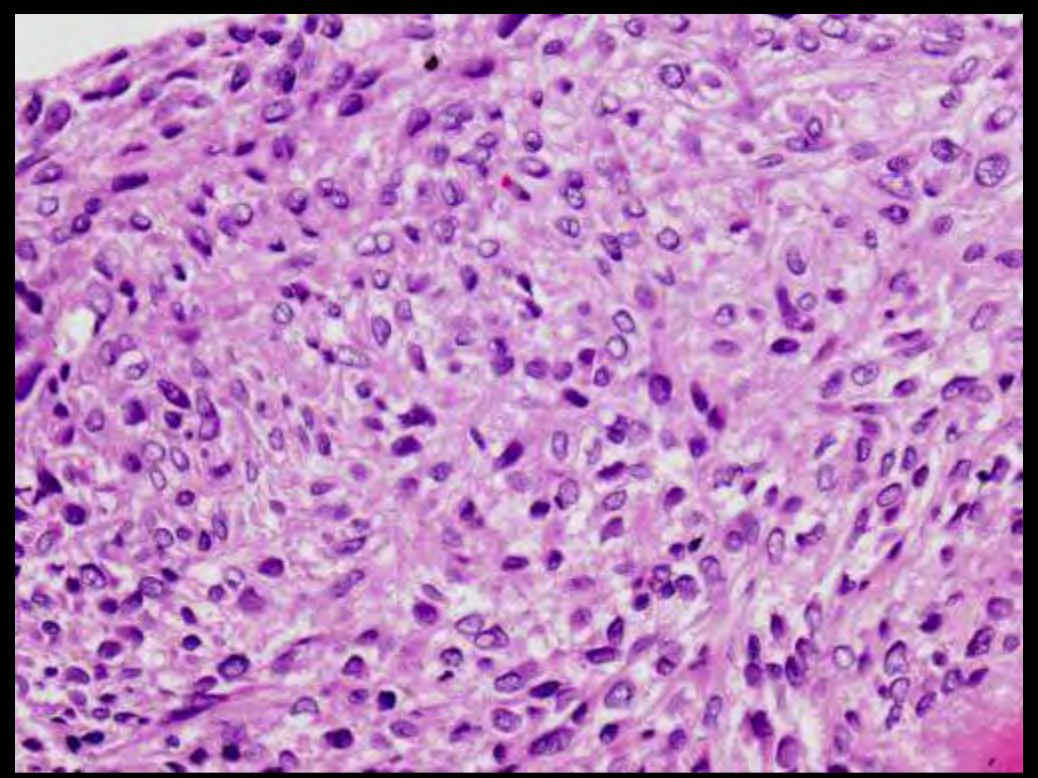
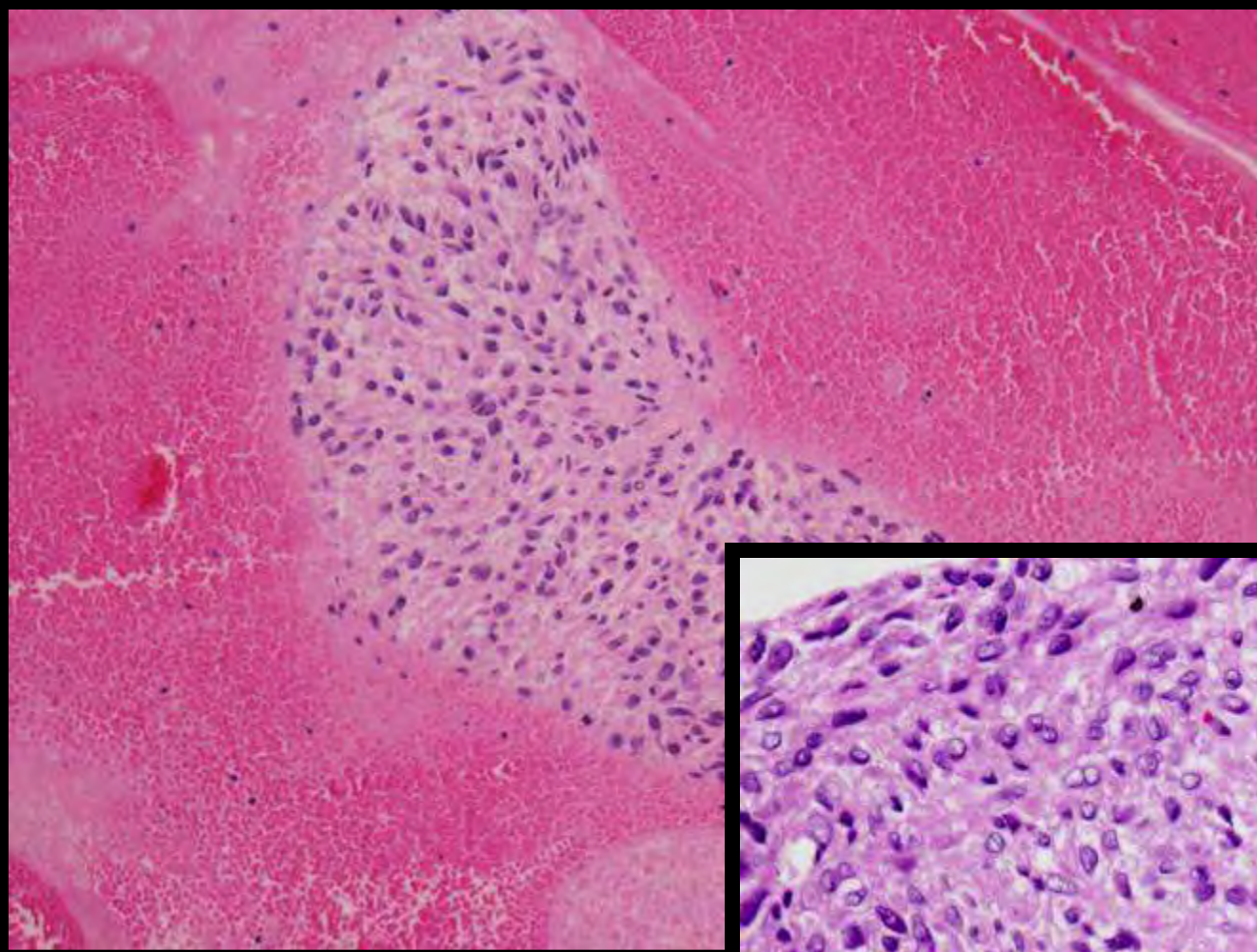




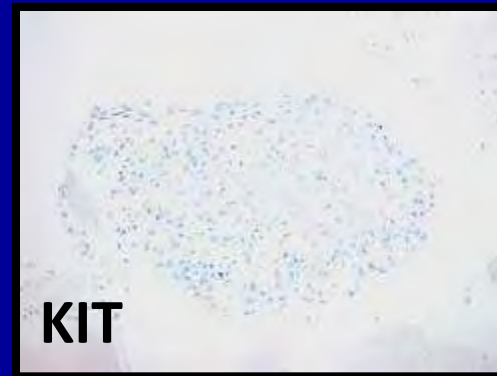
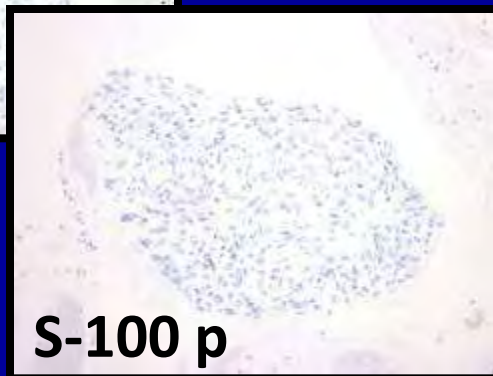
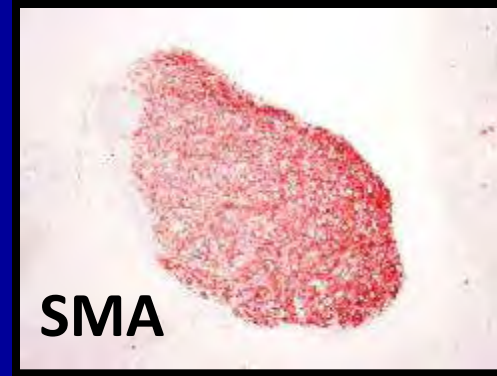
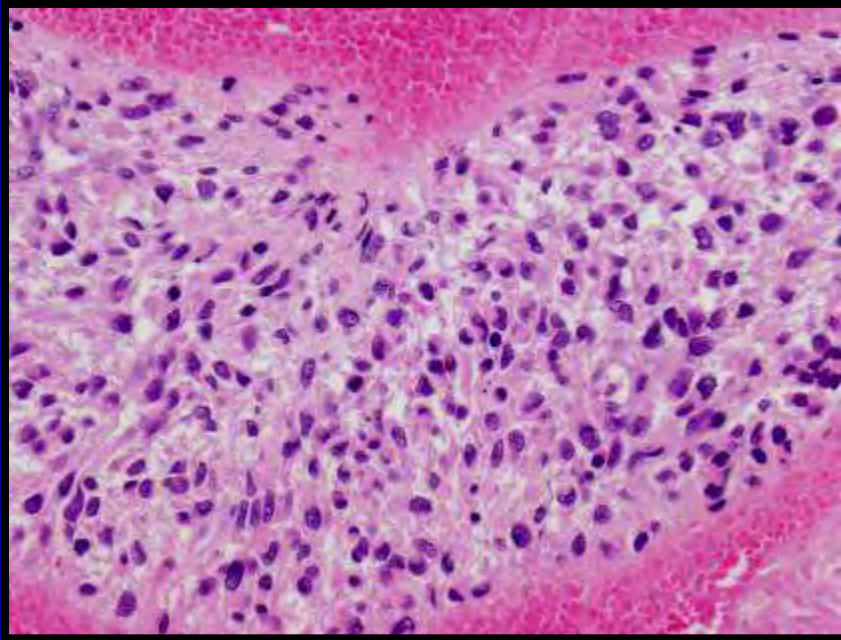
## *Case 3*

**Male, aged 37, with 13 cm gastric wall mass.**

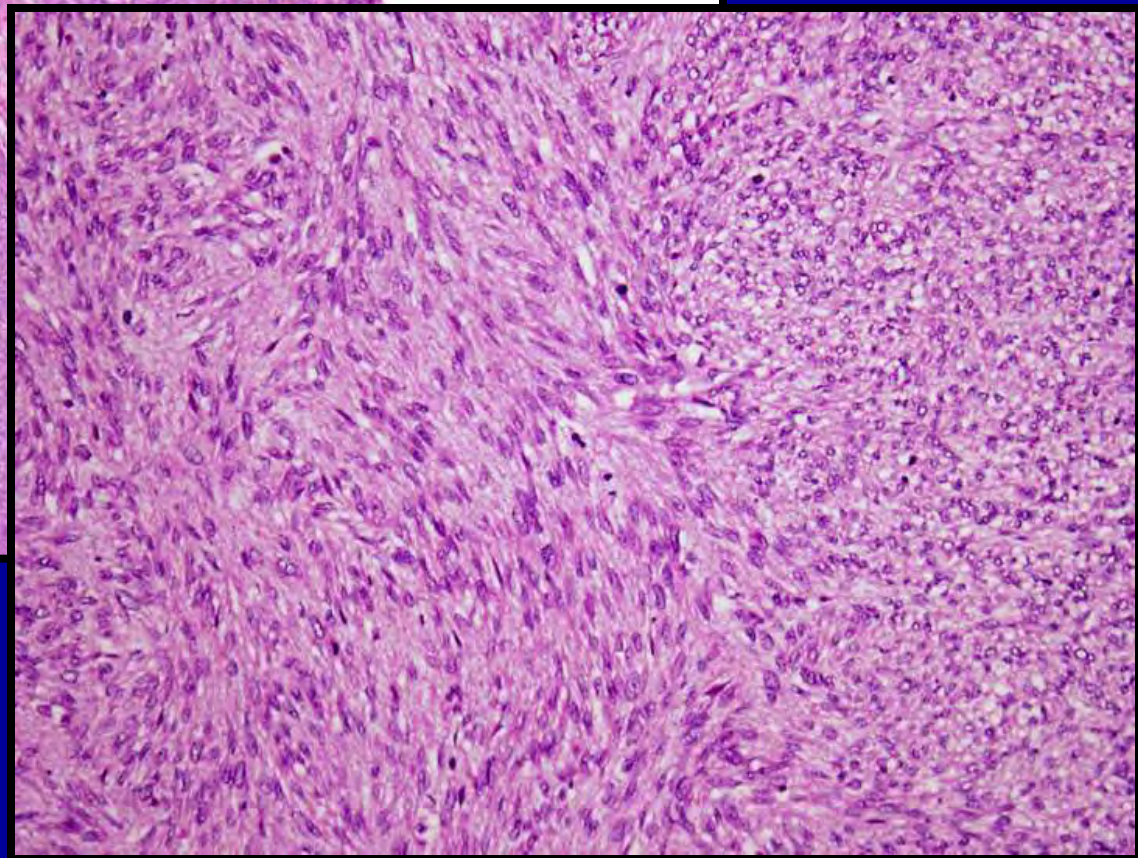
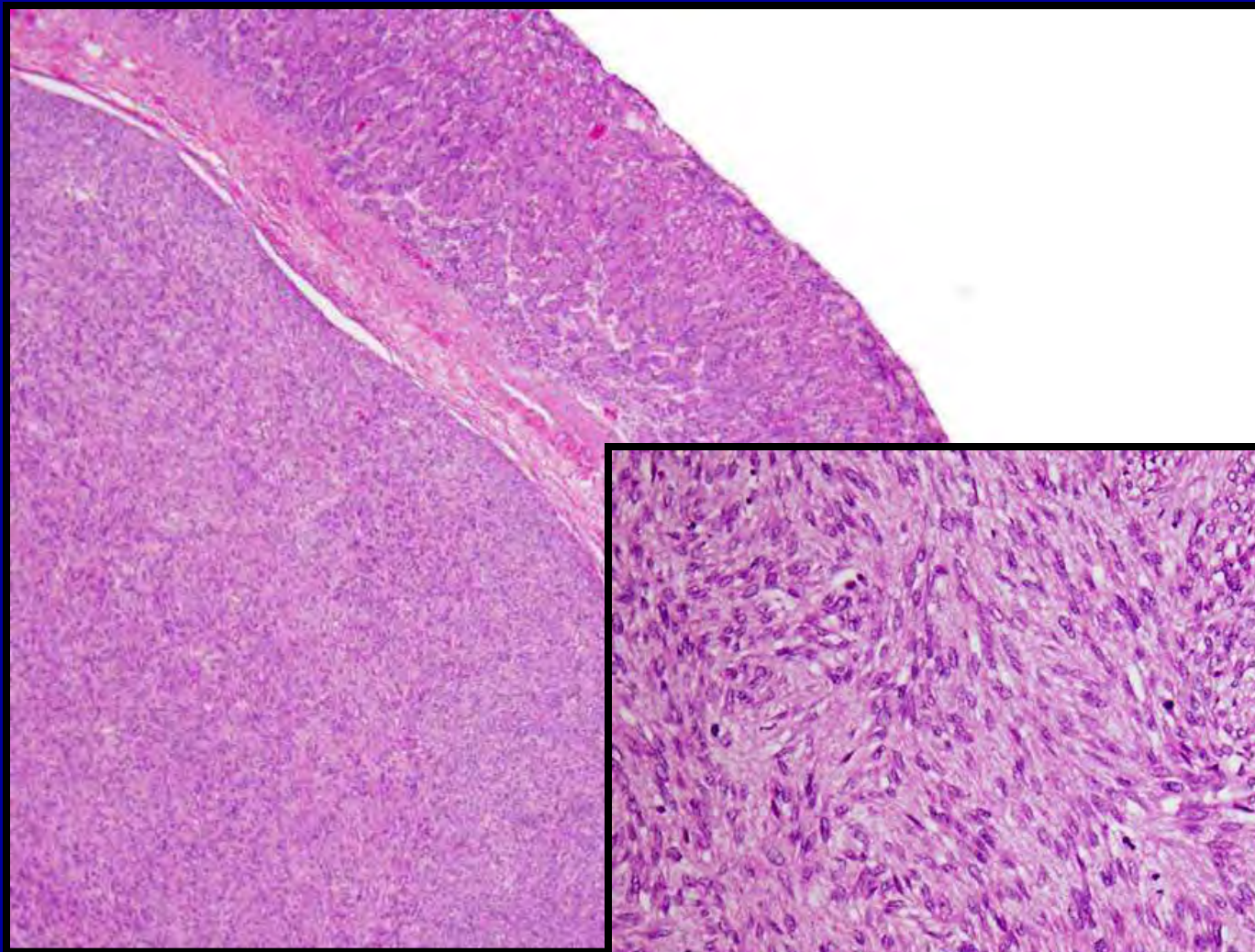




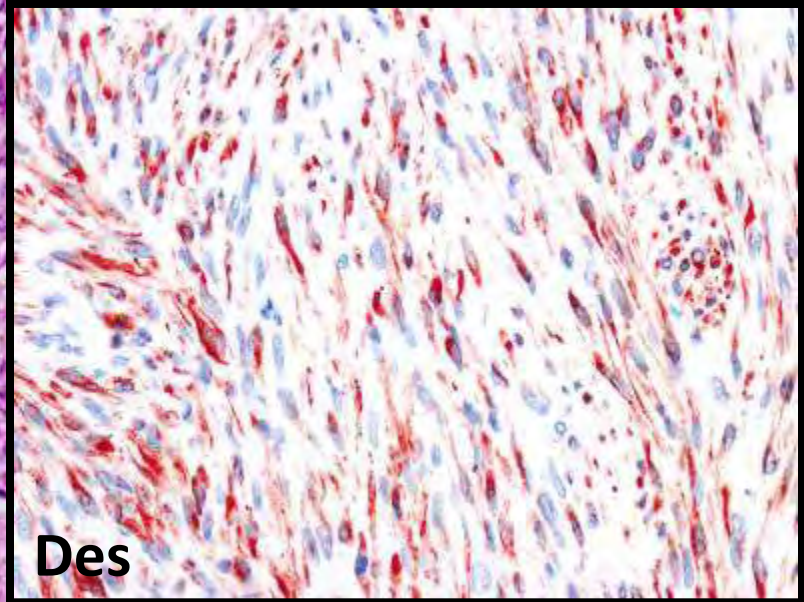
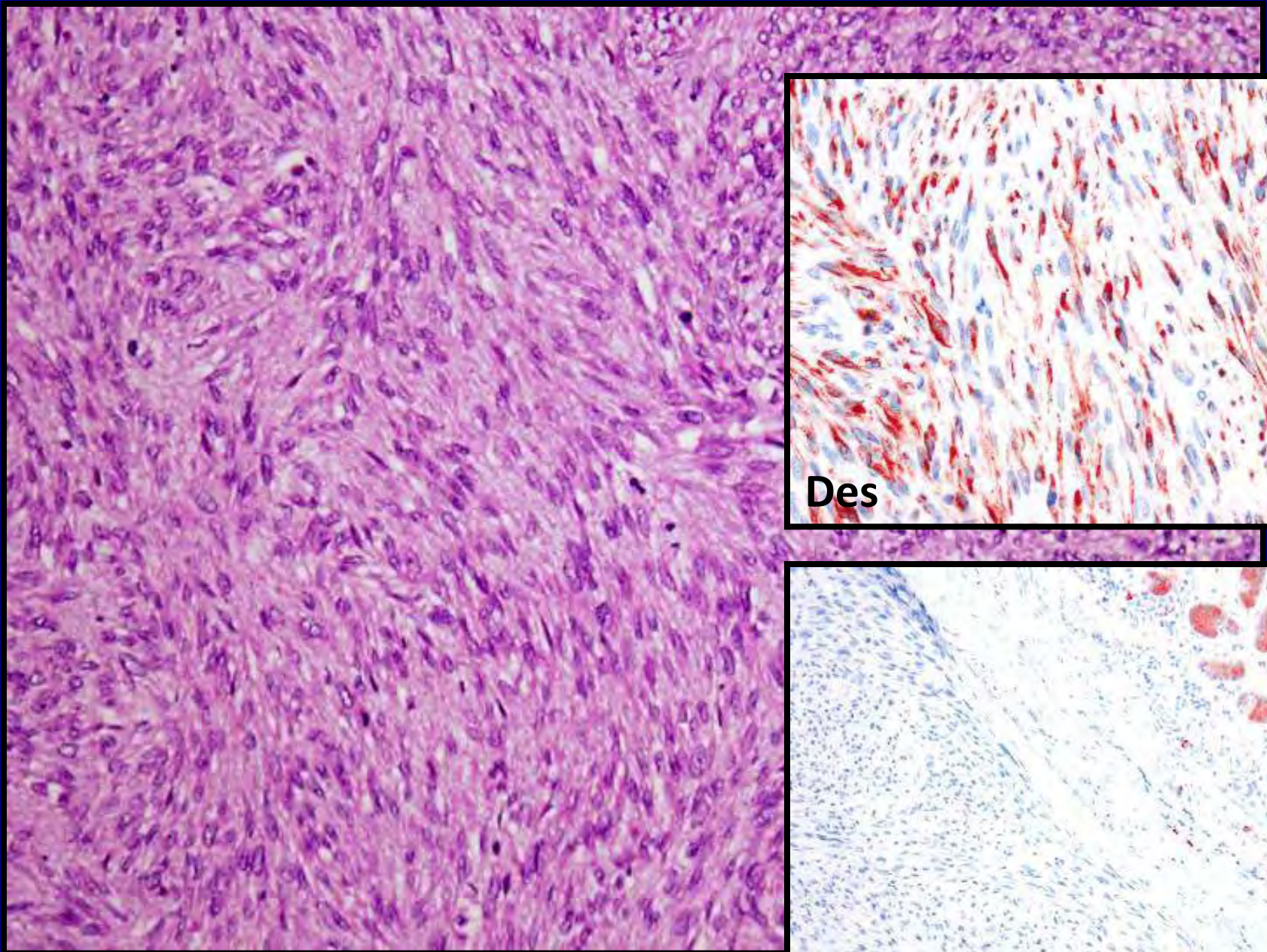




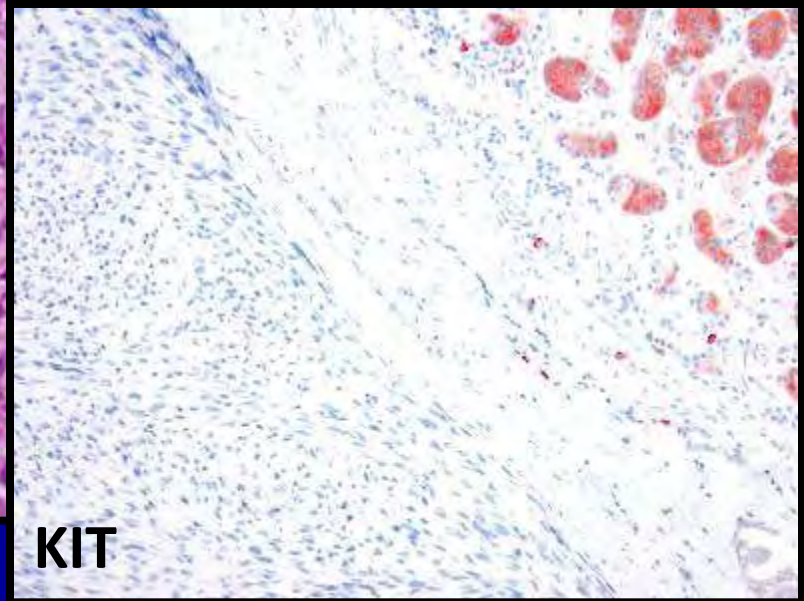






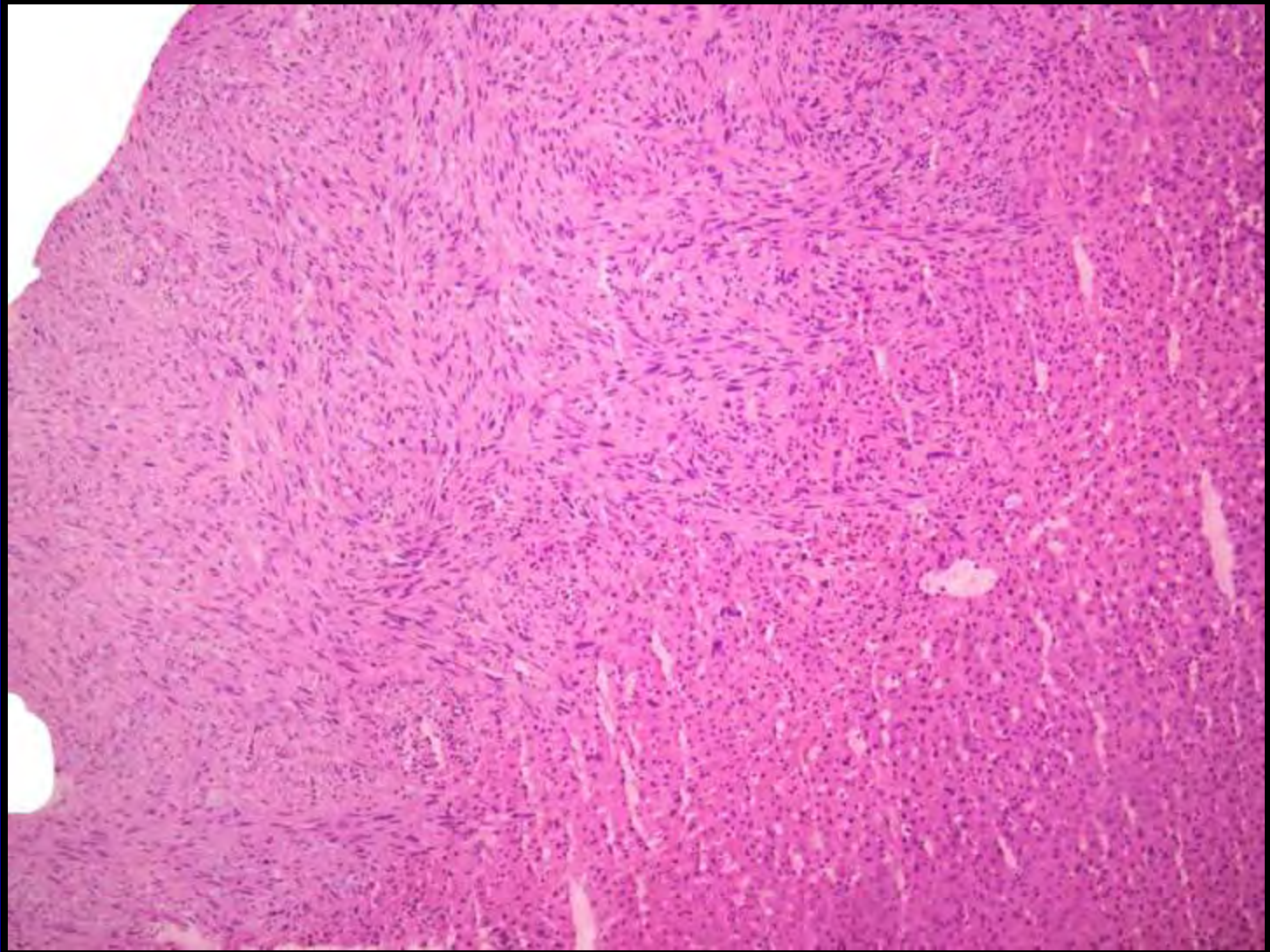


**Des**



**KIT**

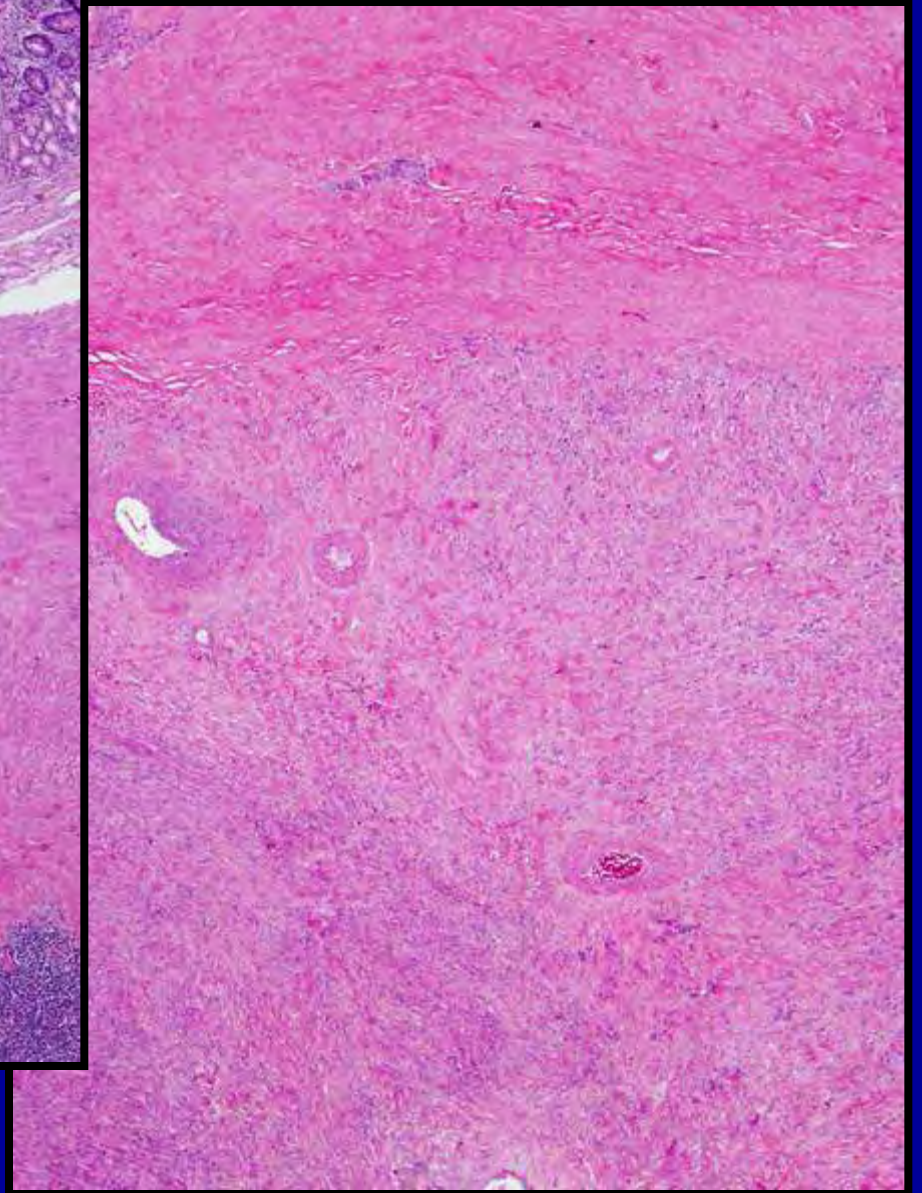
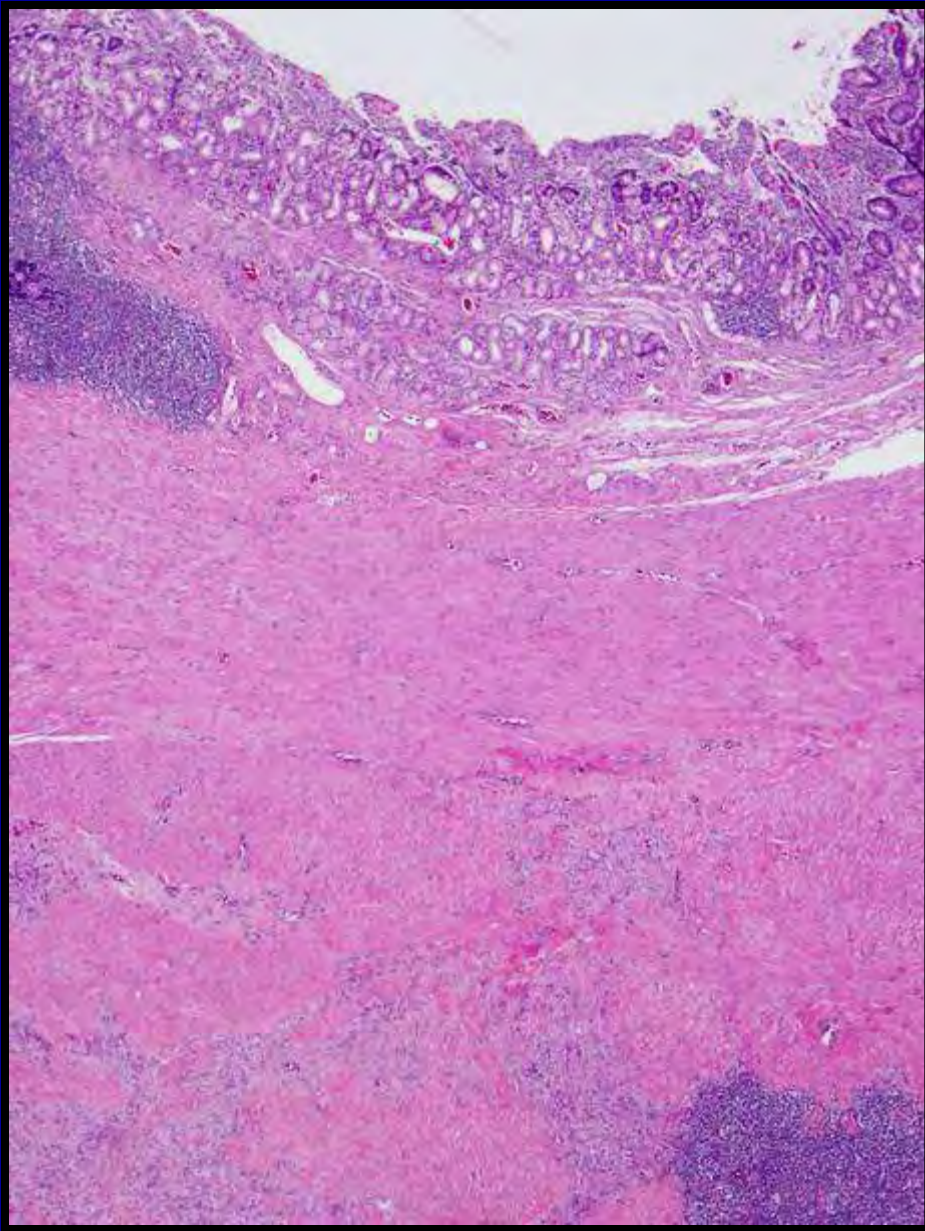




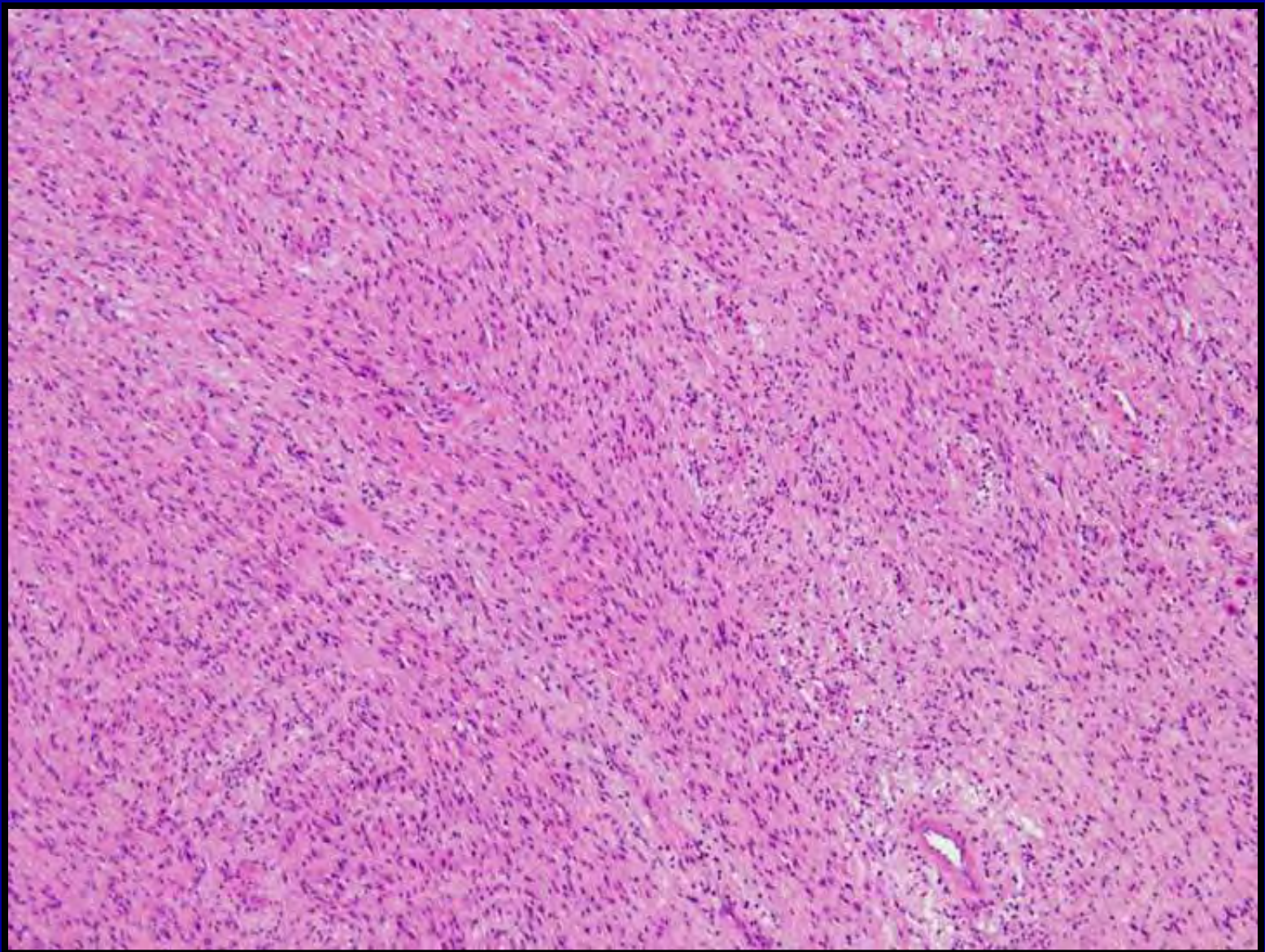
## *Case 4*

**Male, aged 36, with 17 cm gastric wall mass.**

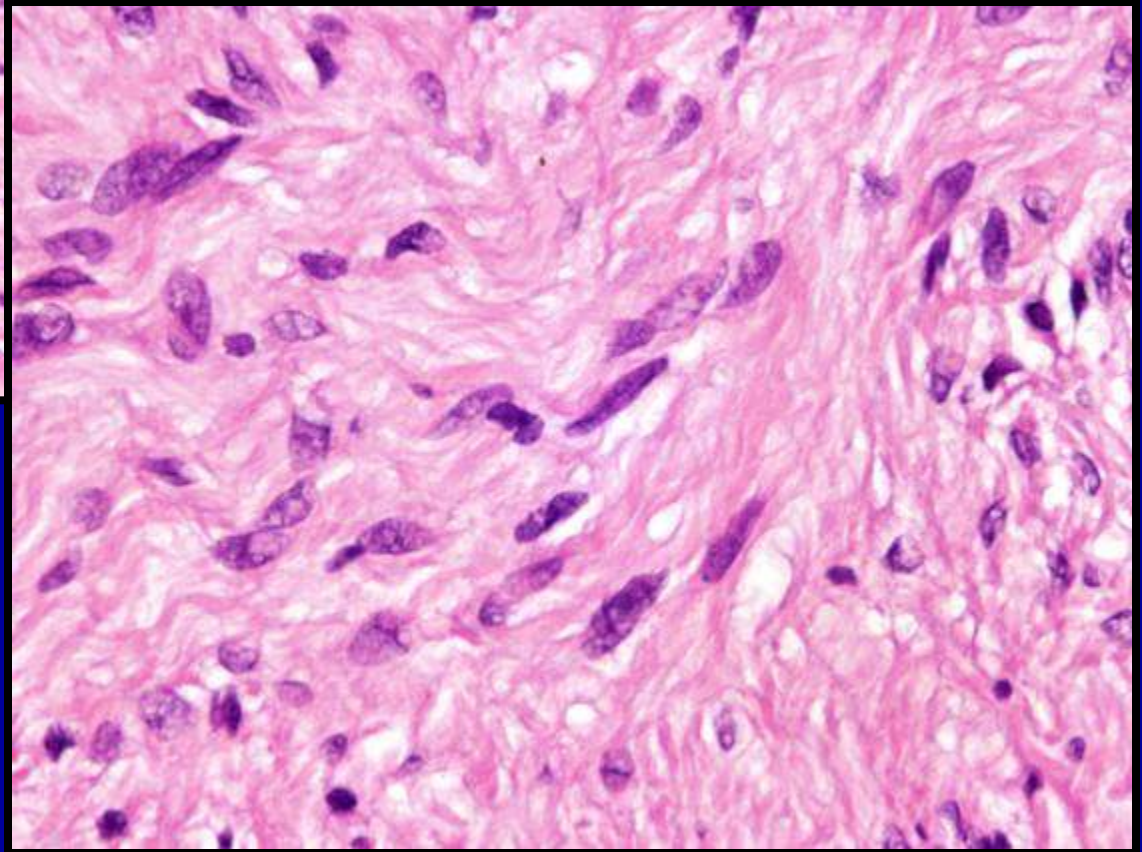
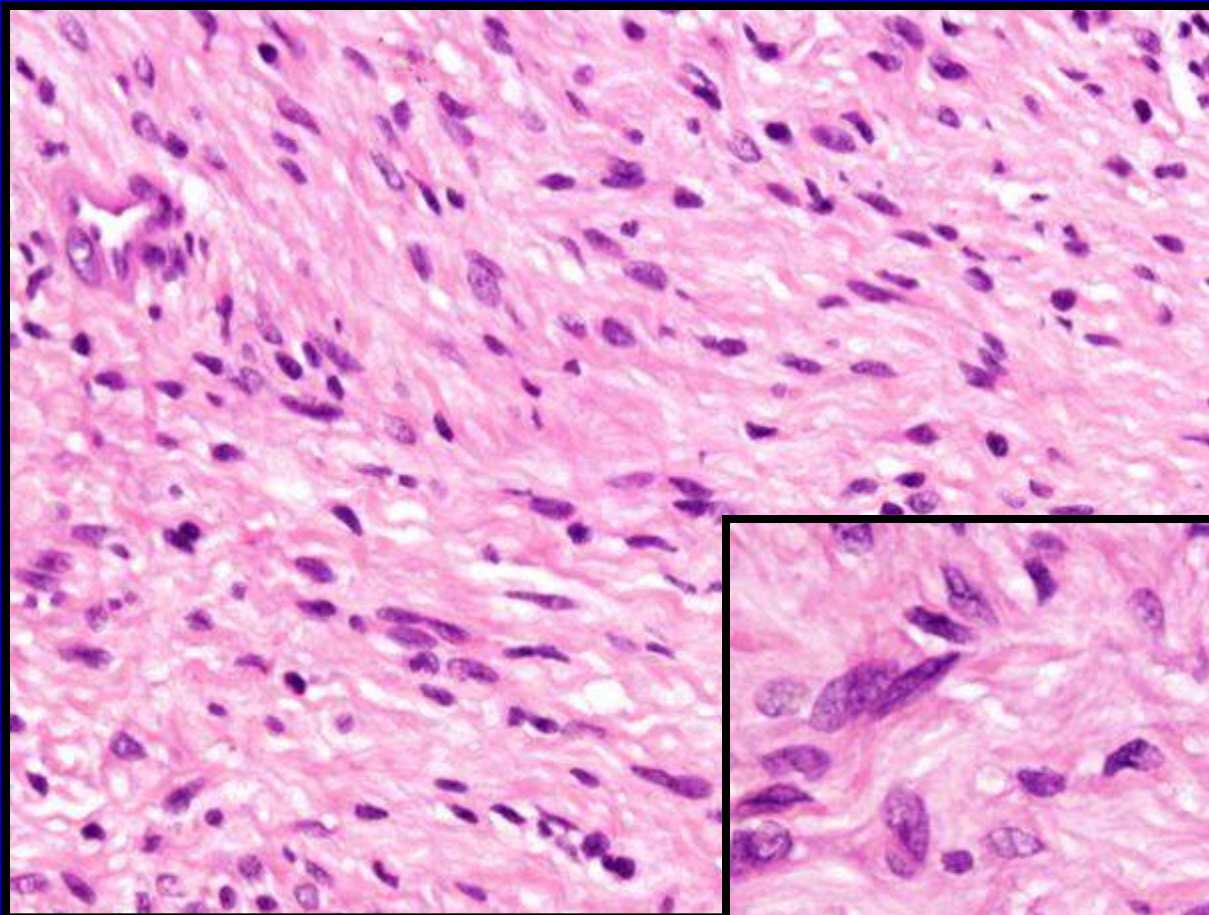








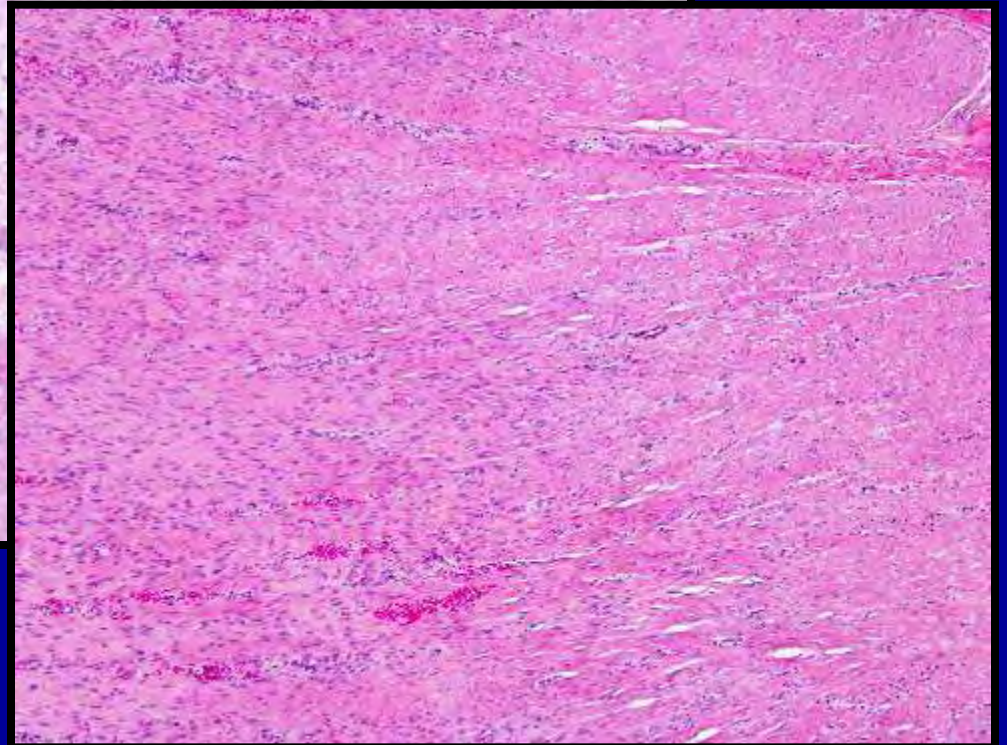
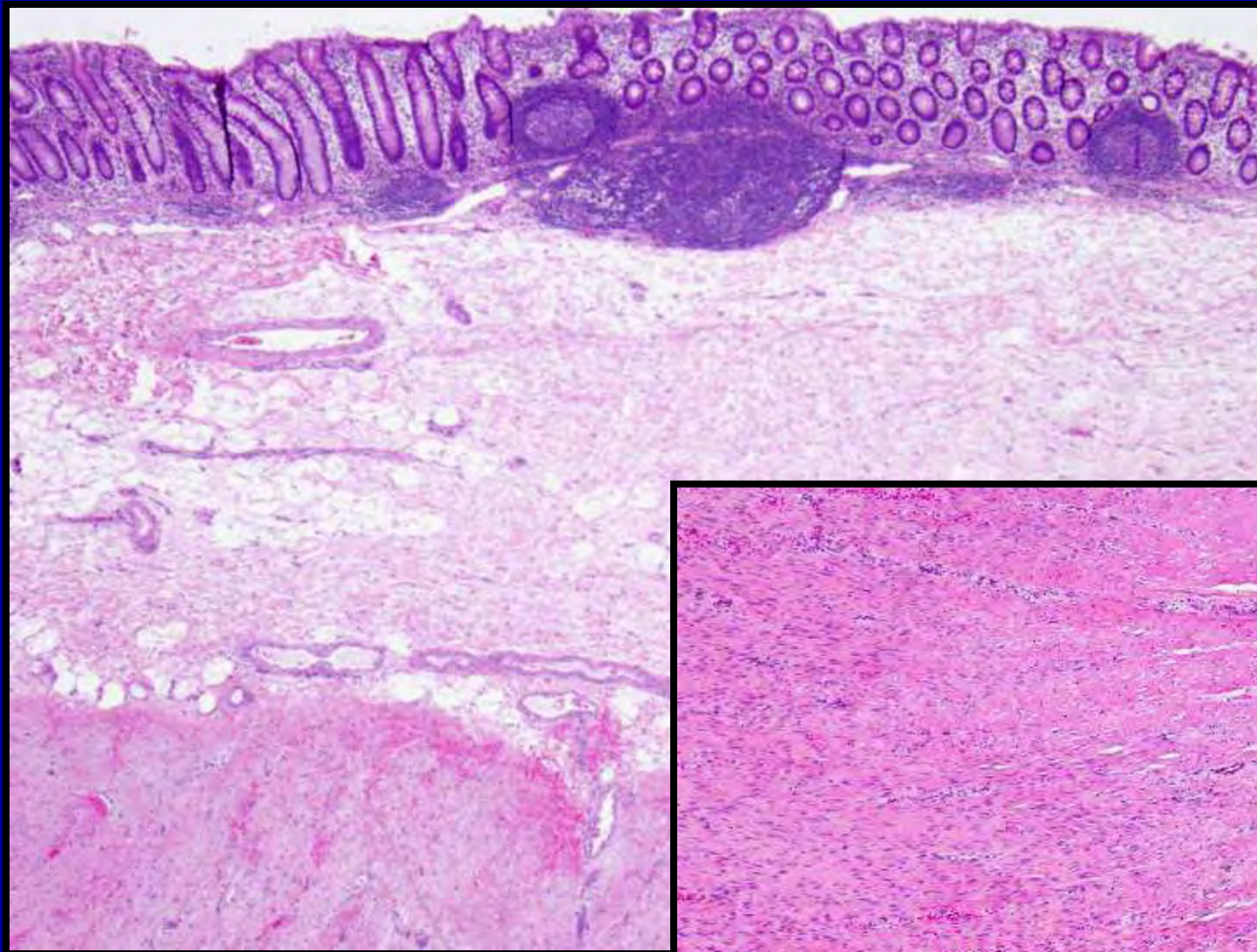




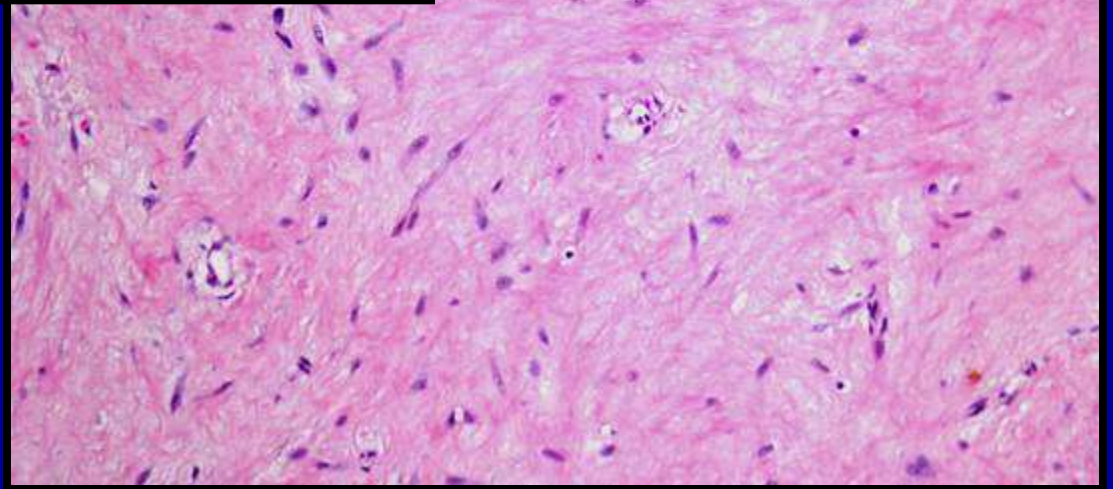
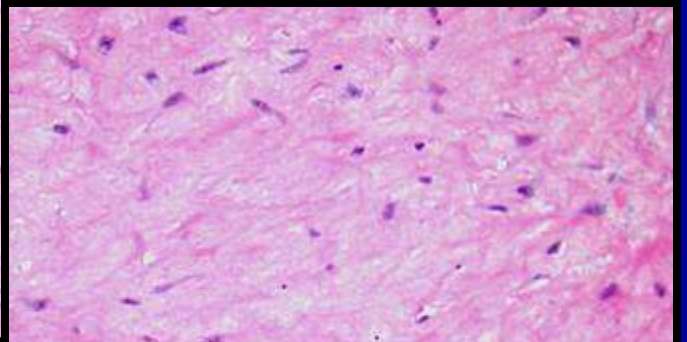
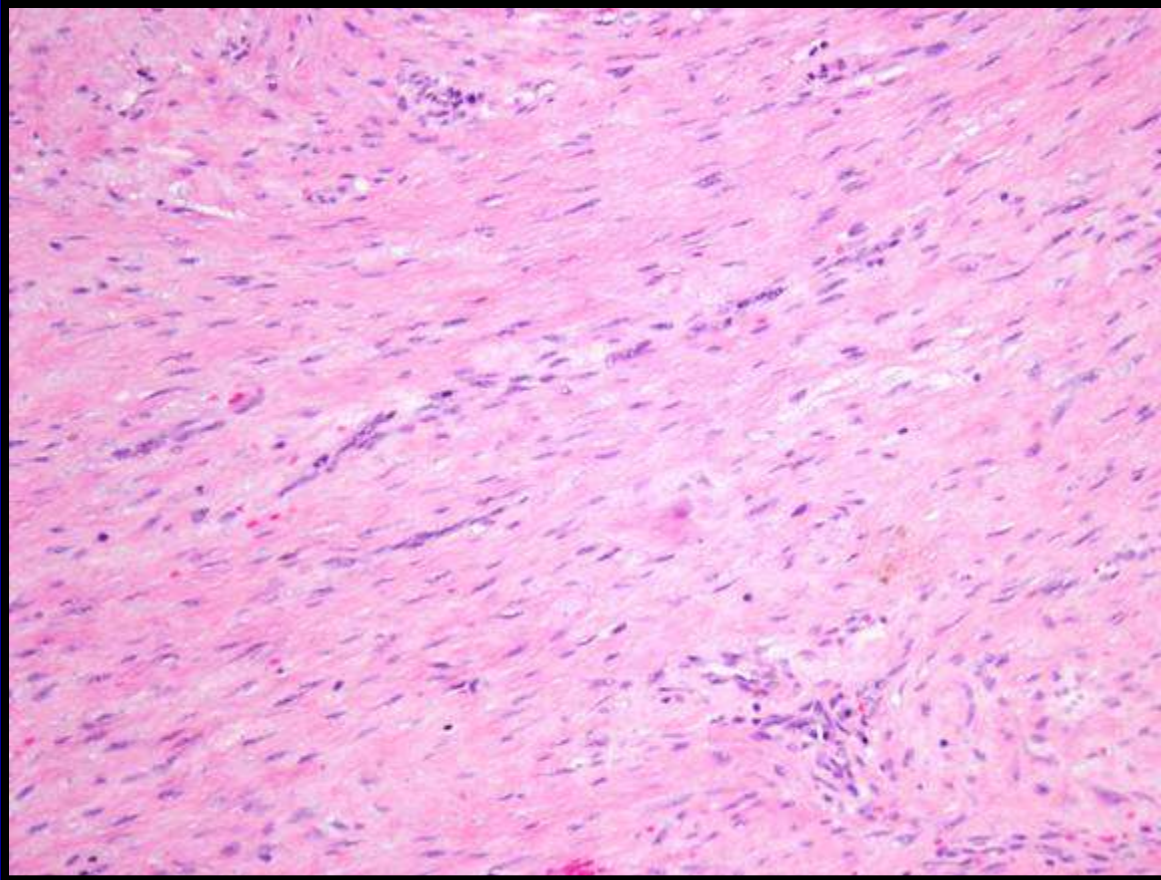
## *Case 5*

**Female, aged 29, with 10 cm gastric wall mass.**

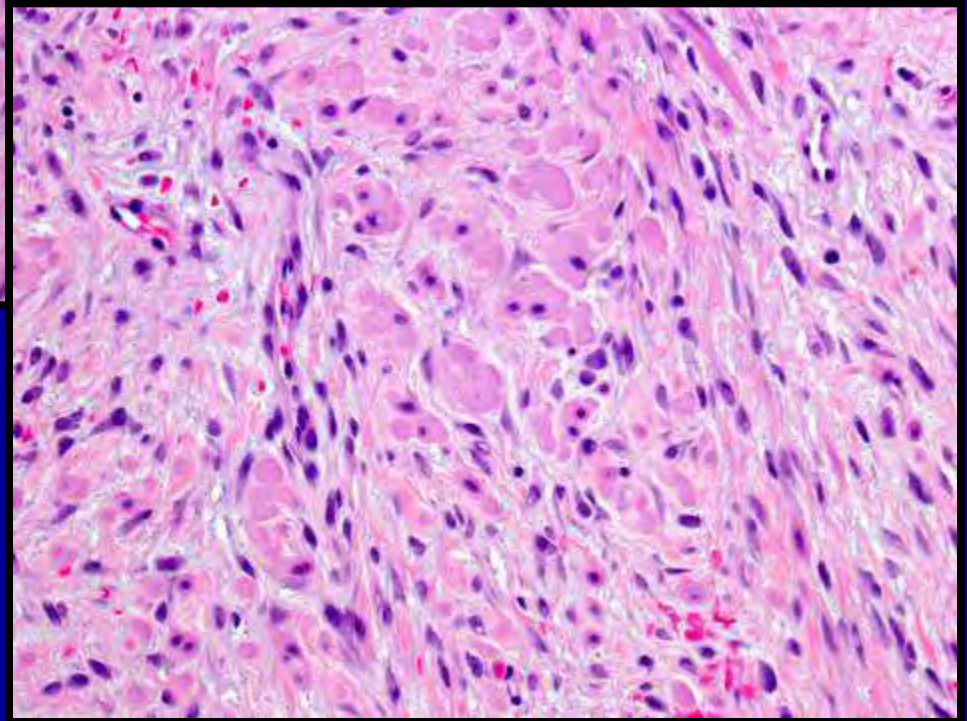
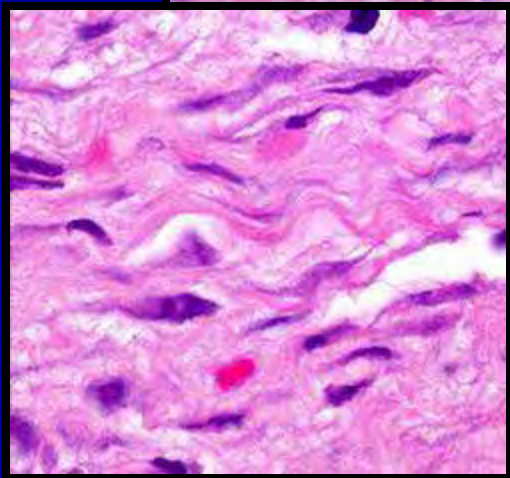
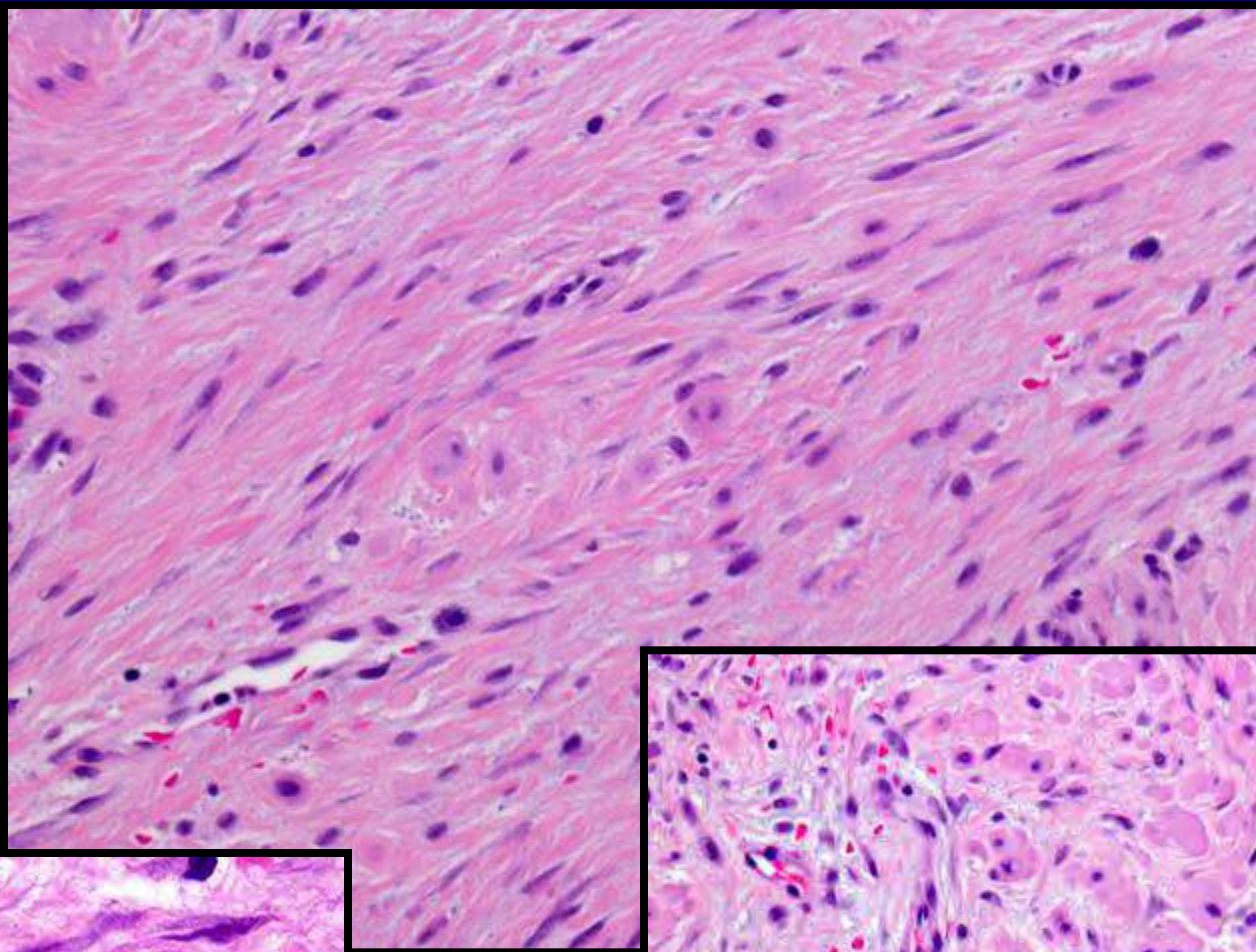




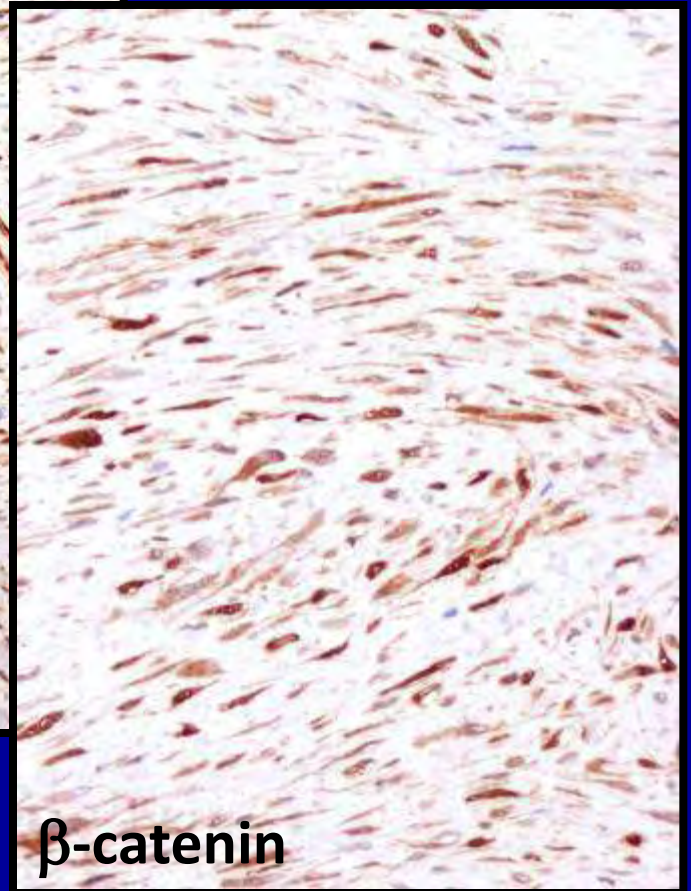
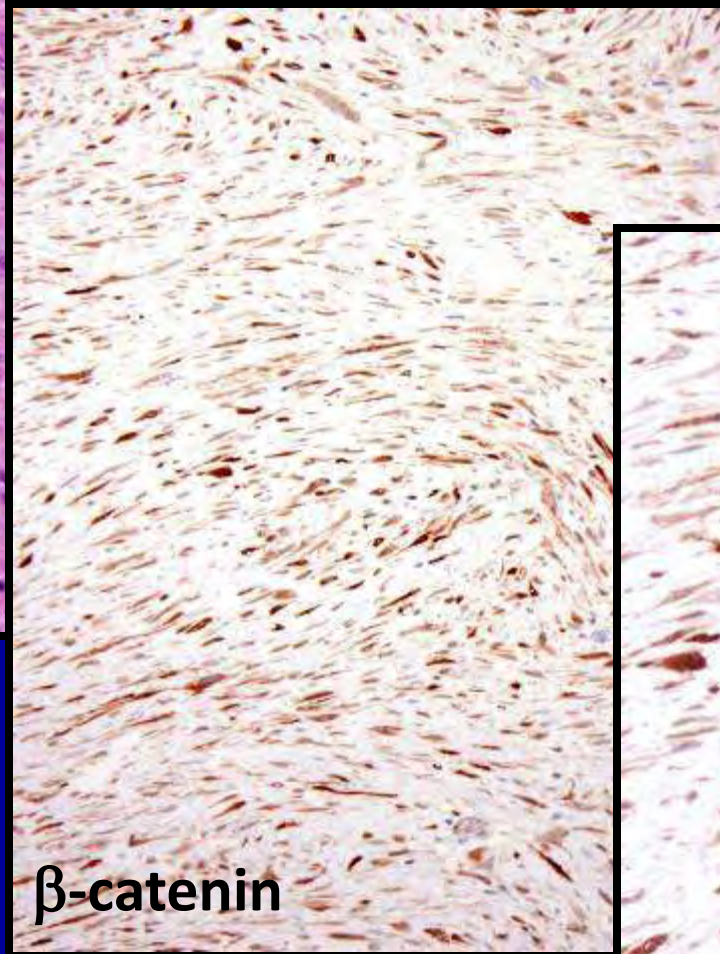
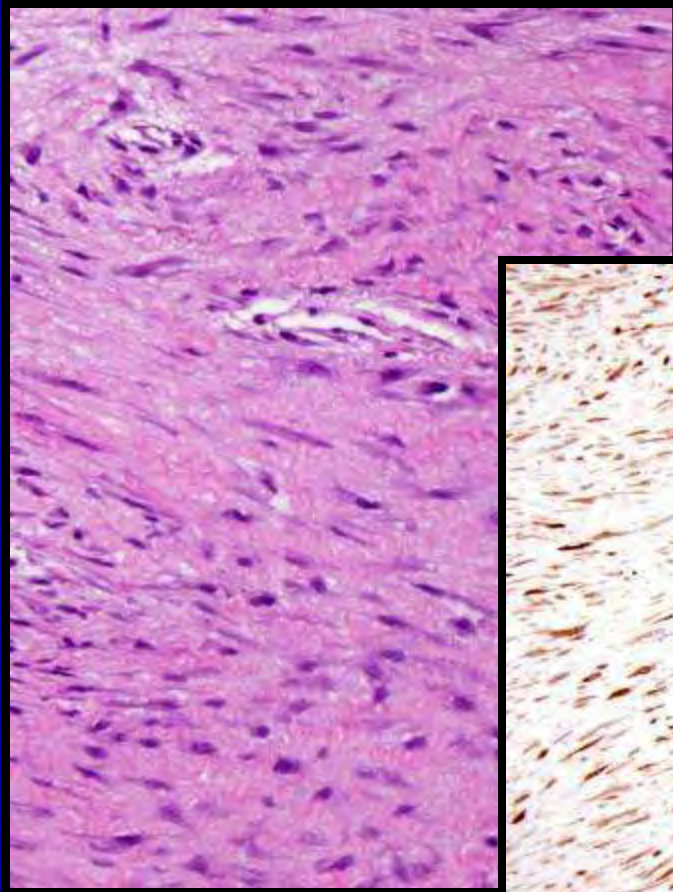


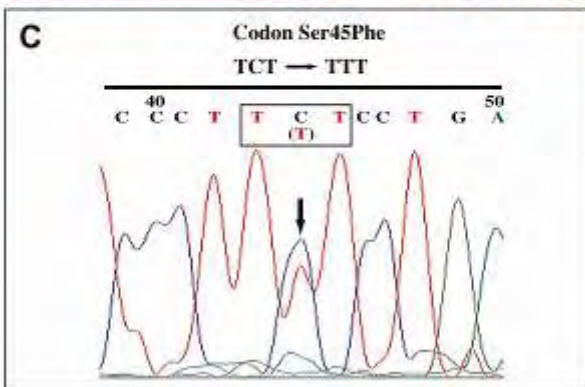
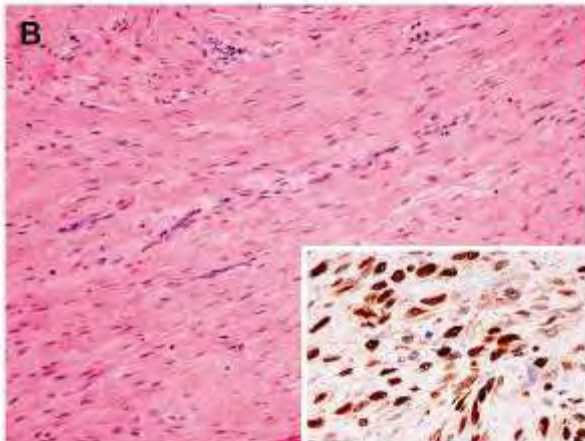
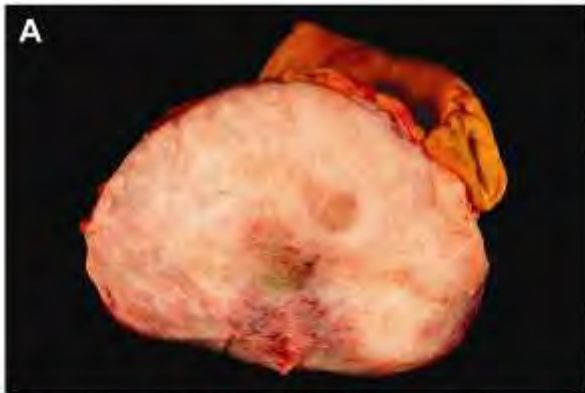






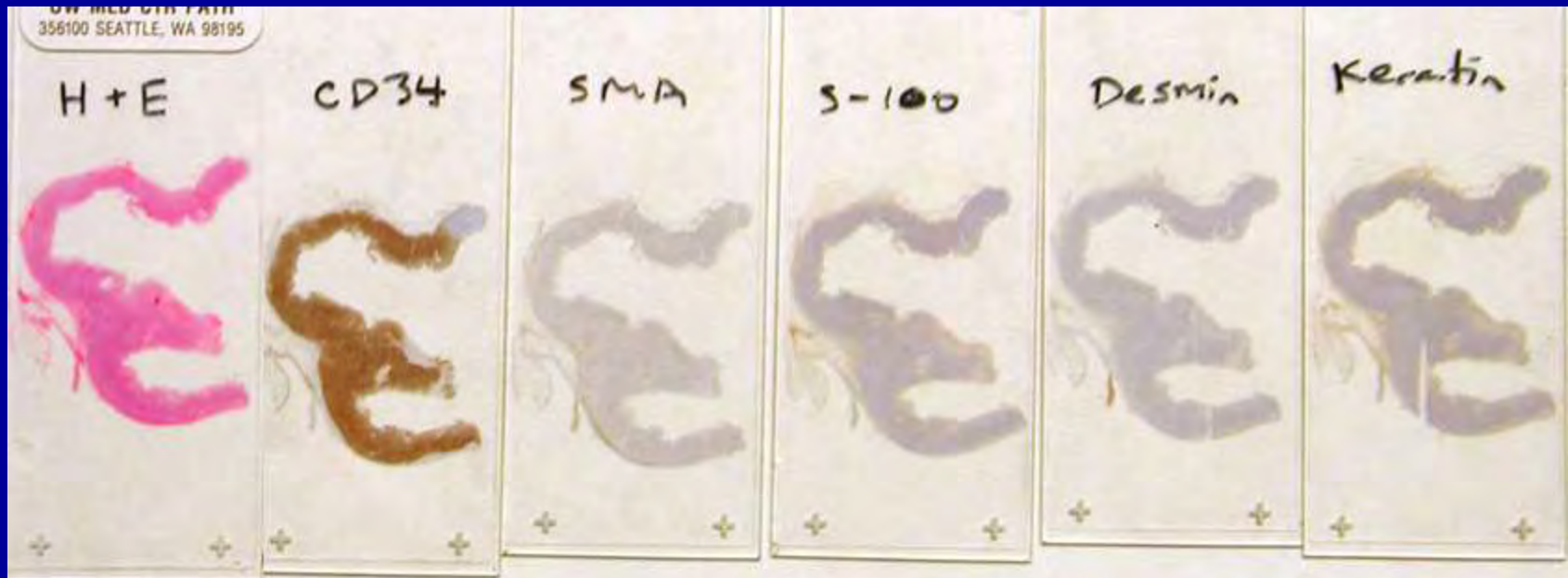








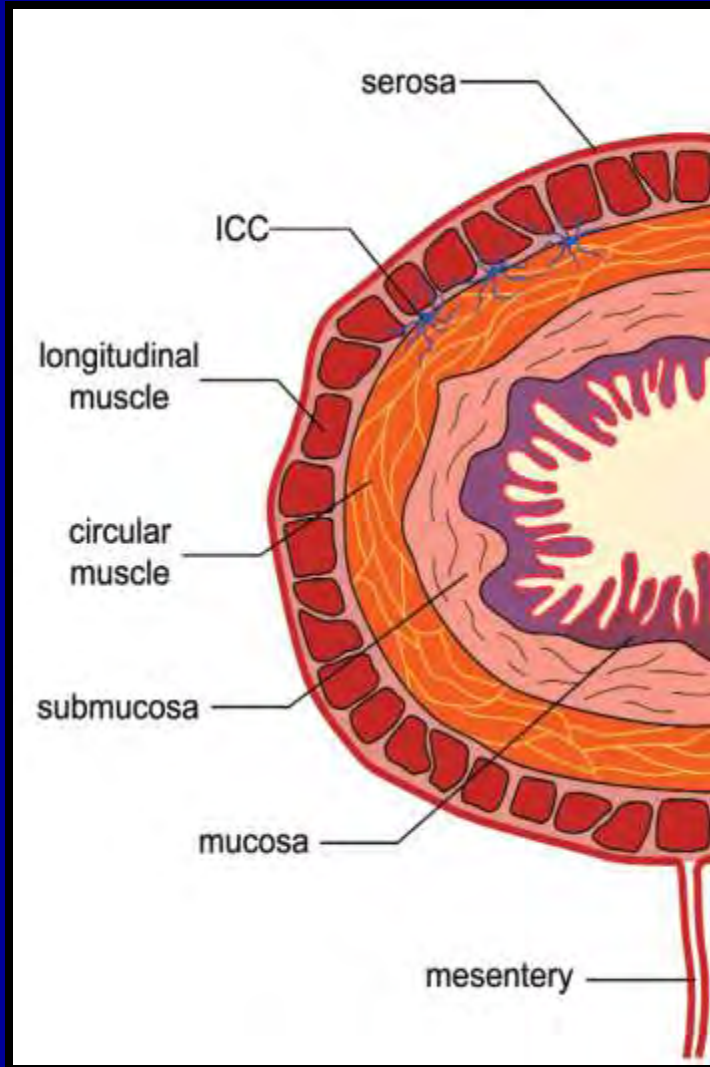
# *Immunohistochemical Profile of GISTs (Circa 1997 and prior)*



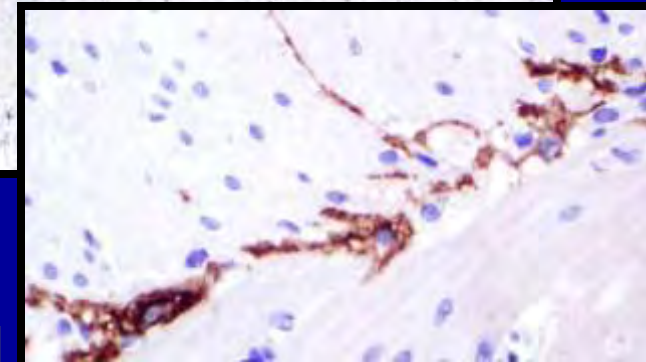
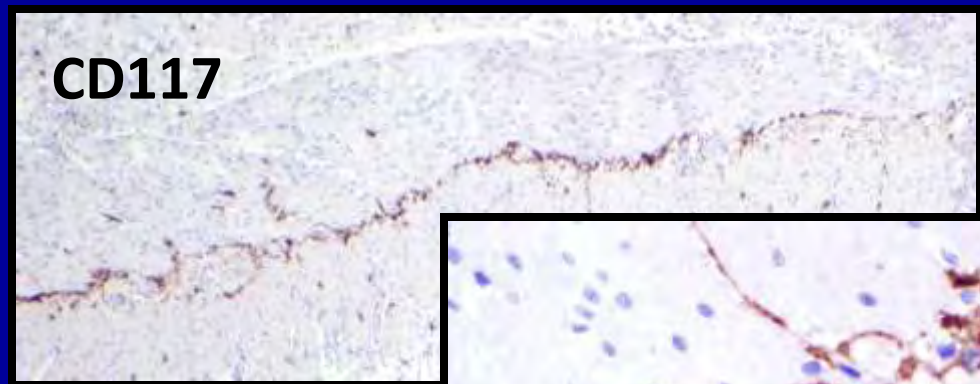
**CD34 +ve (70%)**  
**SMA +ve (30-40%)**  
**Desmin –ve**  
**S-100 protein –ve**  
**Keratin –ve**



# 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%)**

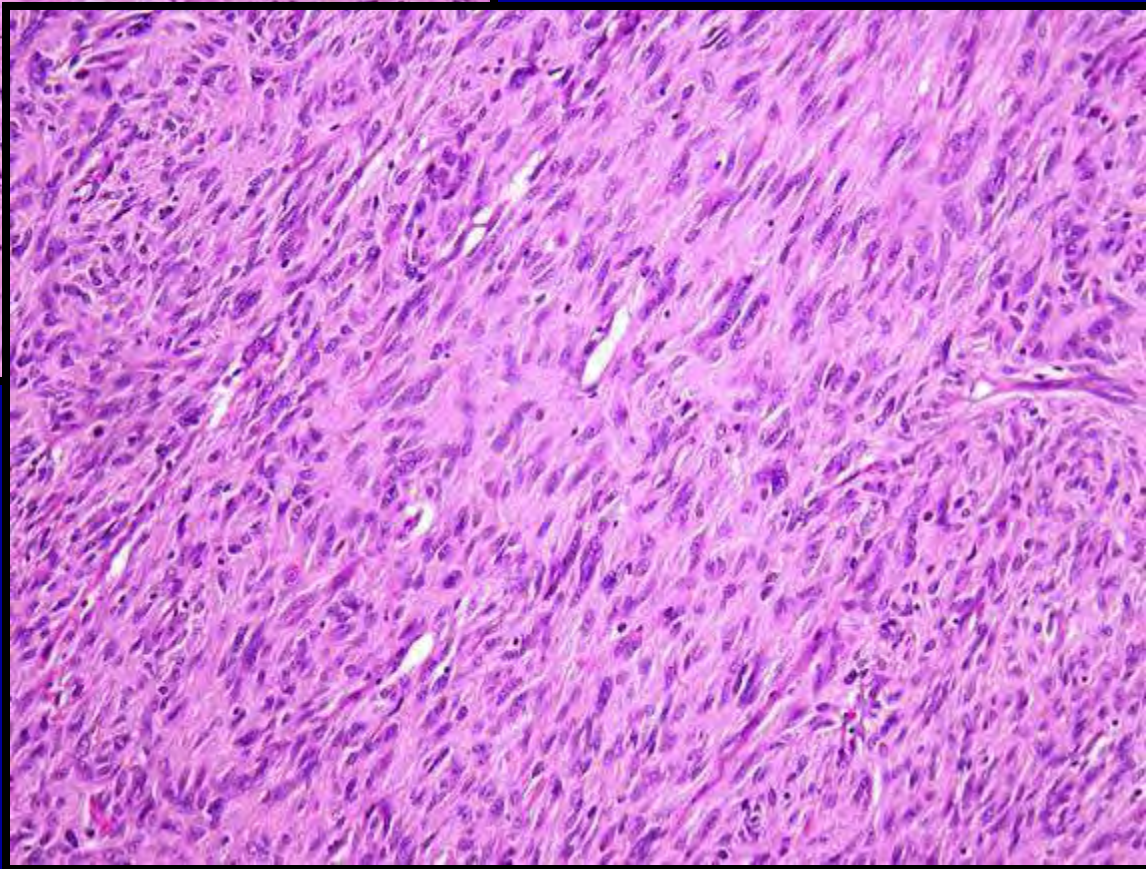
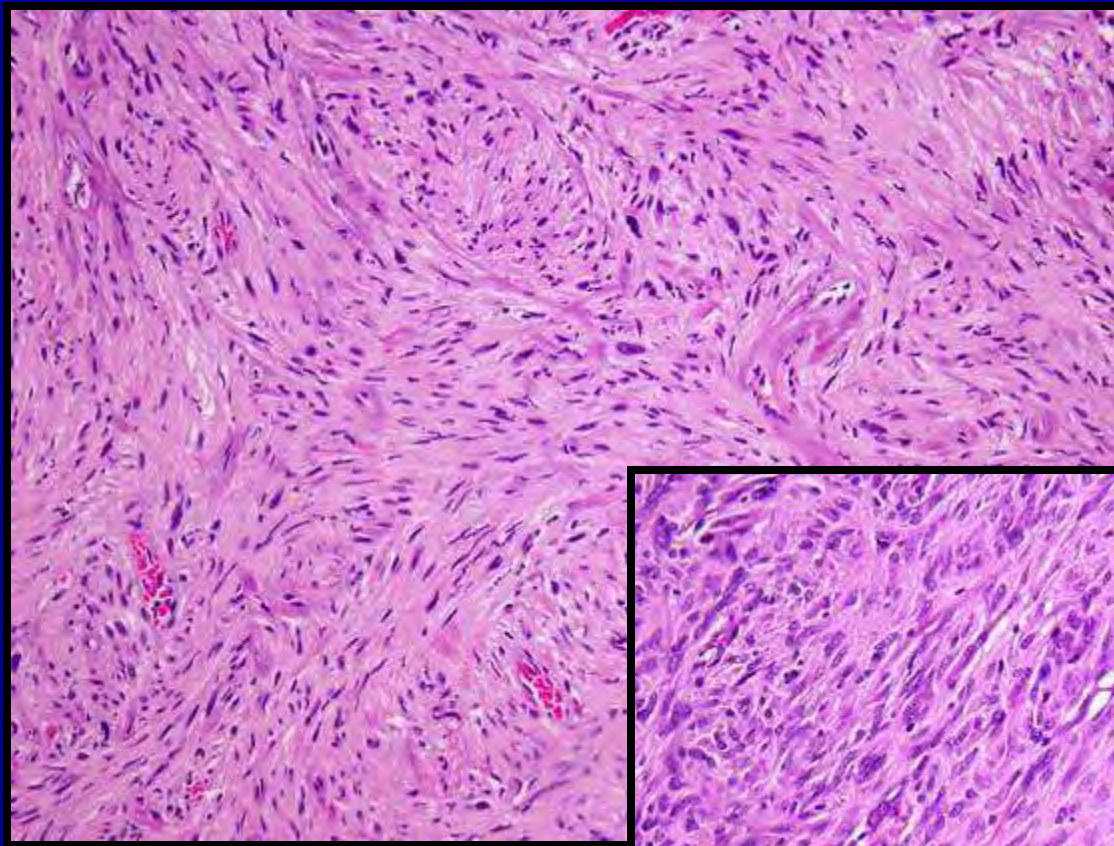
**SMA +ve (30-40%)**

**Desmin -ve**

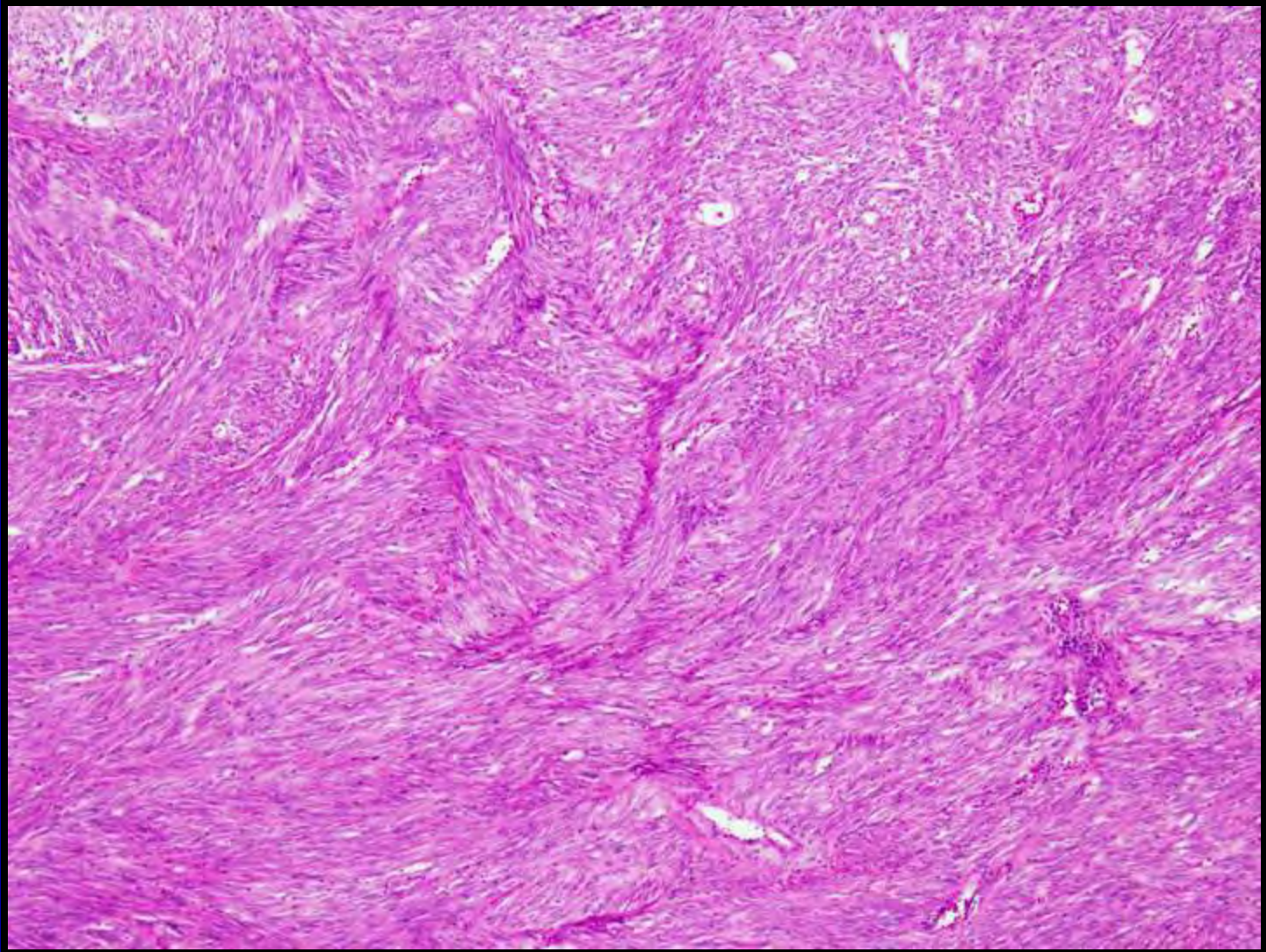
**S-100 protein -ve**

**Keratin -ve**

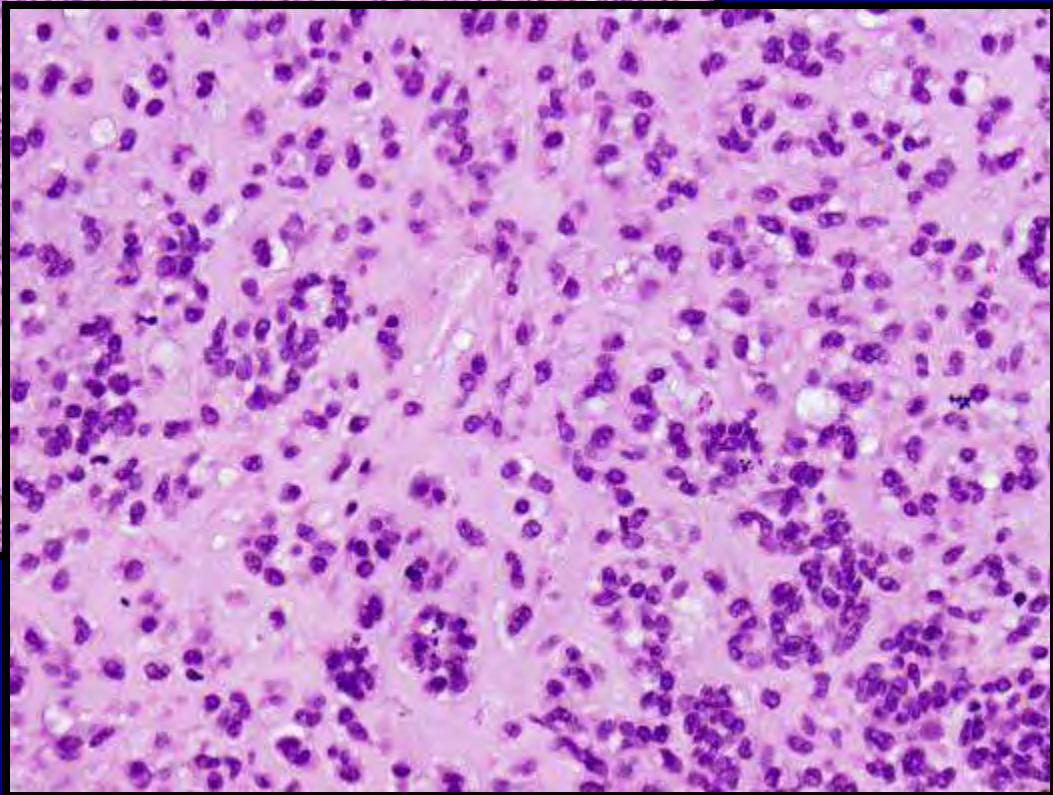
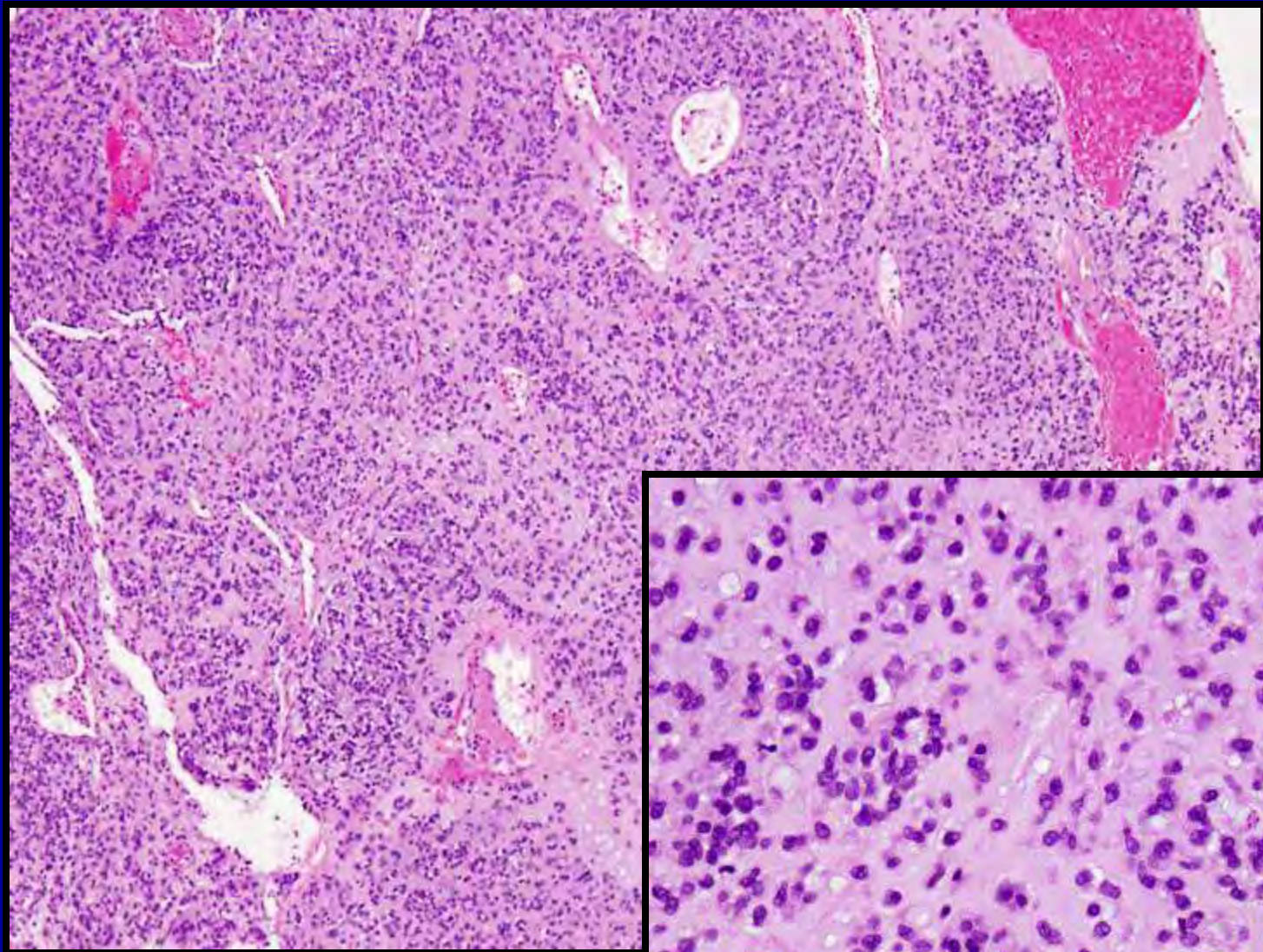
*The many faces of GIST.*



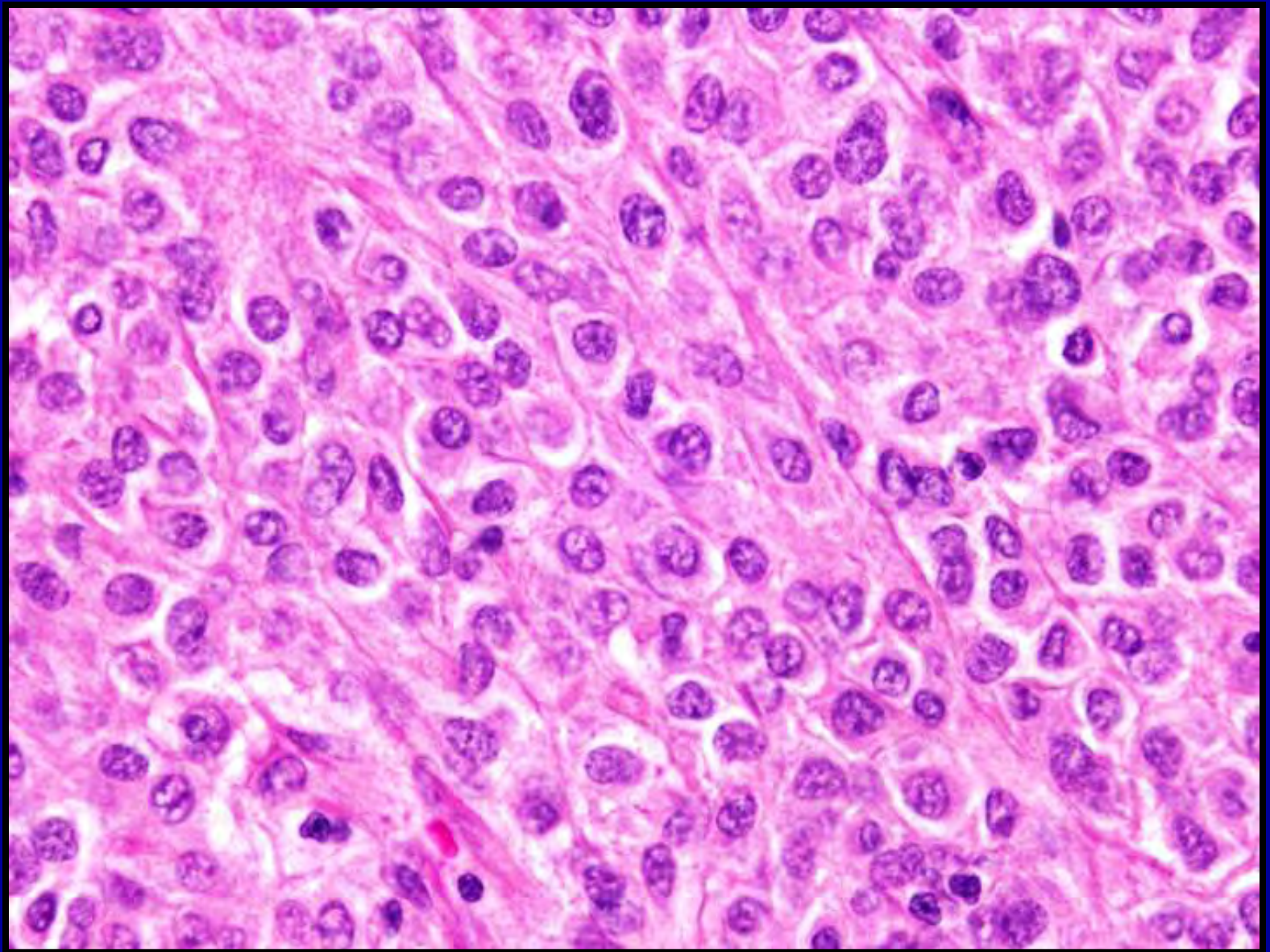




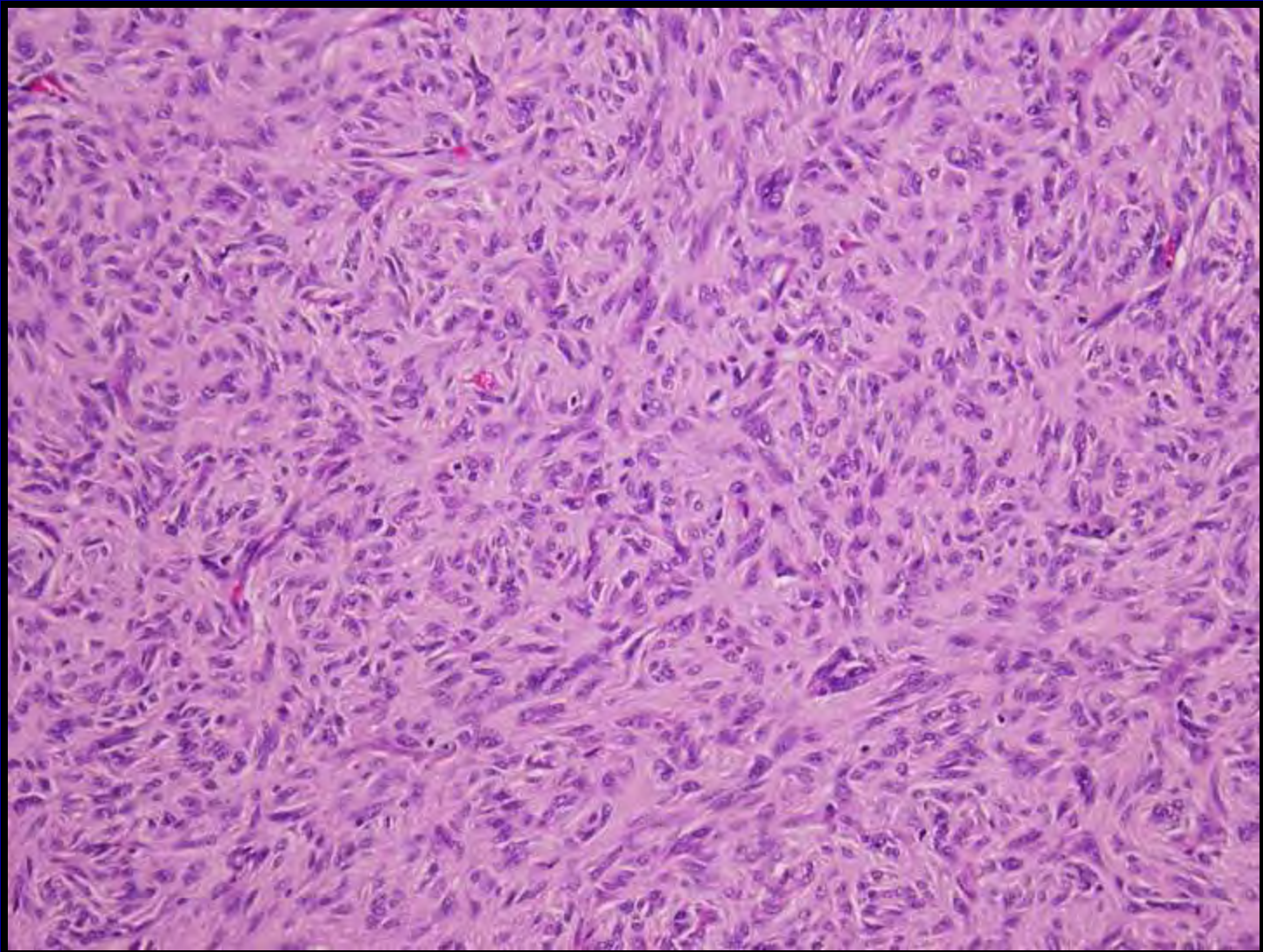




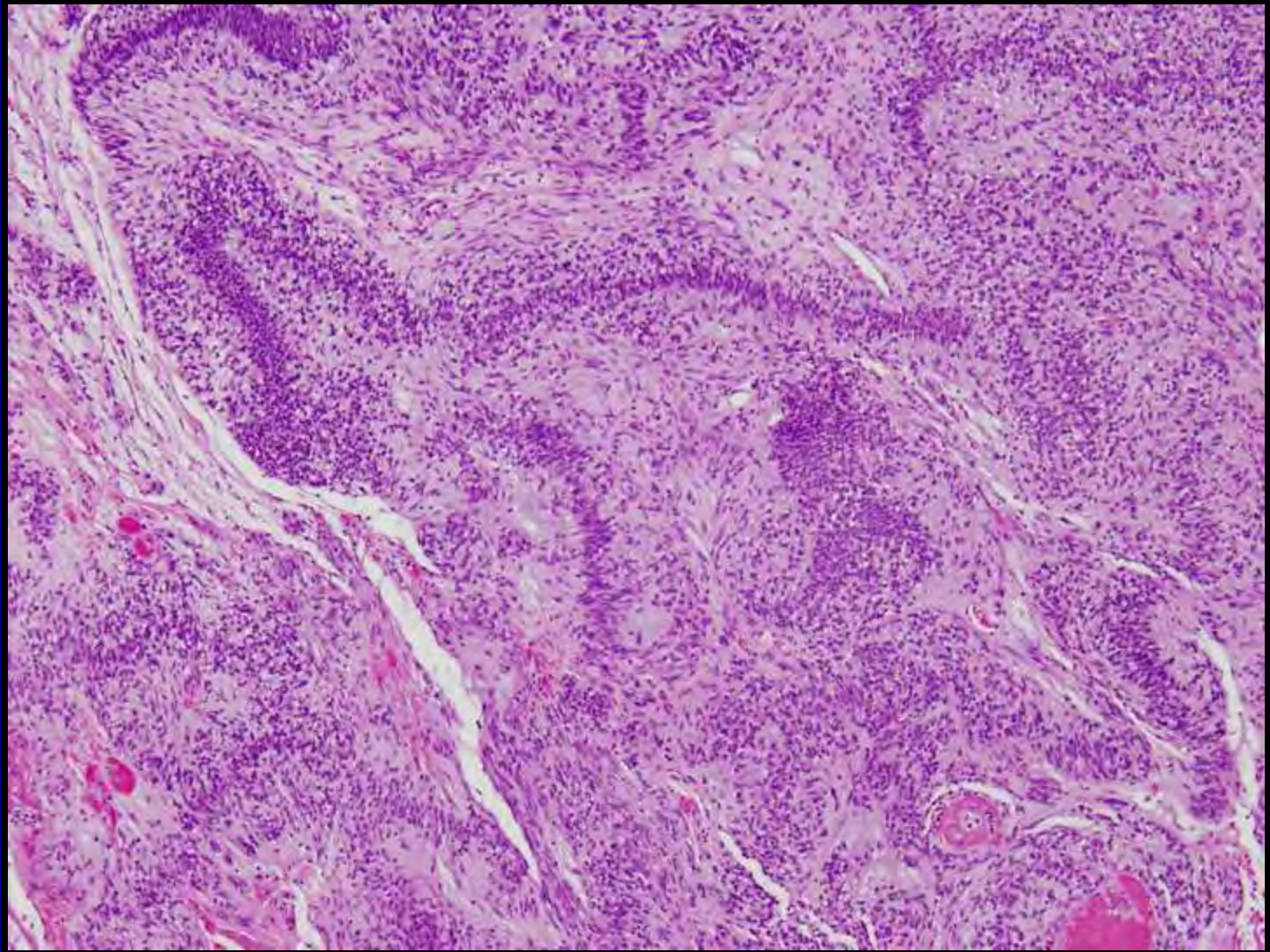




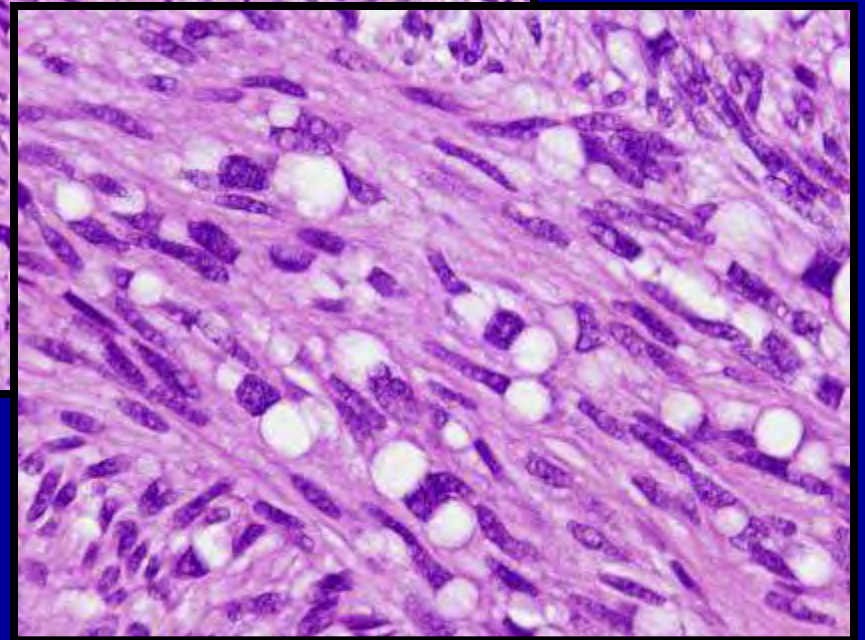
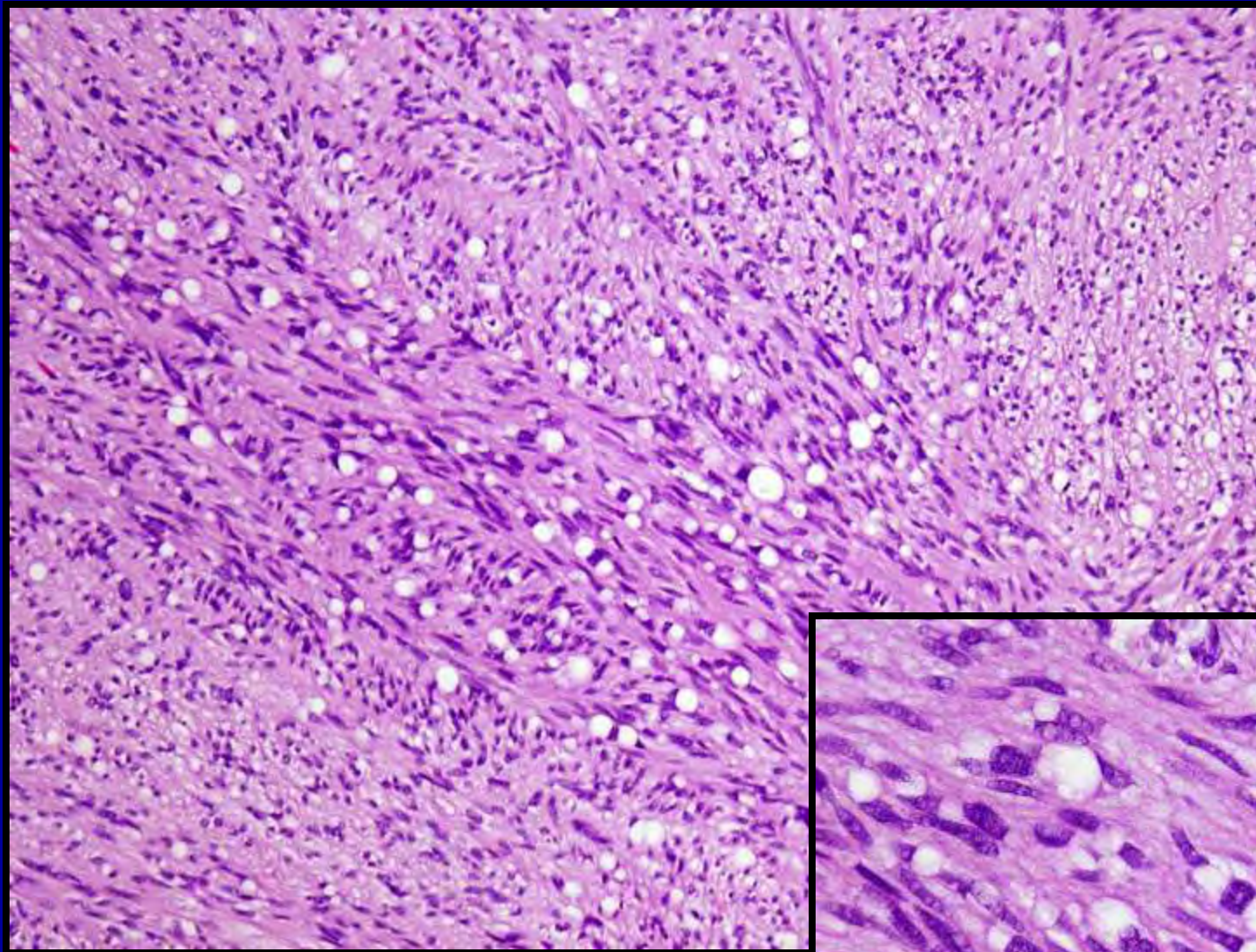




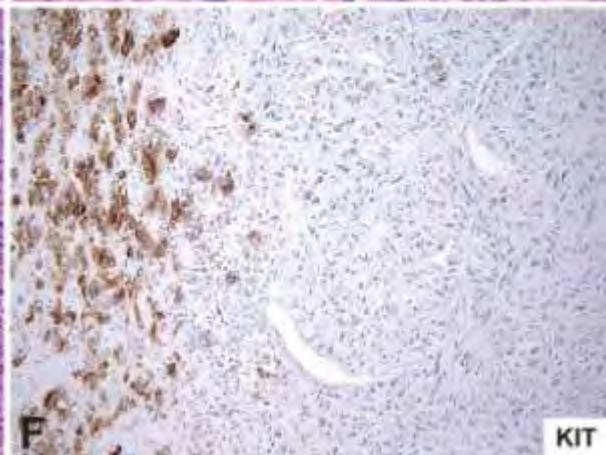
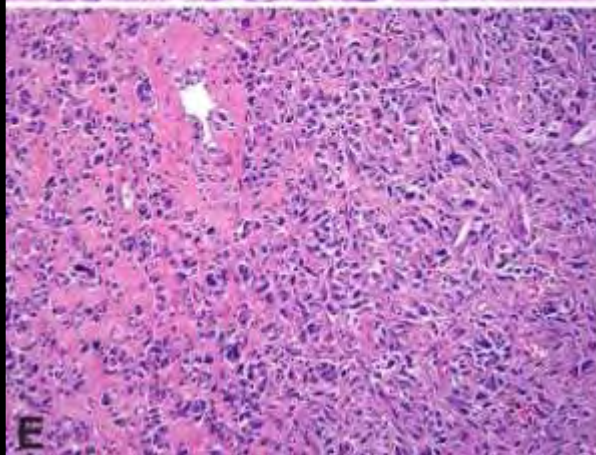
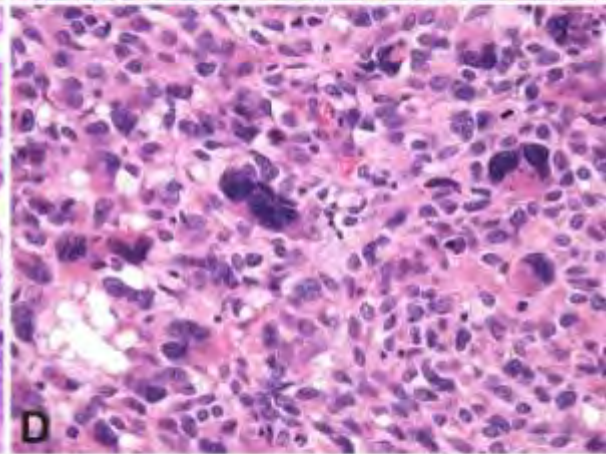
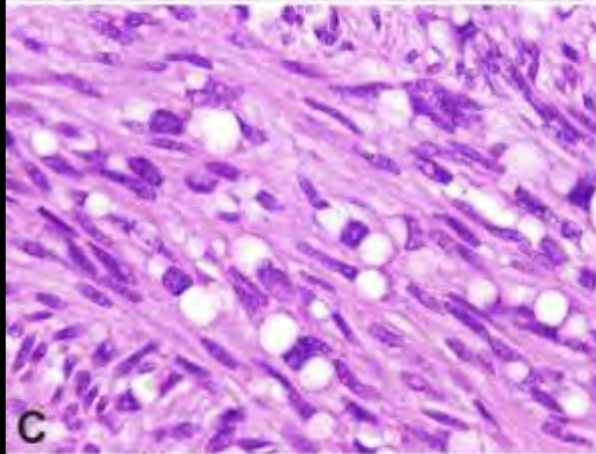
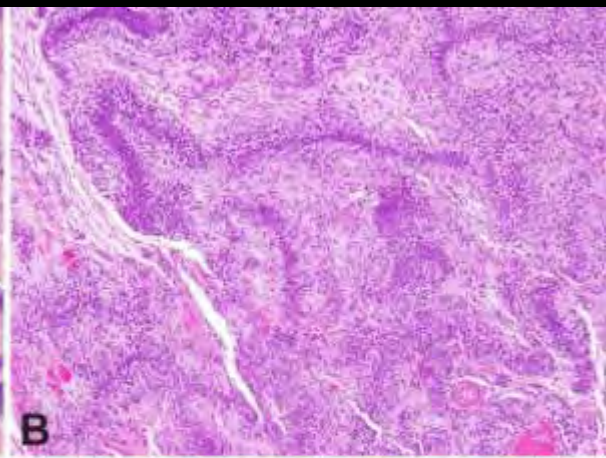
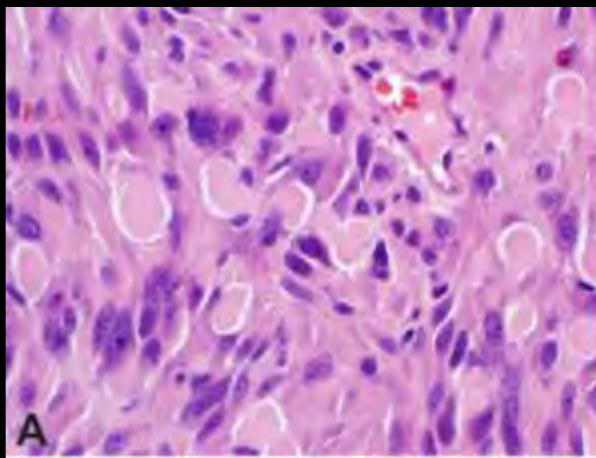




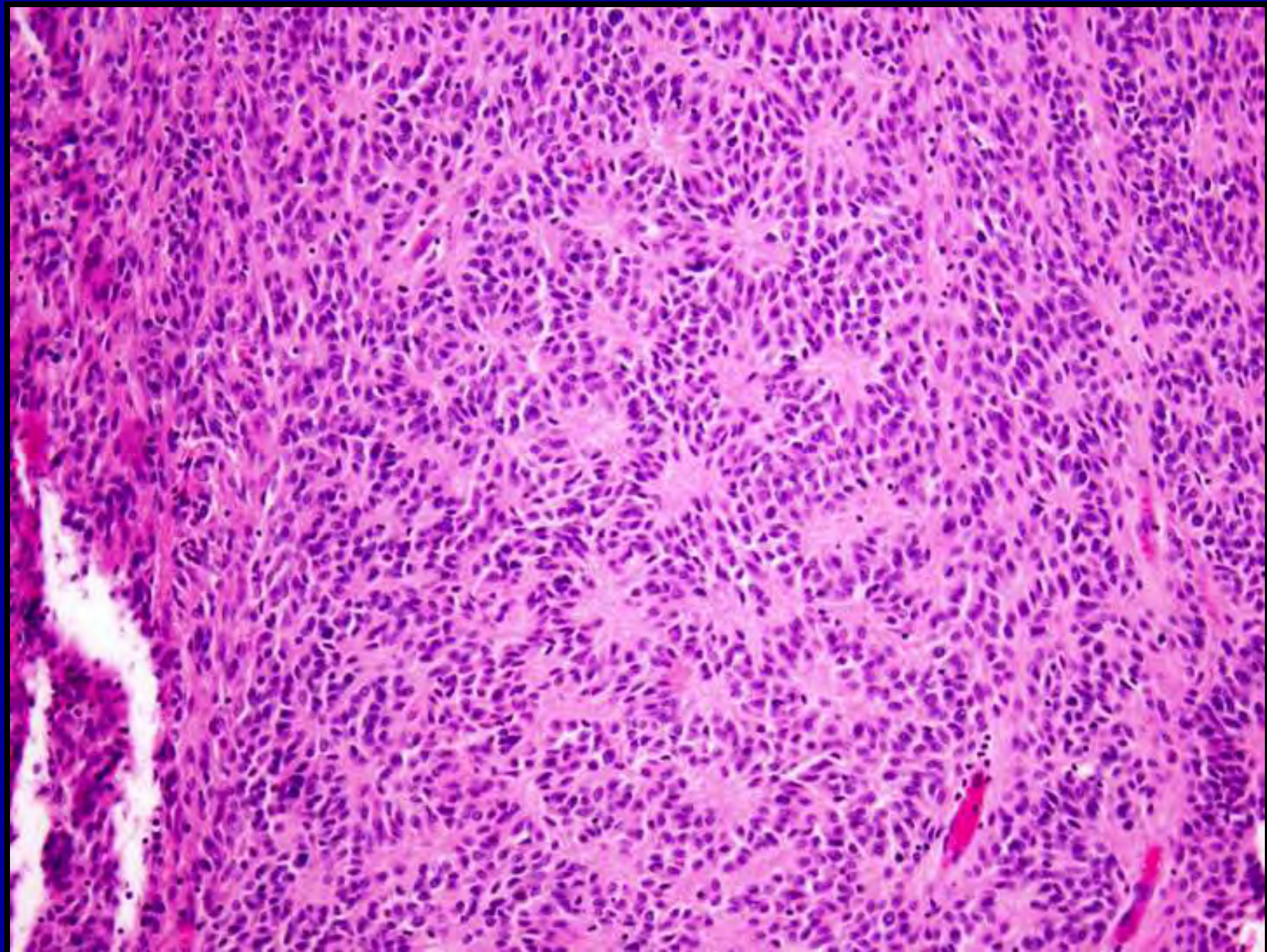




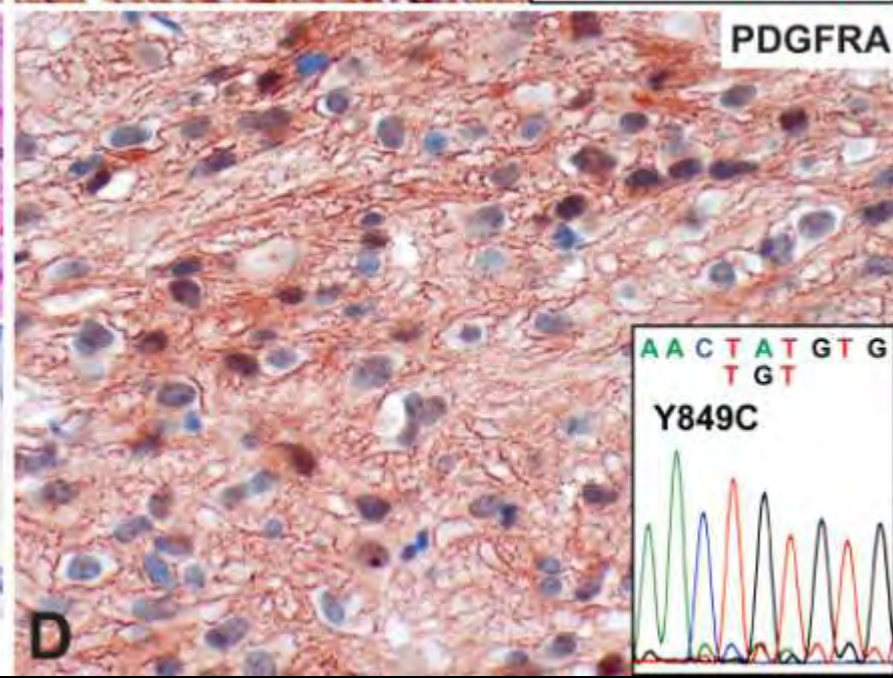
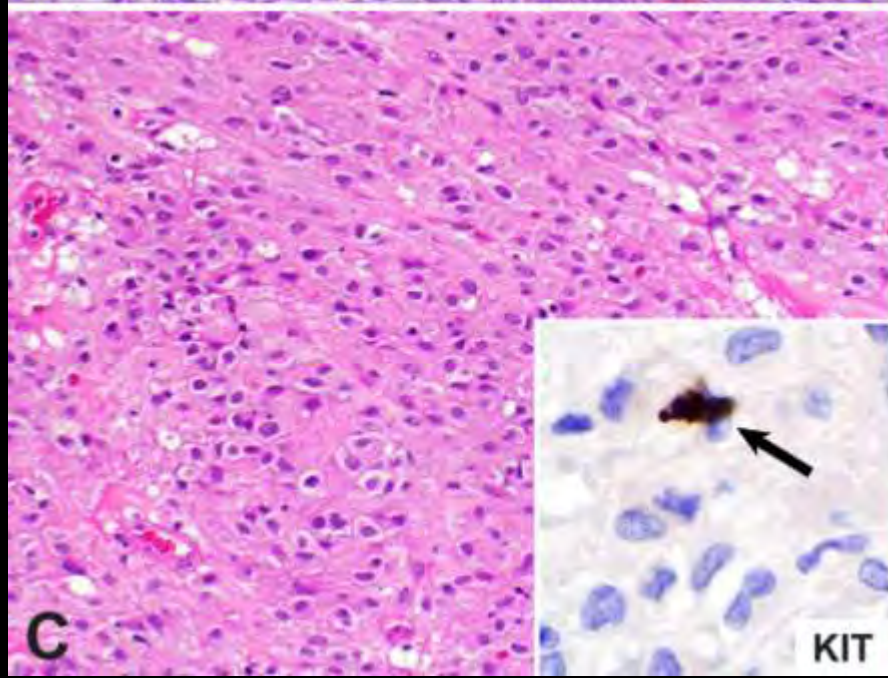
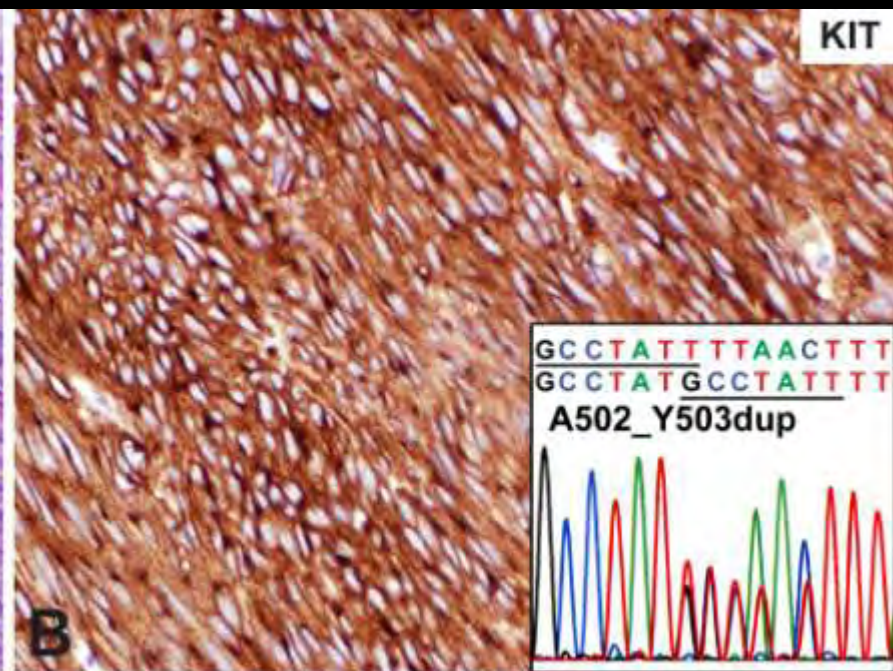
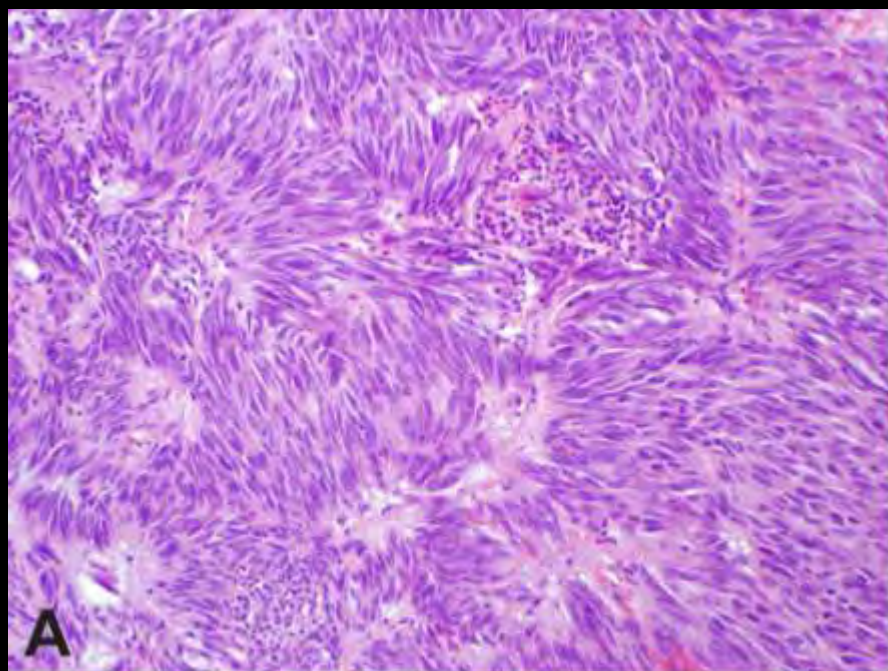




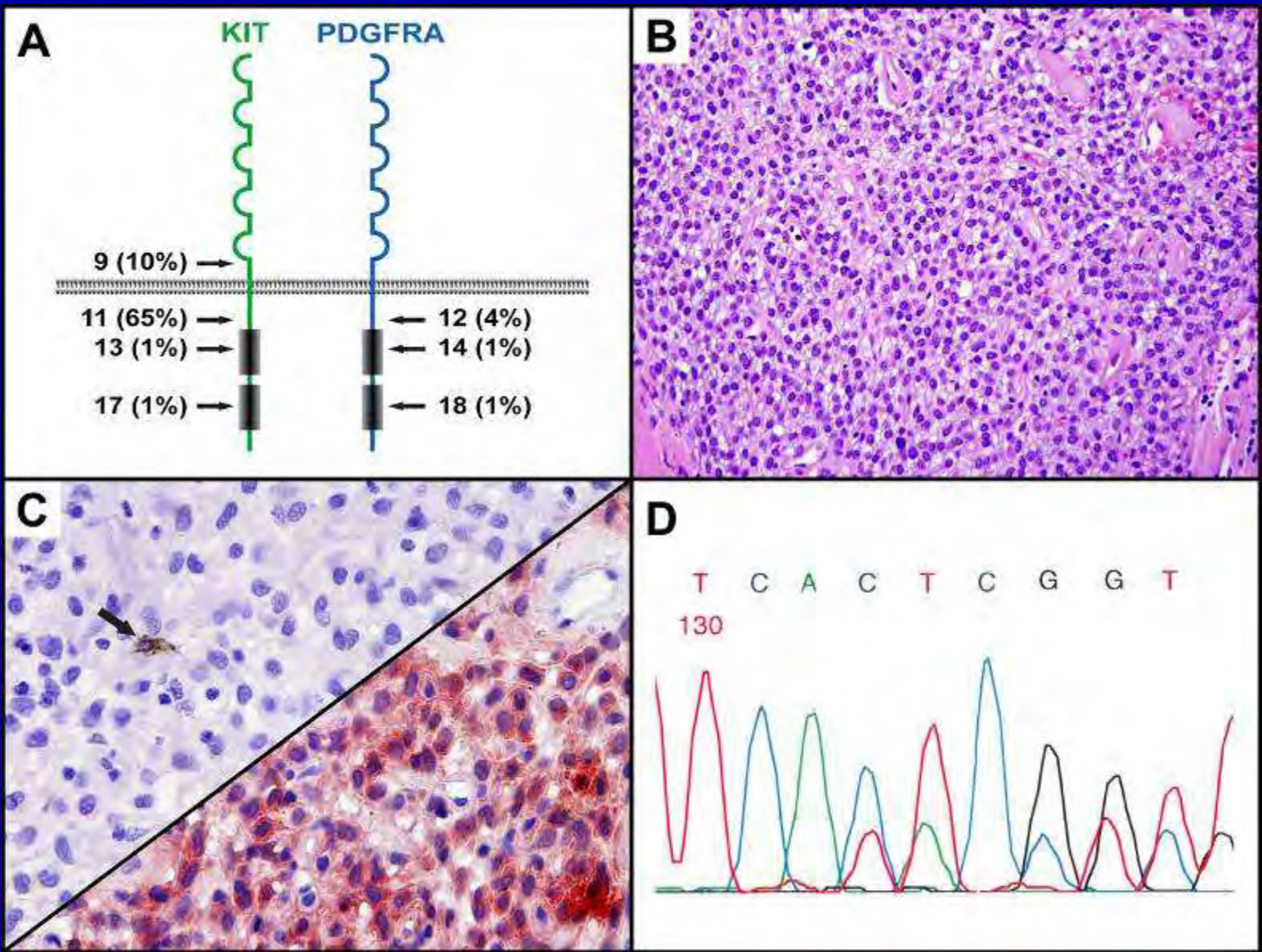




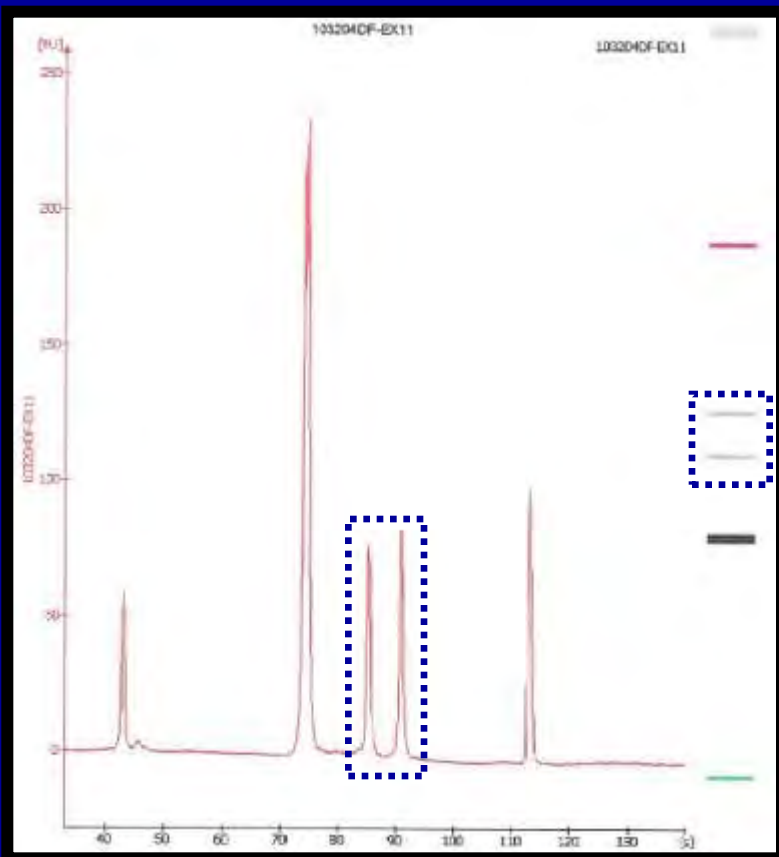






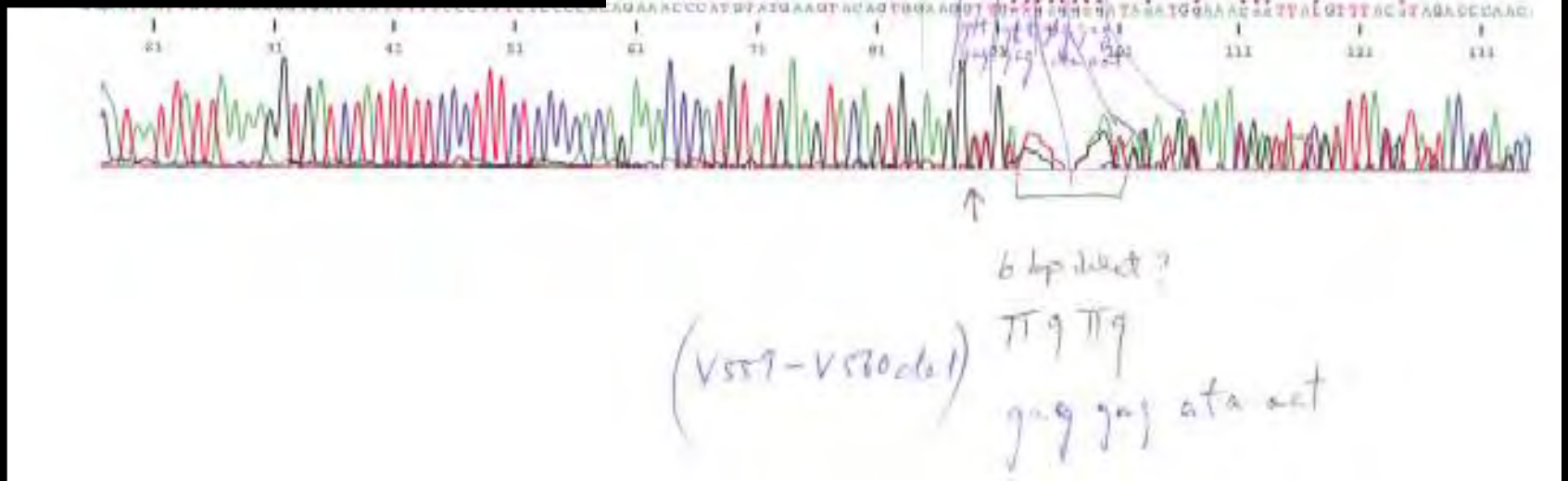






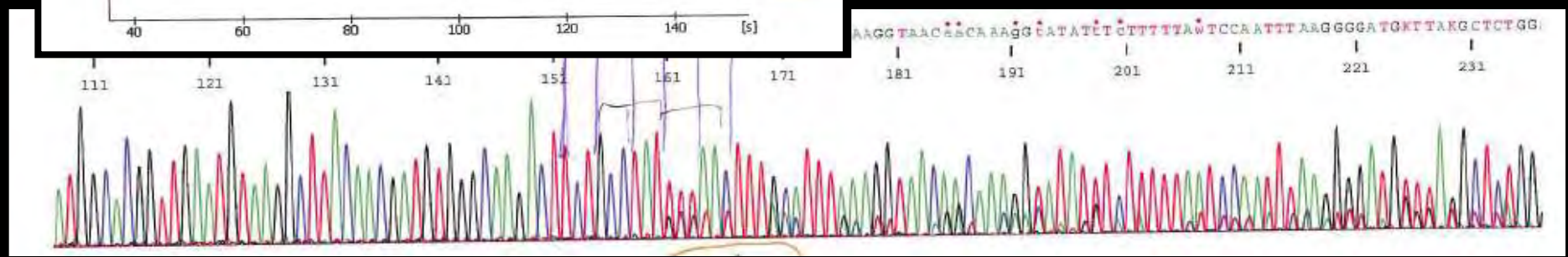
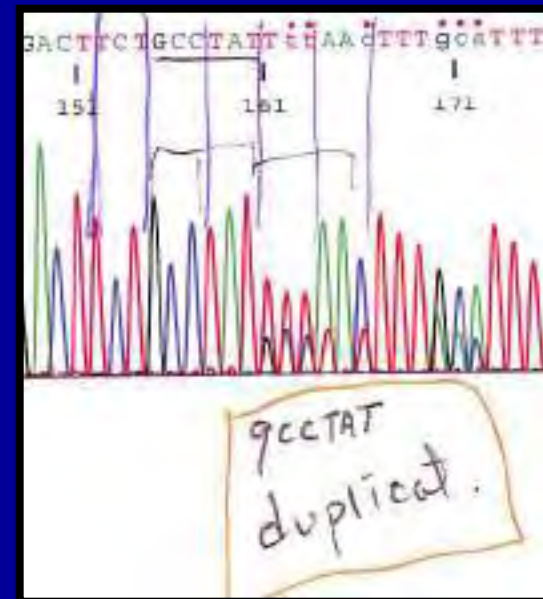
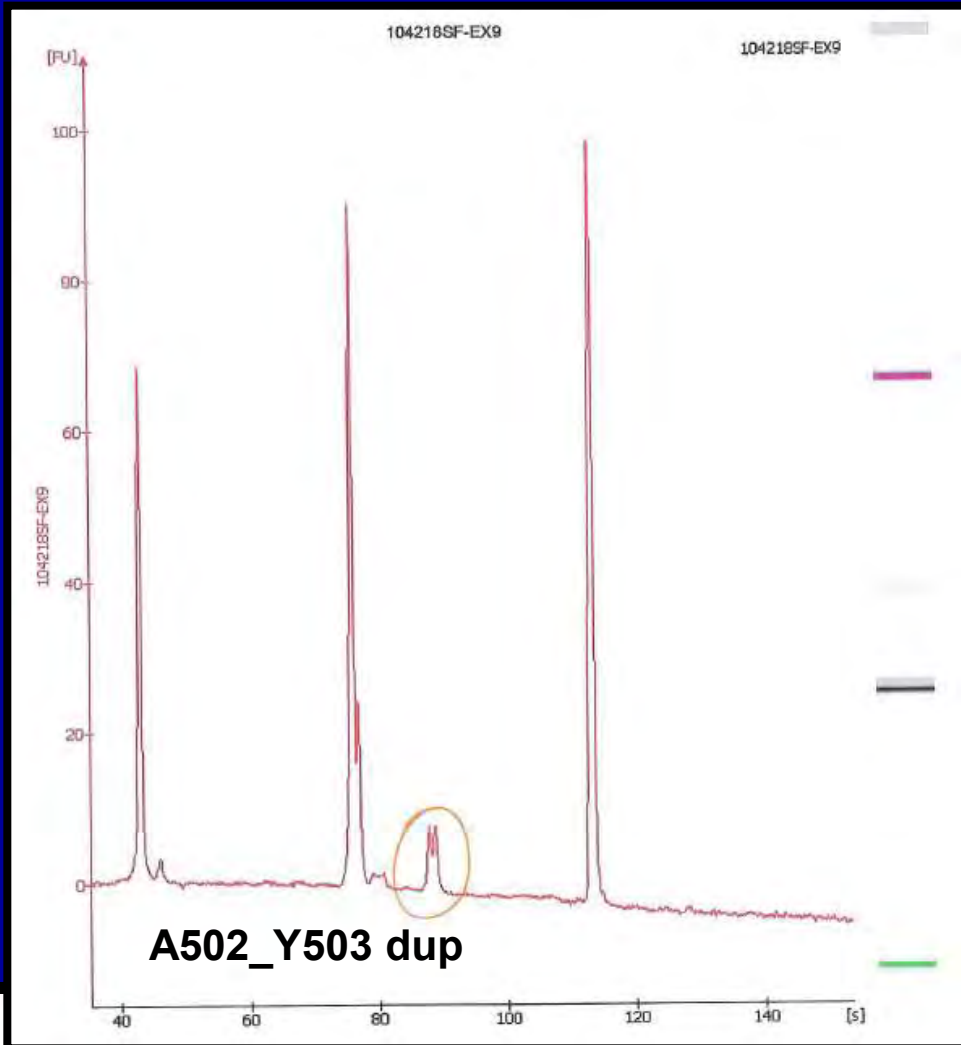
# Exon 11

## V559\_V560del

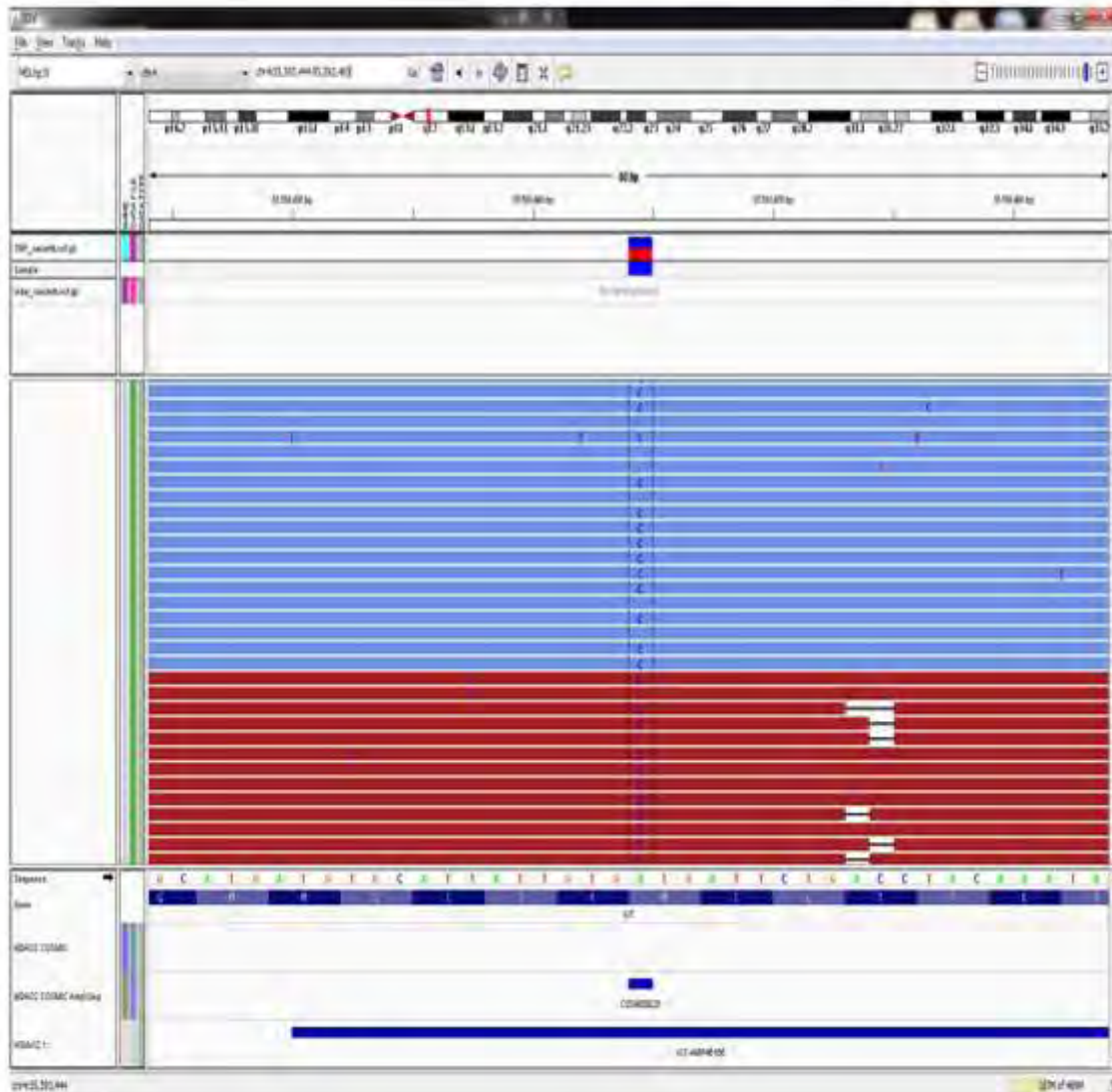


# Exon 9

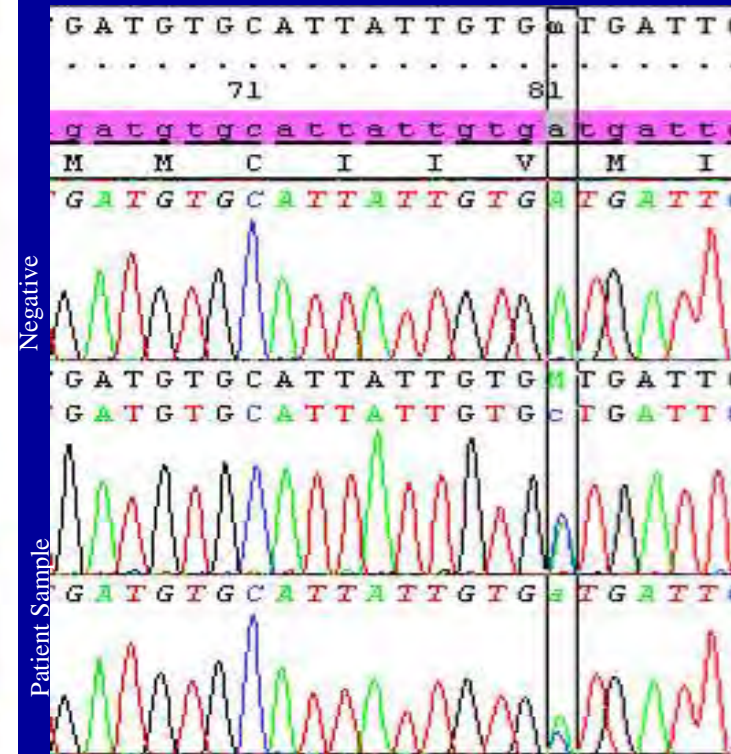
## A502\_Y503dup







Detection of SNV in KIT Exon 10, currently not covered by Sanger

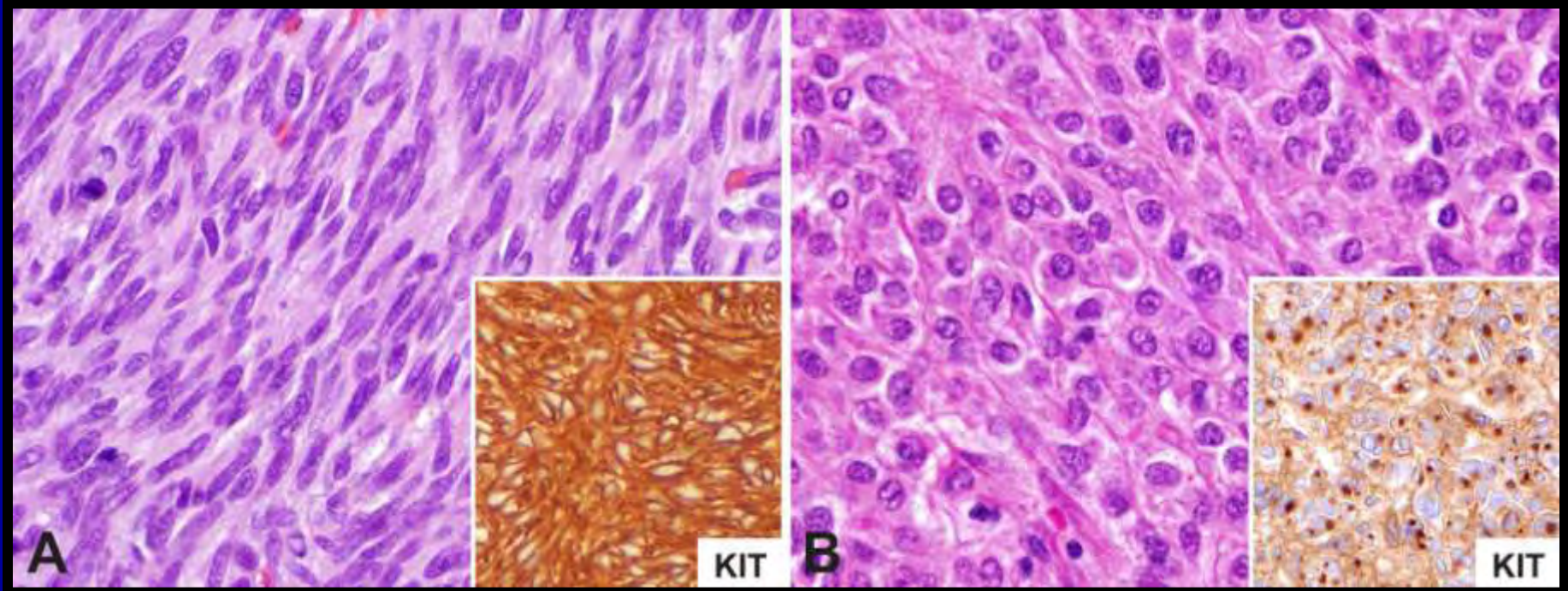


Confirmation by Sanger  
 ATG→CTG, M541L  
 KIT EXON 10

Chromosome	Position	Gene Symb	Ploidy	Ref	Variant	VarFreq	Coverage	RefCov	VarCov
chr4	5559346 4	KIT	Het	A	C	63.42	1077	389	683

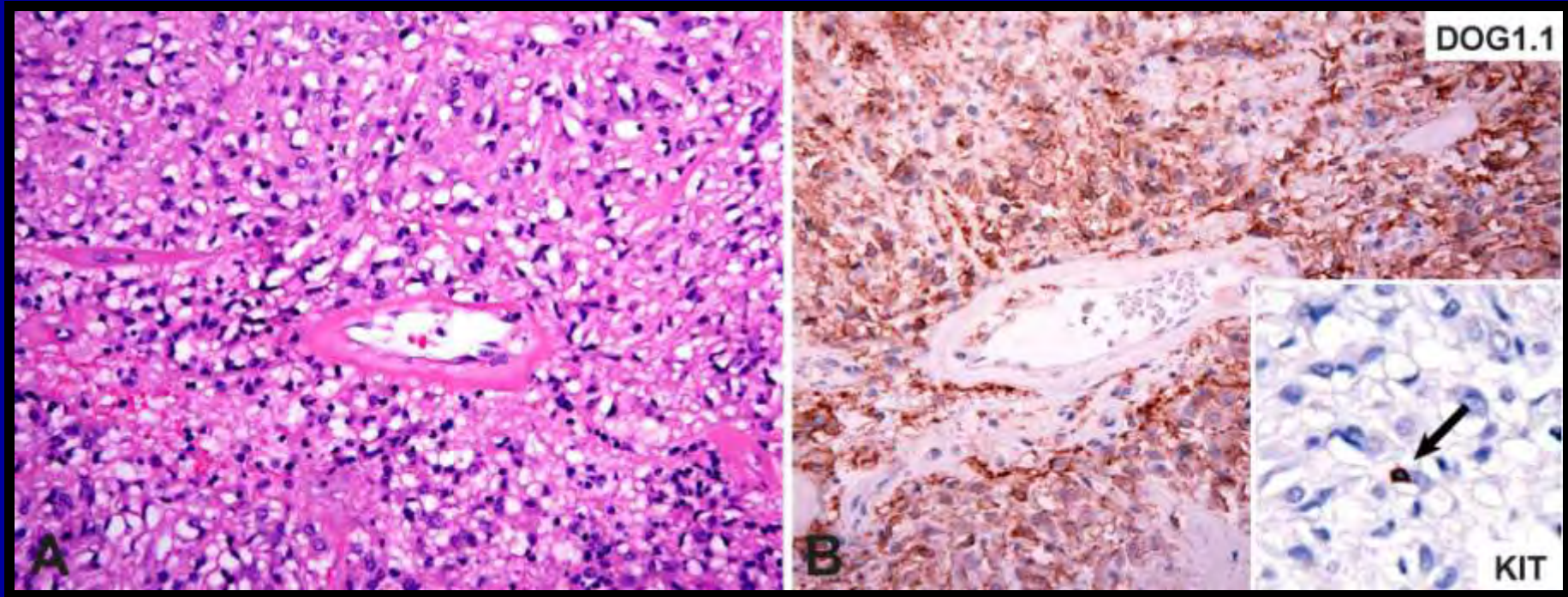
75% Tumor

# *KIT immunoreactivity in GIST*





# *KIT-negative GIST*



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

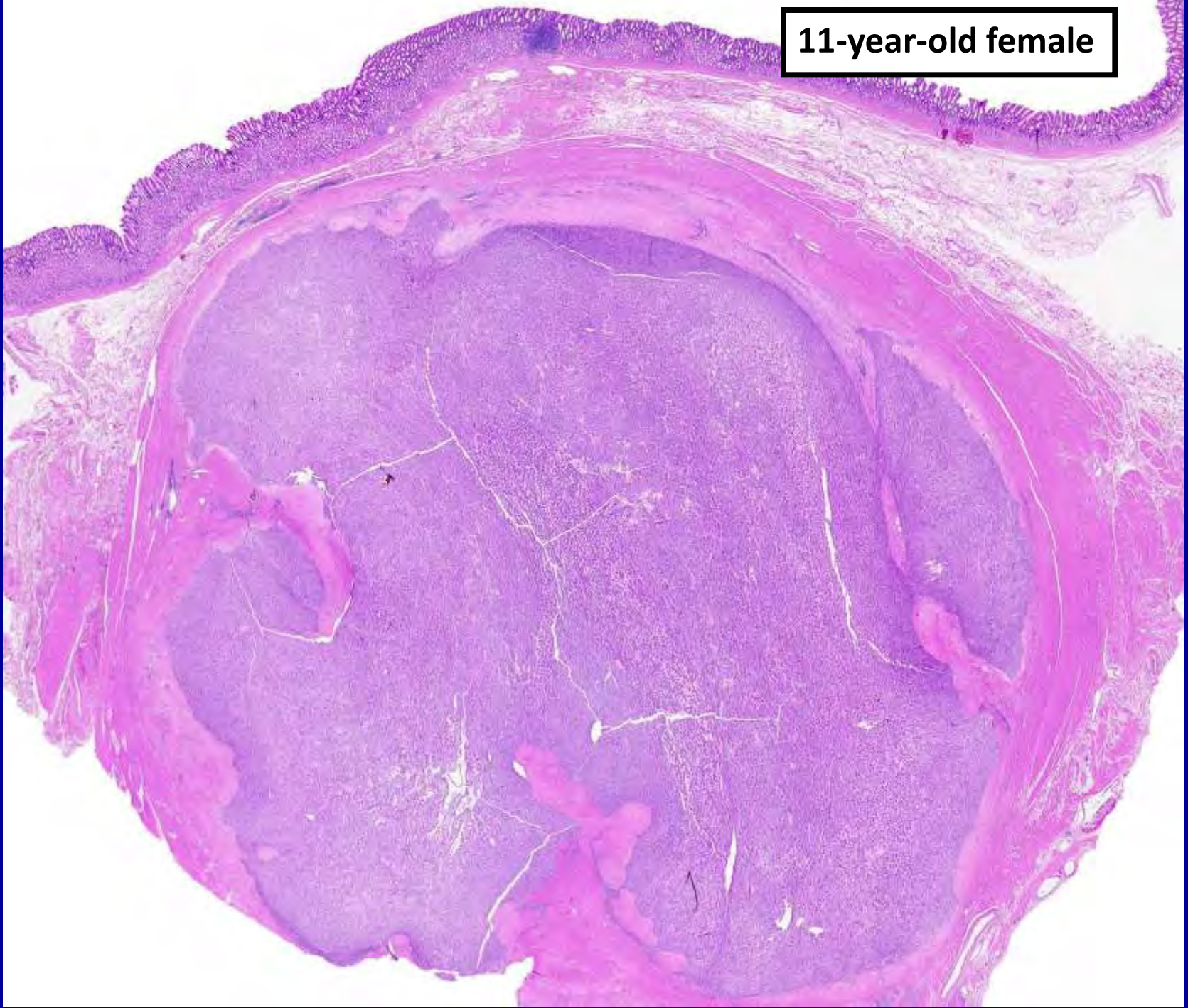
- Pediatric GISTs
  - Female predominance (peak 2<sup>nd</sup> decade)
  - Indolent, but late metastases common
  - Molecular genetic basis unknown
- Carney Triad
  - Gastric GIST, pulmonary chondroma, paraganglioma
  - Molecular genetic basis unknown
- Carney-Stratakis Syndrome
  - Gastric GIST and 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**

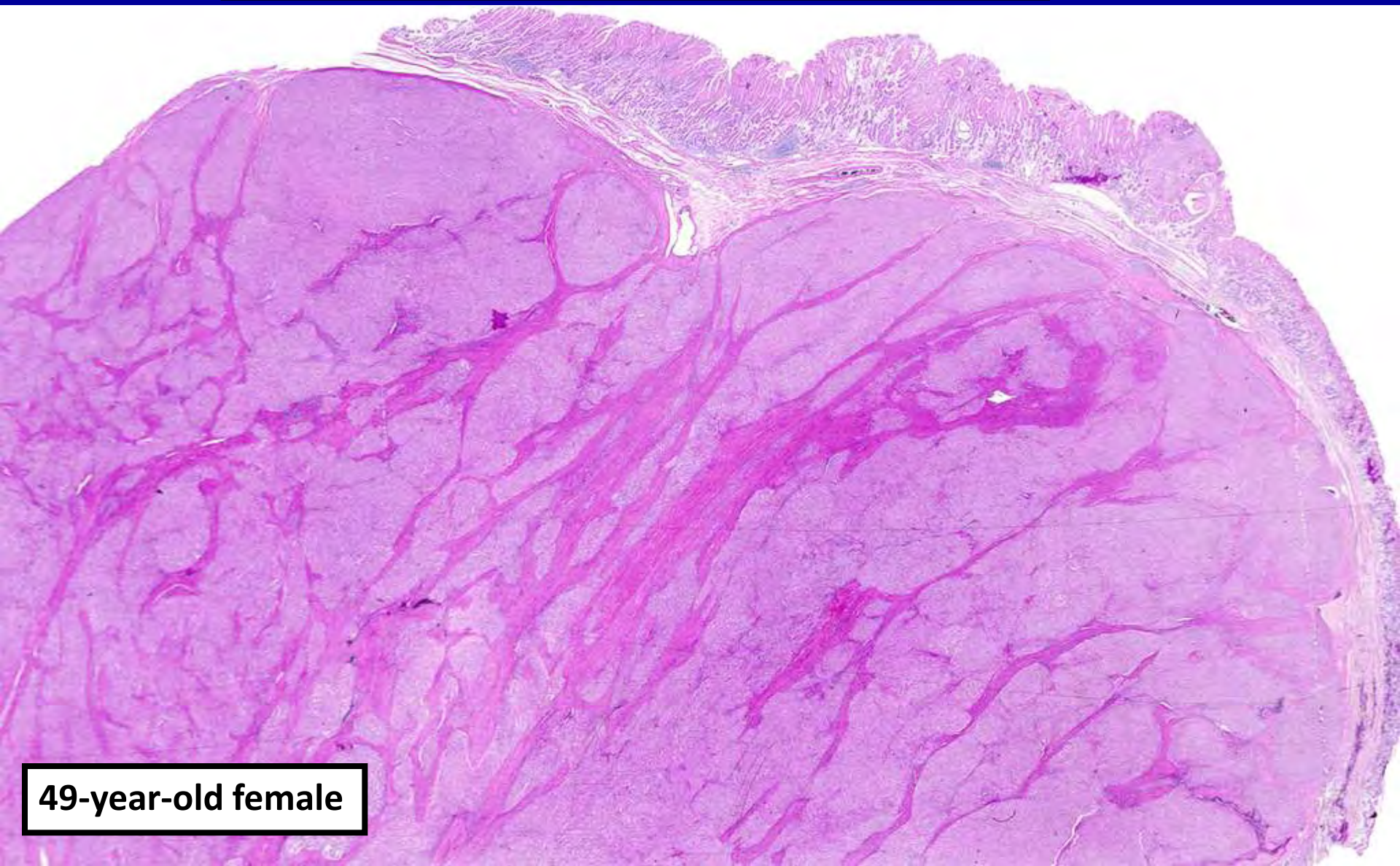
11-year-old female



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

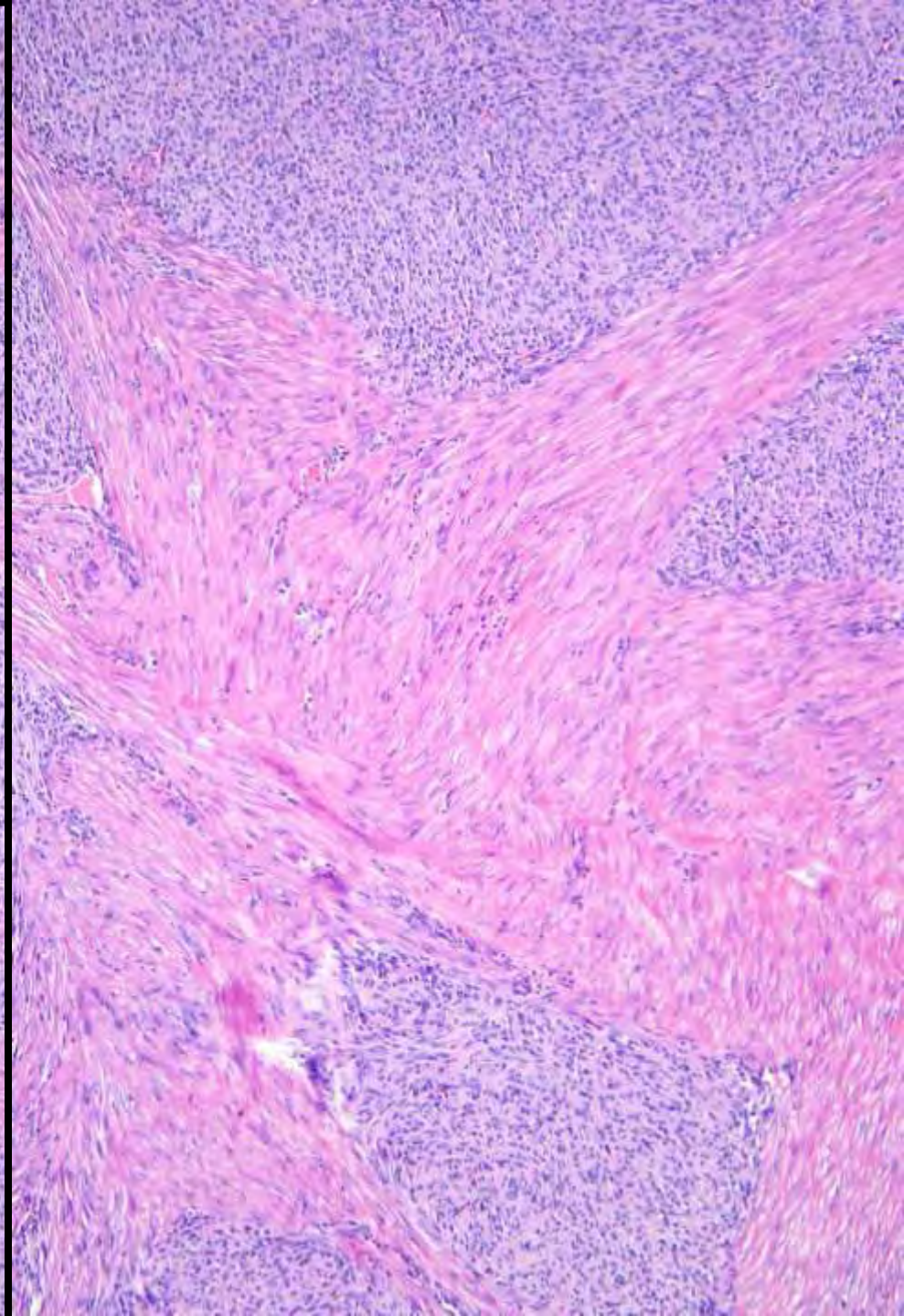
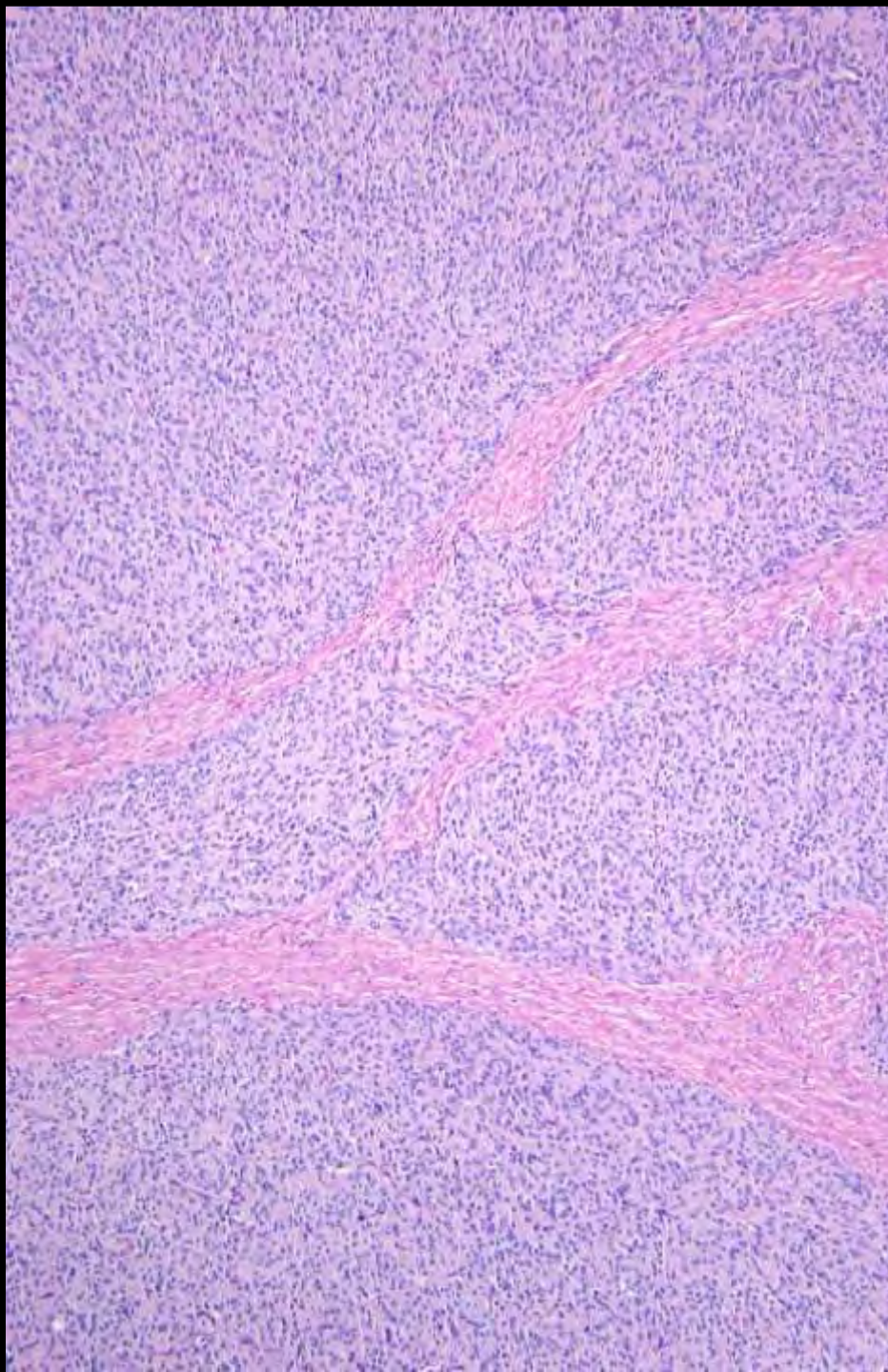


# Pediatric-type GIST in an Adult

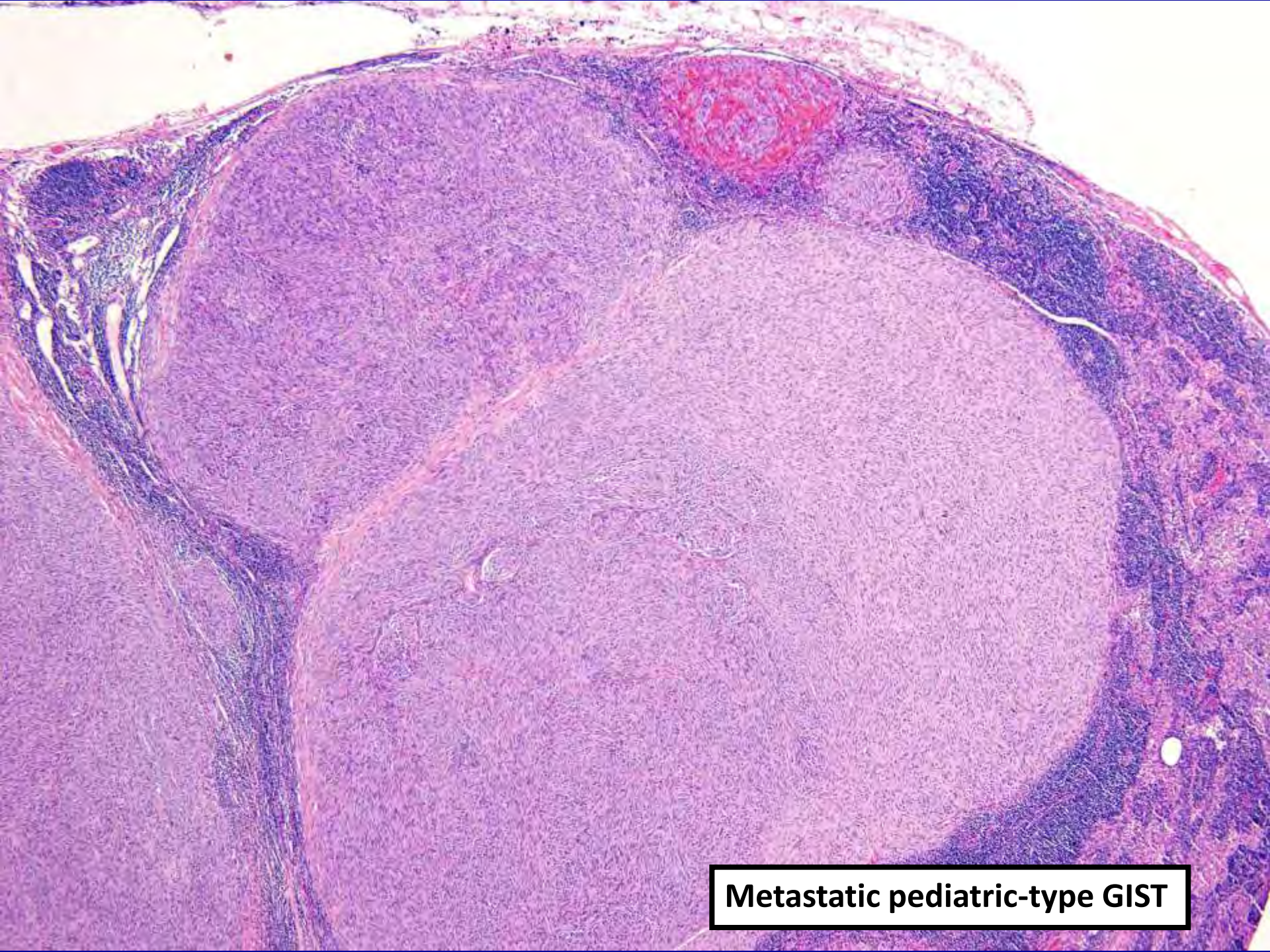


49-year-old female





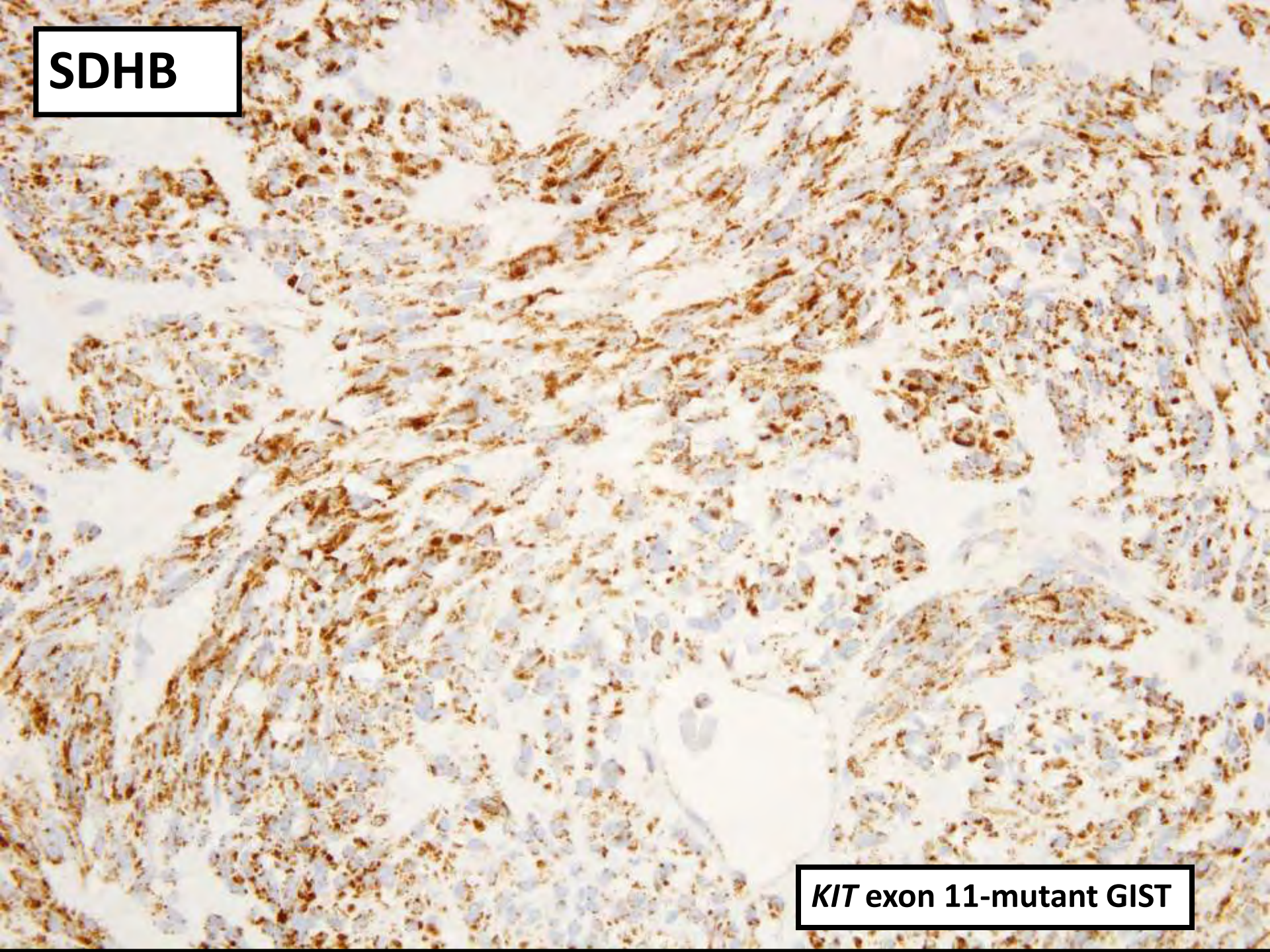




**Metastatic pediatric-type GIST**



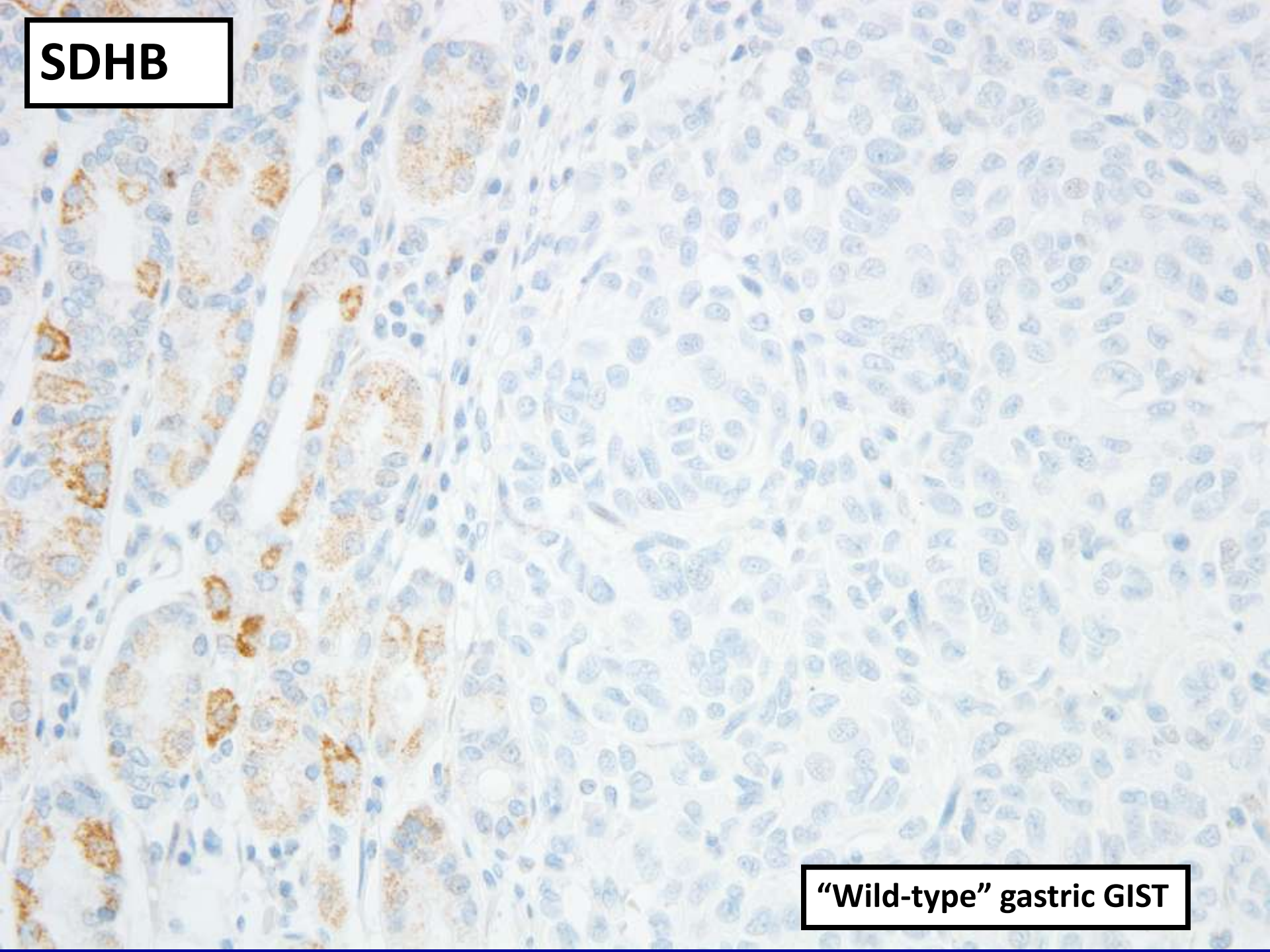
**SDHB**



***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

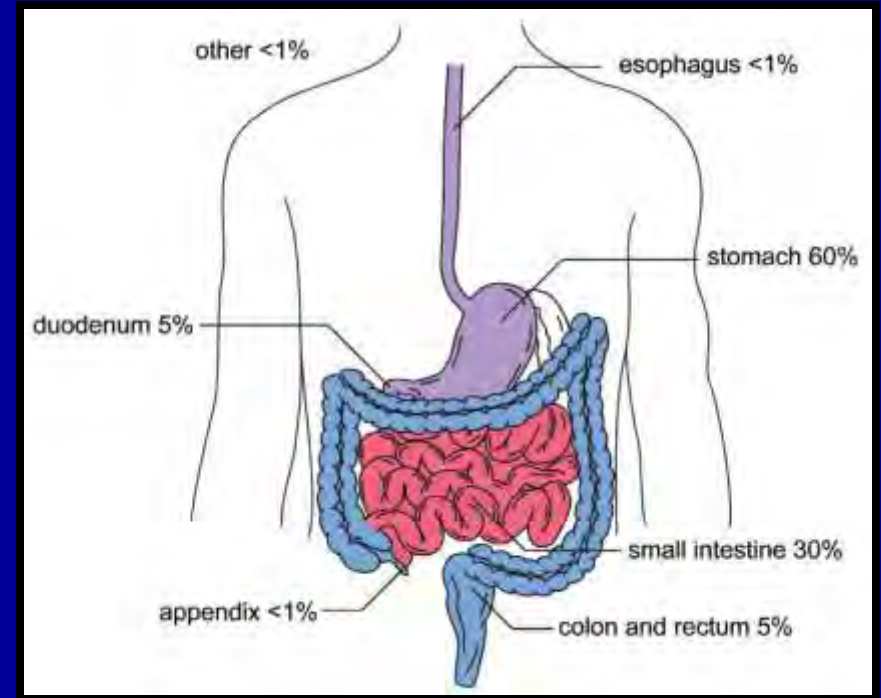
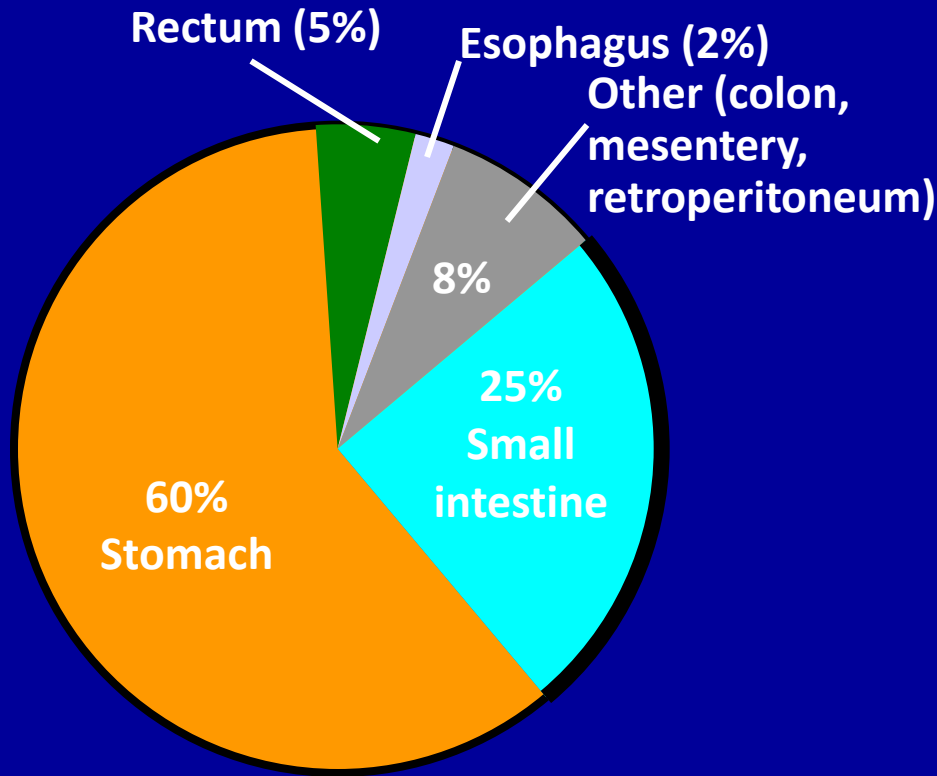
**Problem** – Small GISTs without mitoses  
can metastasize!

# NIH Consensus Risk Assessment

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



# GIST: Sites of Involvement



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

# 2007/2010 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%)

\*\*\* 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





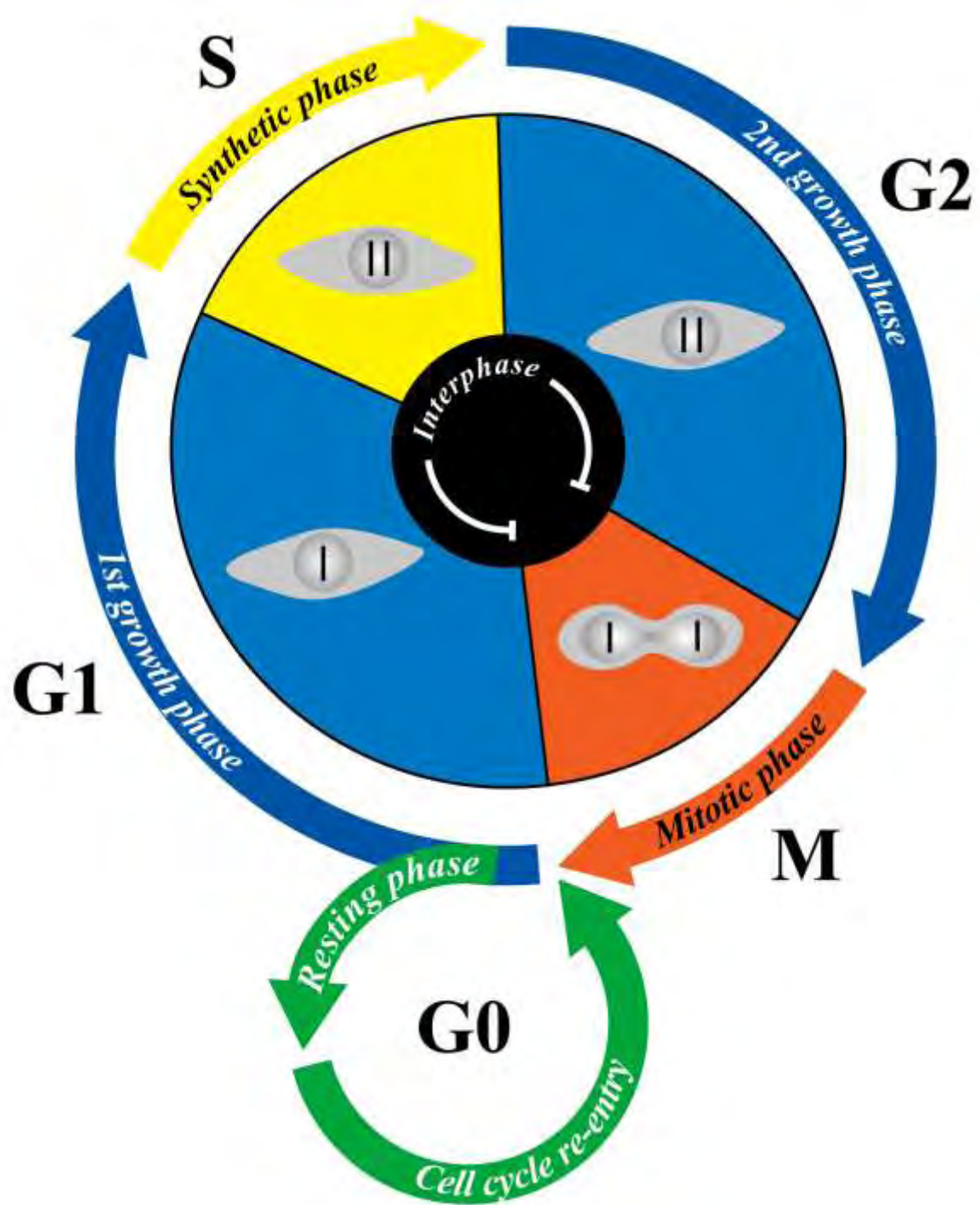


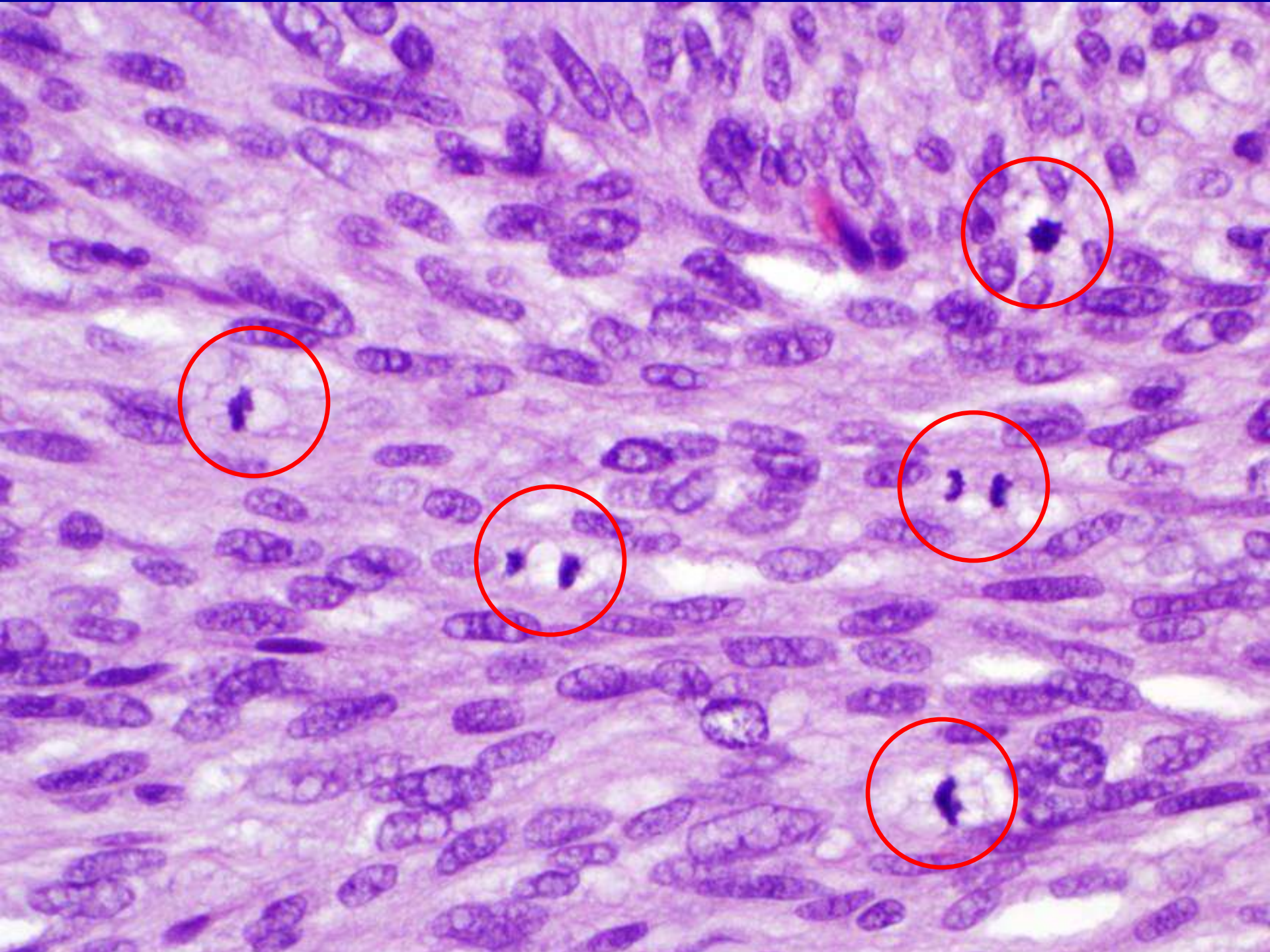
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≤ 5 per 50 hpf	> 5 ≤ 10 cm	Low (3.6%)	(Insuff. data)	Moderate (24%)	(Insuff. data)
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\*\*\* Modified from Miettinen & Lasota, *Semin Diagn Pathol*, 2006 by Dr. Chris Corless, OHSU  
 Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST



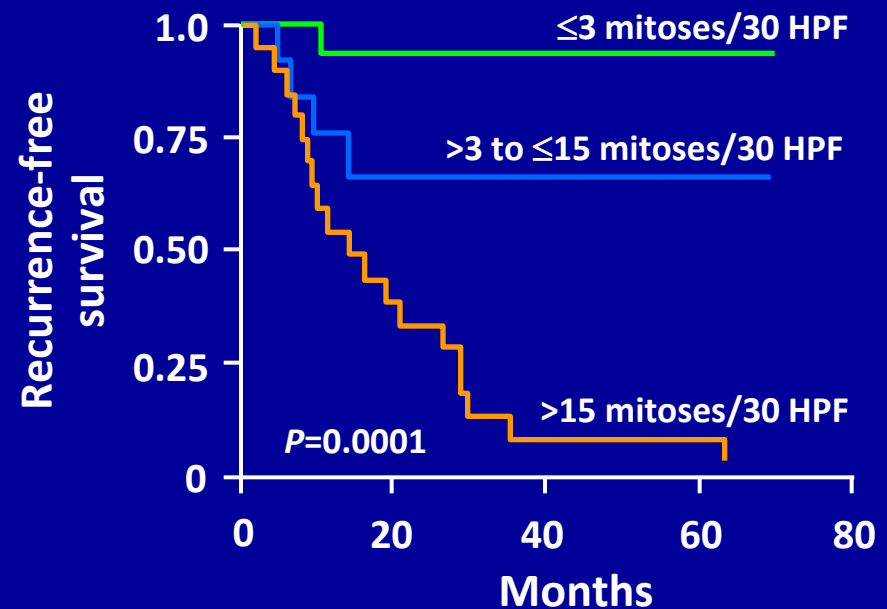
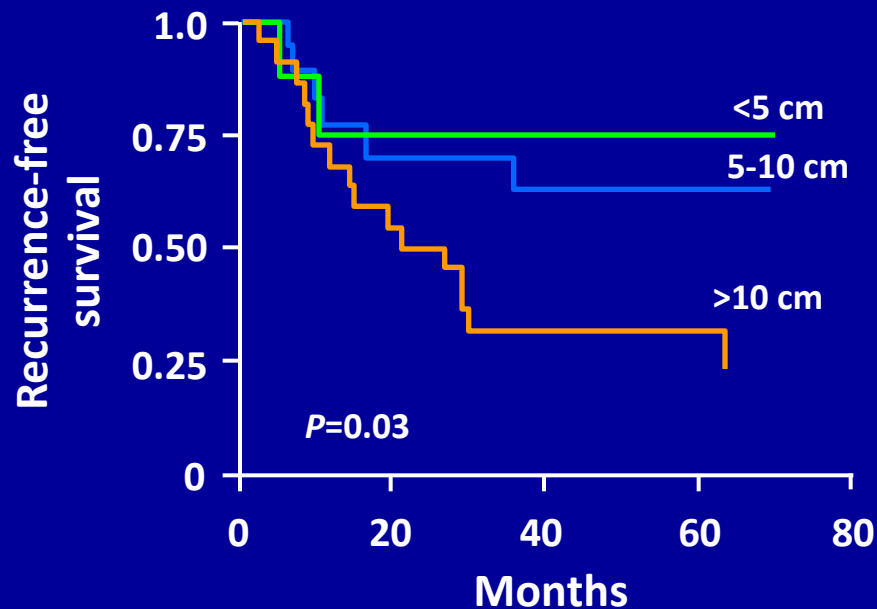






# GIST - Recurrence-Free Survival Following Surgical Treatment of Primary GIST

- 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

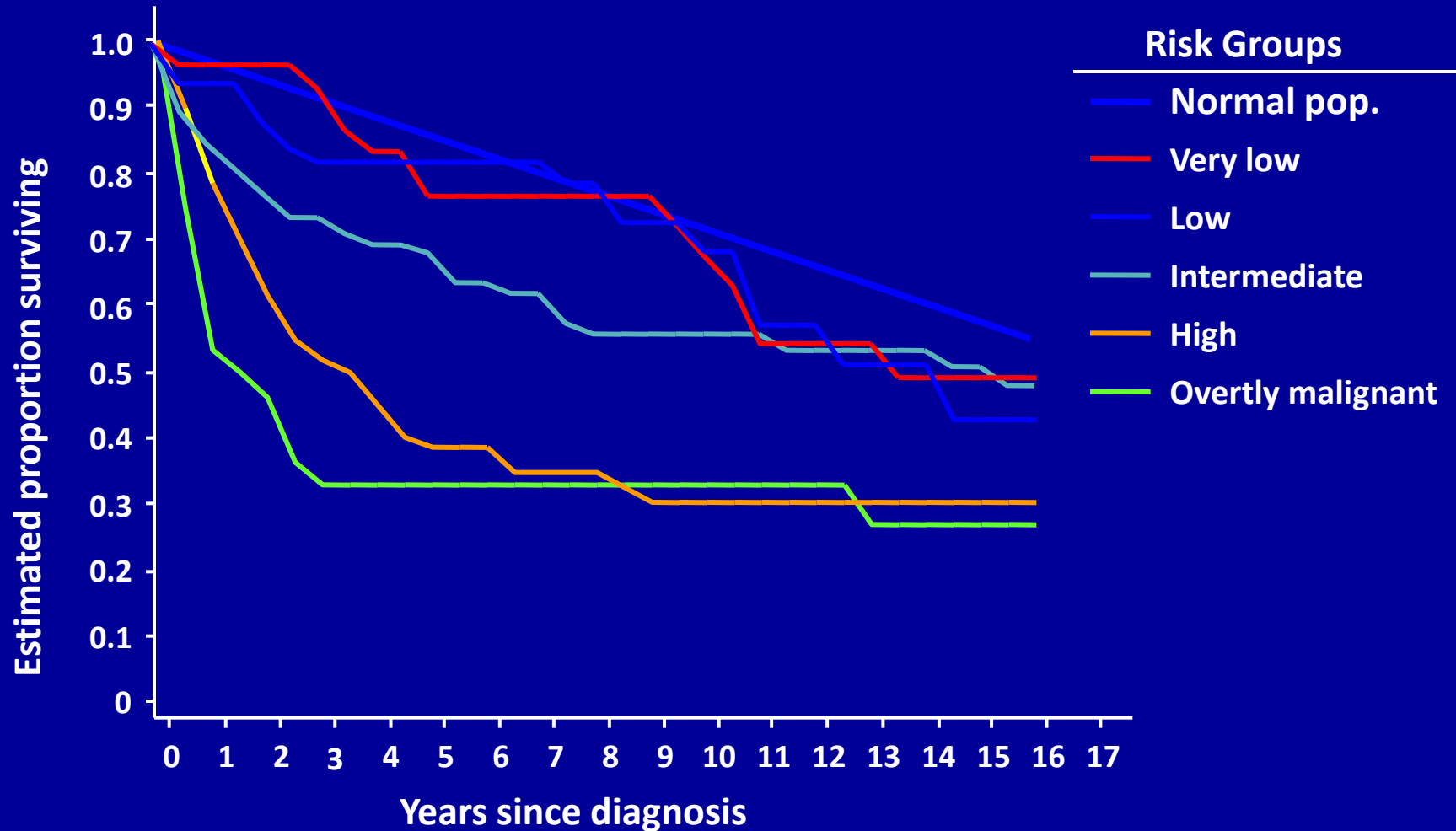
Grade 3 : 6-8

- 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



# *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:**

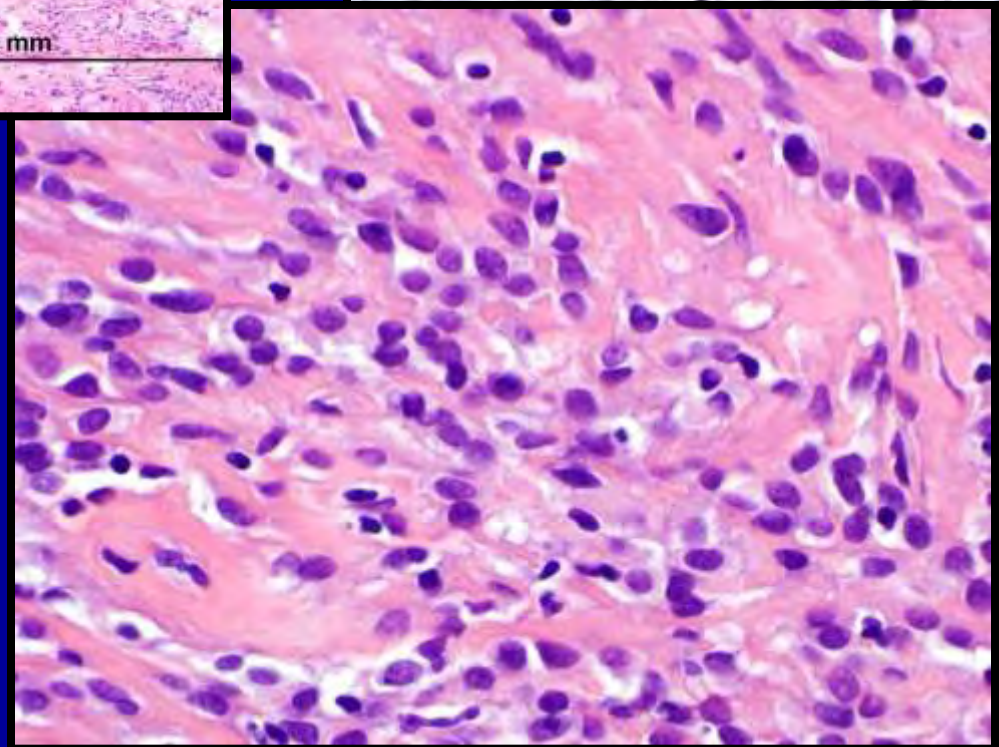
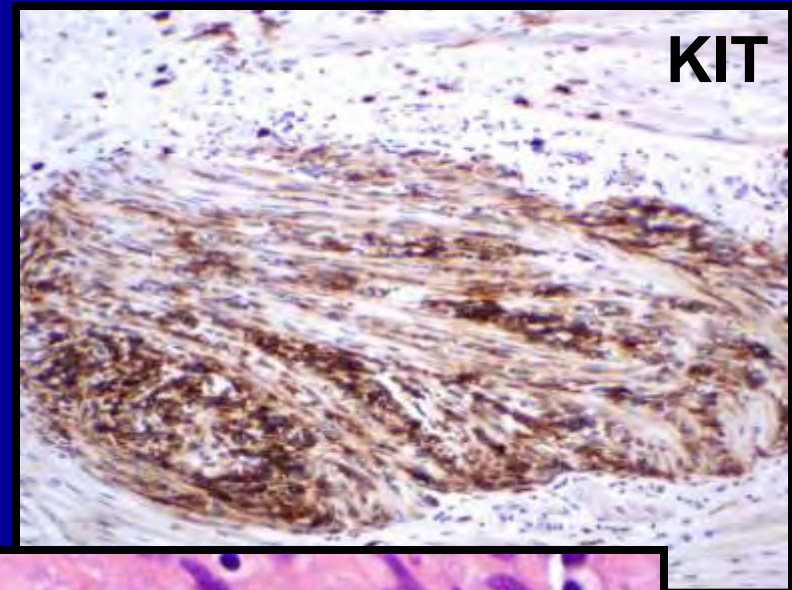
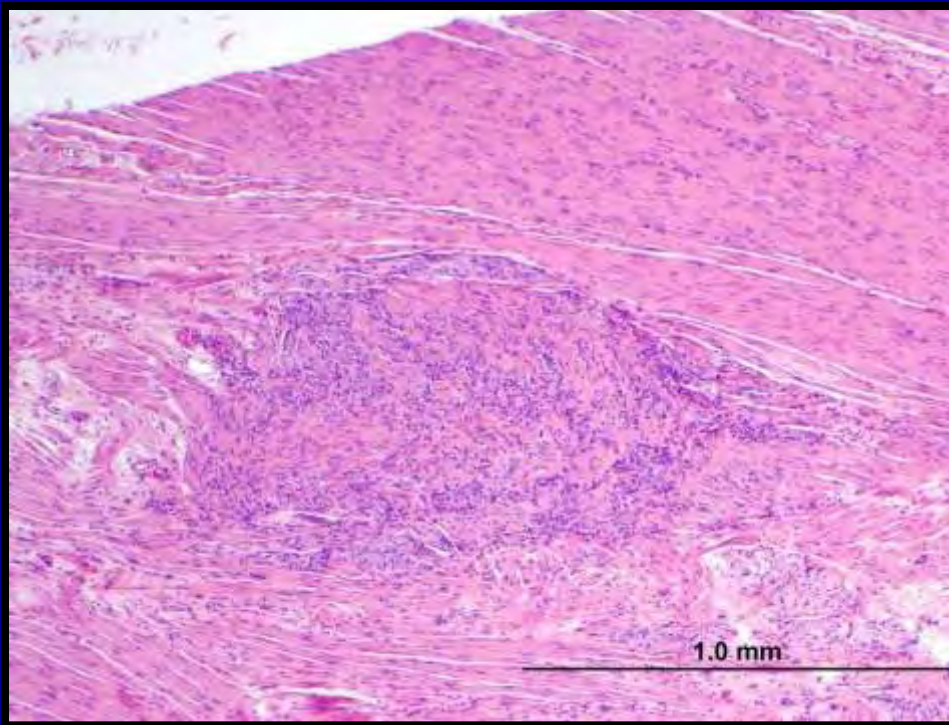
abdominal pain,

gastrointestinal bleeding,

early satiety,

symptoms referable to a mass



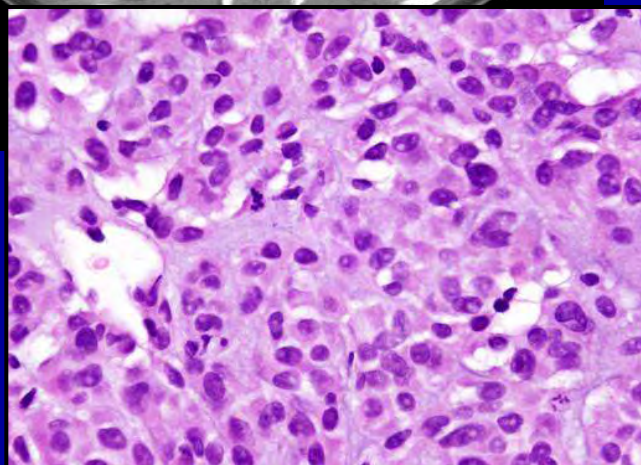
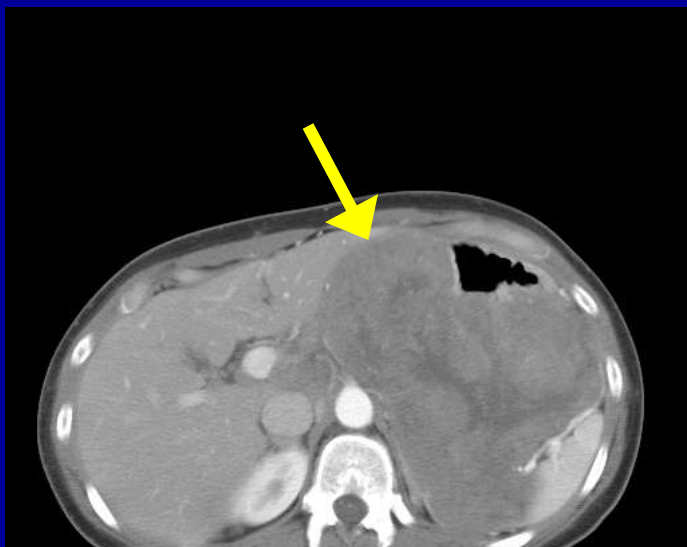


courtesy of Susan Abraham,  
UTMDACC, Houston, TX

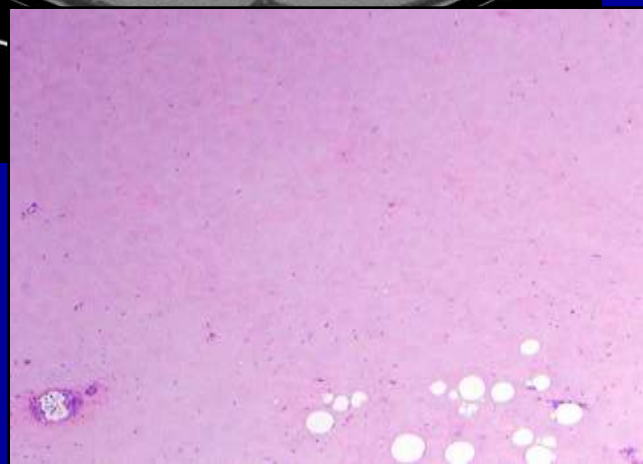
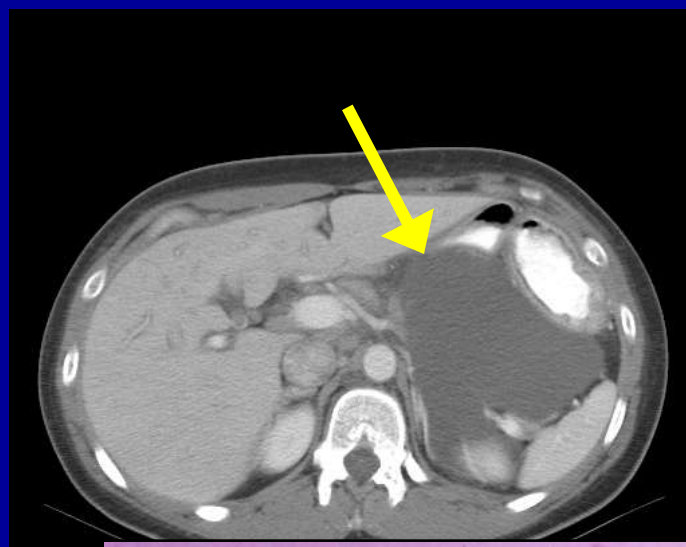
*Treatment can cause big changes.*



# *Treatment effect*

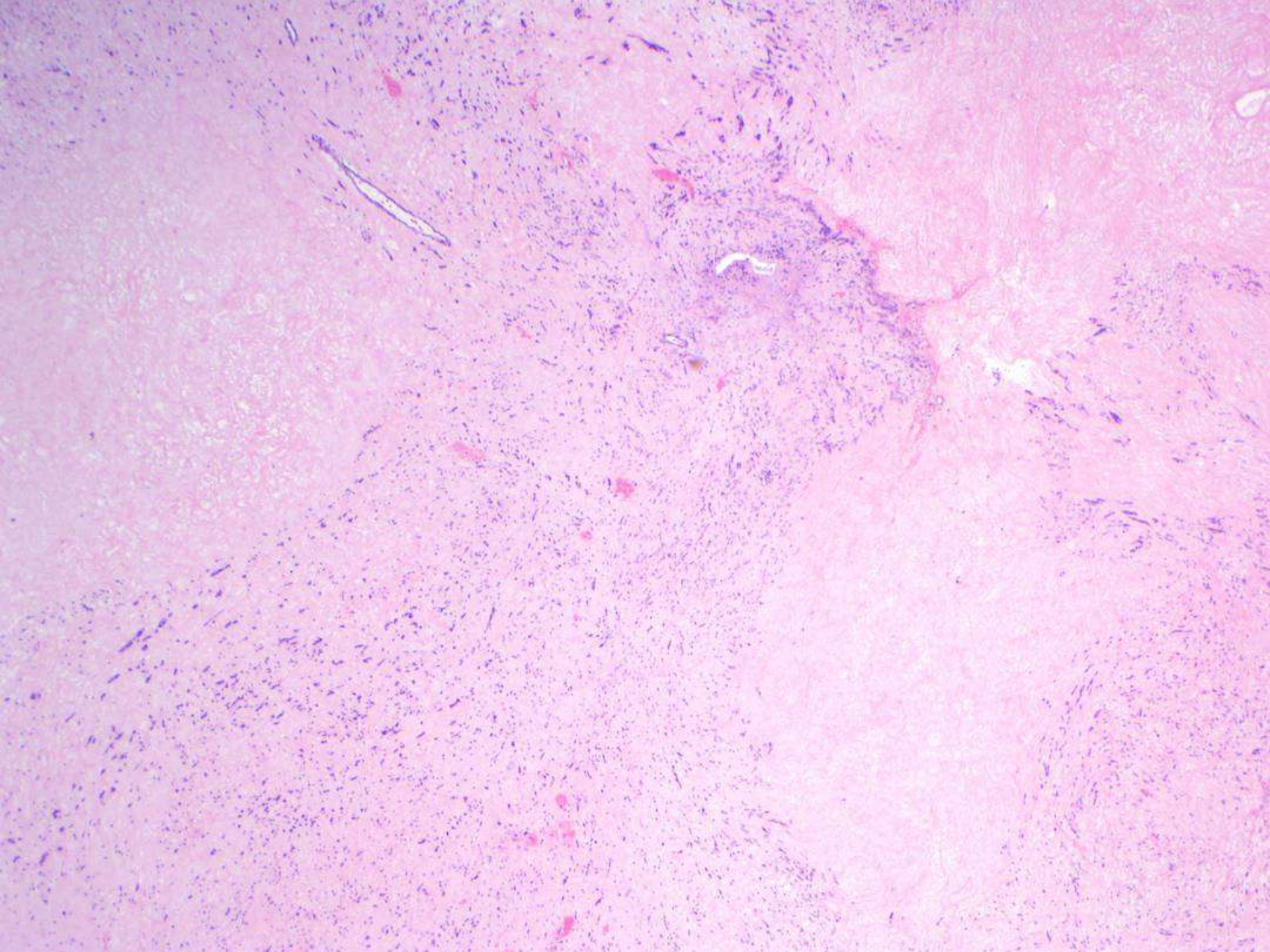


**Pre-Imatinib**

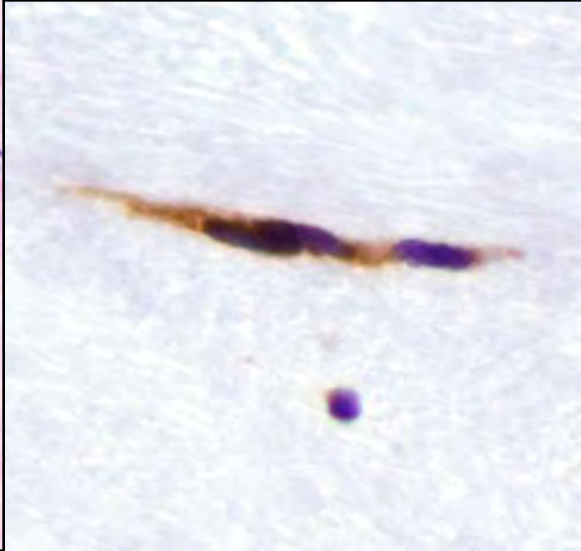
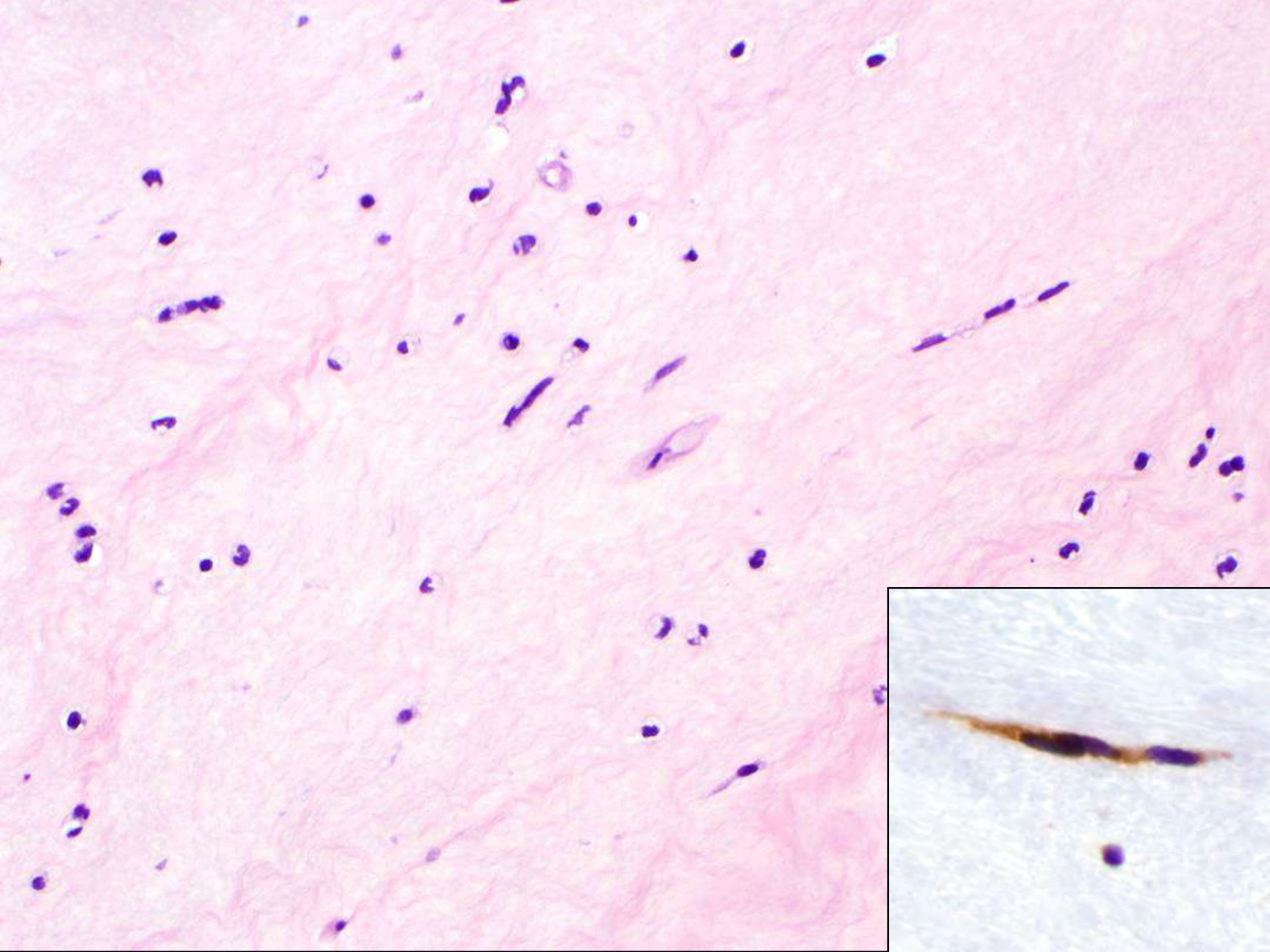


**Post-Imatinib (8 weeks therapy)**



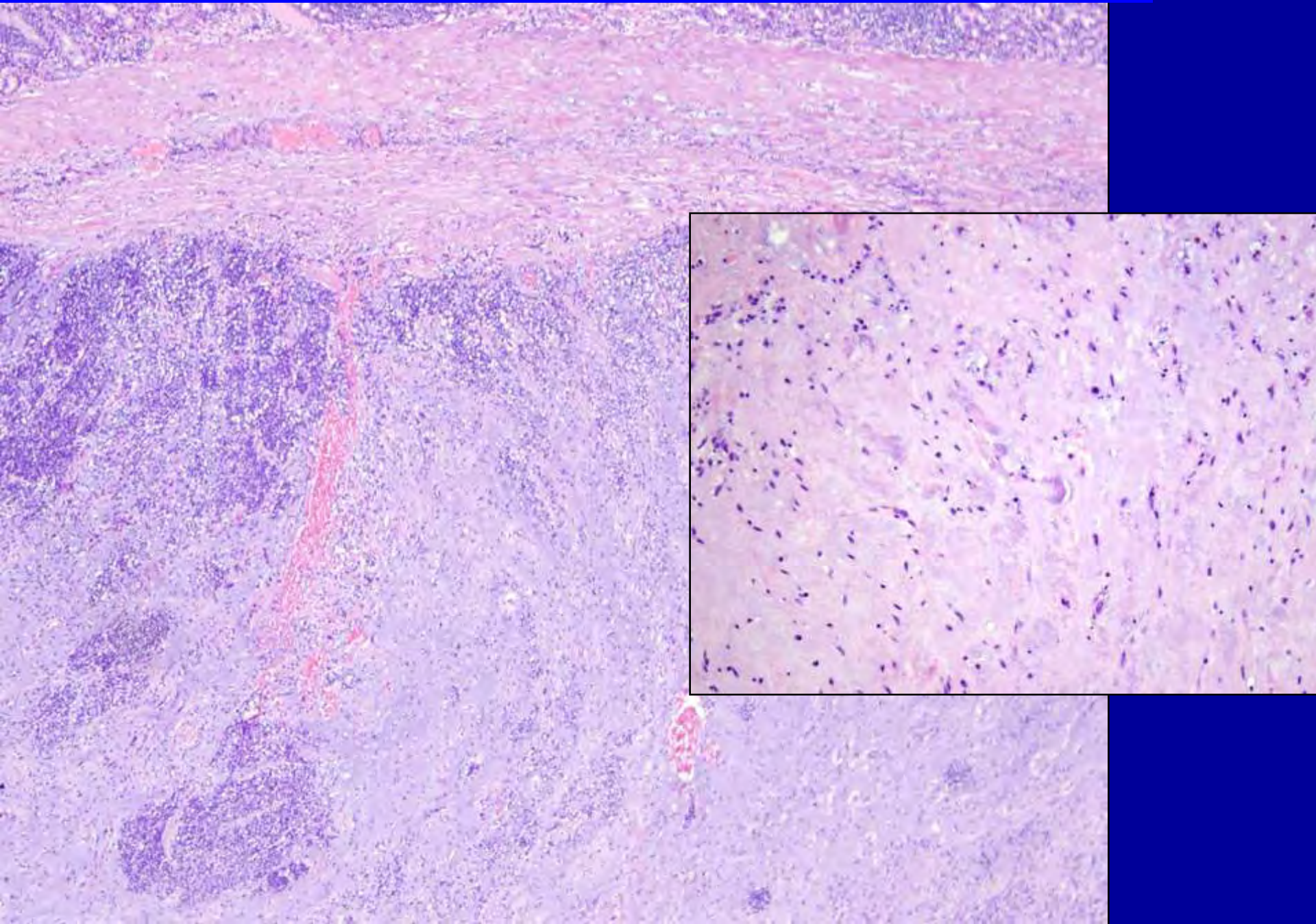






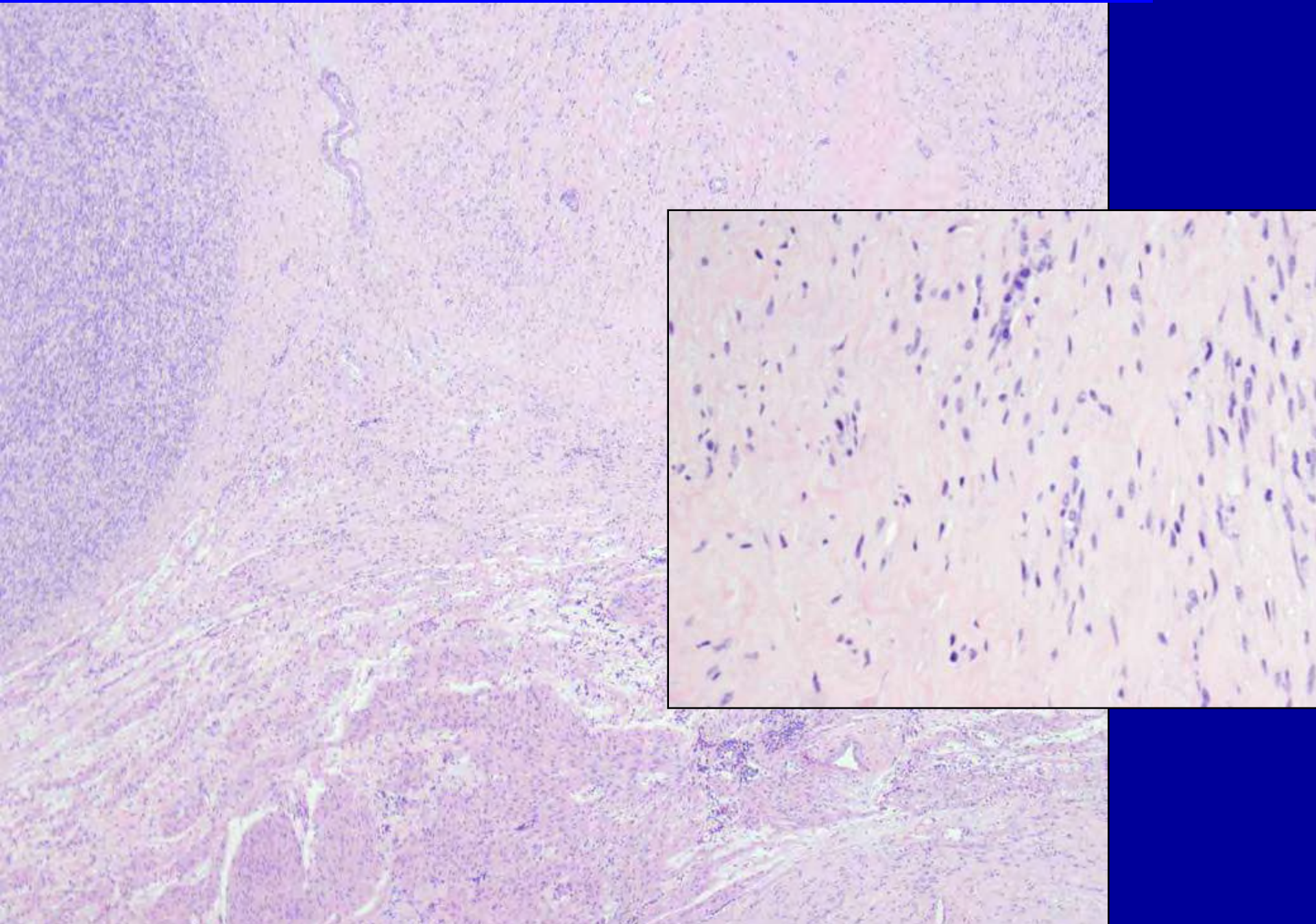


**Case No. 22 - Marked Effect – 7 days pre-op (exon 11)**



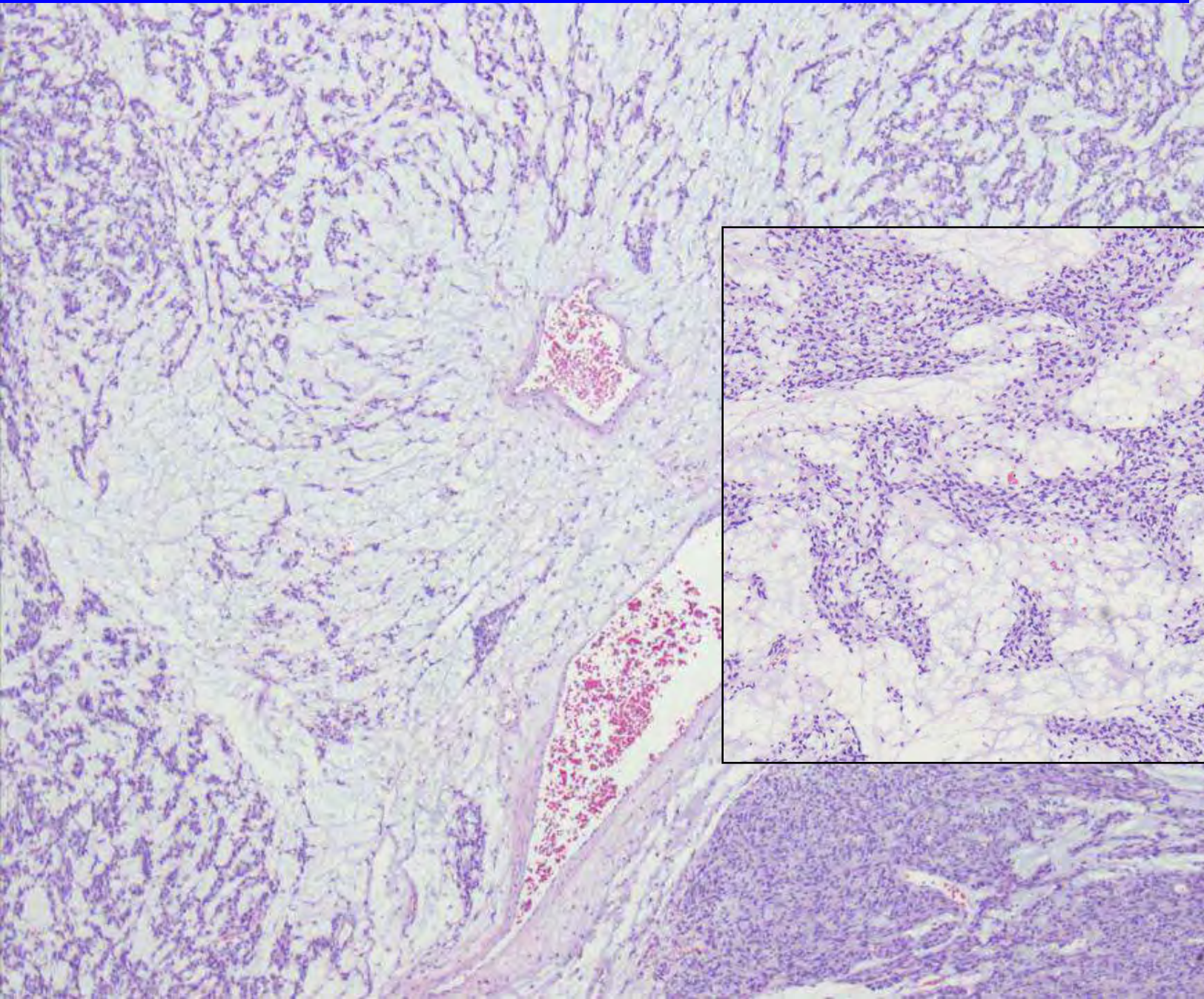


**Case No. 12 - Marked Effect – 5 days pre-op (exon 11)**



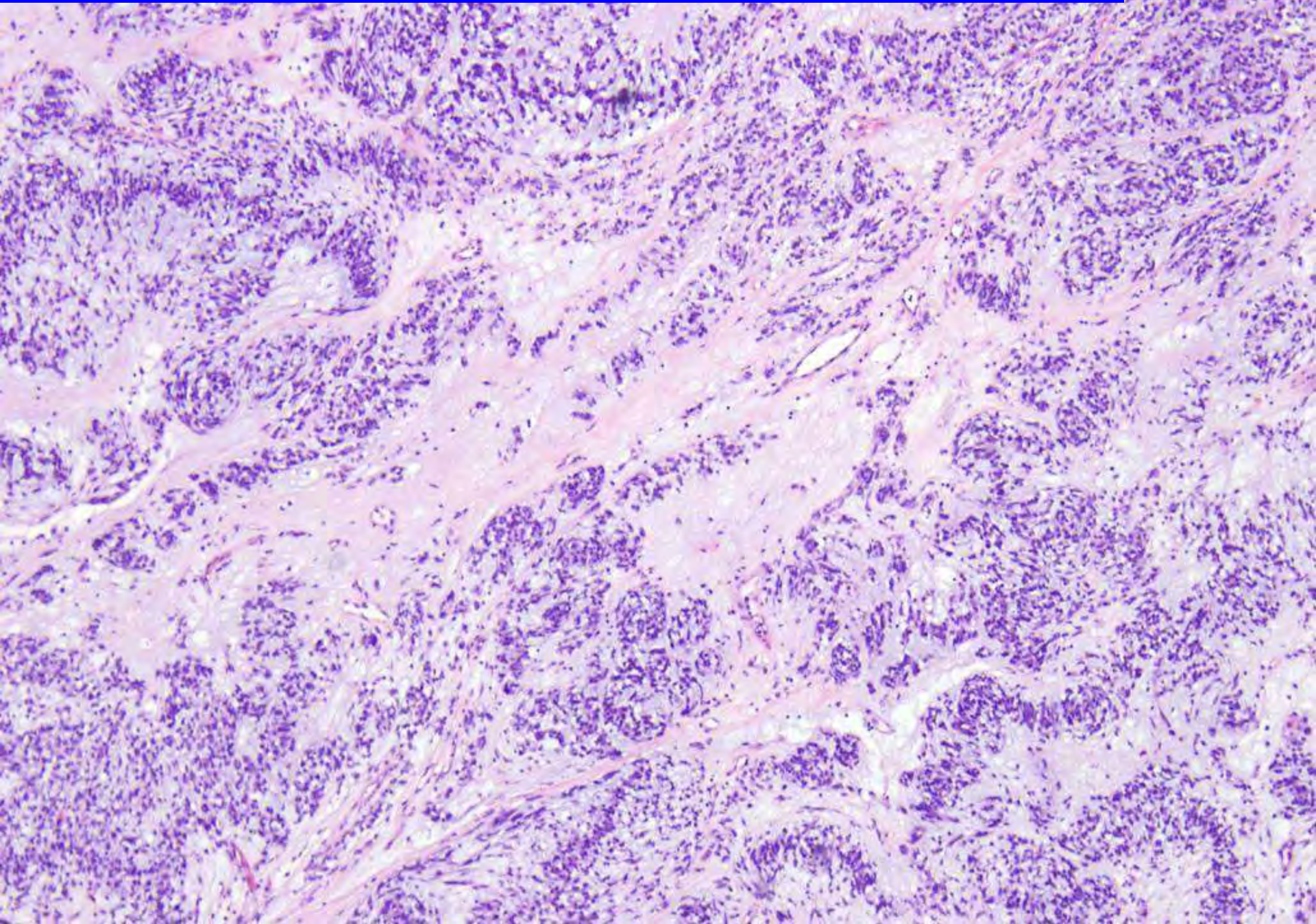


**Case 8. - Moderate Effect – 3 days pre-op (exon 11)**



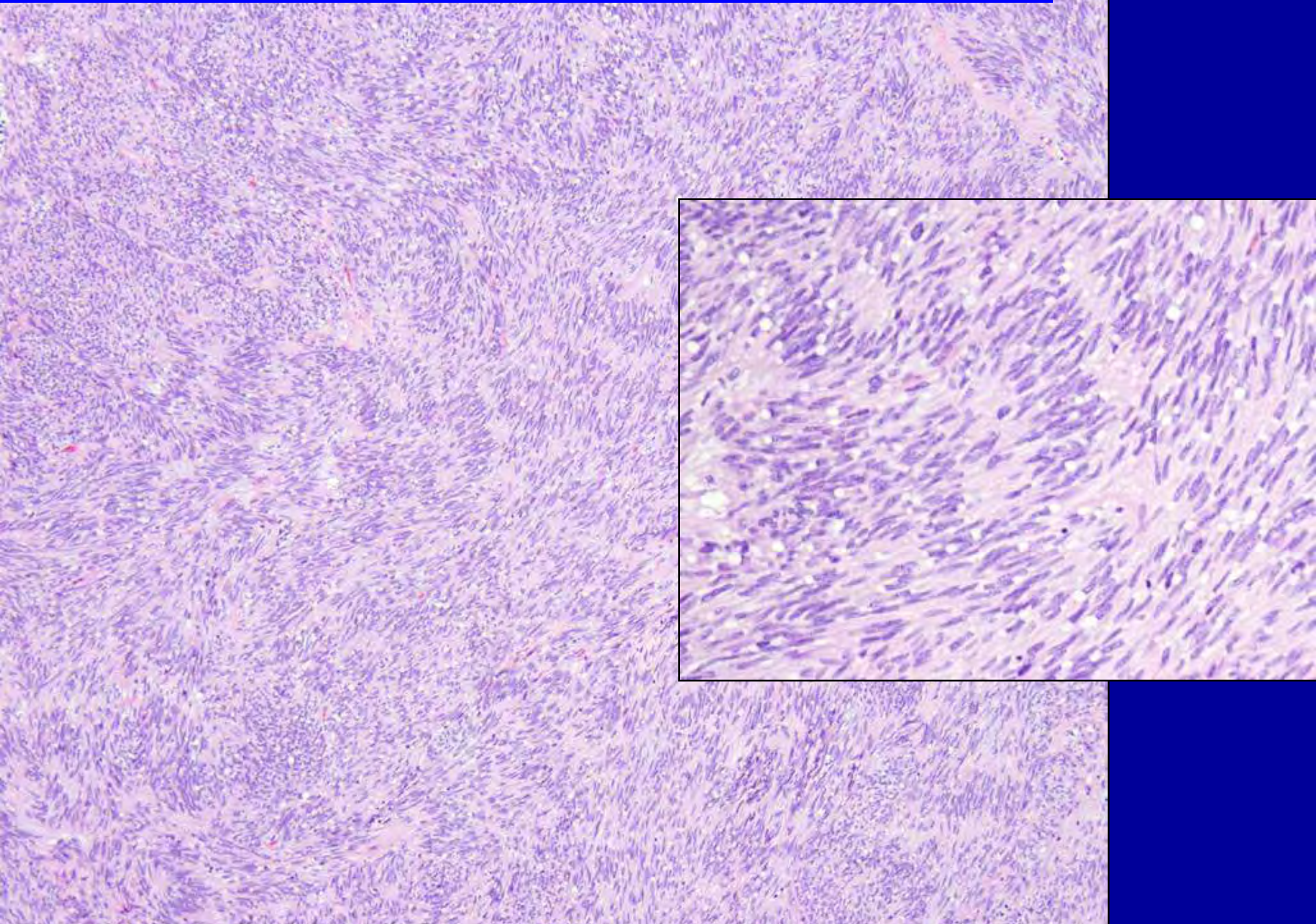


**Case 11. - Moderate Effect – 5 days pre-op (exon 11)**





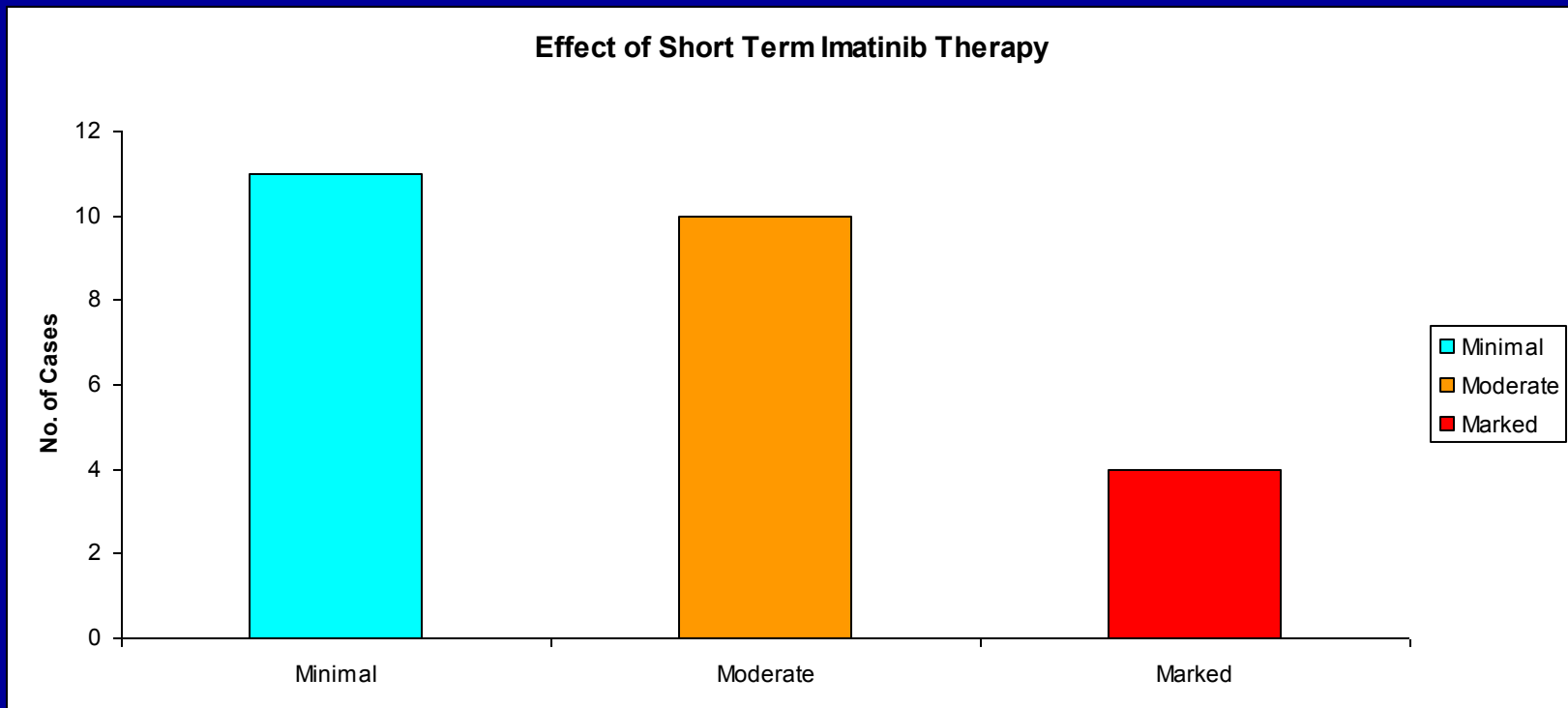
**Case 20. Minimal Effect – 5 days pre-op (exon 11)**





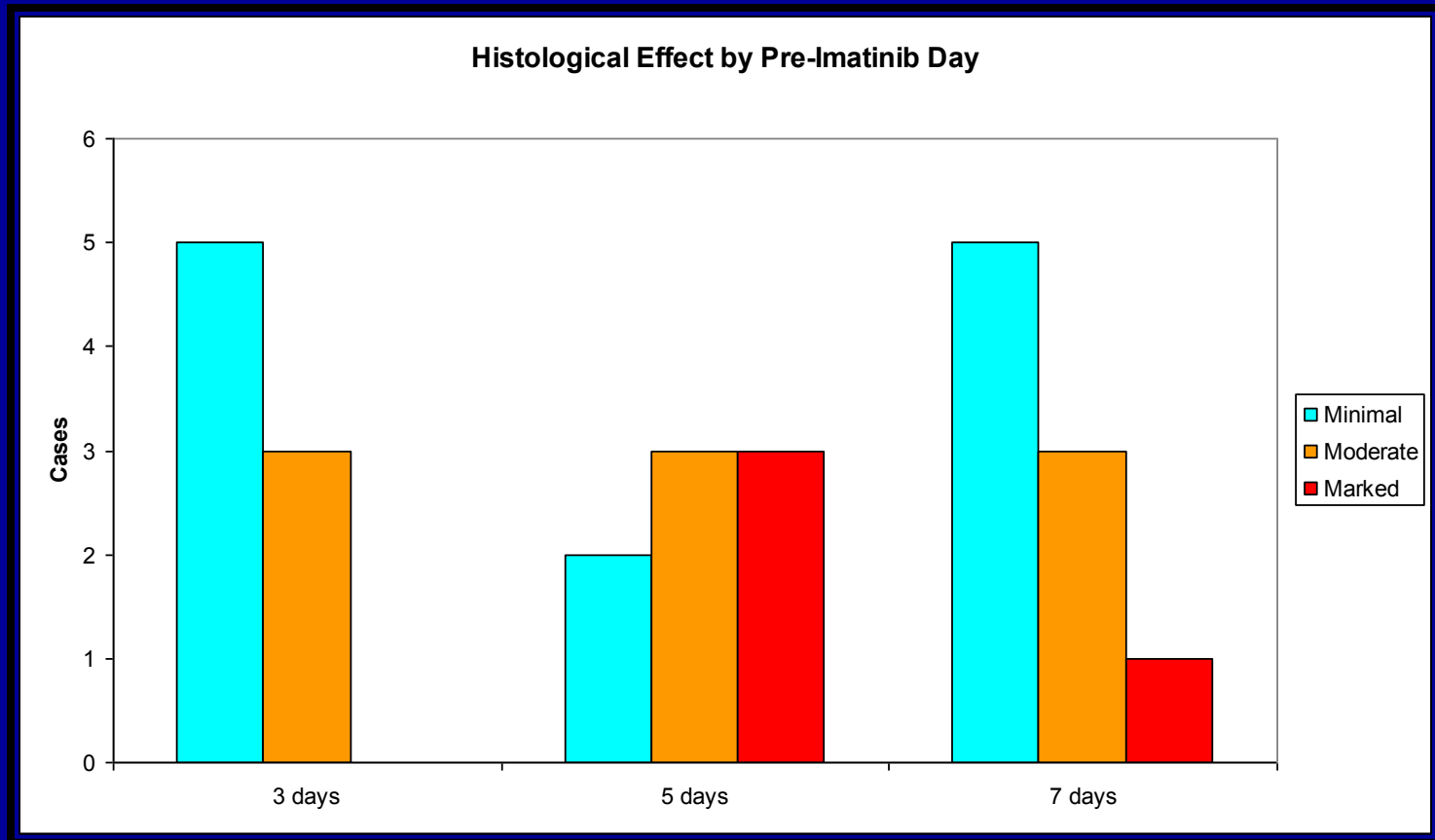
# Results

- **Minimal effect: 11/25 (44%)**
- **Moderate effect: 10/25 (40%)**
- **Marked effect: 4/25 (16%)**
- **No moderate or marked changes seen in control cases (p<0.0009)**



# Early Histologic Effects of Imatinib

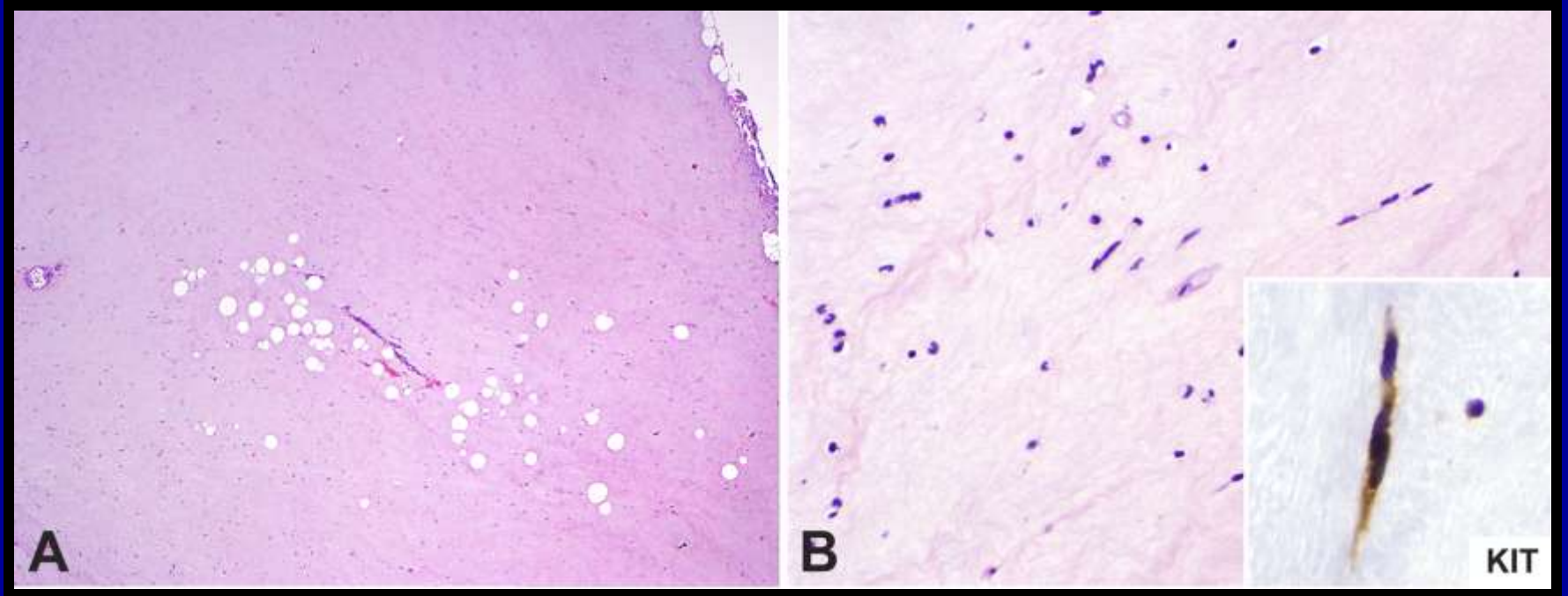
## Duration of Therapy



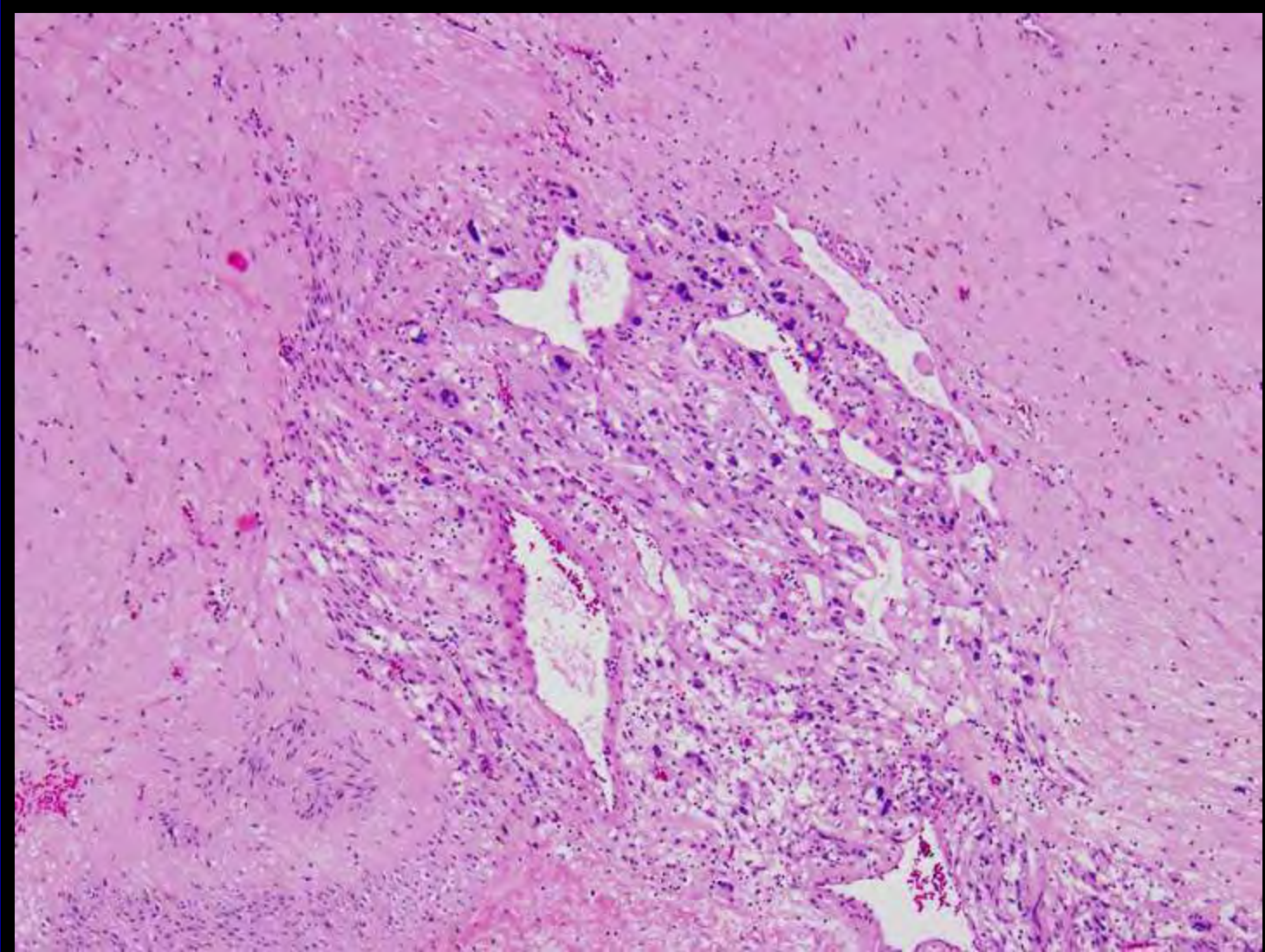
- **Minimal** and **Moderate** effects were seen across all durations of therapy
- **Marked** effect appeared to be a late finding peaking at 5 days



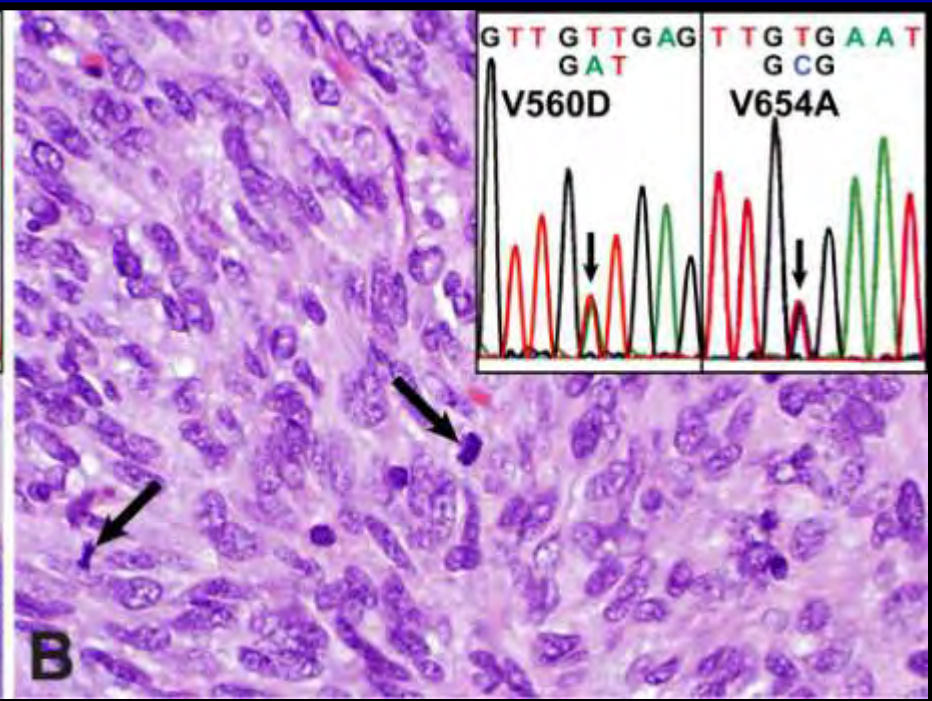
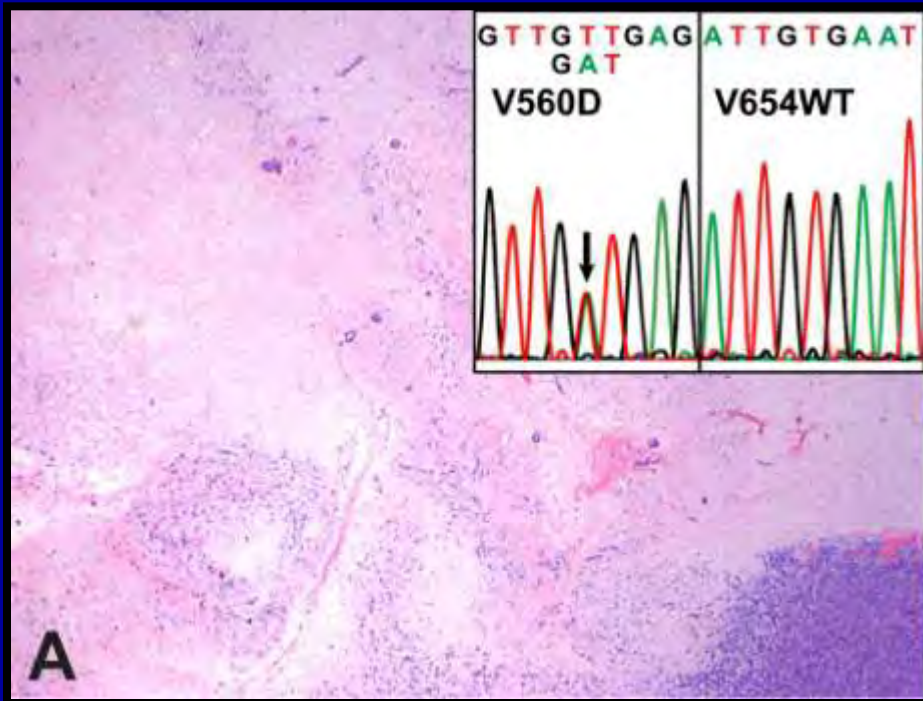
# *Long term Imatinib Tx*

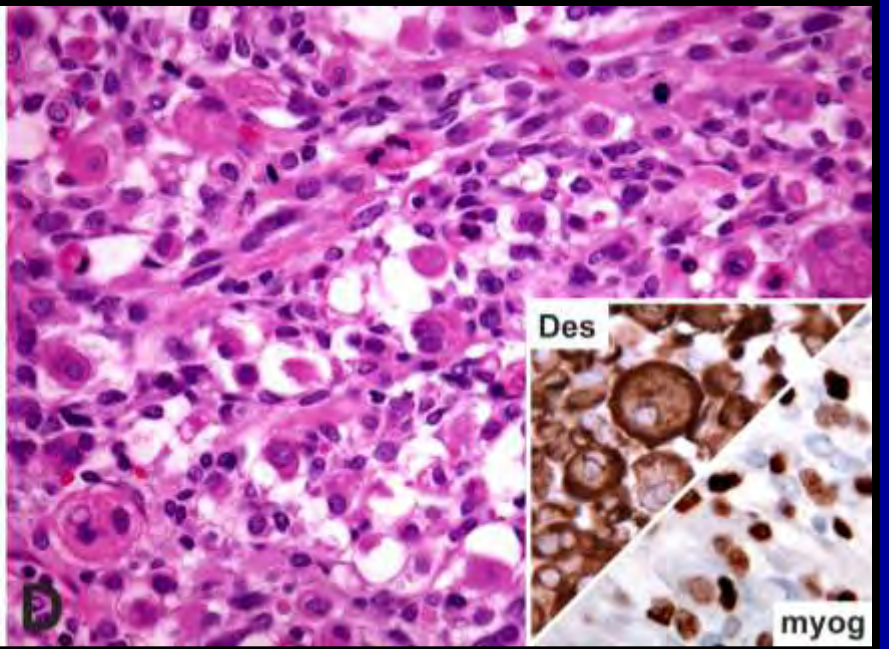
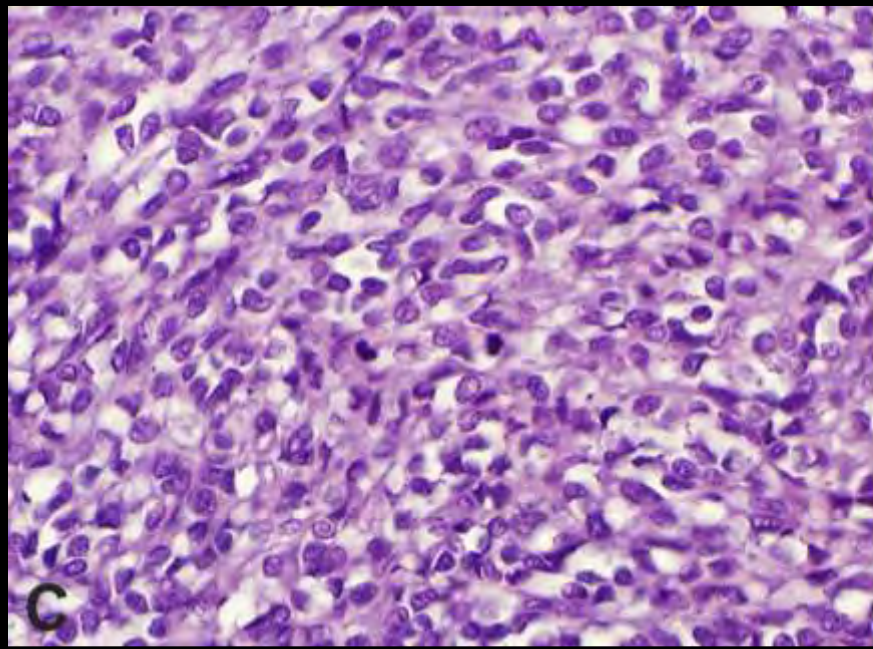


# *Long term Imatinib Tx*





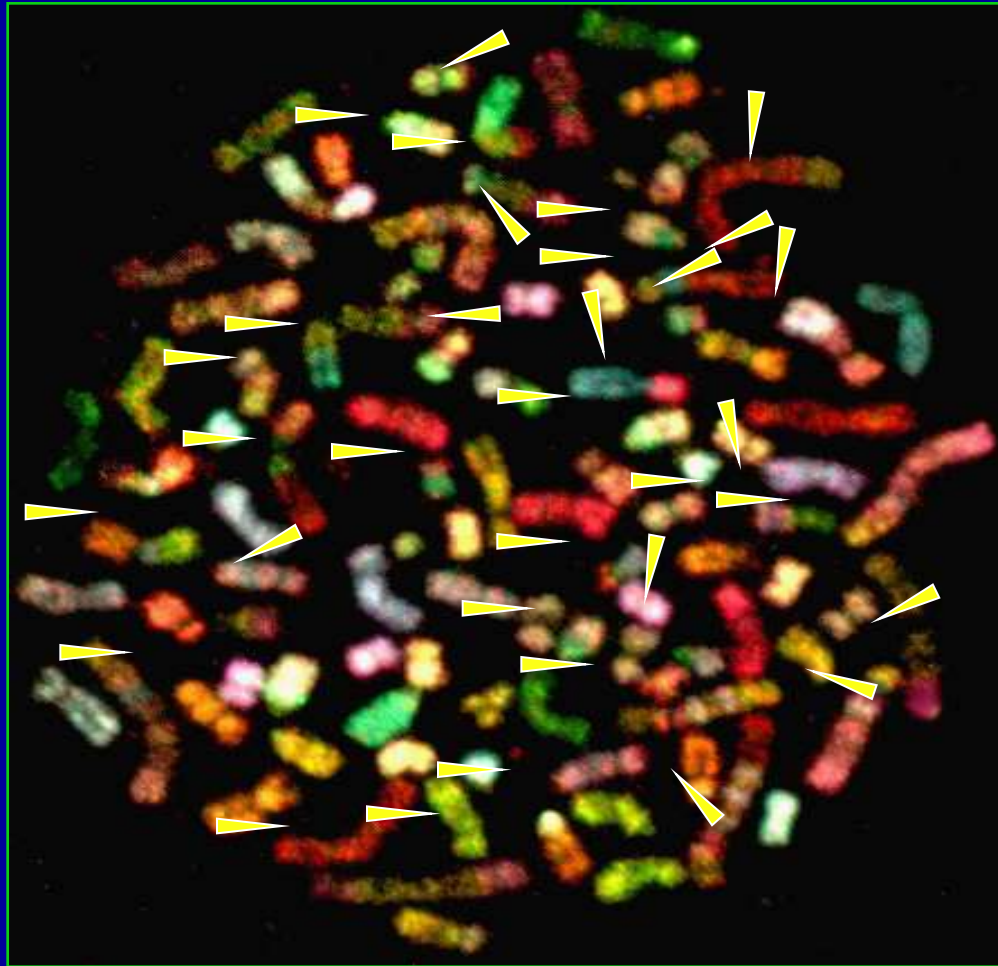






*What is new and exciting in GIST  
pathology?*

# Chromosomal complexity and prognosis



**97 chromosomes and more than 50 translocations**



# 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 ?

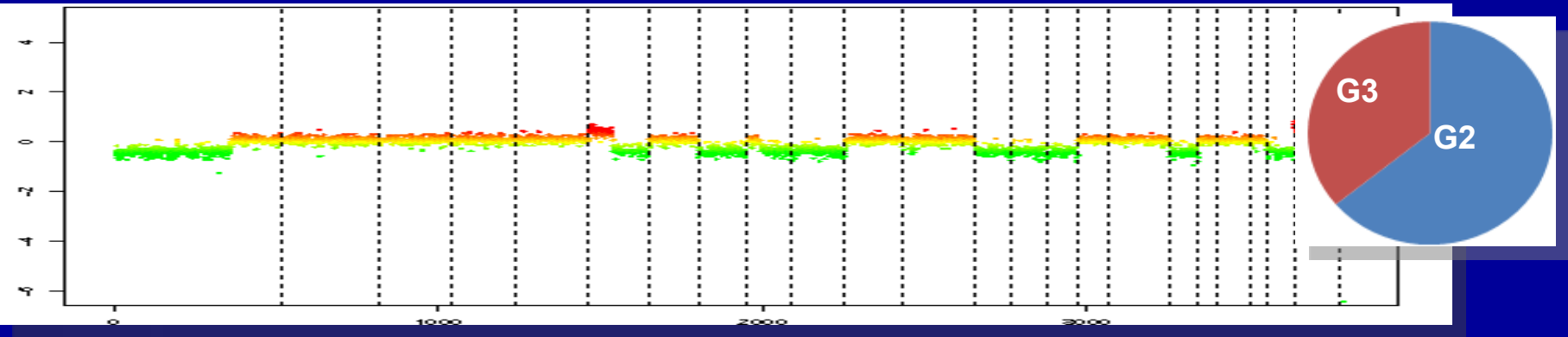
# *Chromosomal instability signature*

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 our series of sarcomas**

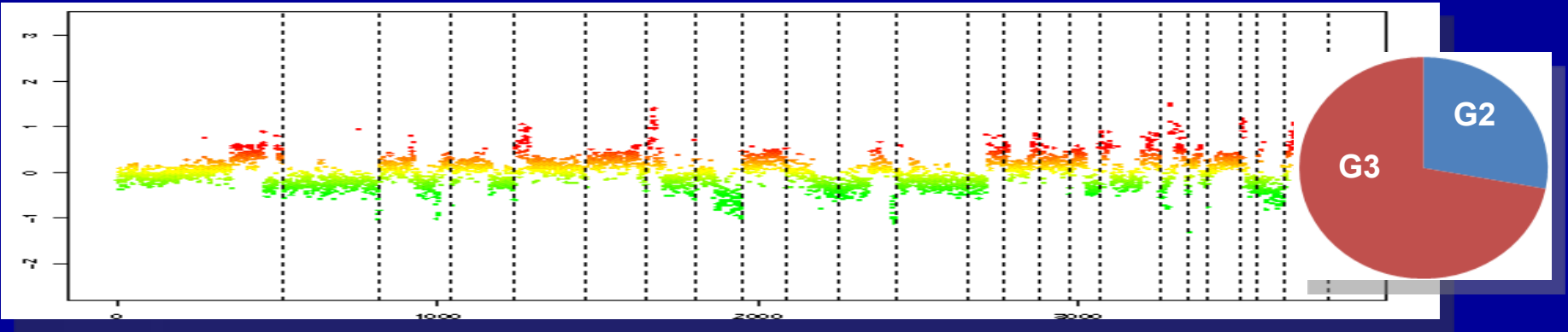


## « Arm » Profile



$p=.001$

## « Rearranged » Profile



# *Genomic complexity and prognosis*

## *Possible approaches*

- **(Histological grading)**
- **Array-CGH**
- **Carter signature**

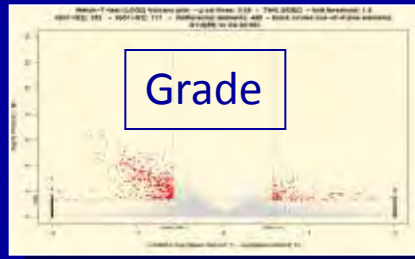


# Molecular grading in sarcomas

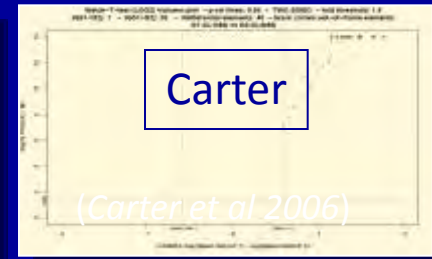
3 t tests to compare the expression profiles of tumors classified according to:



86 genes



73 genes



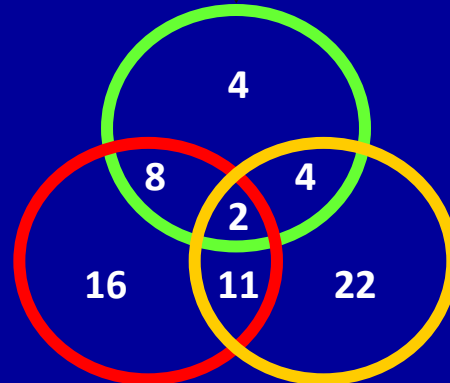
39 genes

**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

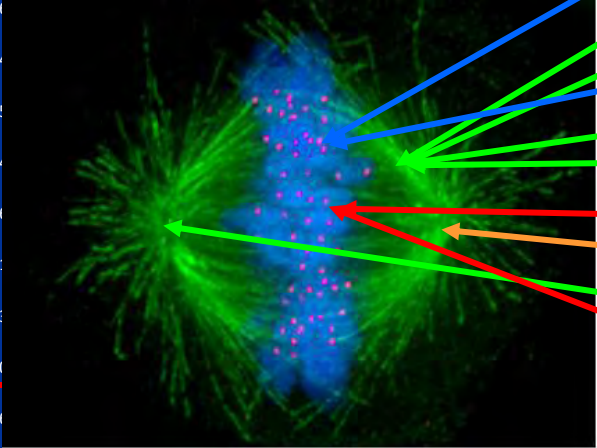


67 genes

Complexity INdex  
In SARComas  
CINSARC

# 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	<a href="#">chromosome, pericentric region</a>
GO:0005819	7	14	3,88E-12	27,03	<a href="#">spindle</a>
GO:0005871	1	1	1,06E-14	25,92	<a href="#">spindle microtubule</a>
GO:0005694	1	1	1,06E-14	22,73	<a href="#">chromosome</a>
GO:0005871	1	1	1,06E-14	11,42	<a href="#">microtubule associated complex</a>
GO:0005871	1	1	1,06E-14	7,90	<a href="#">microtubule</a>
GO:0000771	1	1	1,06E-14	12,42	<a href="#">kinetochore</a>
GO:0005871	1	1	1,06E-14	10,67	<a href="#">kinesin complex</a>
GO:0005811	1	1	1,06E-14	7,96	<a href="#">centrosome</a>
GO:0000941	1	1	1,06E-14	16,72	<a href="#">outer kinetochore of condensed chromosome</a>
GO:0030491	1	1	1,06E-14	10,84	<a href="#">midbody</a>
GO:0005657	2	8	0,0010	10,12	<a href="#">replication fork</a>
GO:0005814	2	8	0,0012	9,52	<a href="#">centriole</a>
GO:0015630	1	1	1,06E-14	10,12	<a href="#">centriole</a>
GO:0000922	1	1	1,06E-14	10,12	<a href="#">centriole</a>
GO:0000785	1	1	1,06E-14	10,12	<a href="#">centriole</a>
GO:0000786	1	1	1,06E-14	10,12	<a href="#">centriole</a>
GO:0001939	1	3	0,0187	8,30	<a href="#">female pronucleus</a>
GO:0005816	1	3	0,0187	8,30	<a href="#">spindle pole body</a>
GO:0000930	1	4	0,0233	7,15	<a href="#">gamma-tubulin complex</a>
GO:0005664	1	4	0,0233	7,15	<a href="#">nuclear origin of replication recognition complex</a>
GO:0015030	1	4	0,0233	7,15	<a href="#">Cajal body</a>
GO:0005881	1	6	0,0325	5,78	<a href="#">cytoplasmic microtubule</a>
GO:0043234	2	64	0,0385	3,10	<a href="#">protein complex</a>

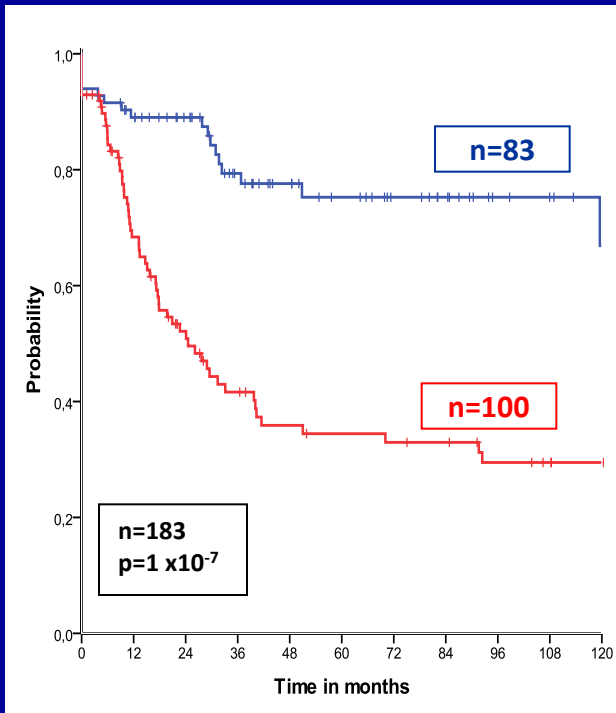


**CINSARC is a signature related to chromosome management and mitosis control associated with genome complexity**

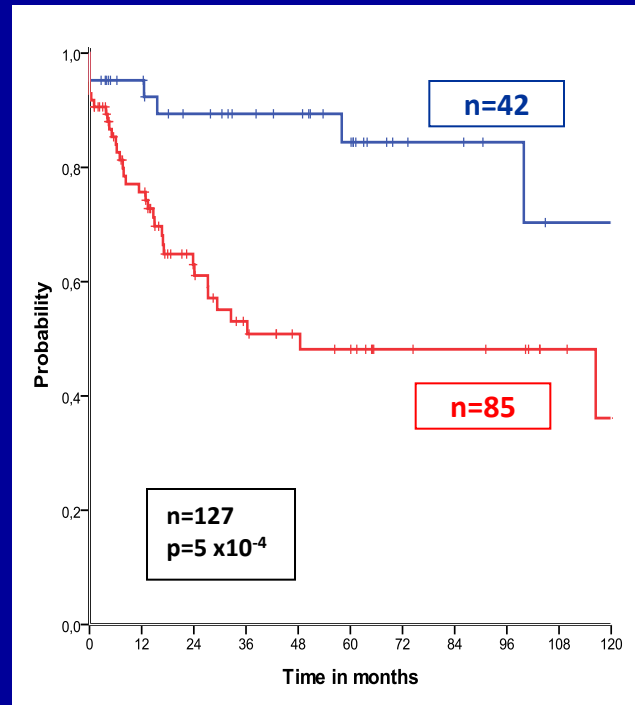


## Prognostic value of CINSARC: Metastasis free survival

### Cohort 1



### Cohort 2

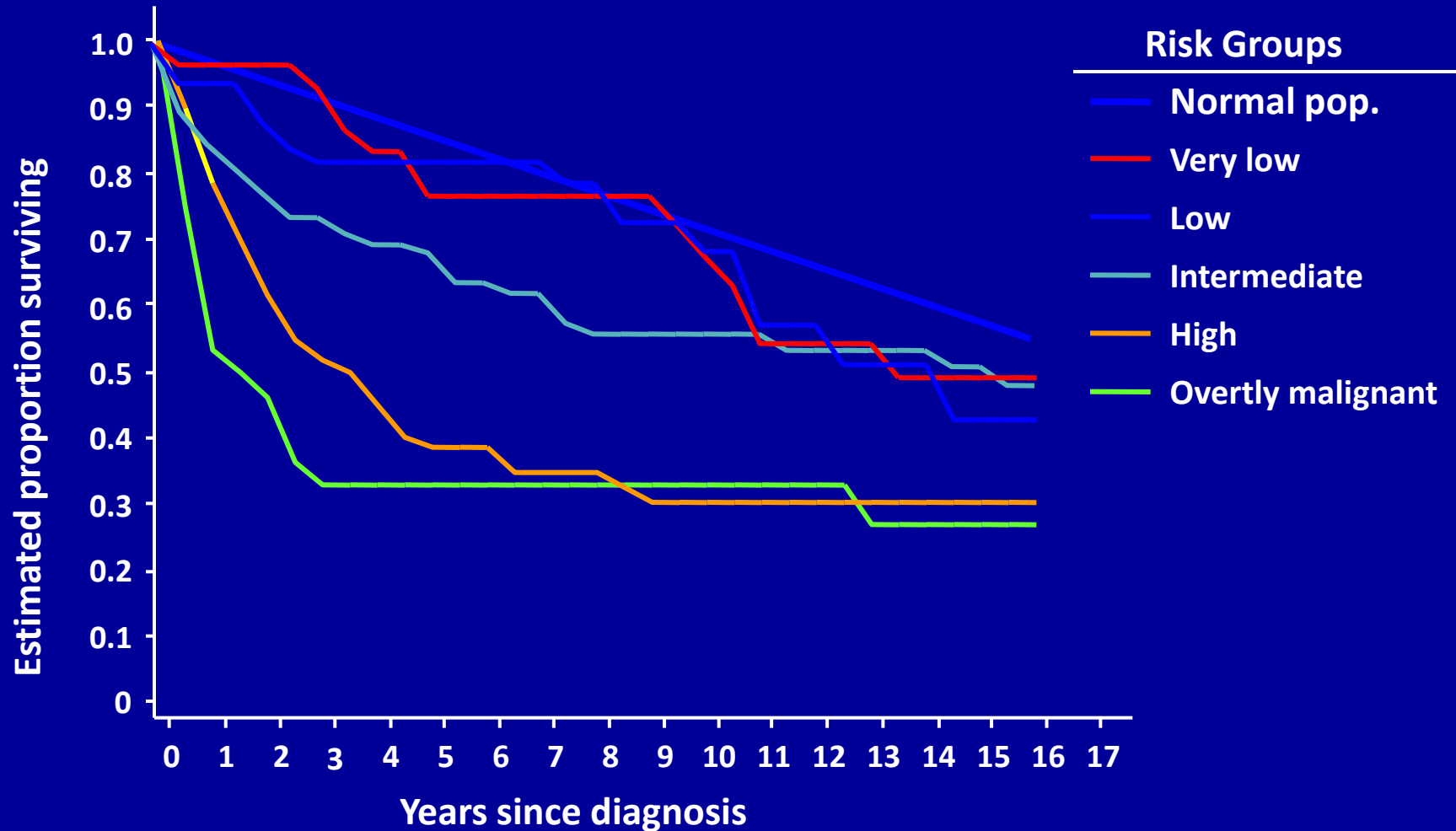


## Multivariate analysis

HR = 3.1; 95% CI [1.8 – 5.4]

**CINSARC is an independent prognostic factor**

# GIST - Overall Survival by Risk Group

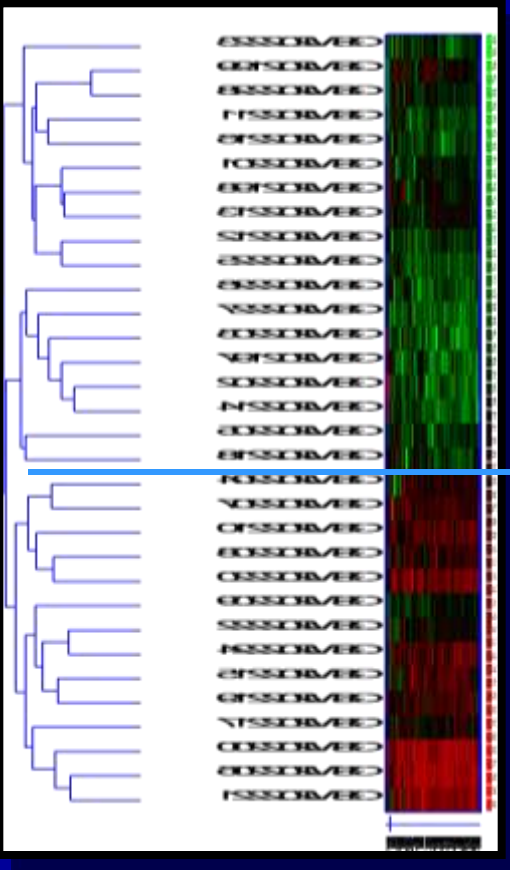




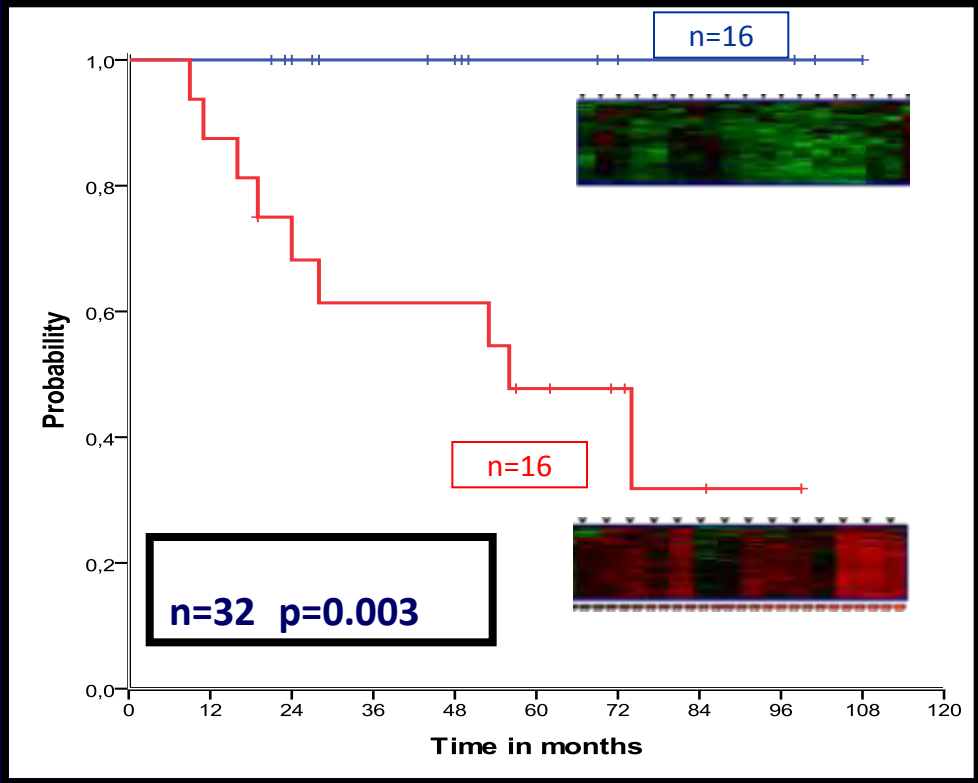
# CINSARC and GIST

## In-silico study of 32 GISTs

(Yamaguchi *et al* 2008)

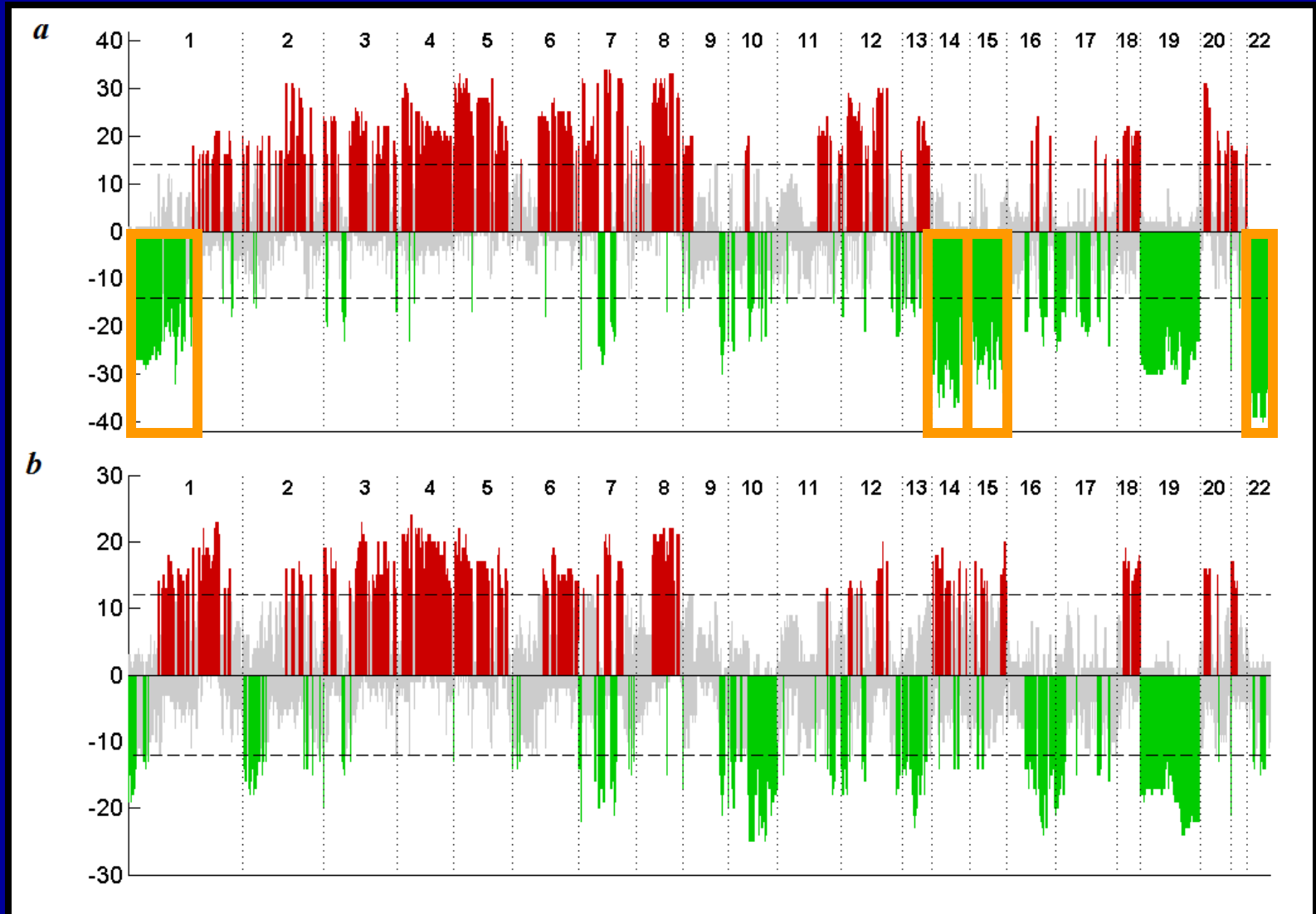


Metastasis free survival



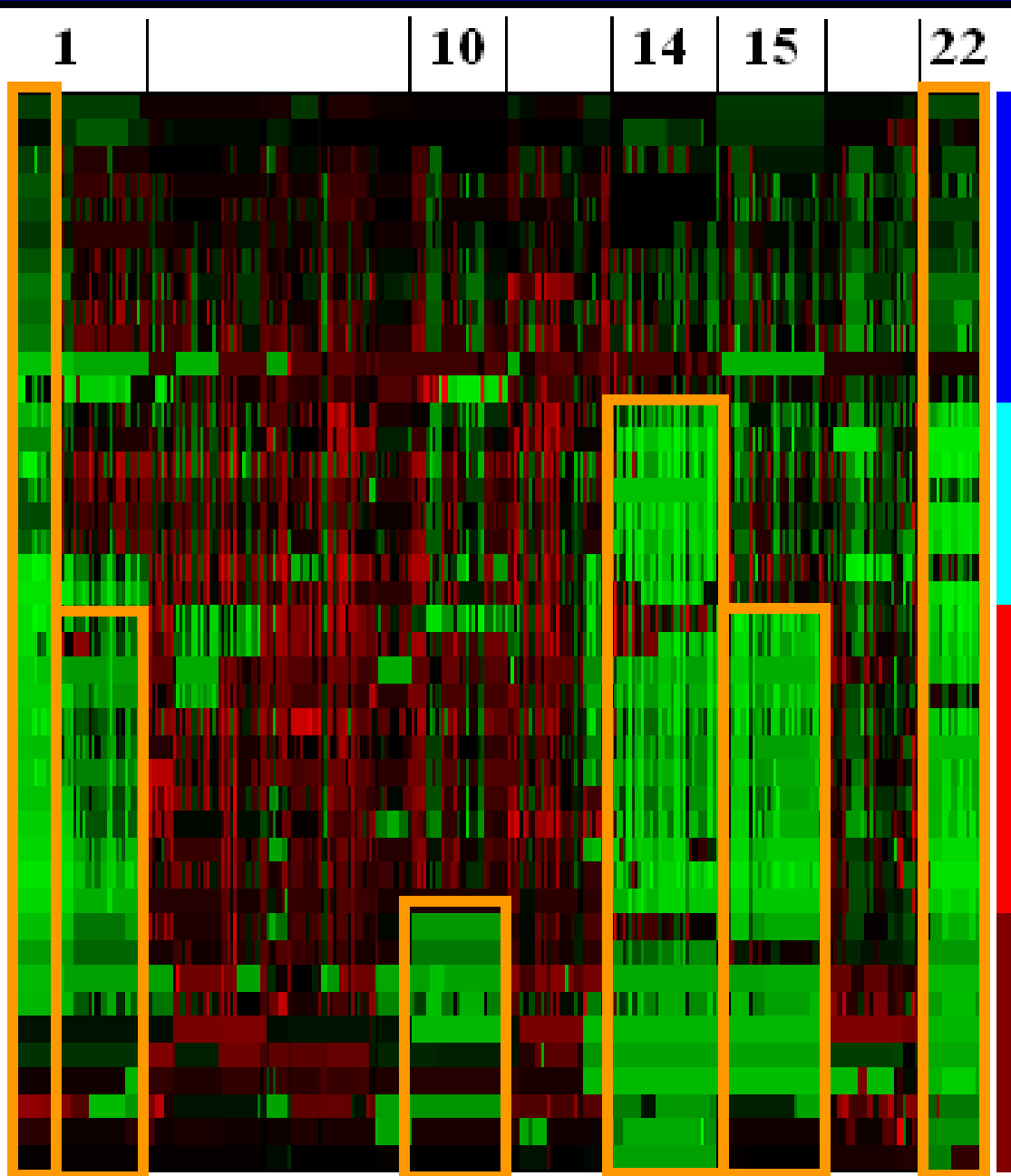
Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)

# GIST (n=42)



# LMS (n=30)



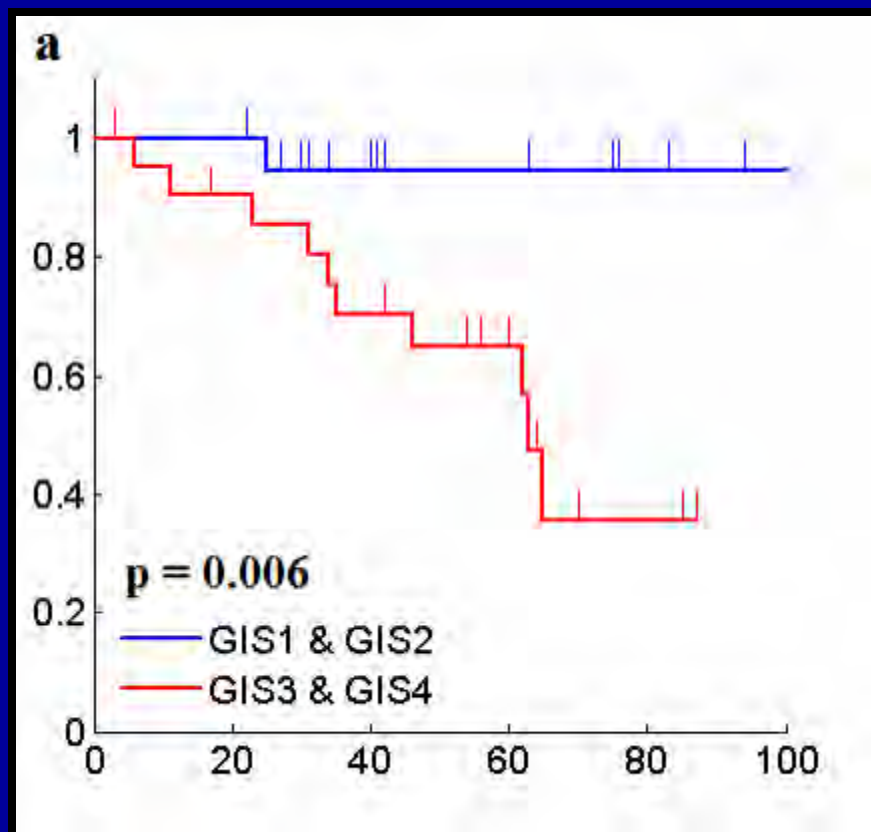
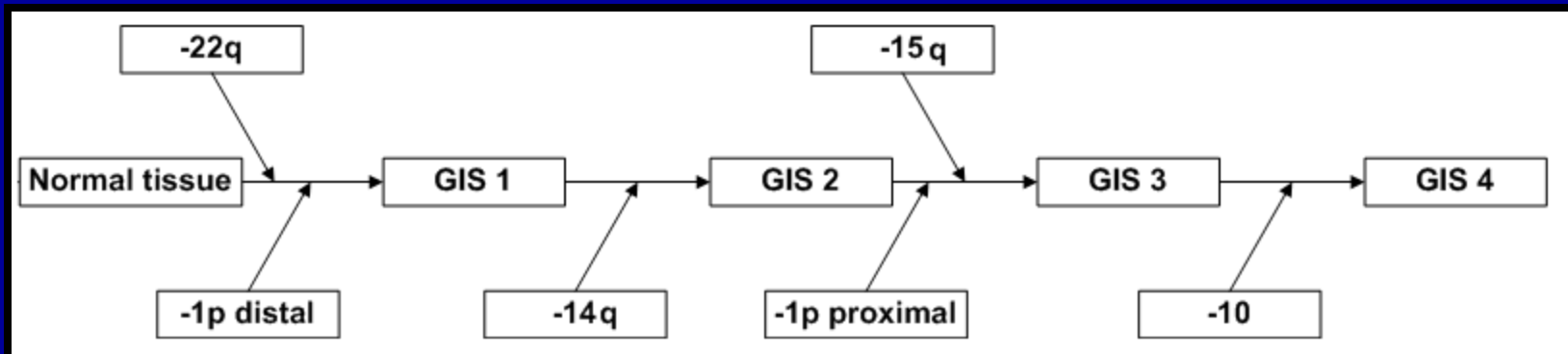


**GIS 1:**  
-1p distal, -22q

**GIS 2:**  
-1p distal, -22q,  
-14q

**GIS 3:**  
-1p, -22q, -14q,  
-15q

**GIS 4:**  
-1p, -22q, -14q,  
-15q, -10



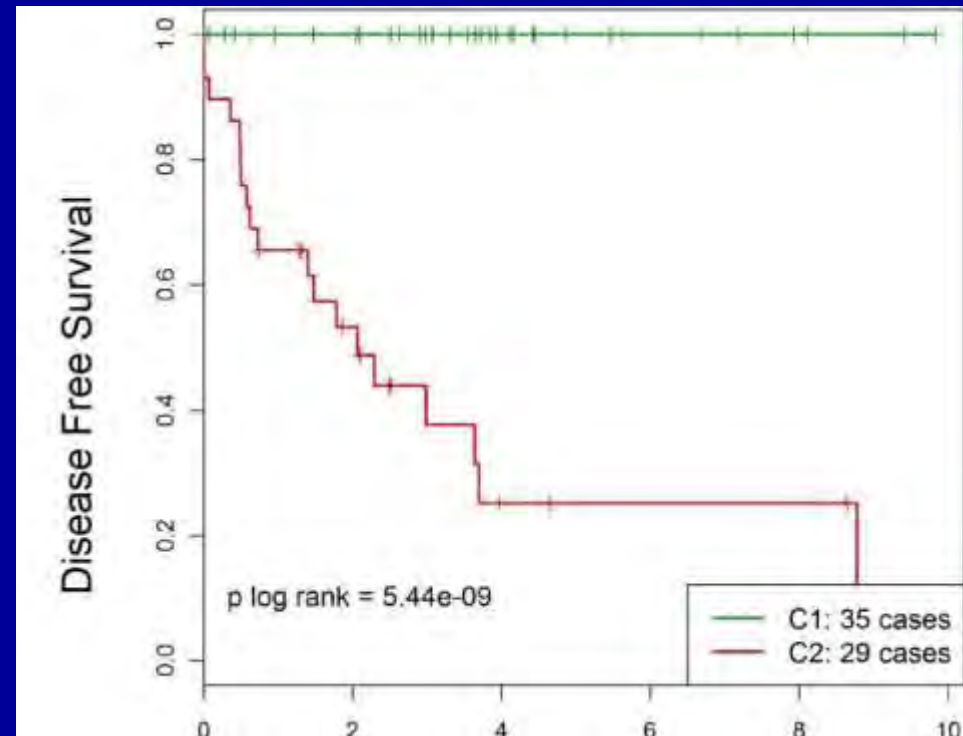


# *GIST and molecular signature*

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

CINSARC

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

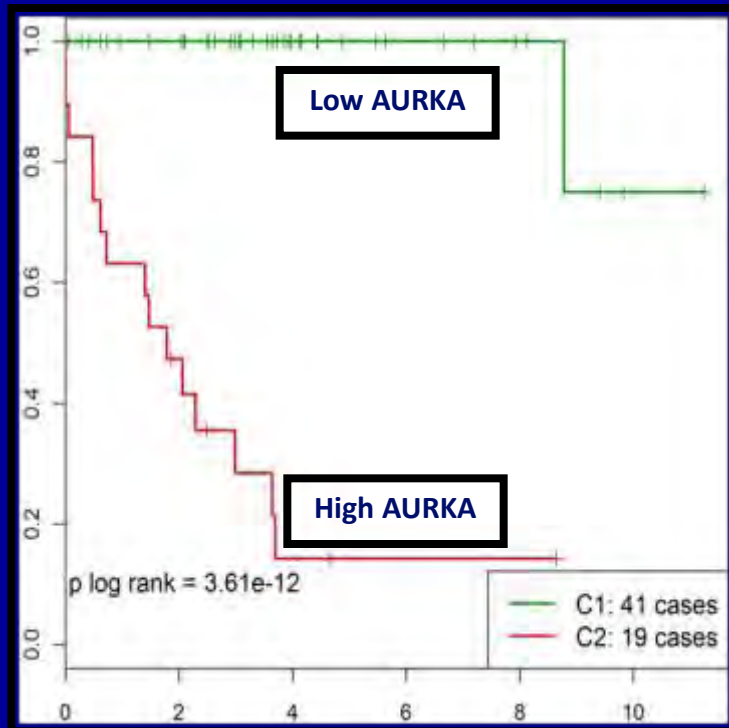


Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)

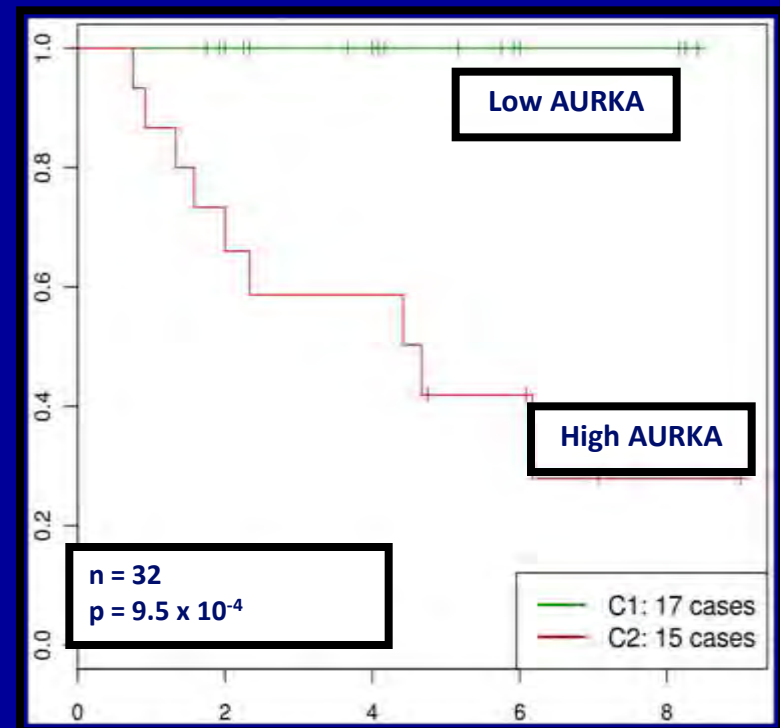
# GIST and molecular signature

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

AURKA is a prognostic factor in GIST



Bergonié + Leuven



Yamagushi et al JCO 2008



# **AURKA – top ranked gene in CINSARC**

- **Gene maps to chromosome 20q13**
- **Mitotic centrosomal protein kinase**
- **Control of chromosome segregation**
- **Overexpression induces centrosome duplication/distribution abnormalities and aneuploidy**
- **Overexpression associated with poor prognosis in several cancers**

# *Prognosis in GIST*

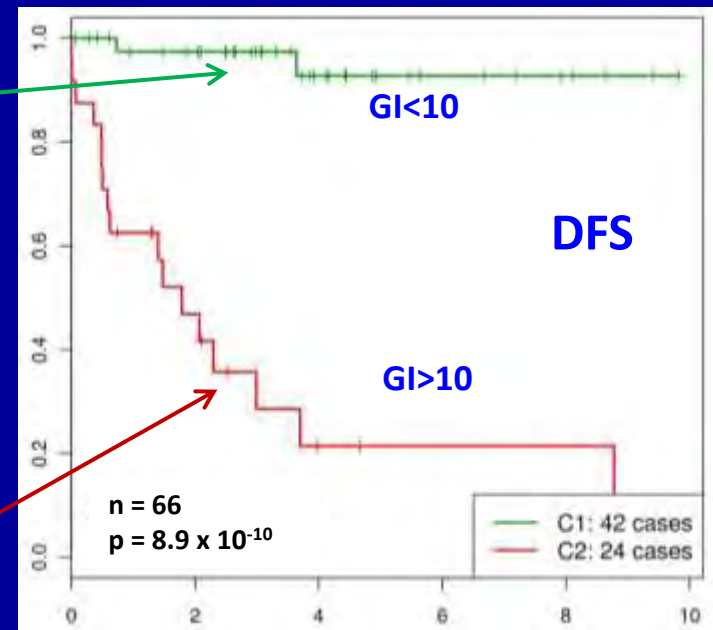
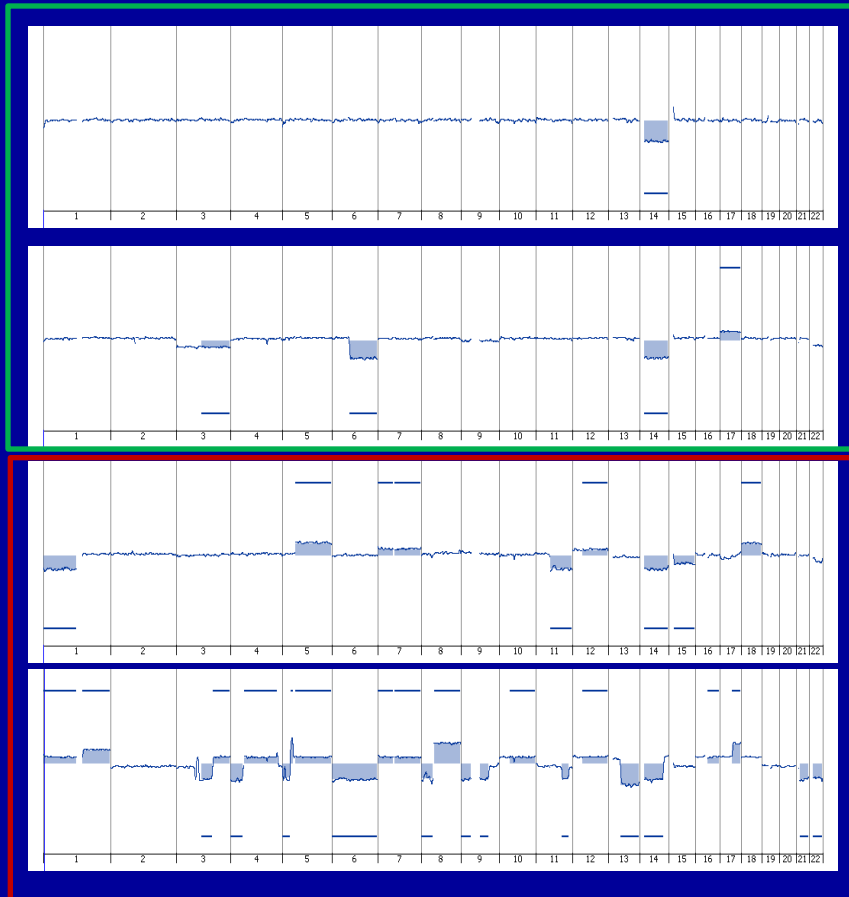
- *AURKA* is overexpressed in aggressive GIST
- No amplification of *AURKA*
- Deletion of p16 (*CDKN2A*) or *RB1*
- Likely causal events leading to increase *AURKA* and *CINSARC* gene expression, chromosomal instability and complexity, and finally to metastasis



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

$$GI = \text{Alt}^2 / \text{nb of altered chr.}$$

- Frozen tissue is rarely available
- Method applicable on paraffin tissue ?
- Genomic Index (GI) on CGH

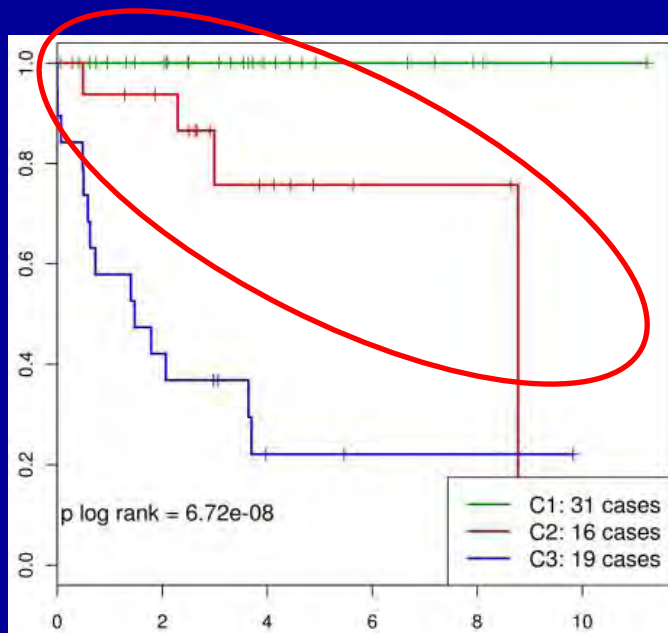


Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

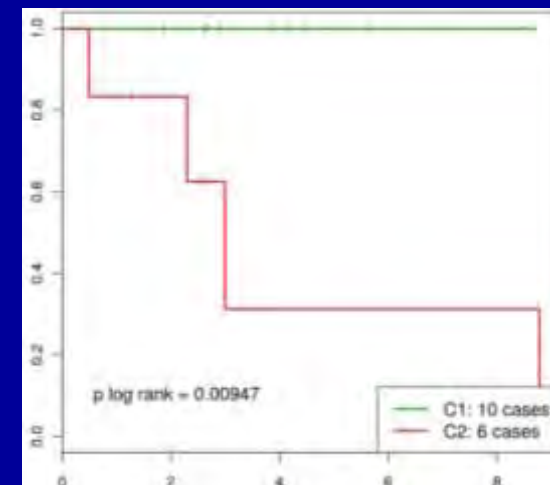
# *GIST and molecular signature*

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

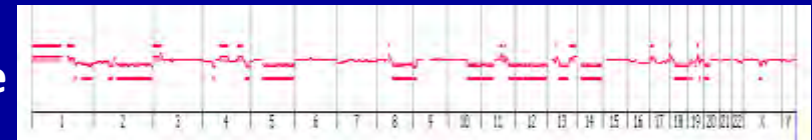
## Miettinen classification



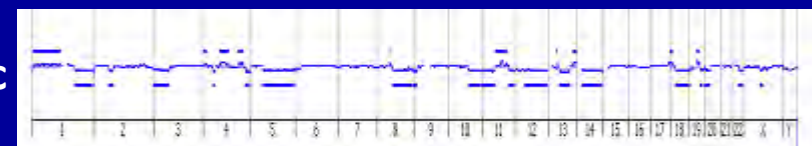
## CGH-Genomic Index



## Frozen Tissue



## FFPE bloc



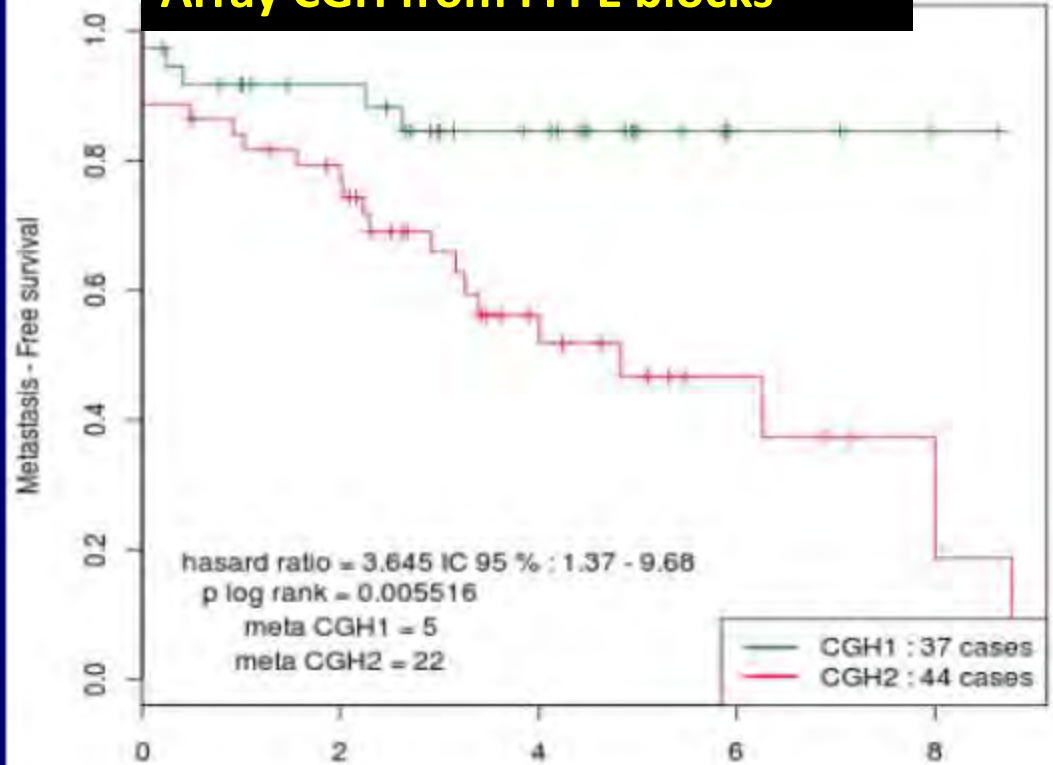
Courtesy of J-M Coindre & F Chibon,  
Bordeaux, France (Fresch Sarcoma Group)



# Intermediate GIST and array-CGH

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

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



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

# *Thank You*

- **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.**
- **Colleagues at UTMDACC.**