



A nighttime photograph of the MD Anderson Cancer Center building, illuminated with warm lights. The building is a large, multi-story structure with many windows lit up. In the foreground, there is a landscaped area with a fountain and some trees. The sky is dark, and the overall scene is lit by the building's lights and streetlights.

GIST 201: The Pathology of GIST: 10th Anniversary GIST Summit (GSI)

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Saturday 22 September 2018**



Disclosures

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

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 is examined by a pathologist.

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



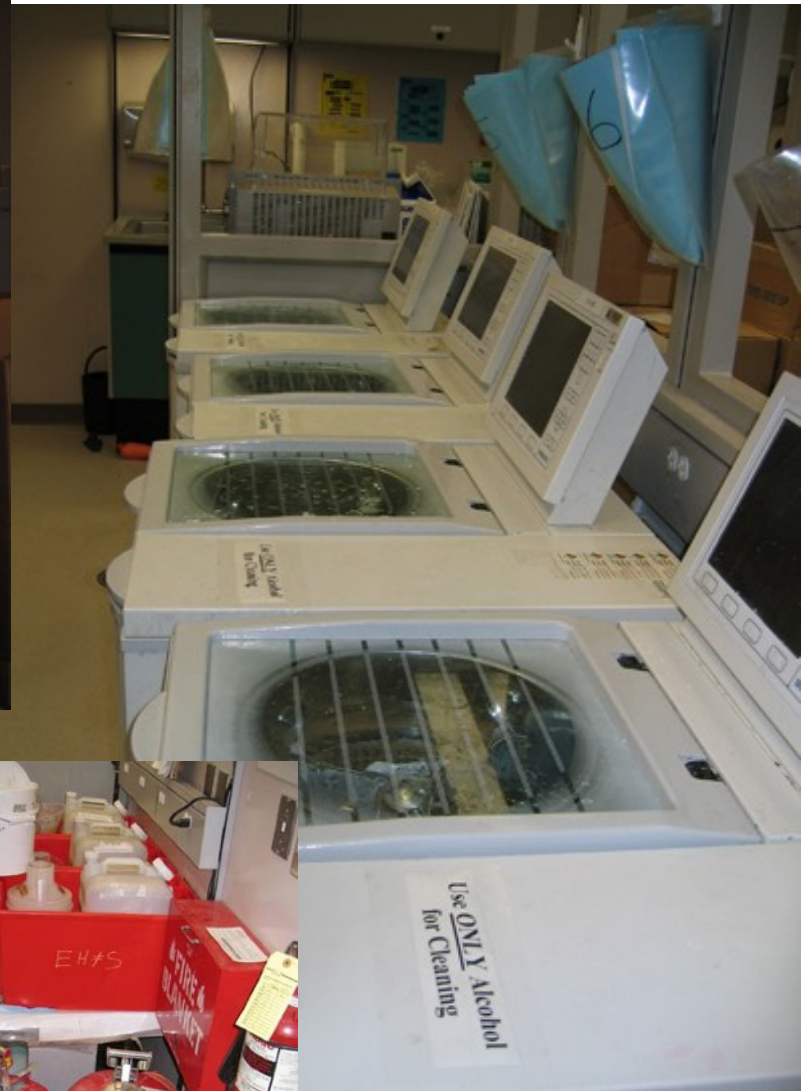


Tumor is sampled and placed in plastic cassettes for further processing.

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.



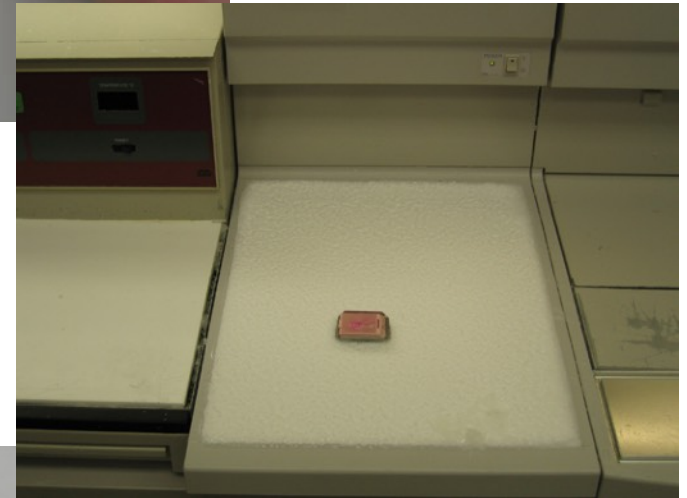
Tissue processing is done overnight and utilizes graded treatments of formalin, ethanol, xylene and paraffin.



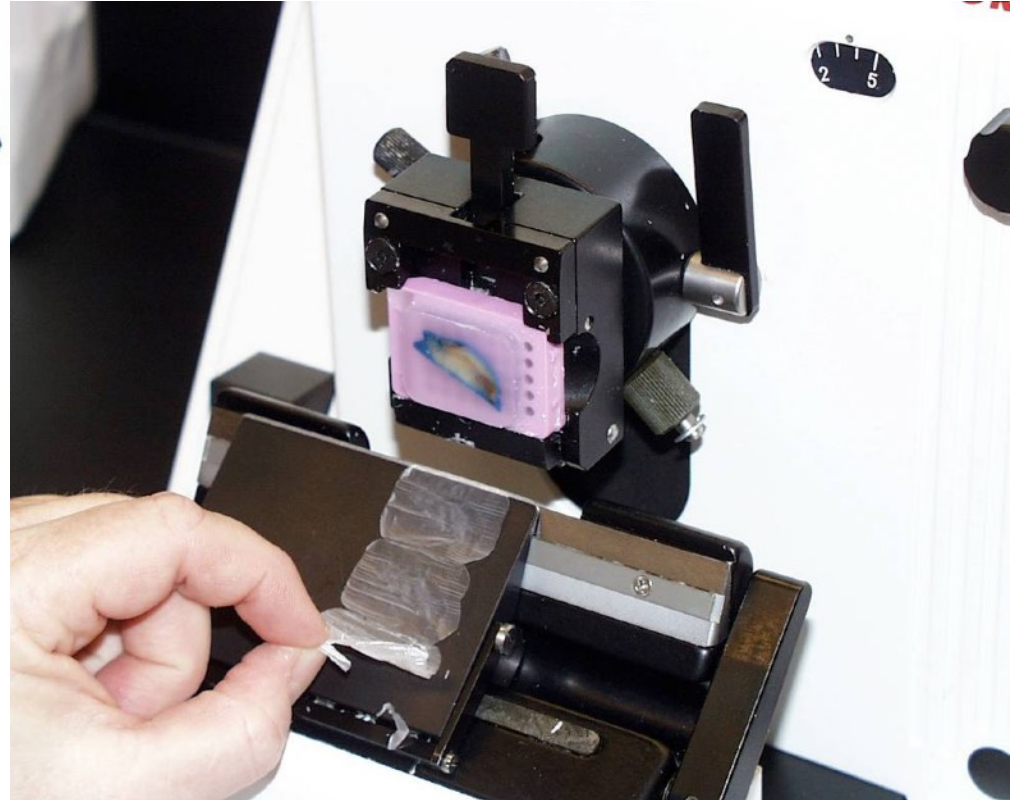
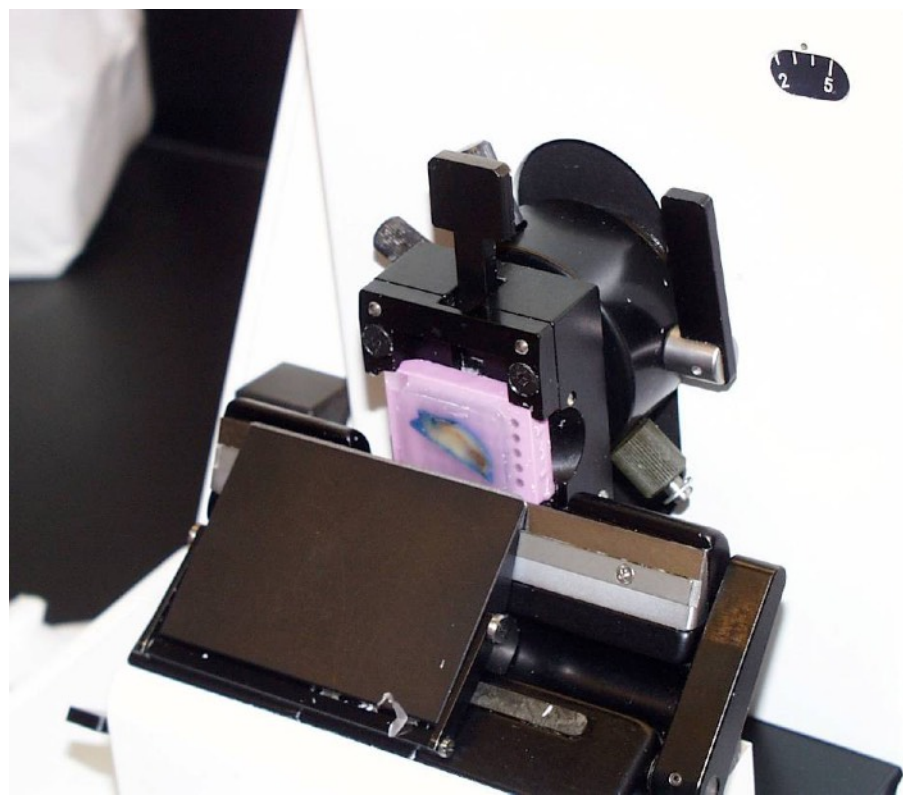


Blocks are retrieved from the tissue processor.





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



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

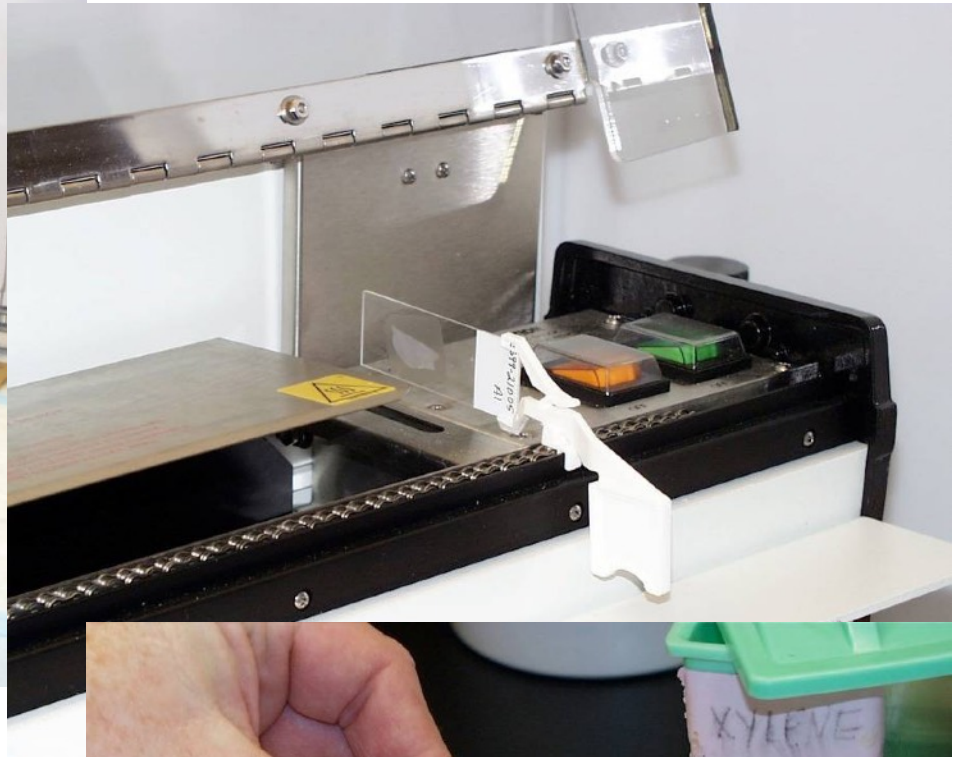


Tissue paraffin ribbons are placed in a warm waterbath and then picked up on glass slides.



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?***



cap

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

Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: June 2012

Procedures

- Biopsy
- Resection

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

+ Necrosis

+ ___ Not identified

+ ___ Present

+ Extent: ___%

+ ___ Cannot be determined

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

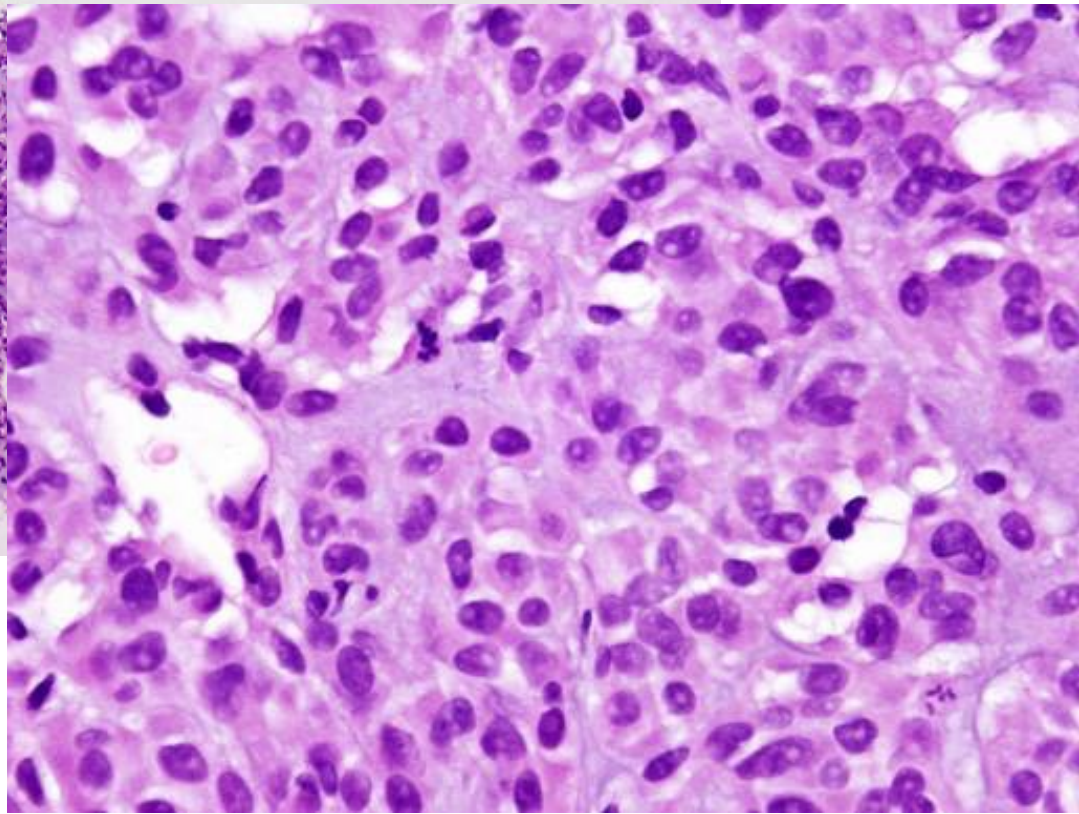
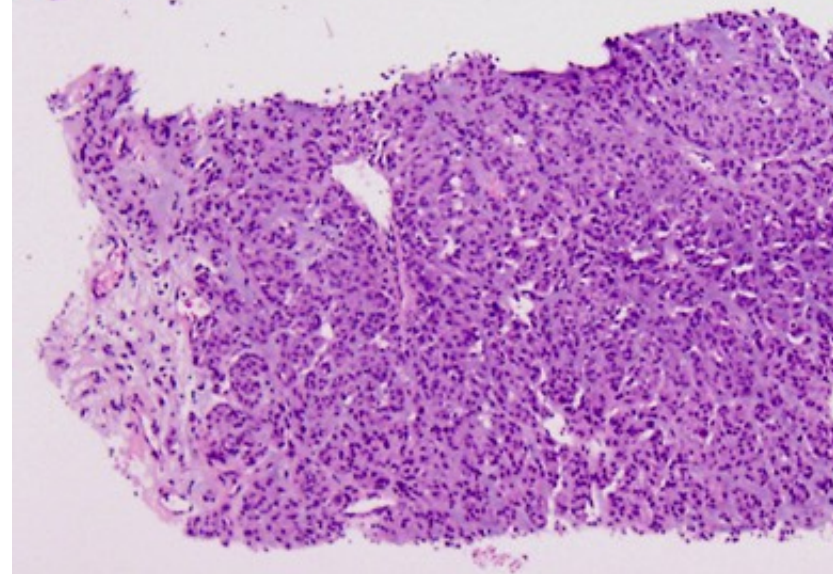
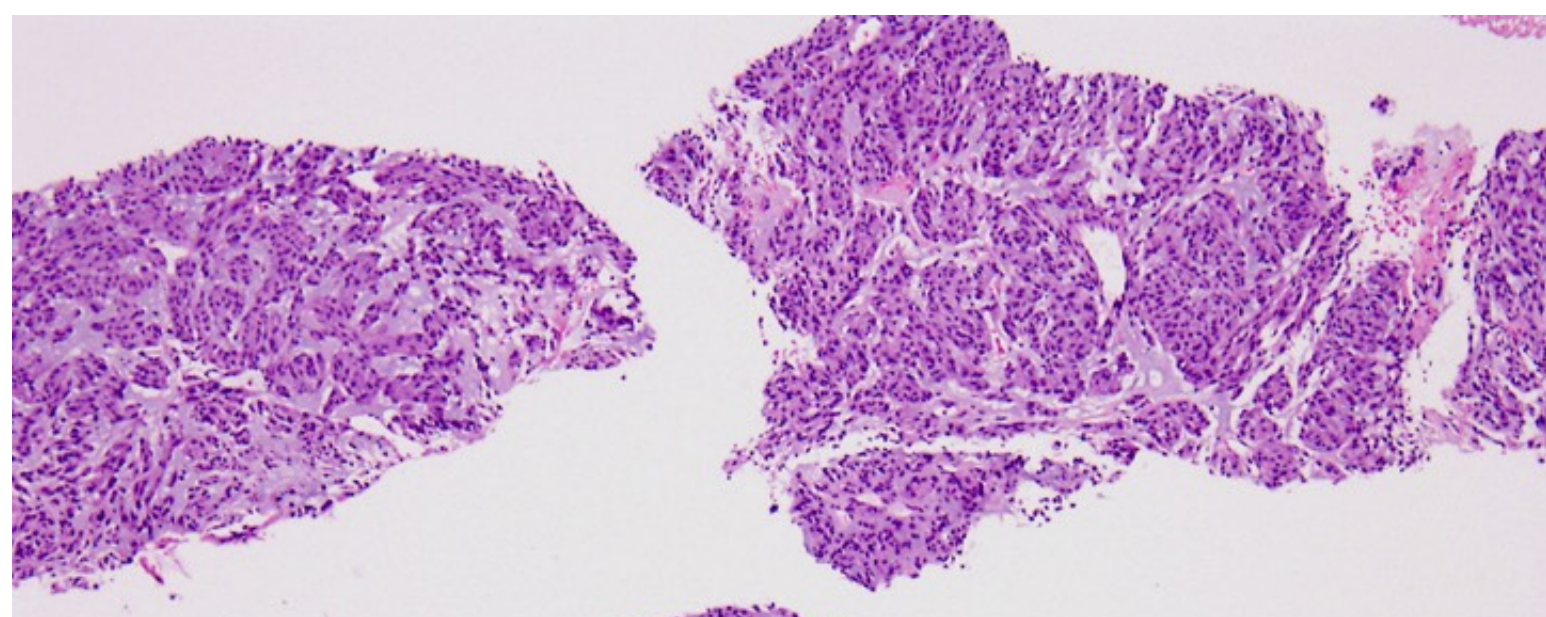
+ Treatment Effect (Note F)

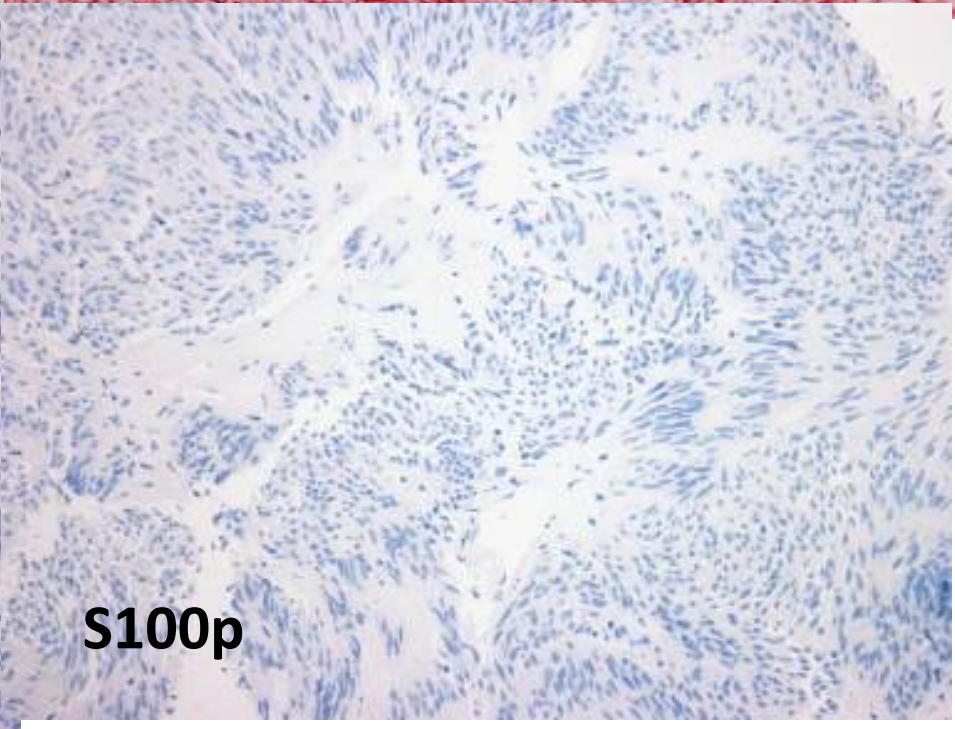
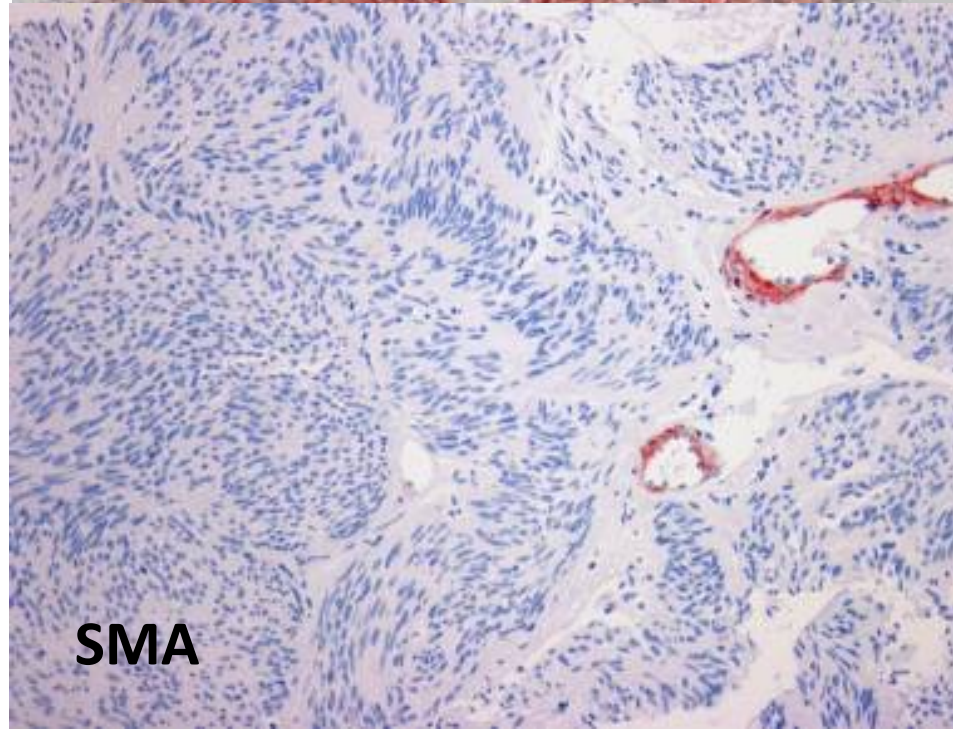
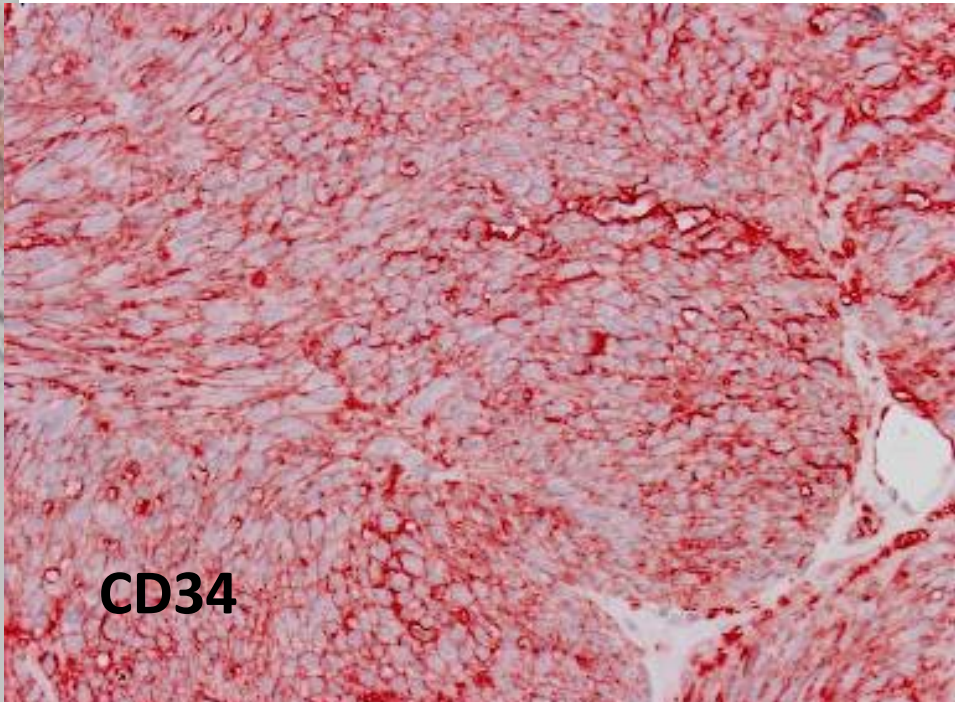
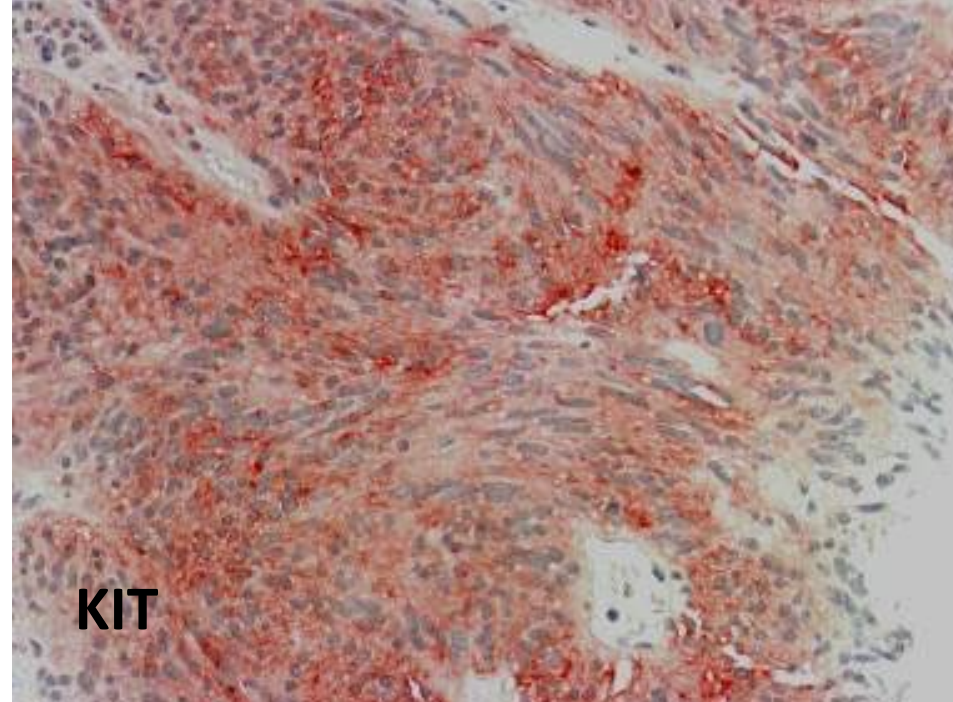
- + Specify percentage of viable tumor: ___%

+ Comment(s)

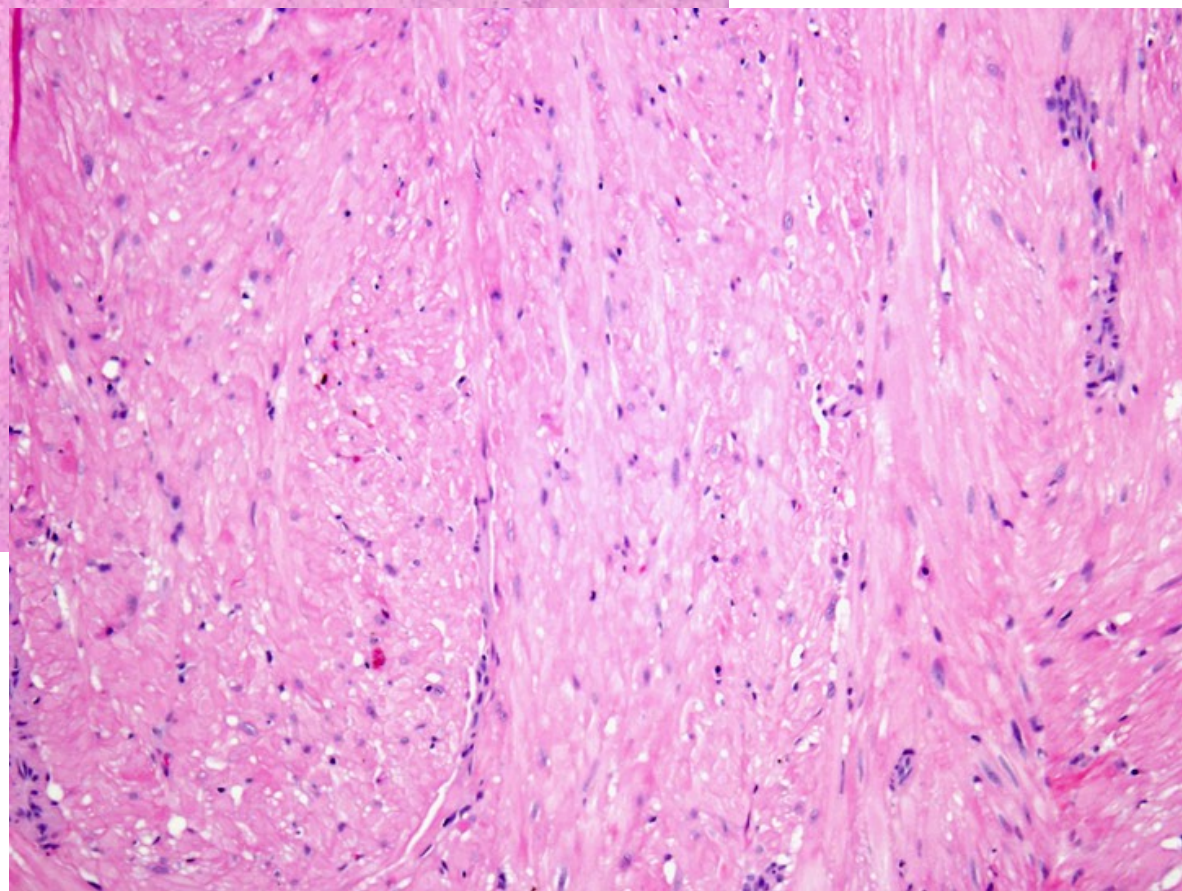
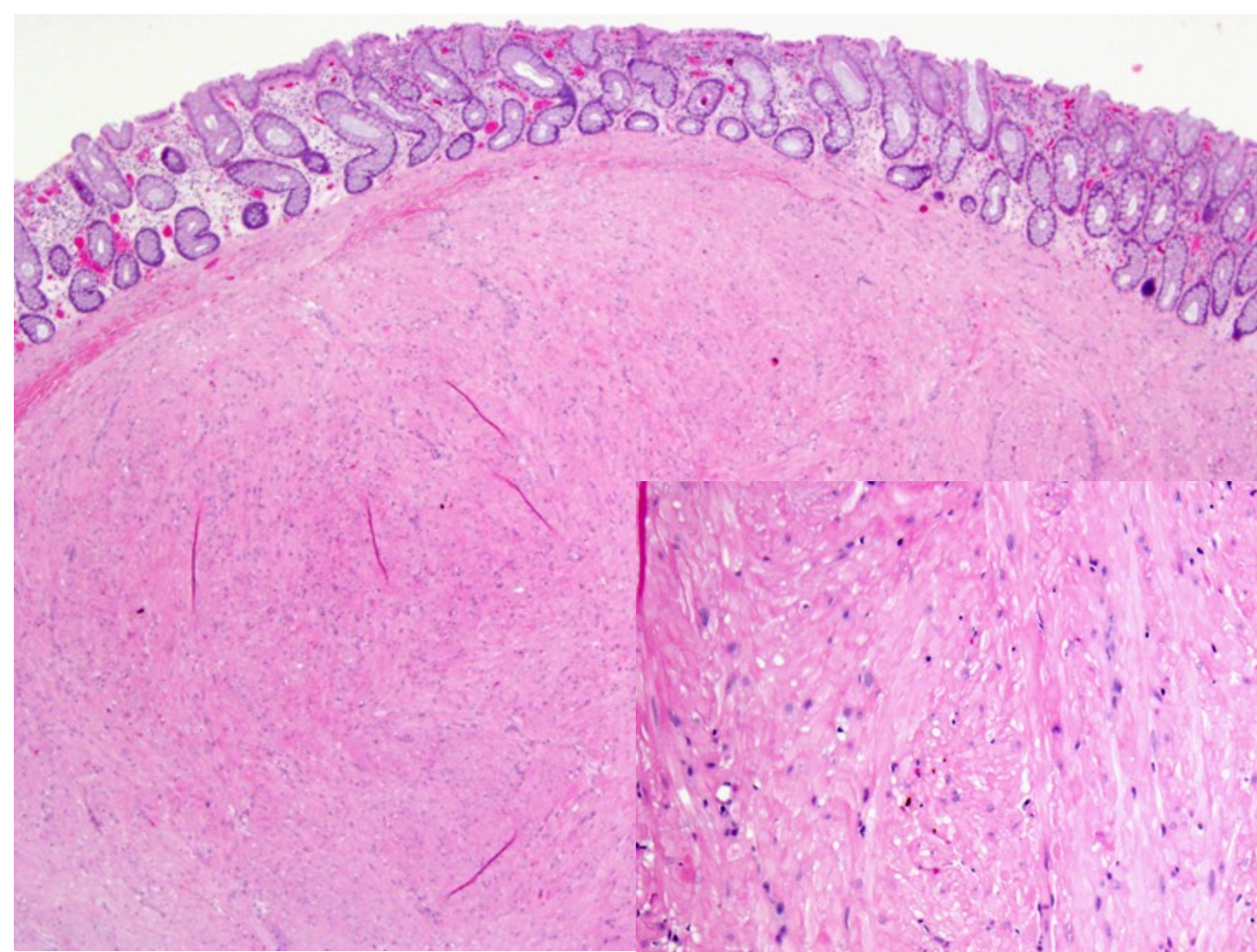
Getting the diagnosis right

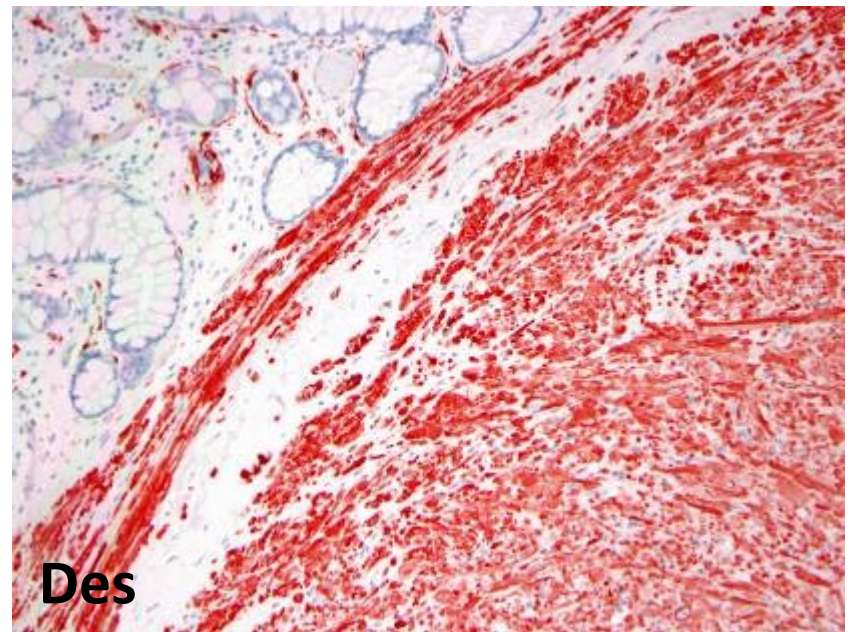
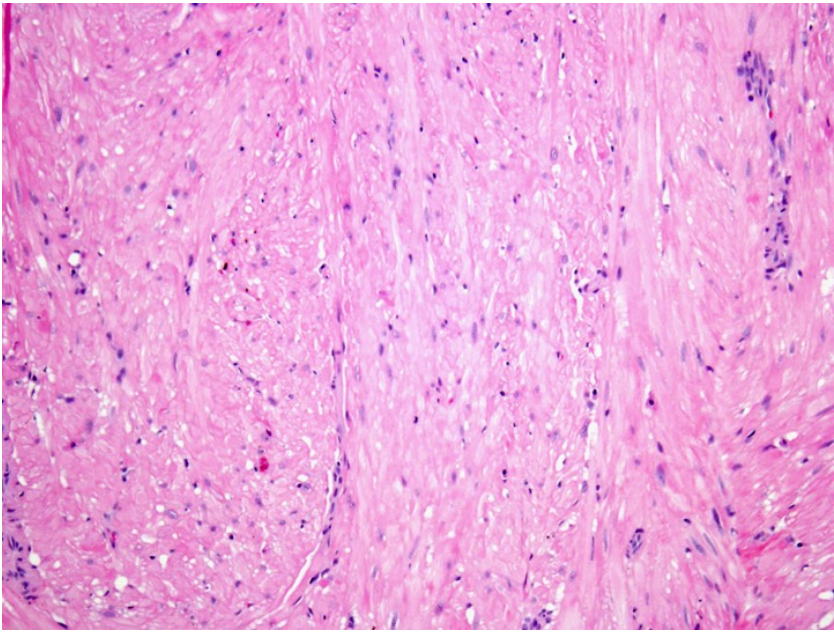
Case 1



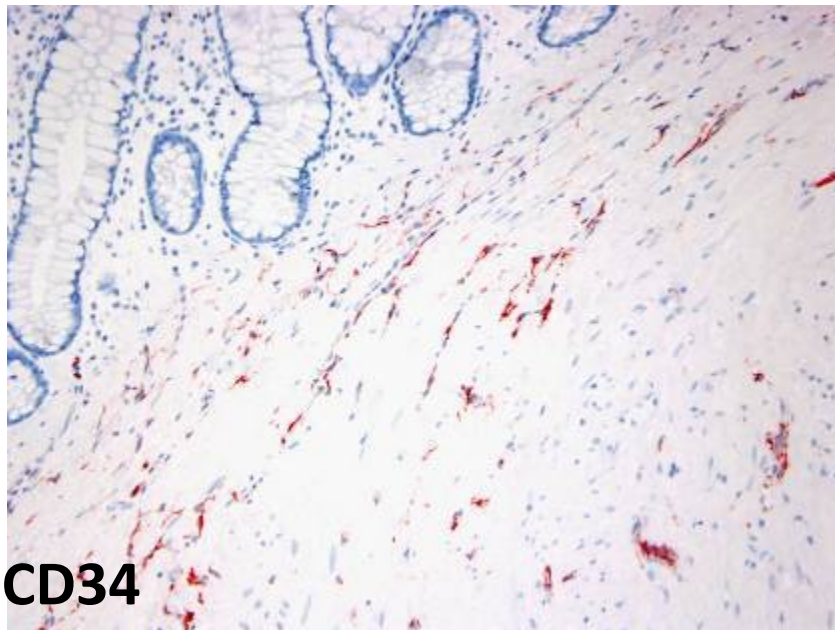


Case 2

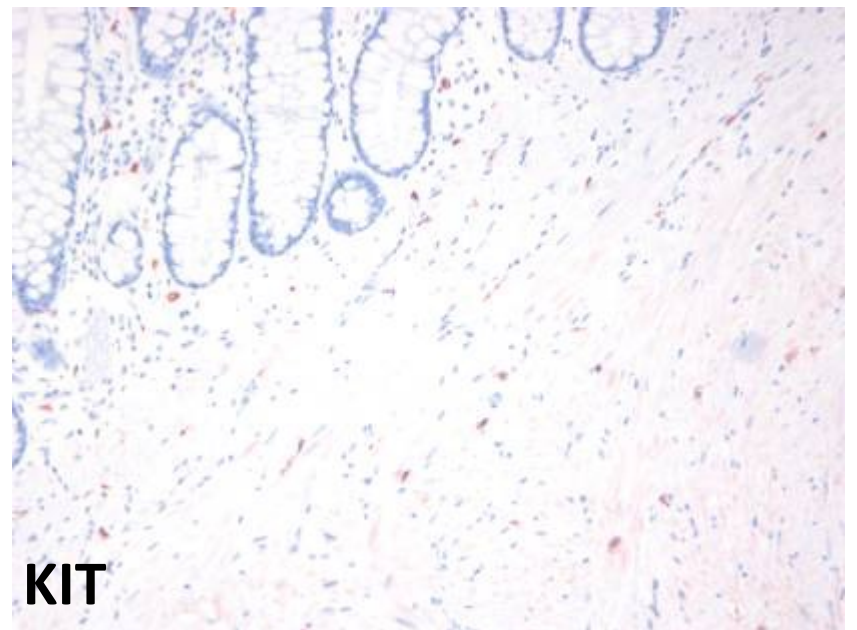




Des

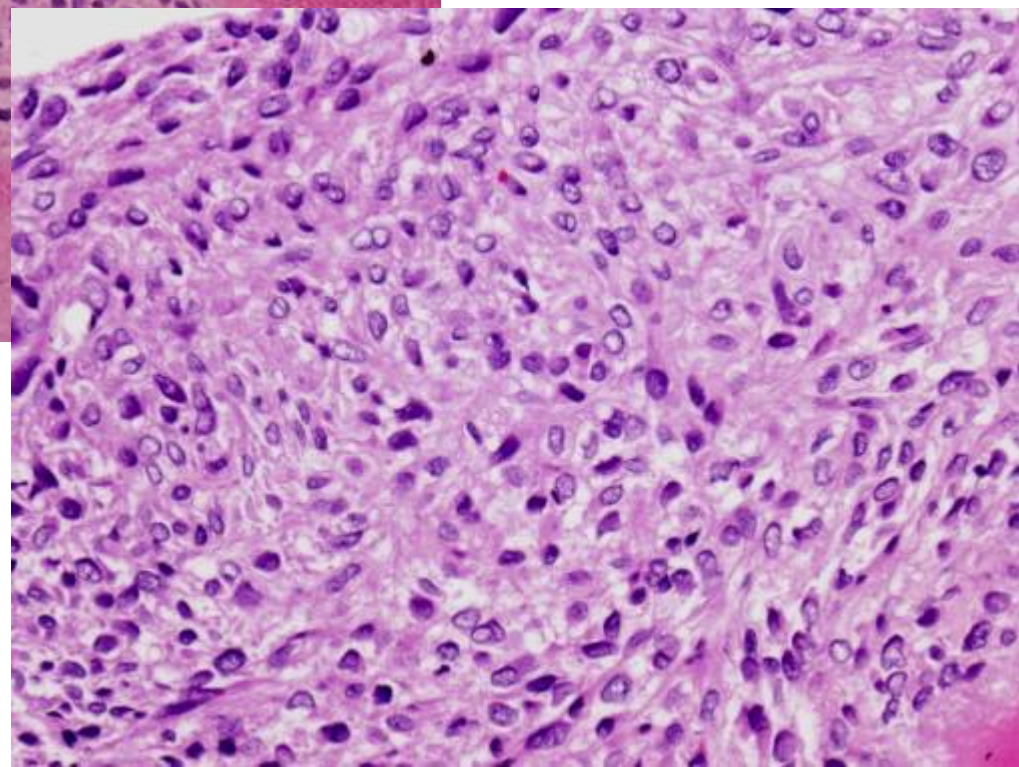
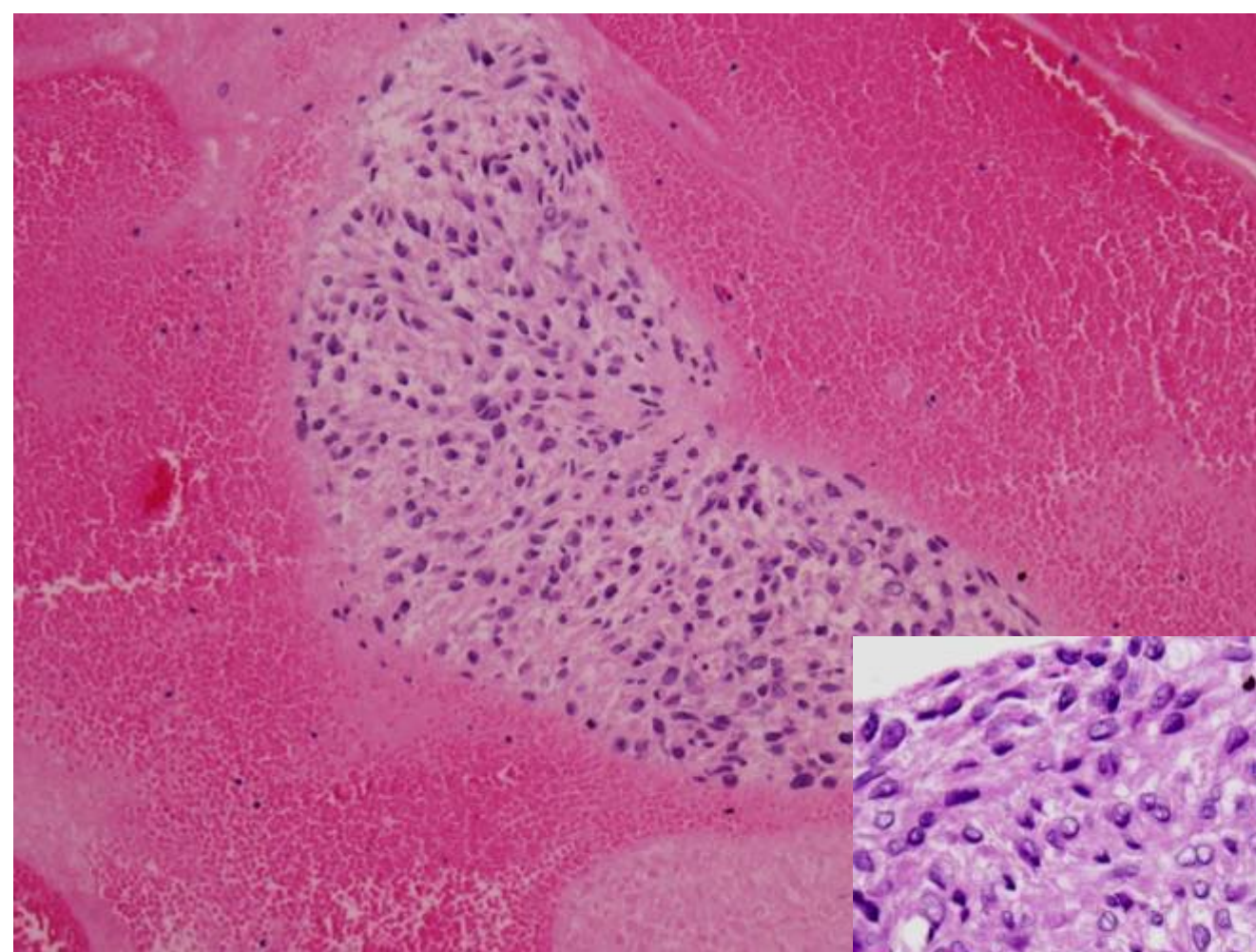


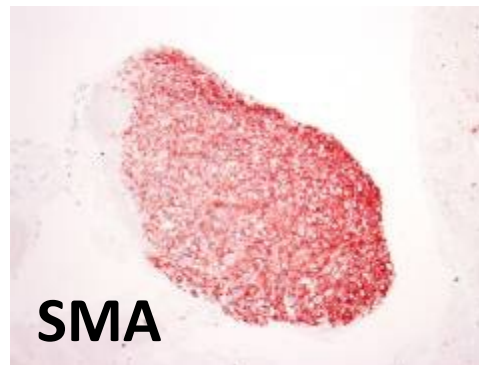
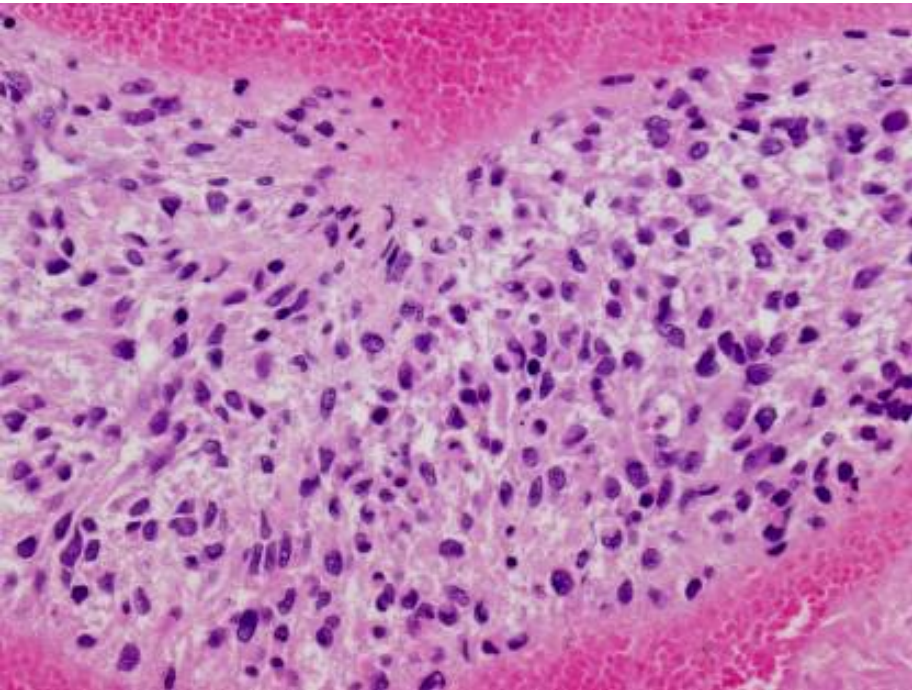
CD34



KIT

Case 3





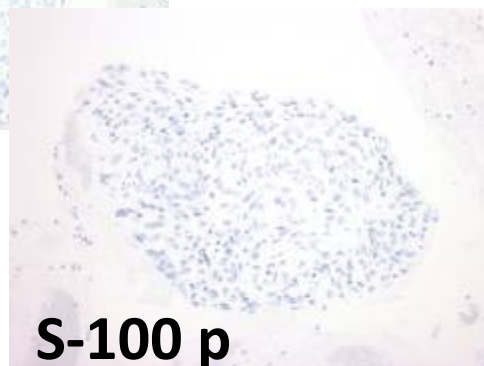
SMA



Des



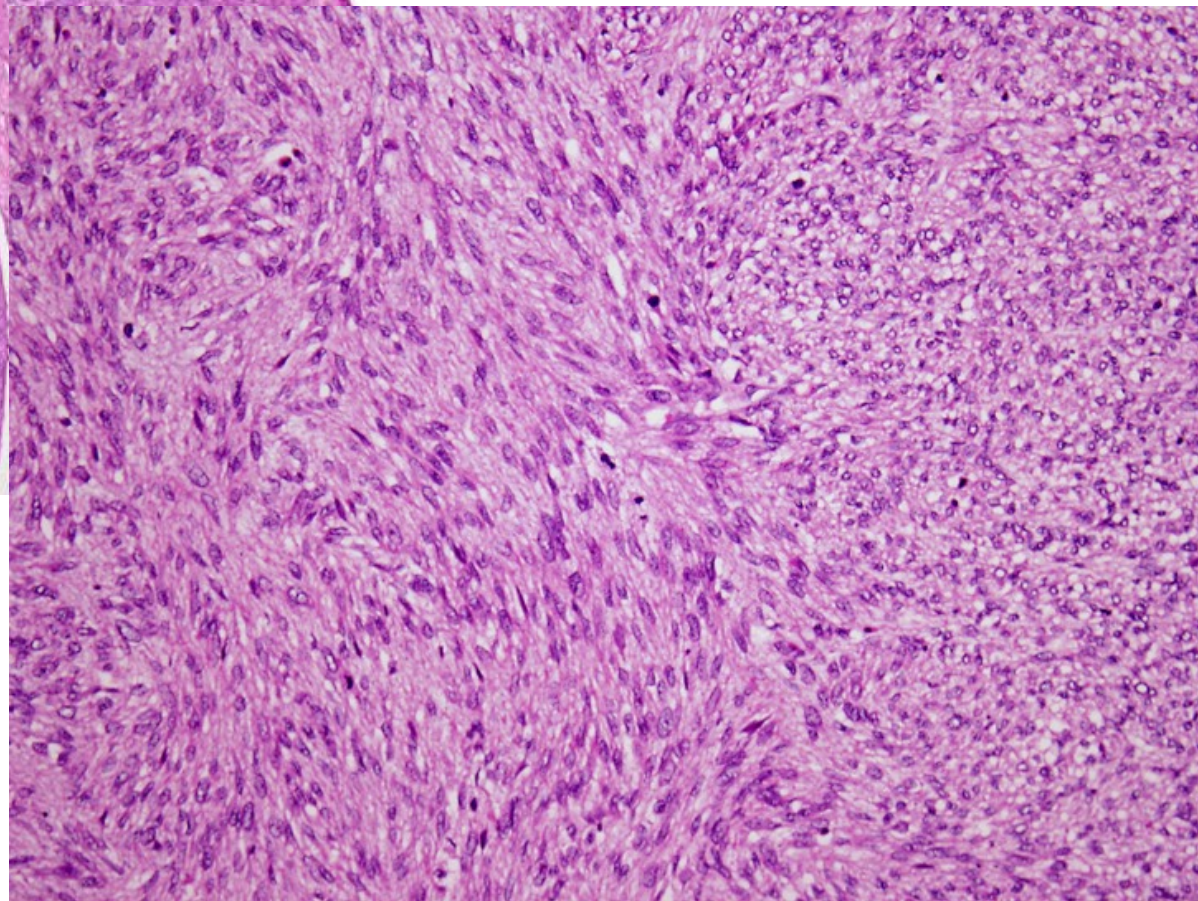
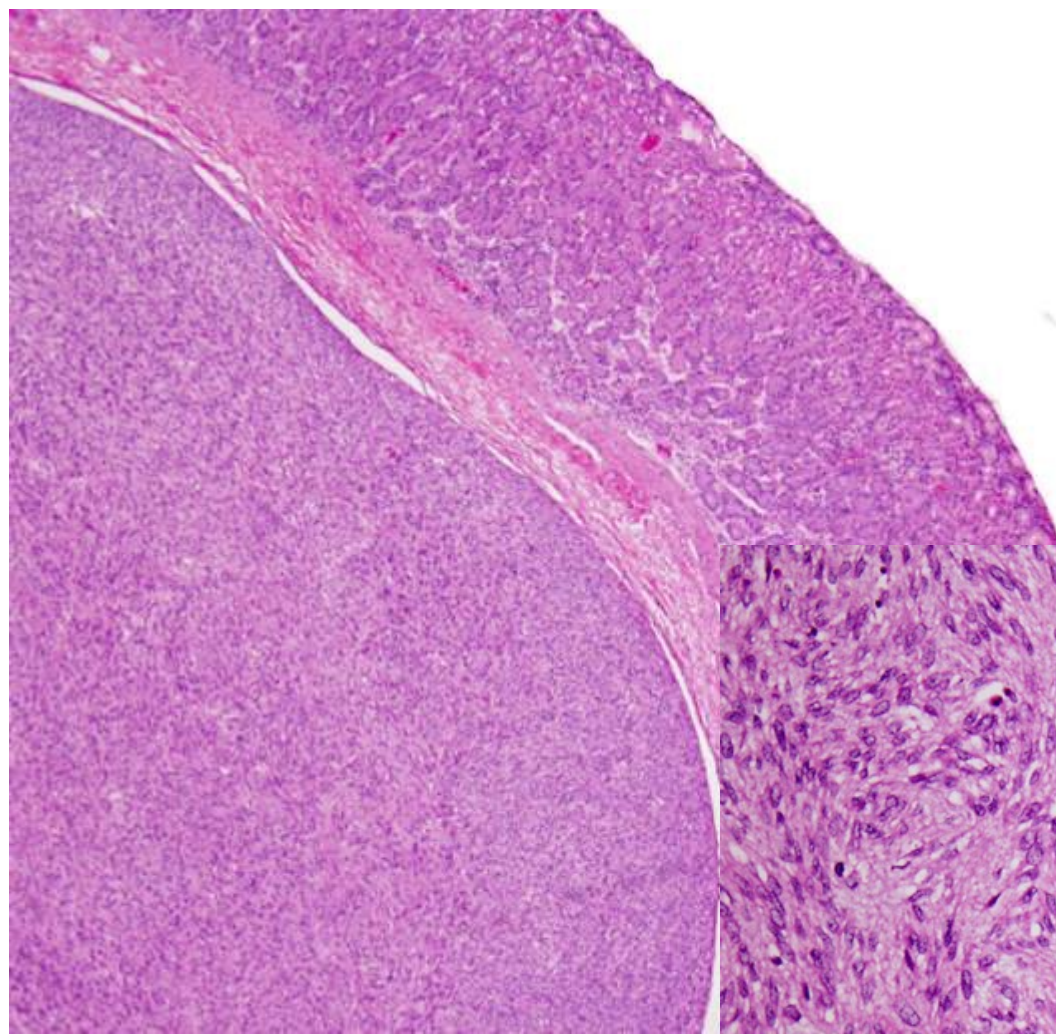
panK

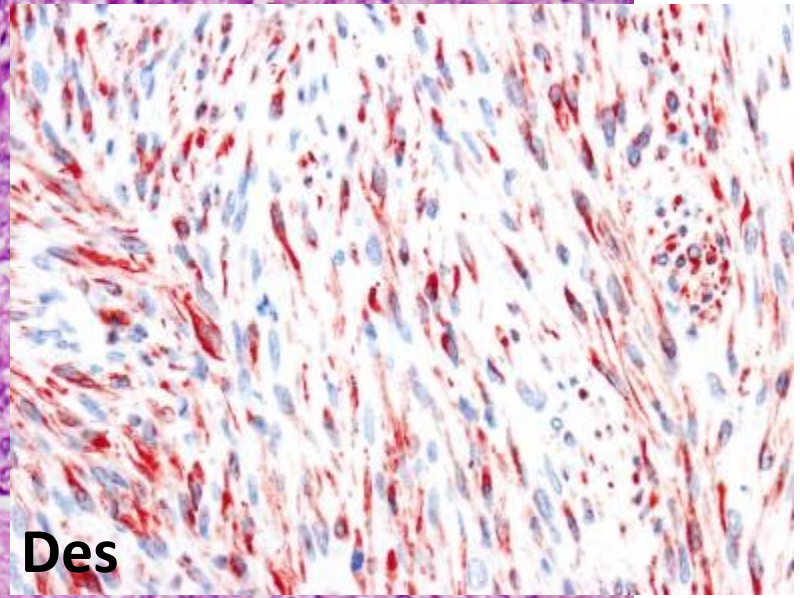
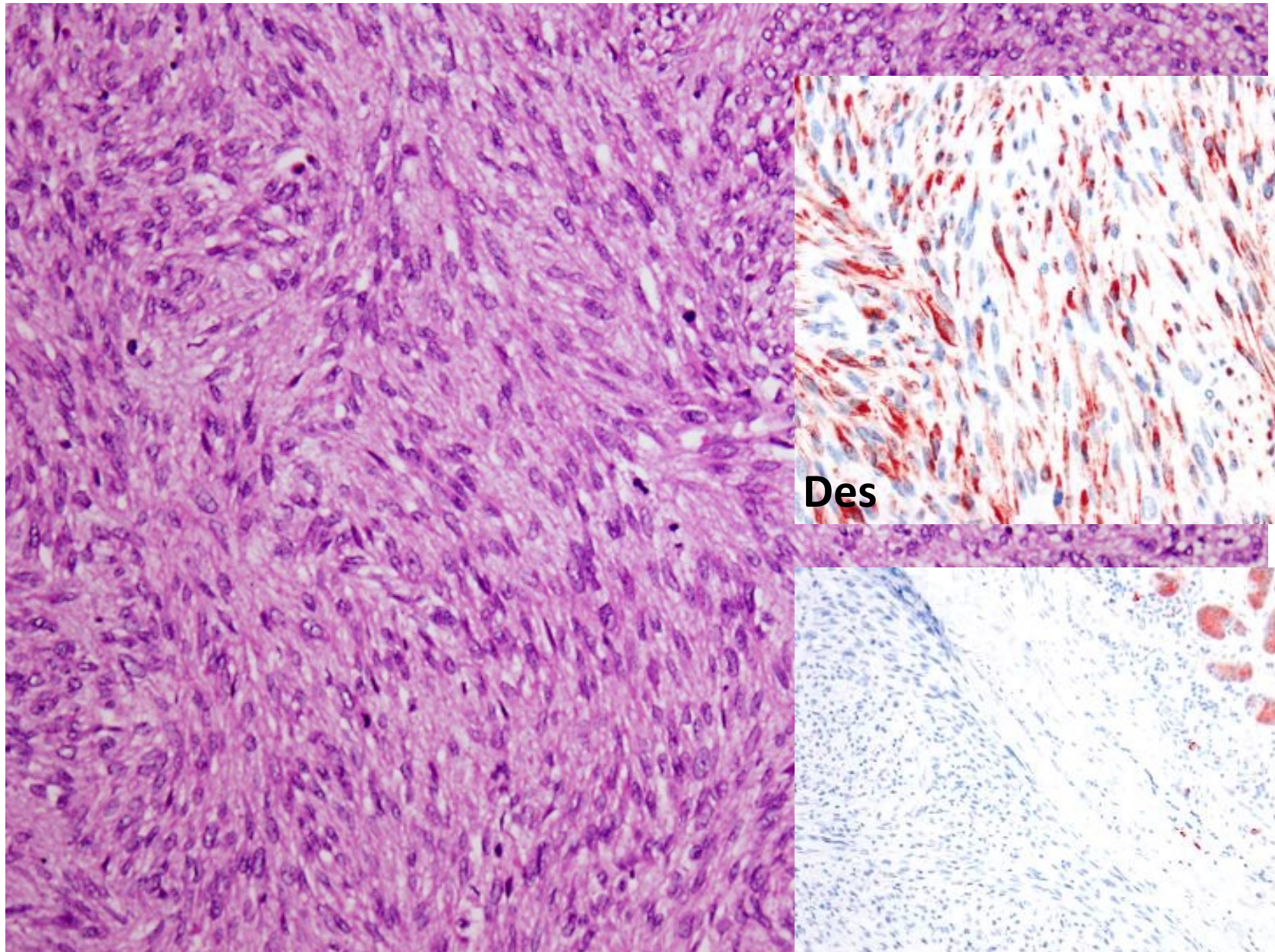


S-100 p

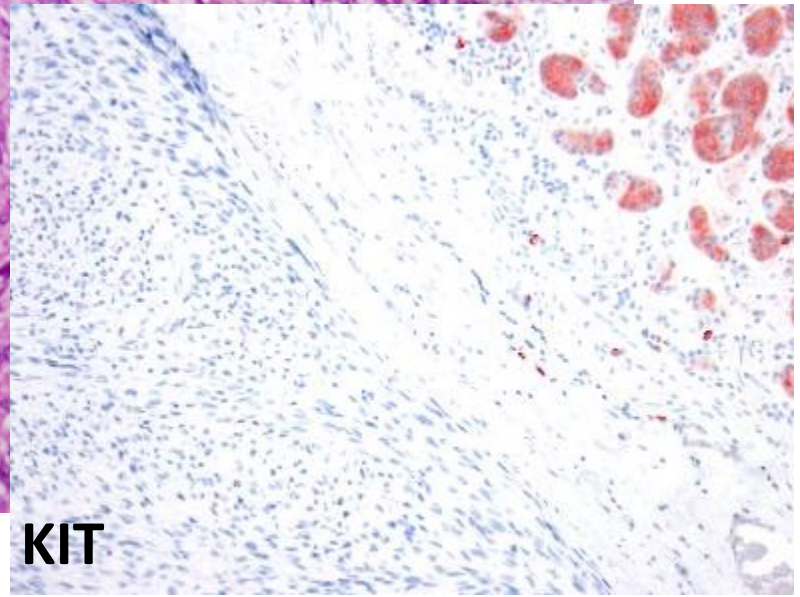


KIT

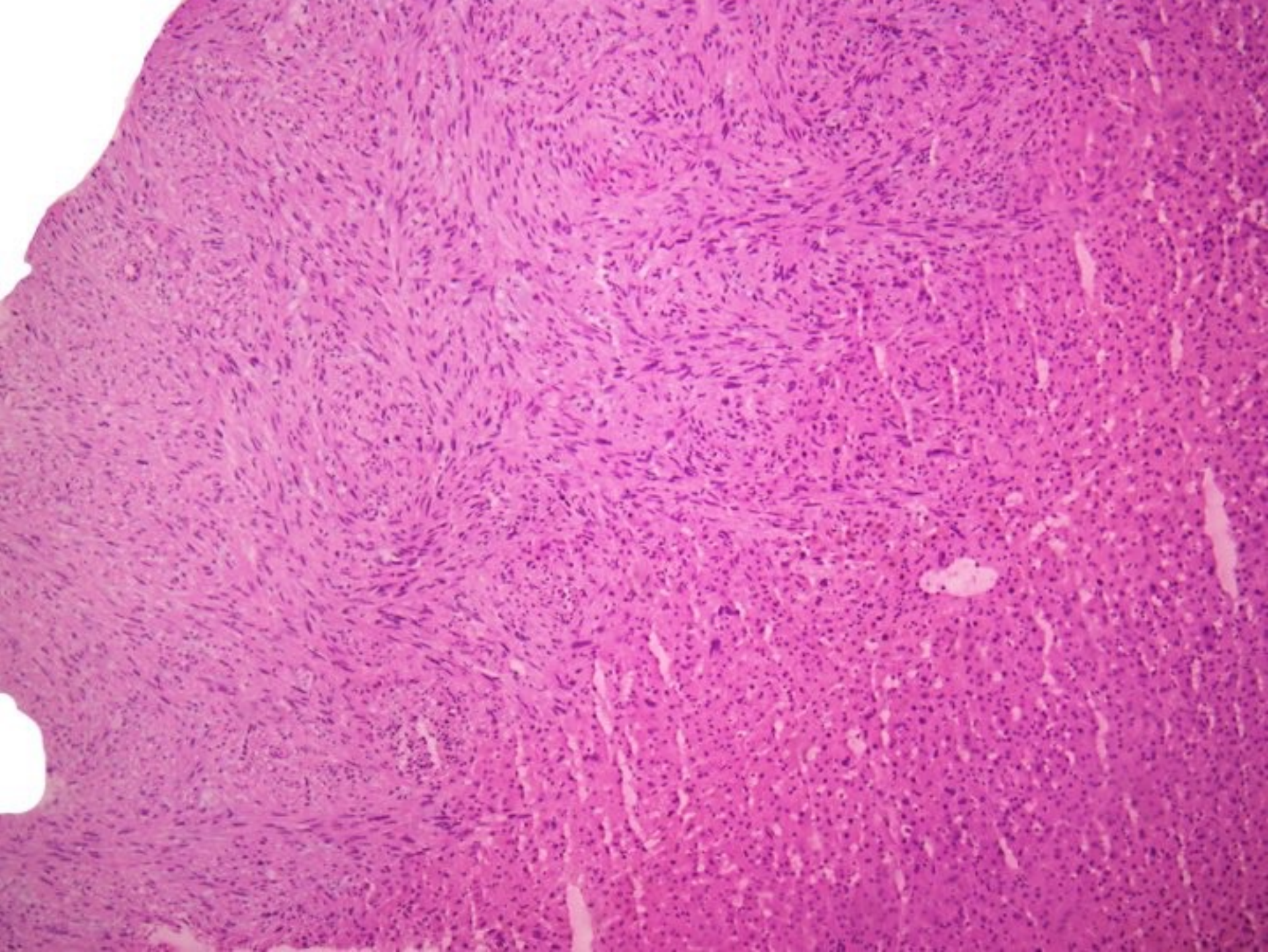




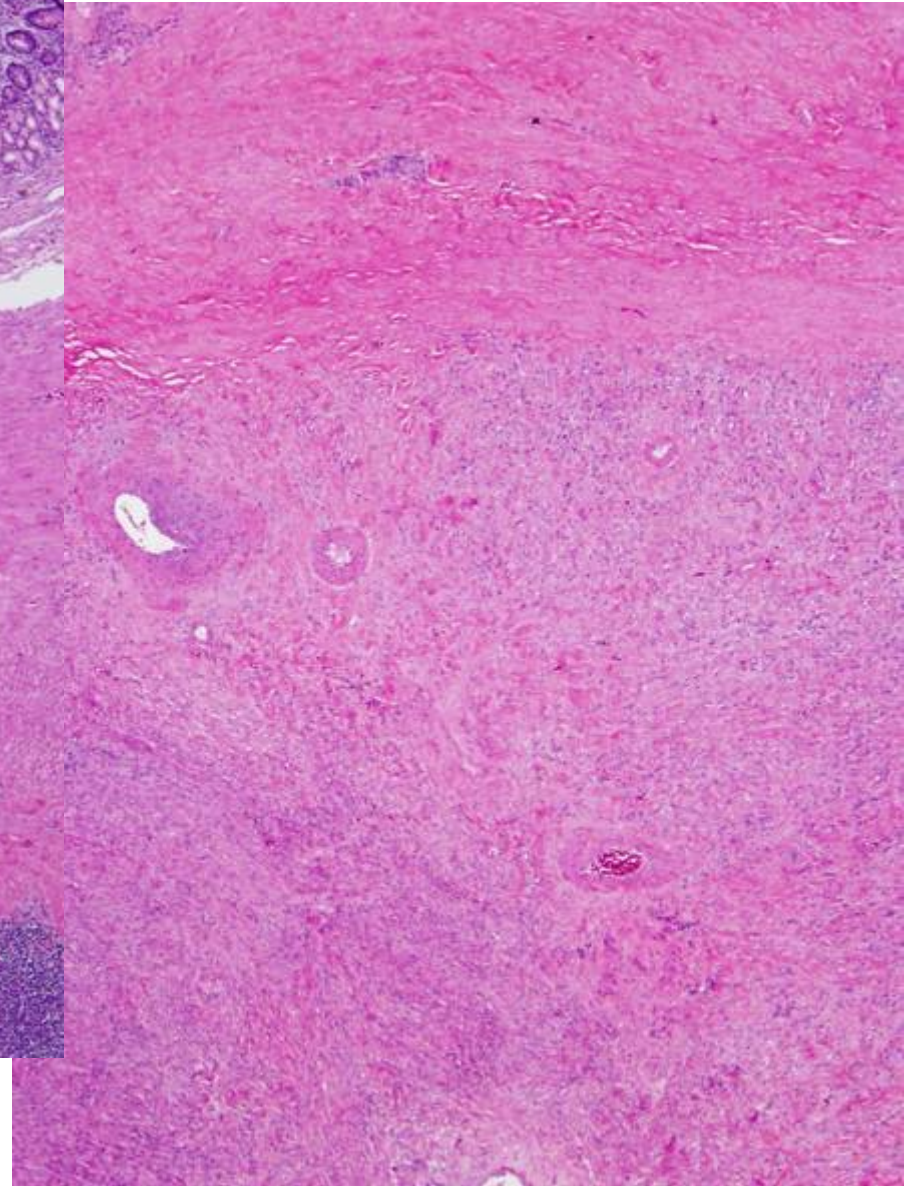
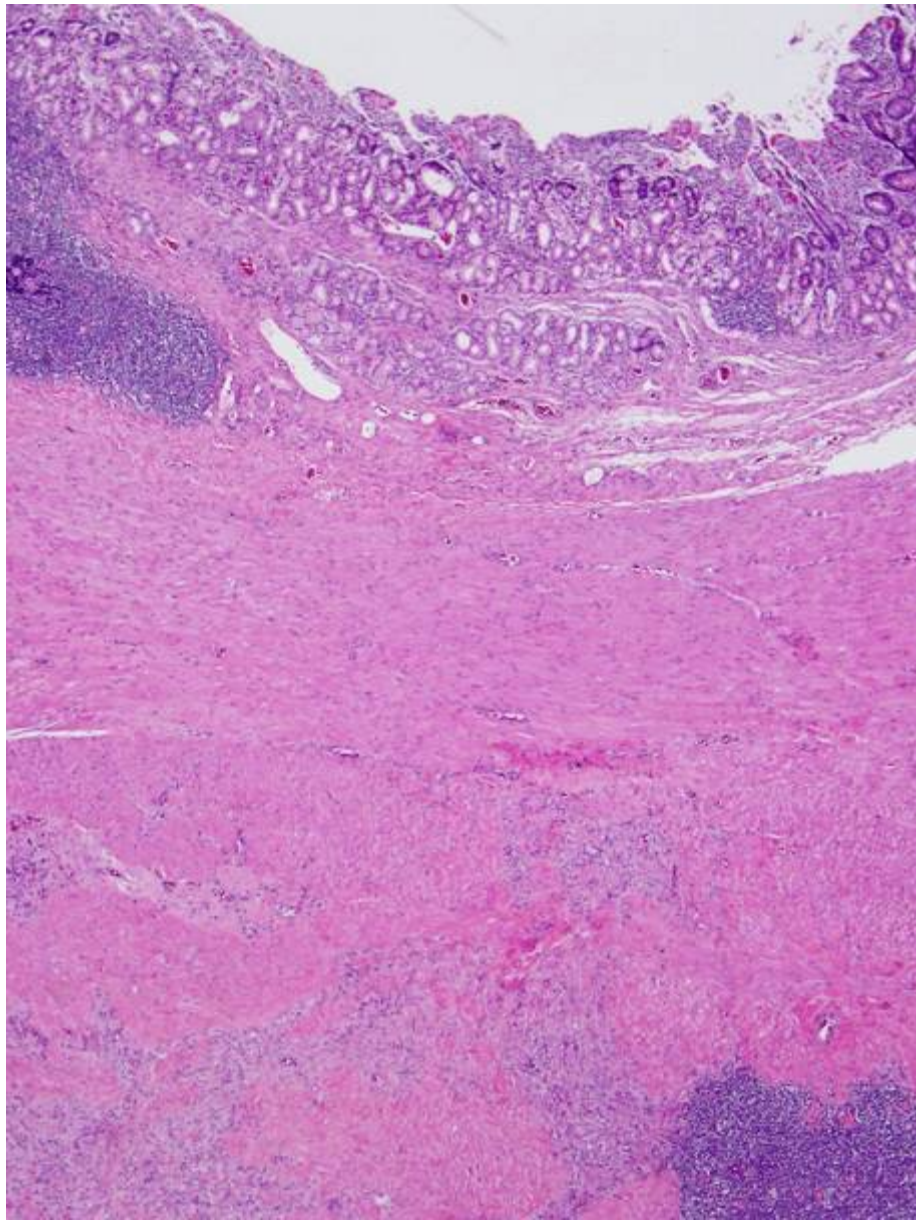
Des

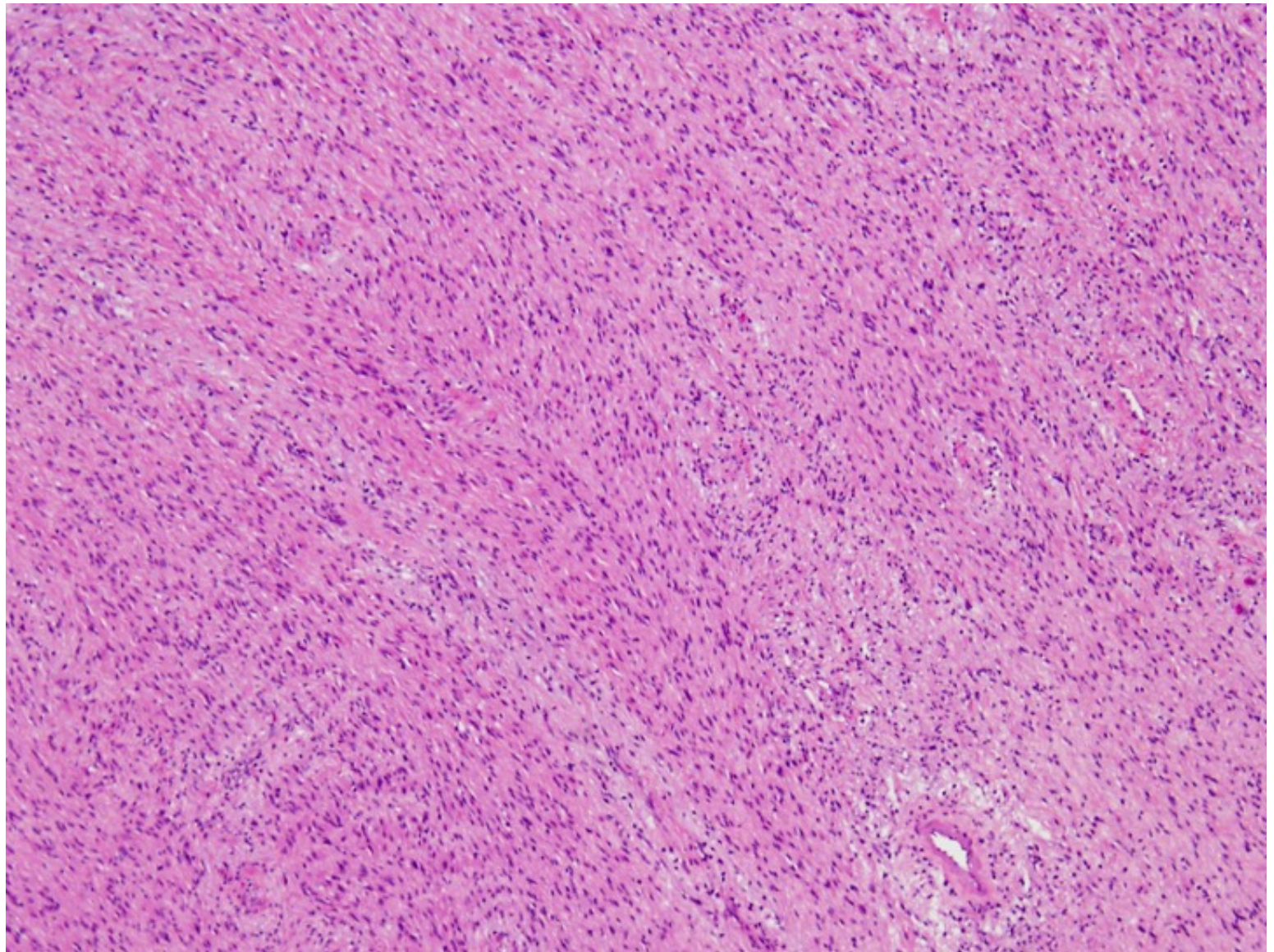


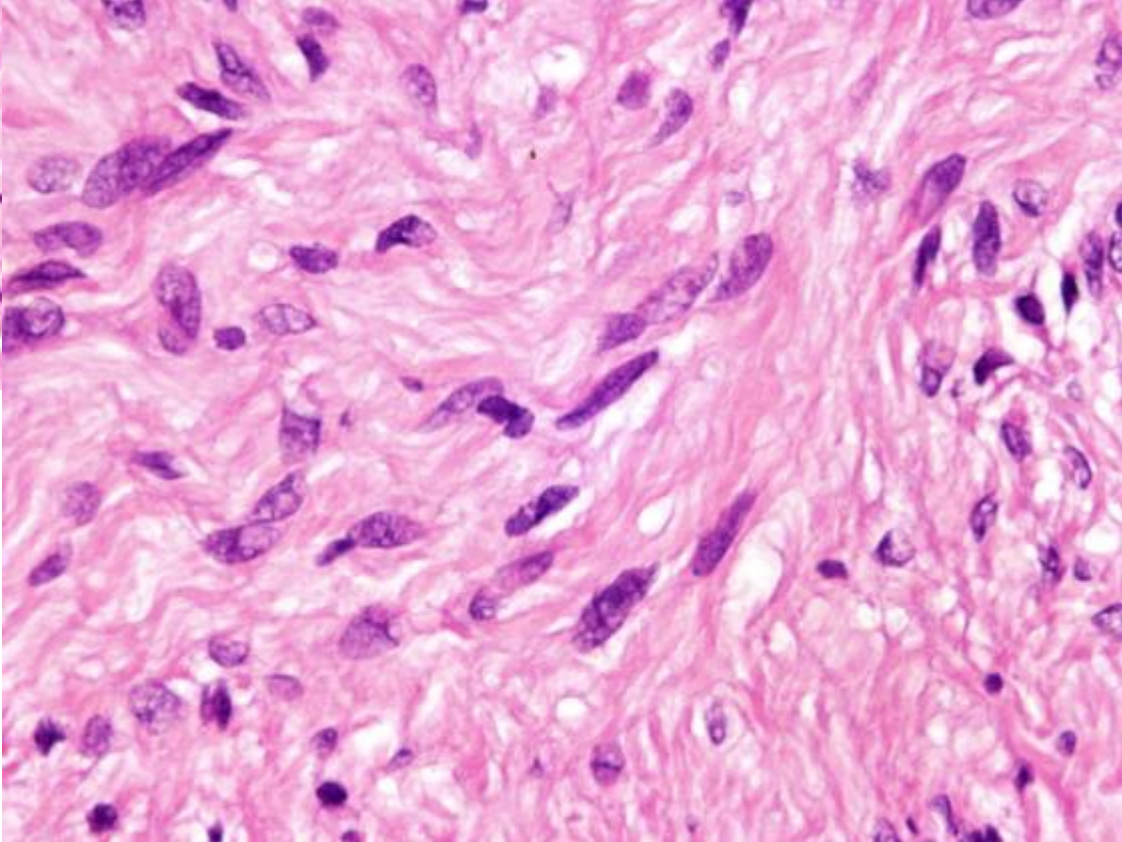
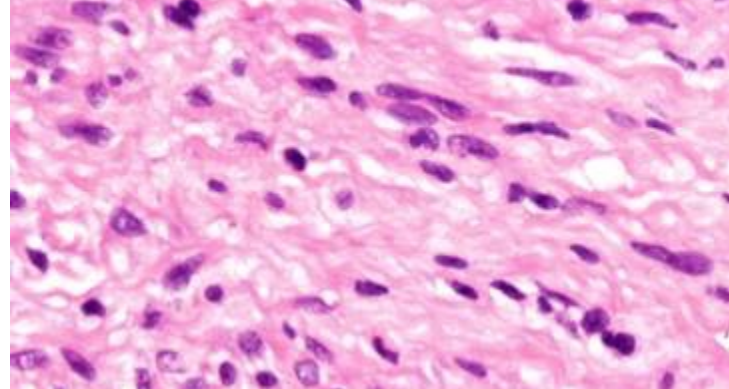
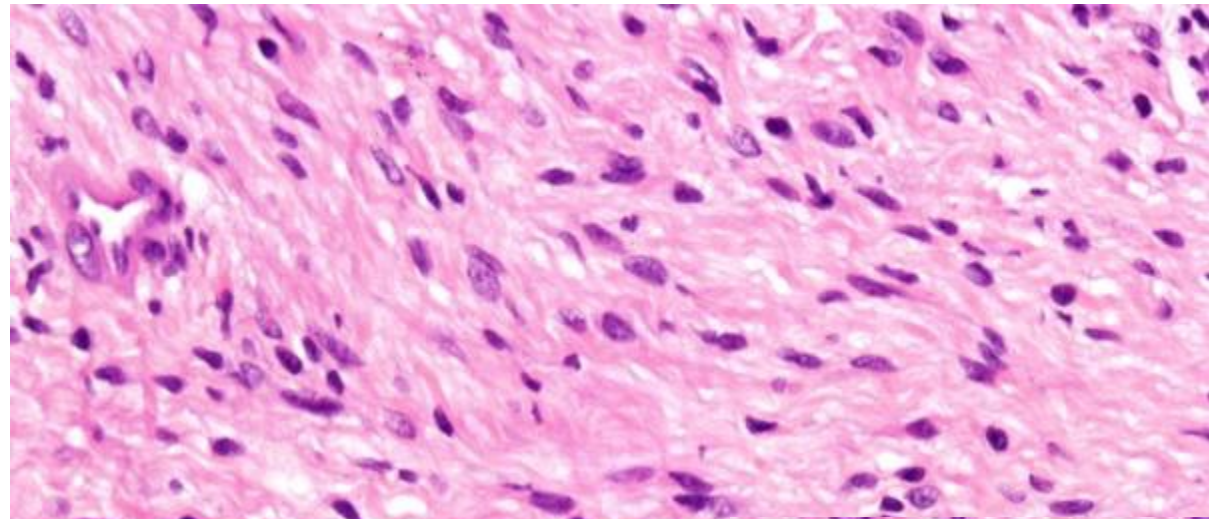
KIT



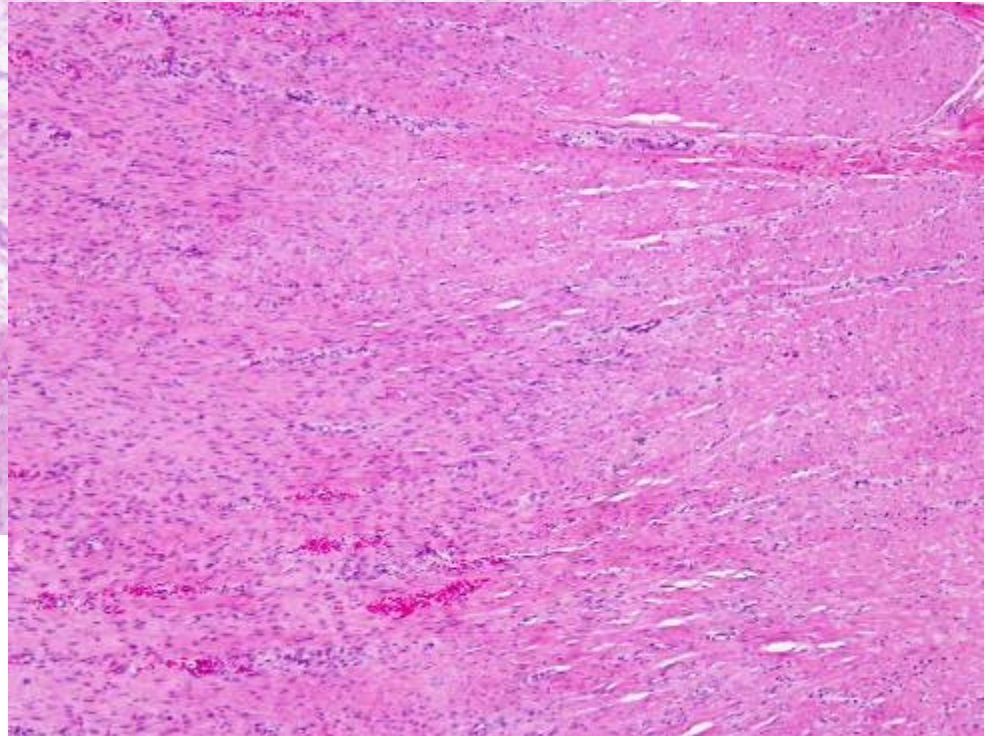
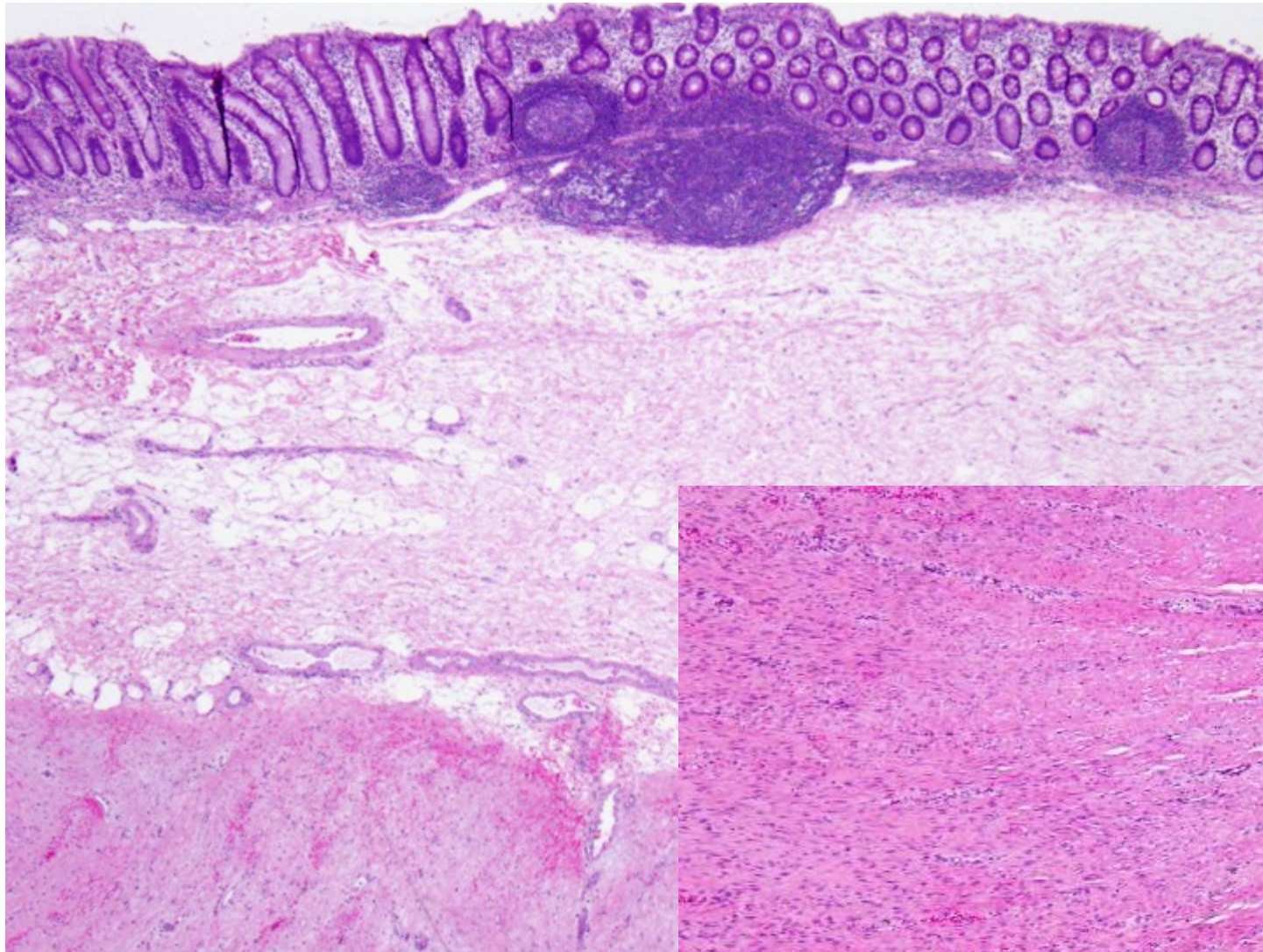
Case 4

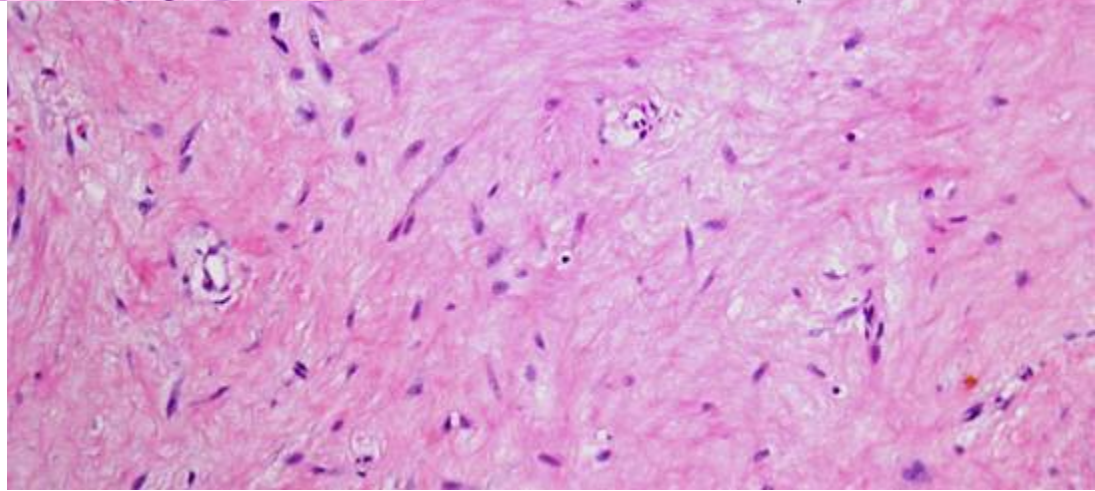
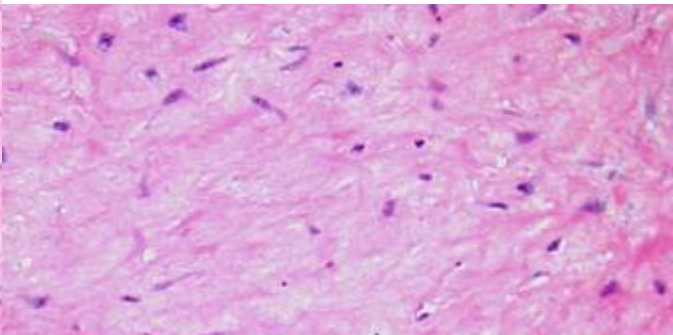
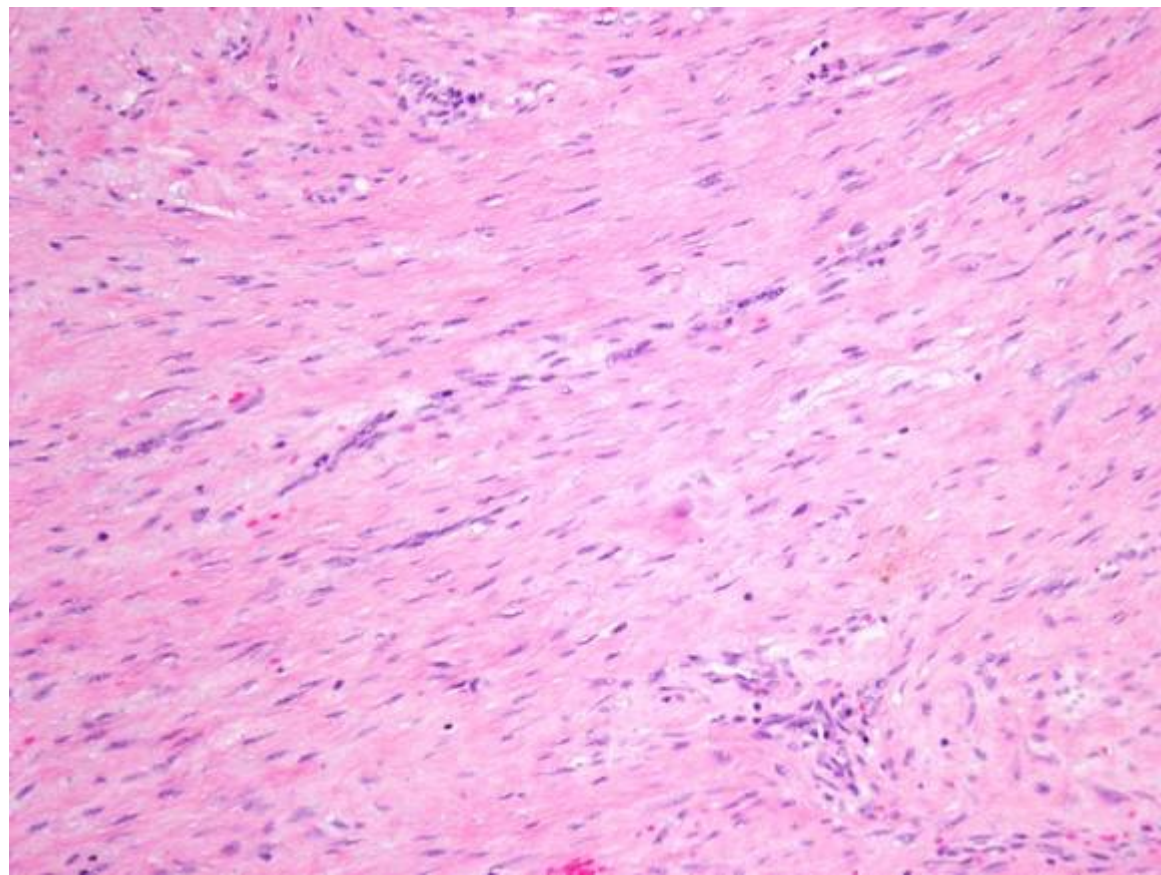


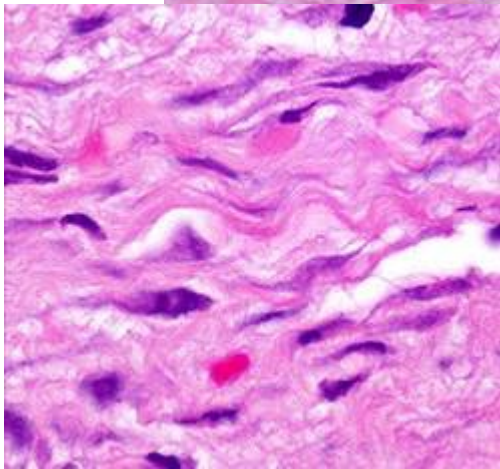
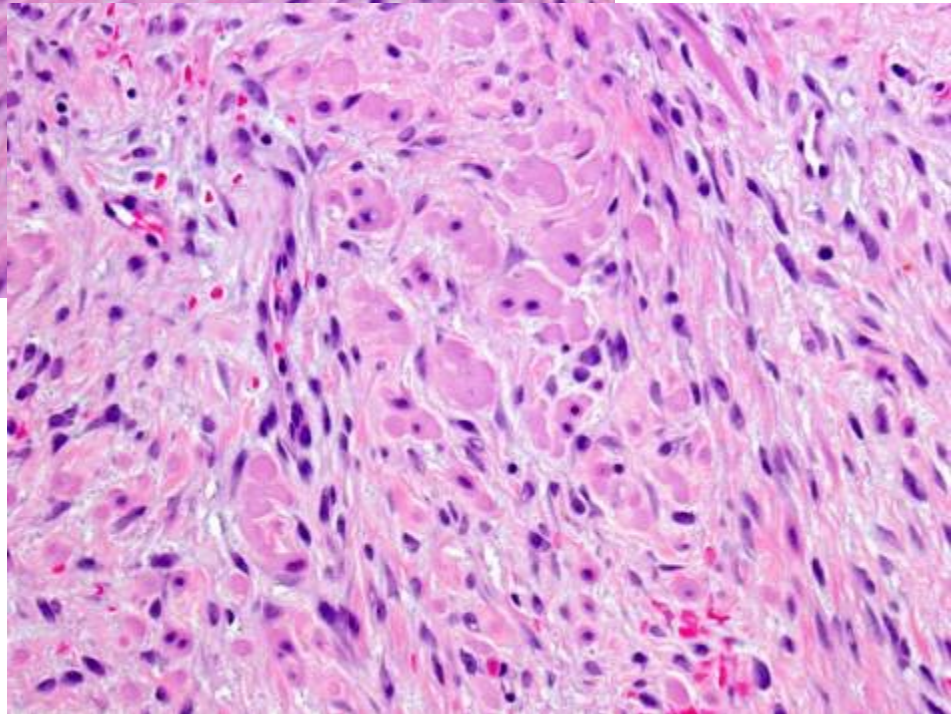
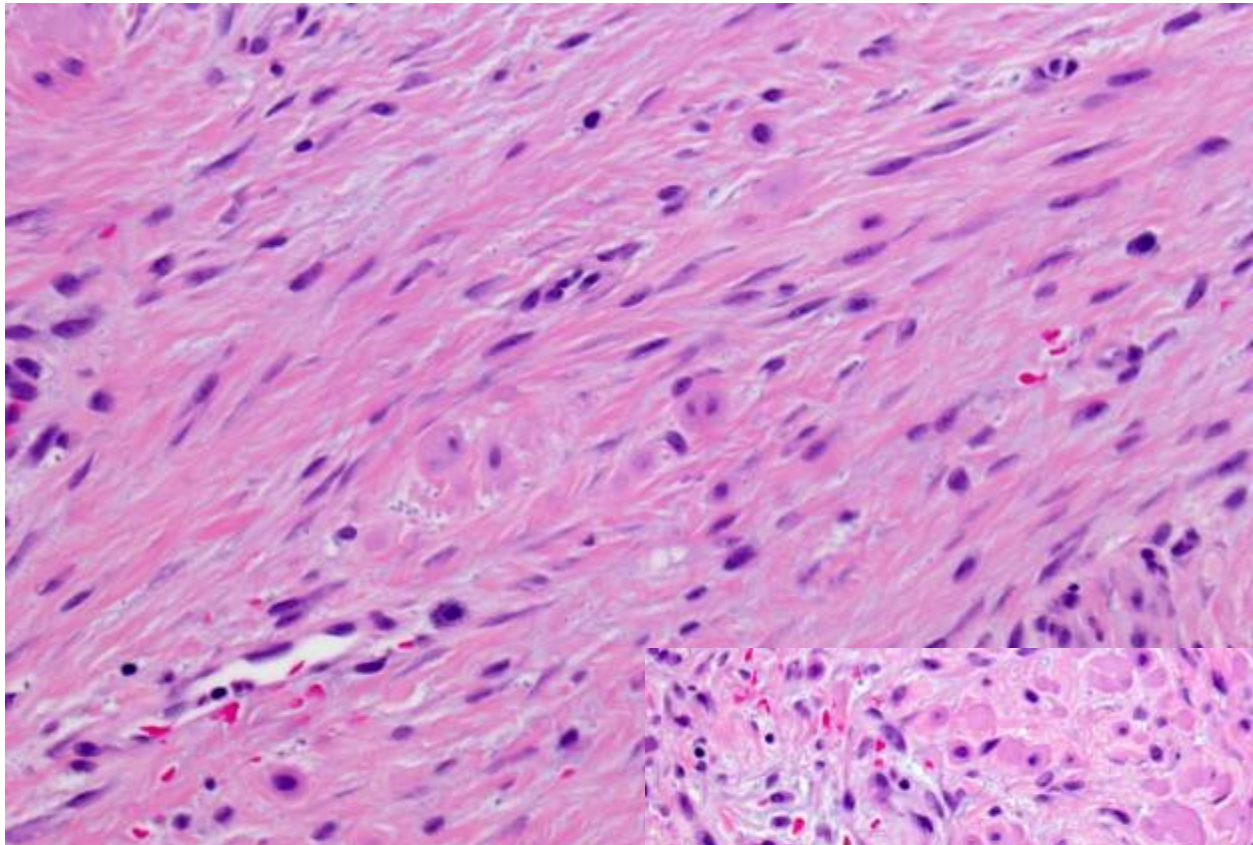


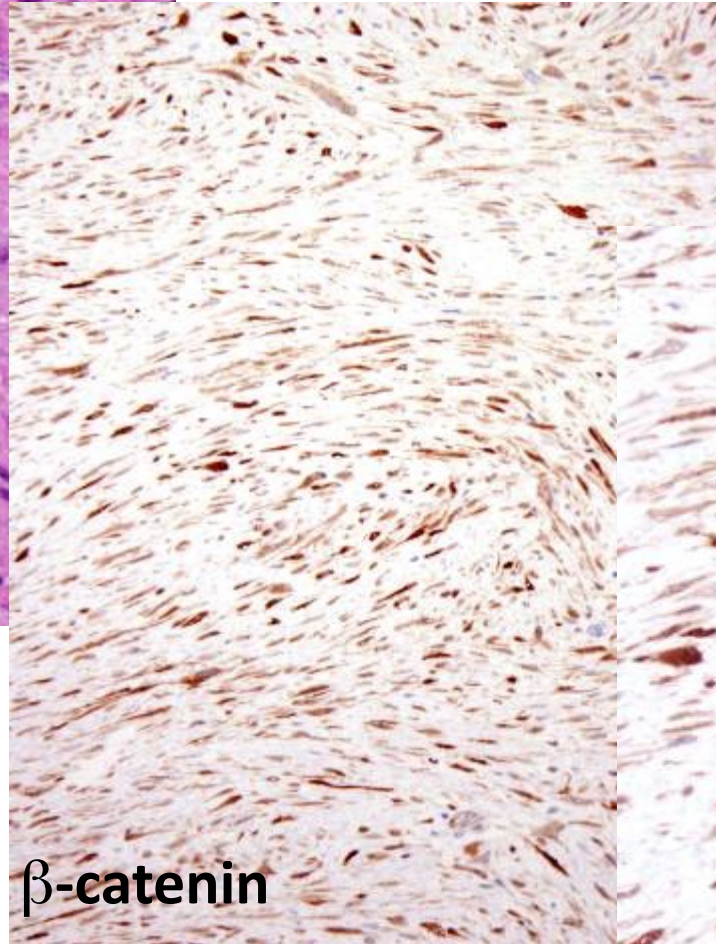
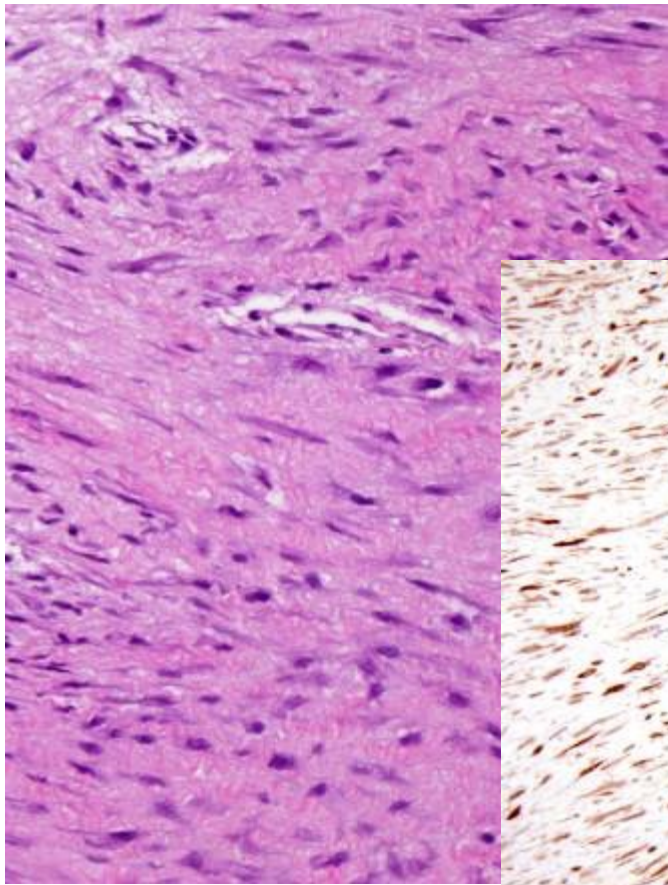


Case 5

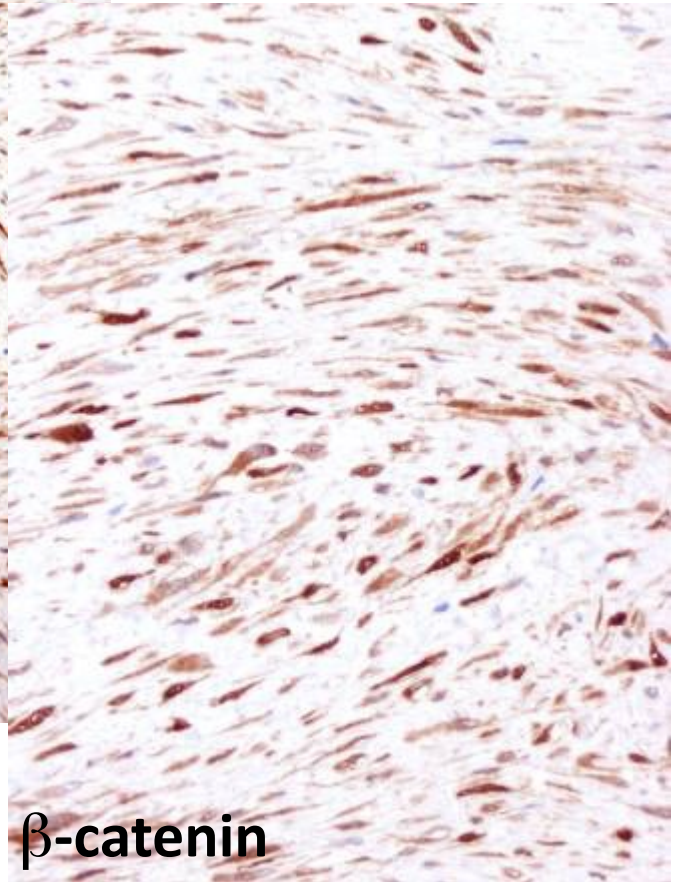




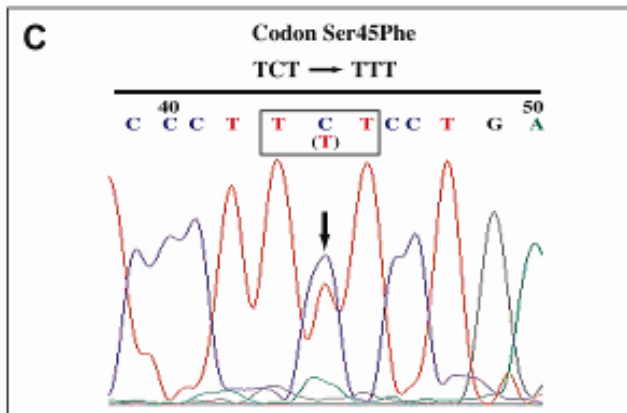
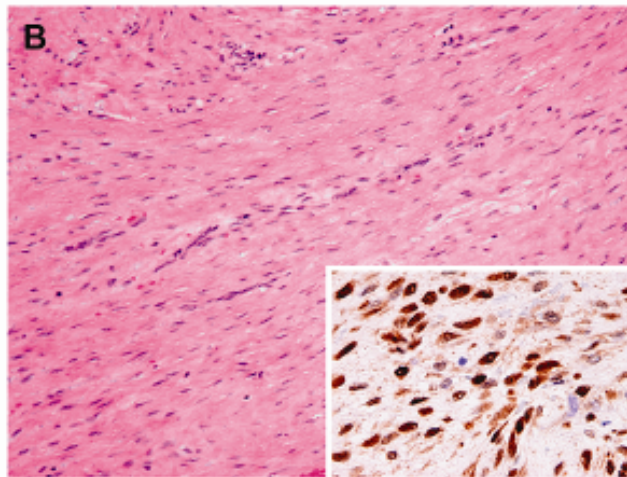
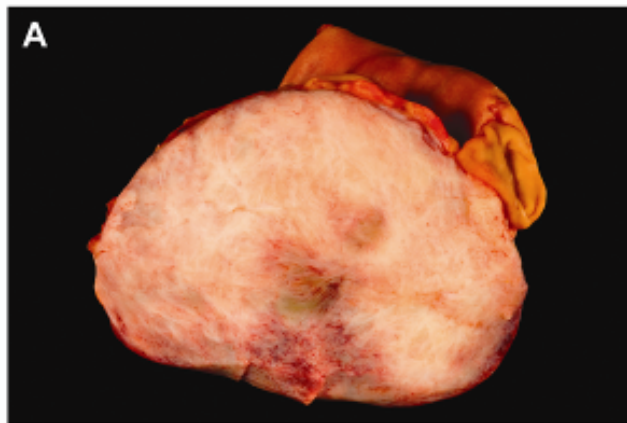




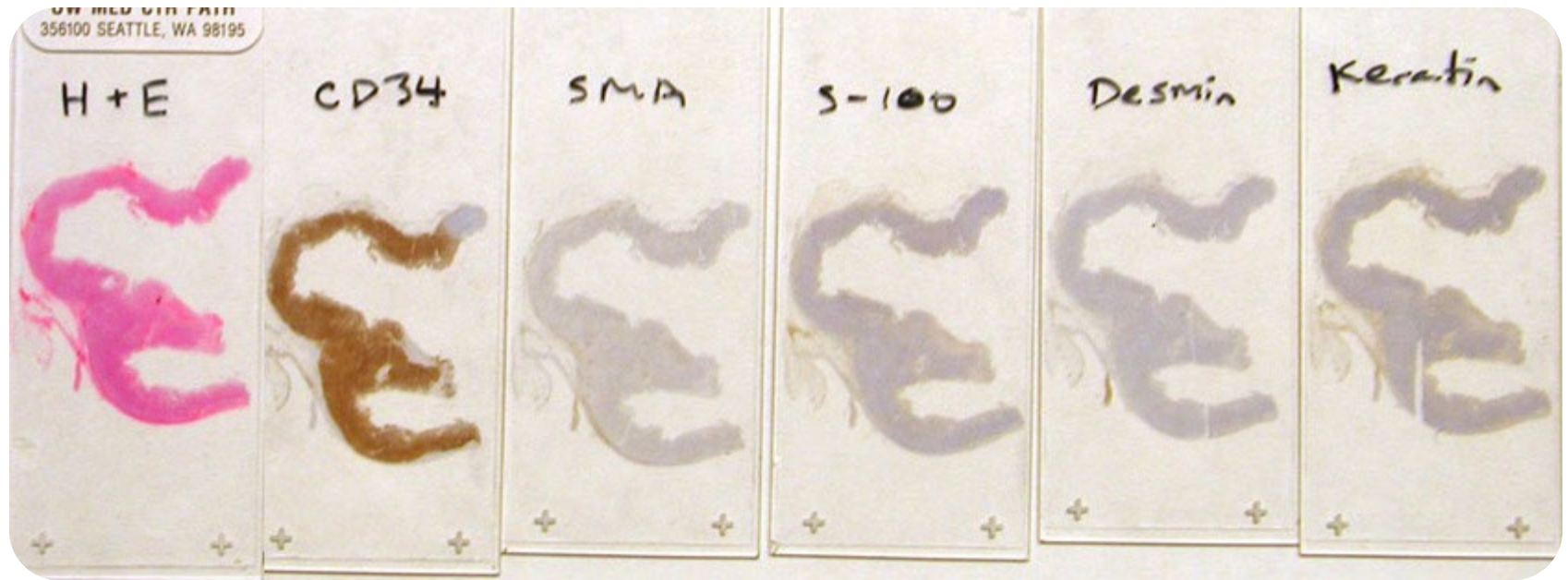
β -catenin



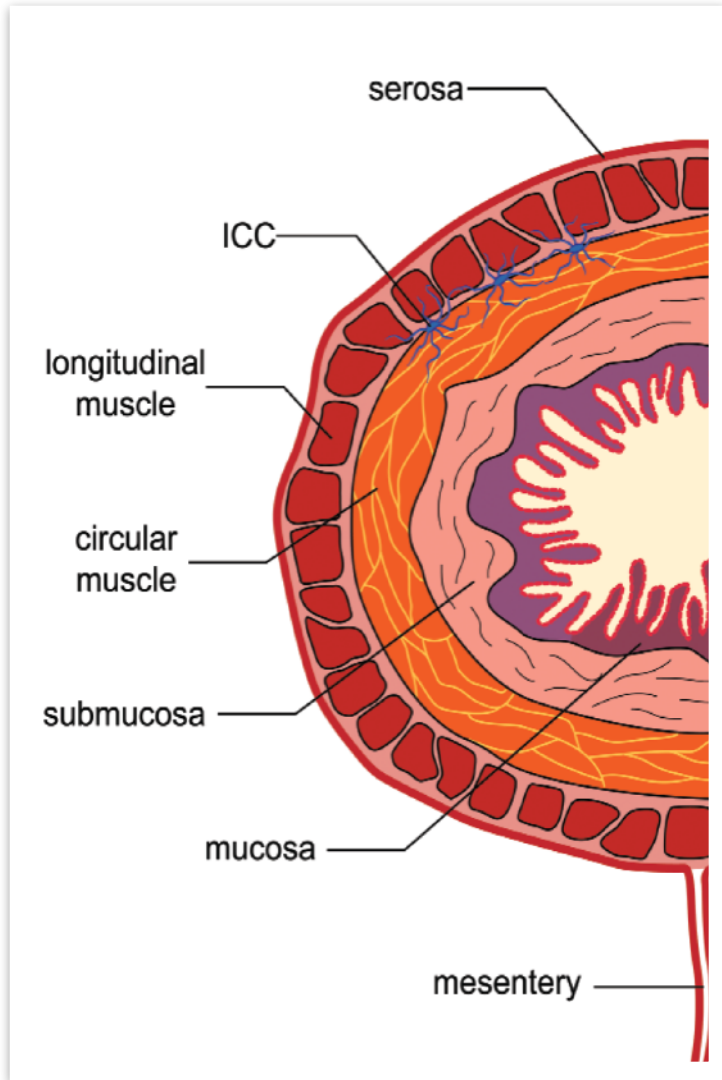
β -catenin



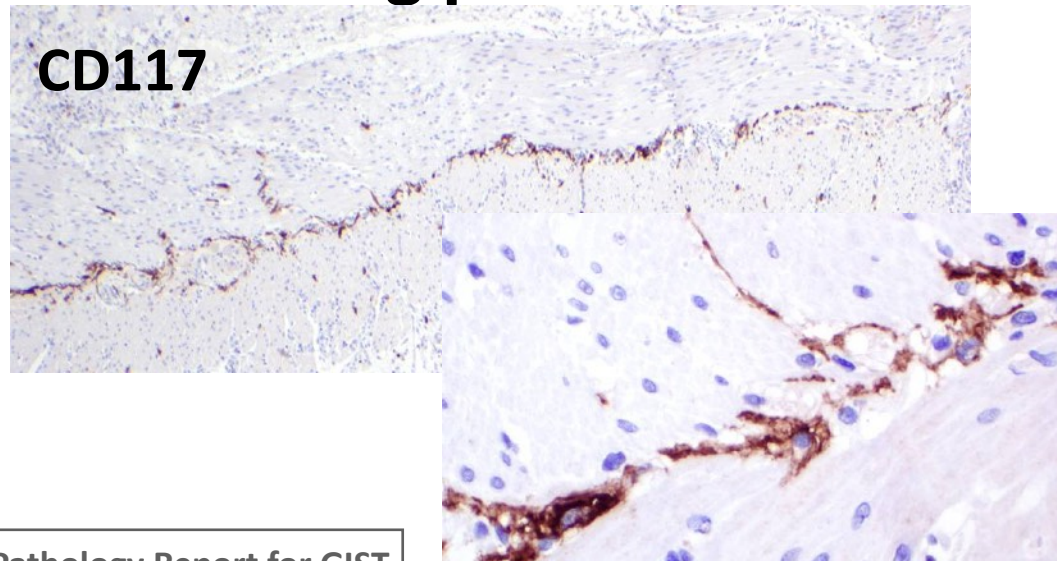
Immunohistochemical Profile of GISTs (Circa 1997 and prior)



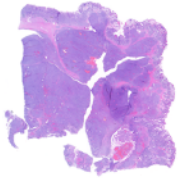
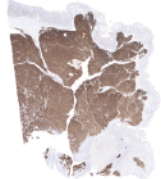
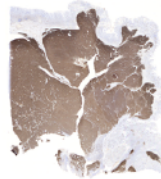
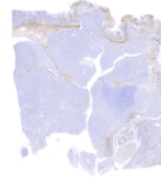
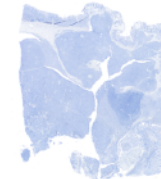
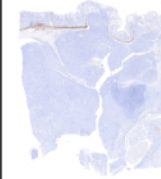
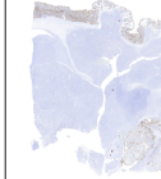
Gastrointestinal Stromal Tumor



- **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%)

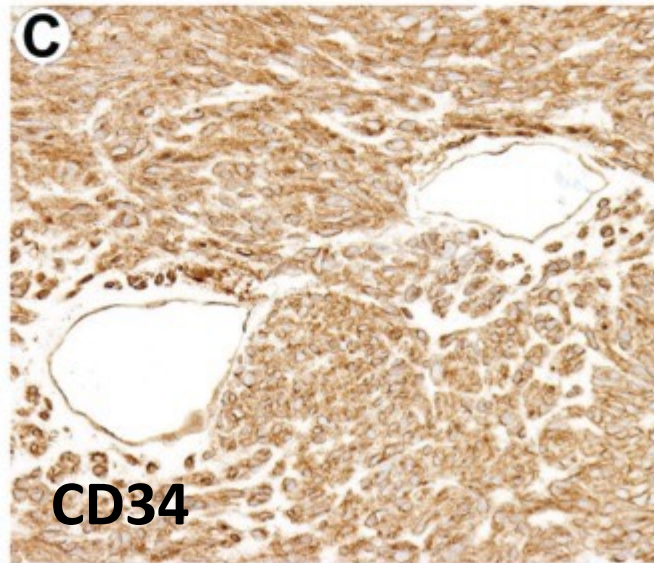
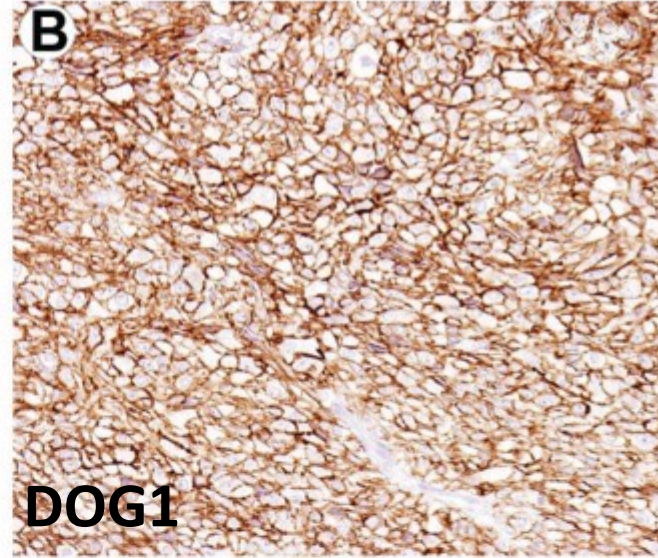
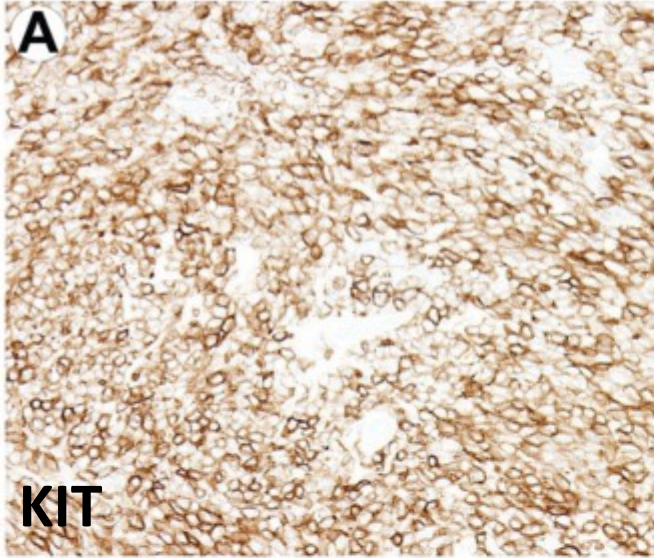
CD34 +ve (70%)

SMA +ve (30-40%)

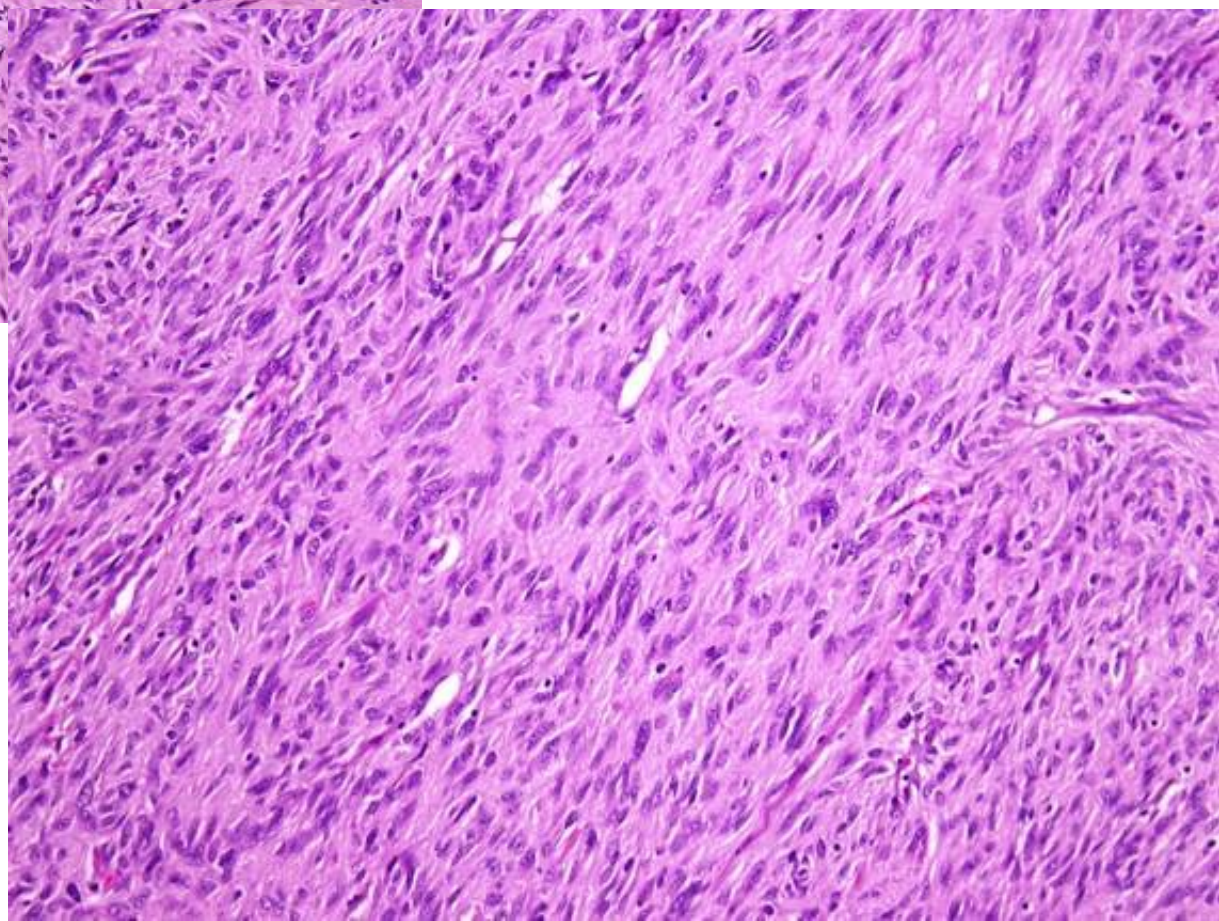
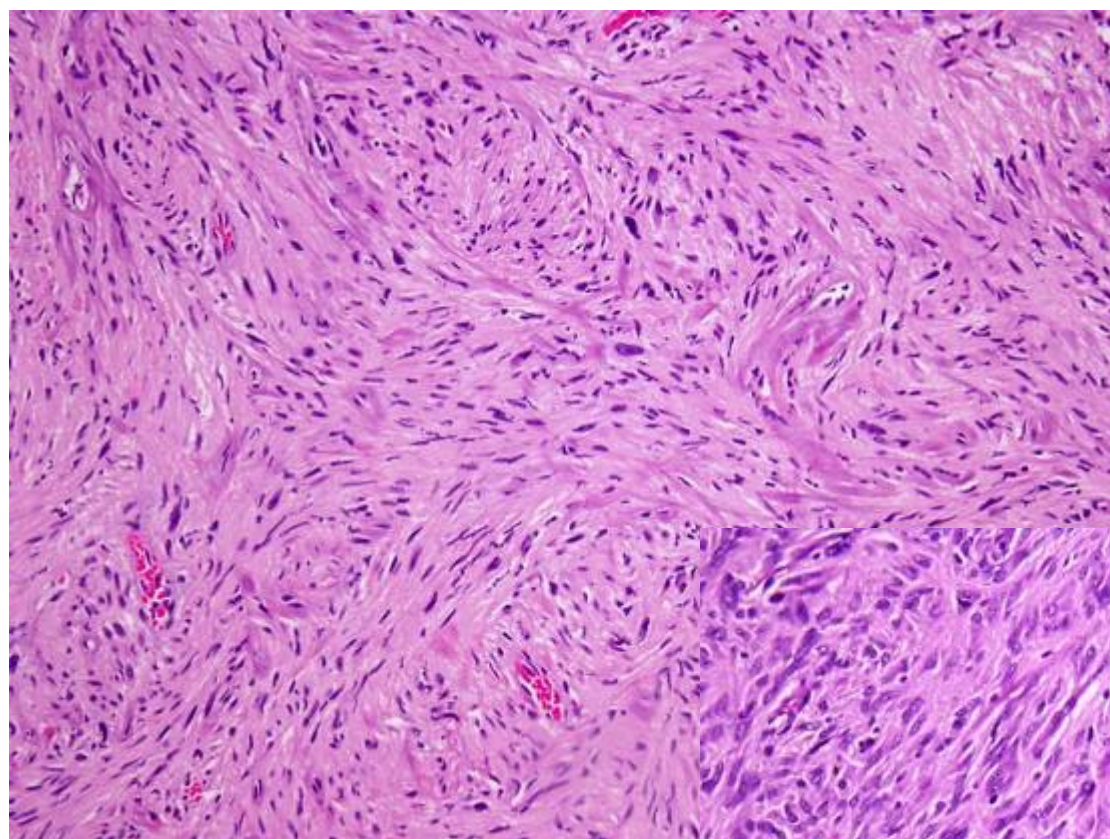
Desmin -ve

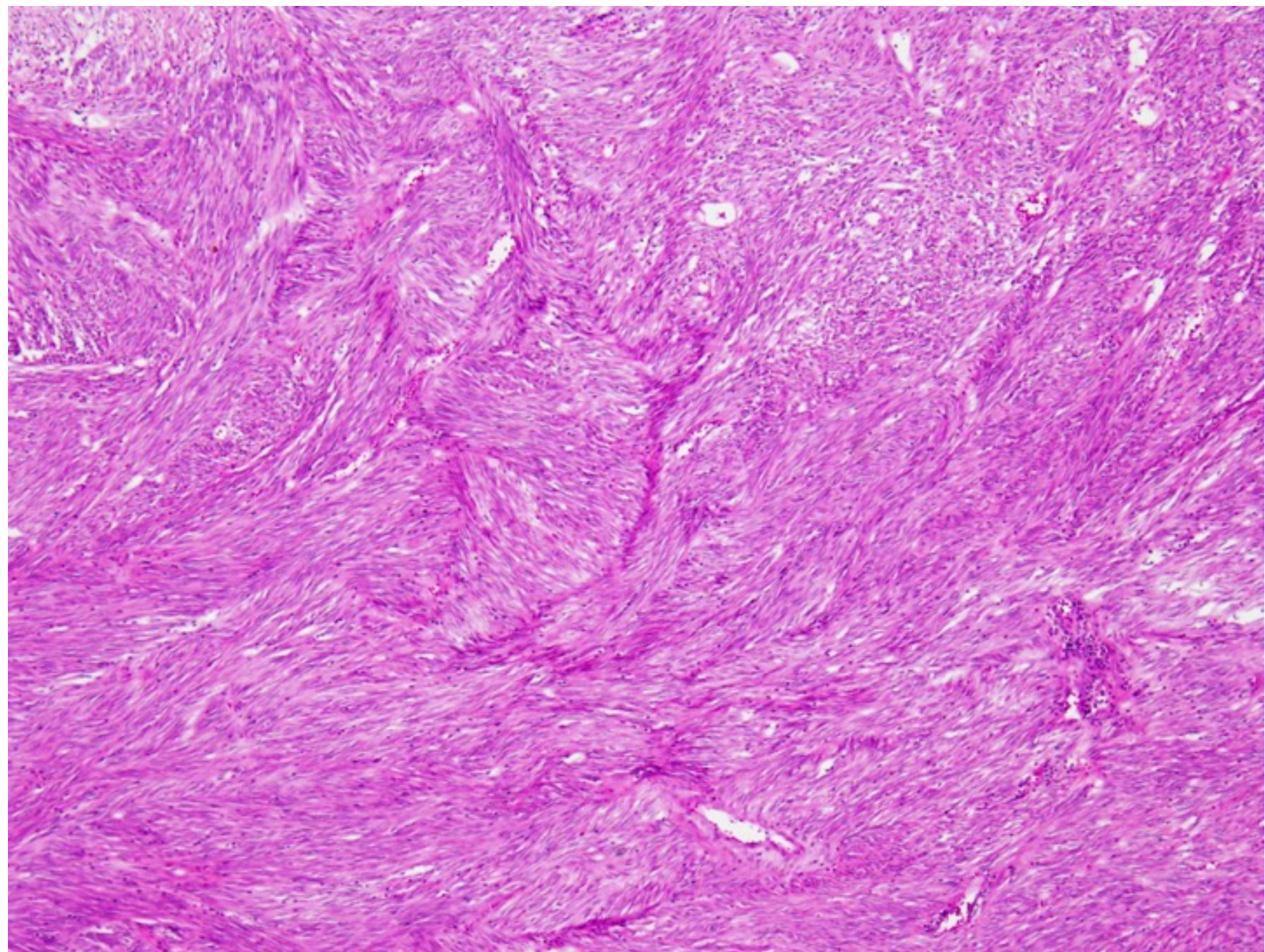
S-100 protein -ve

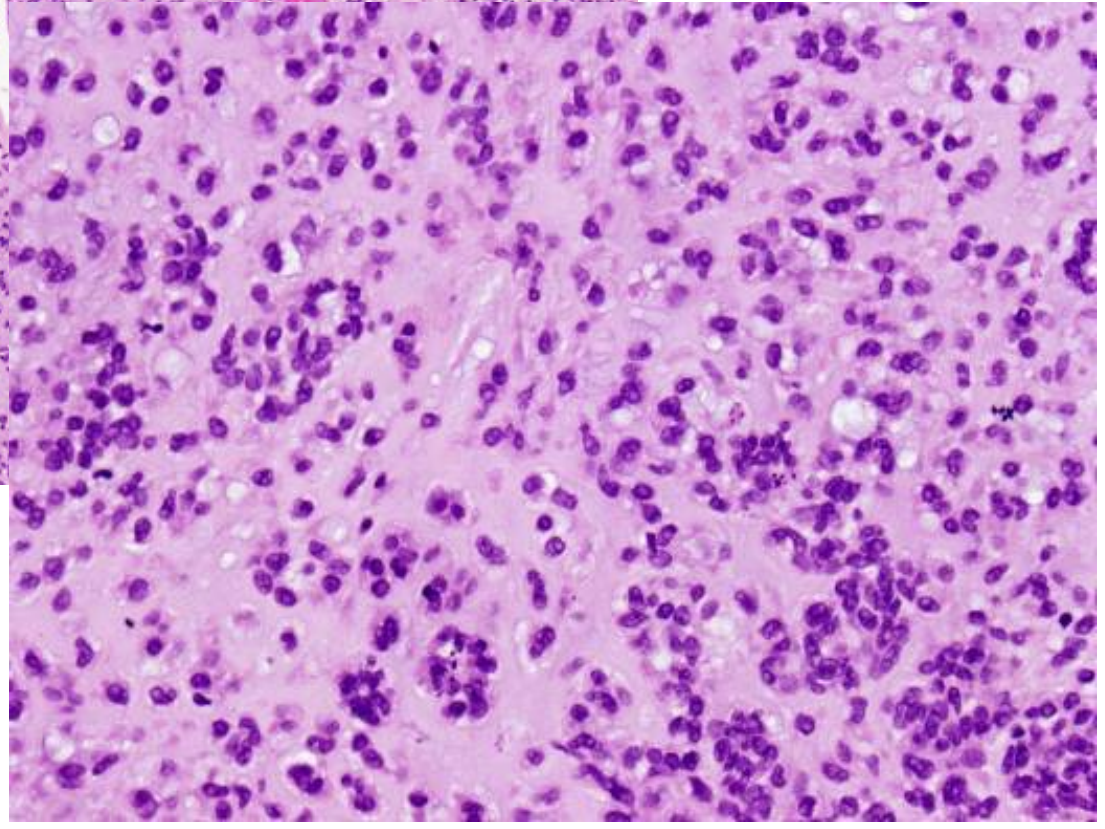
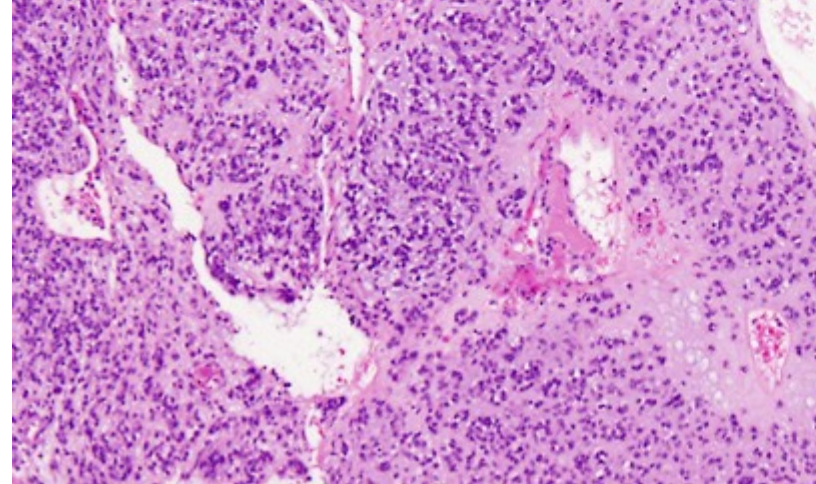
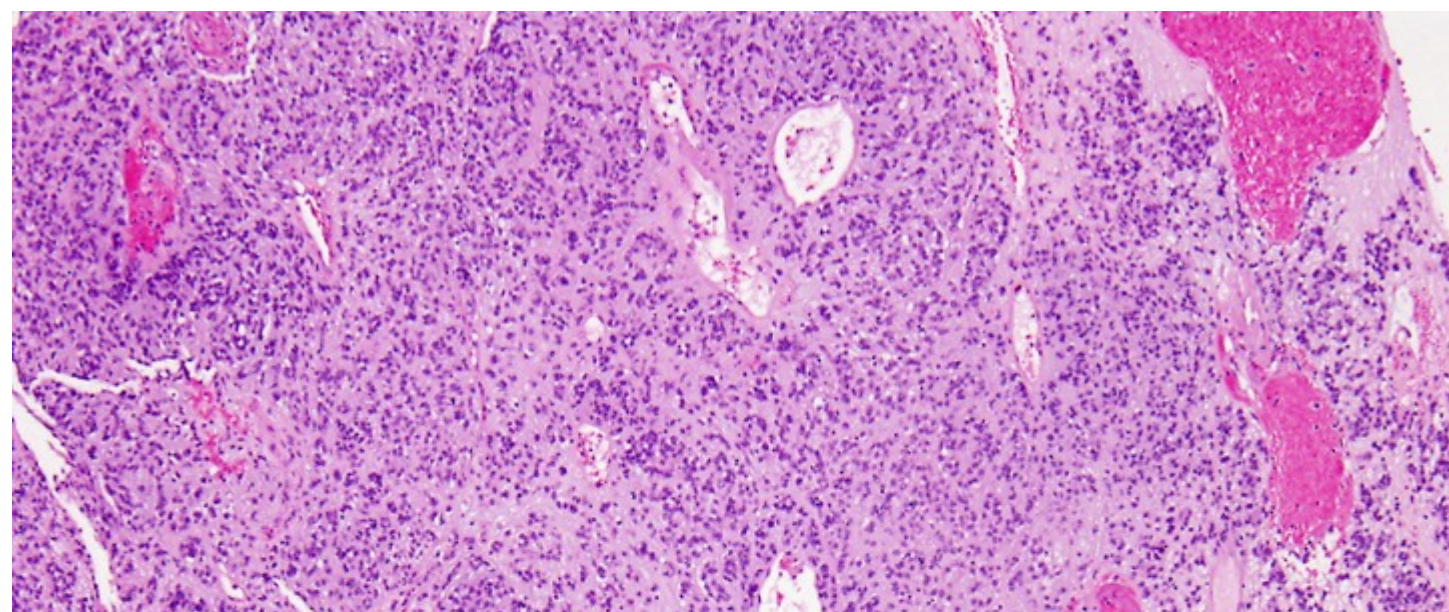
Keratin -ve

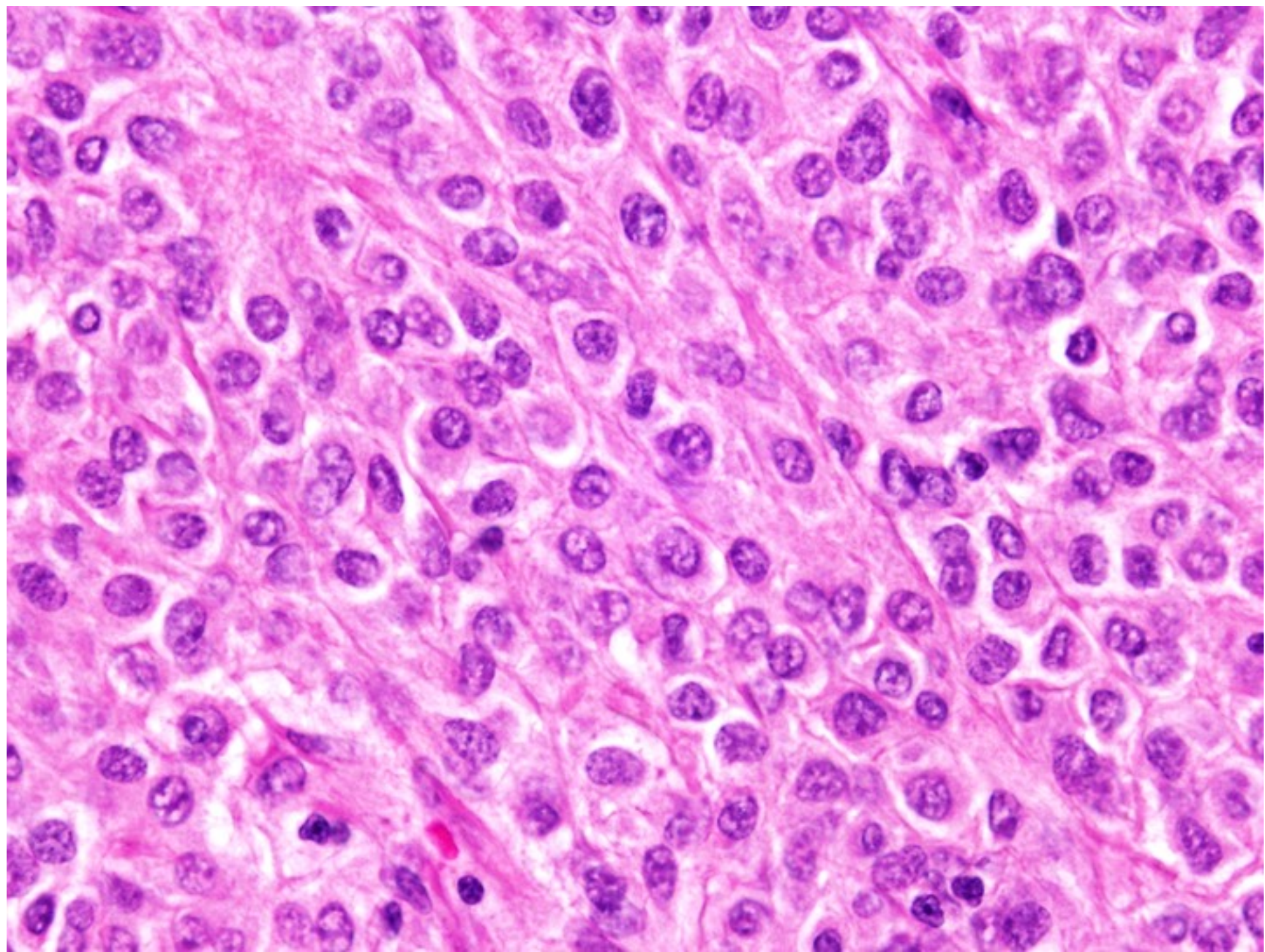


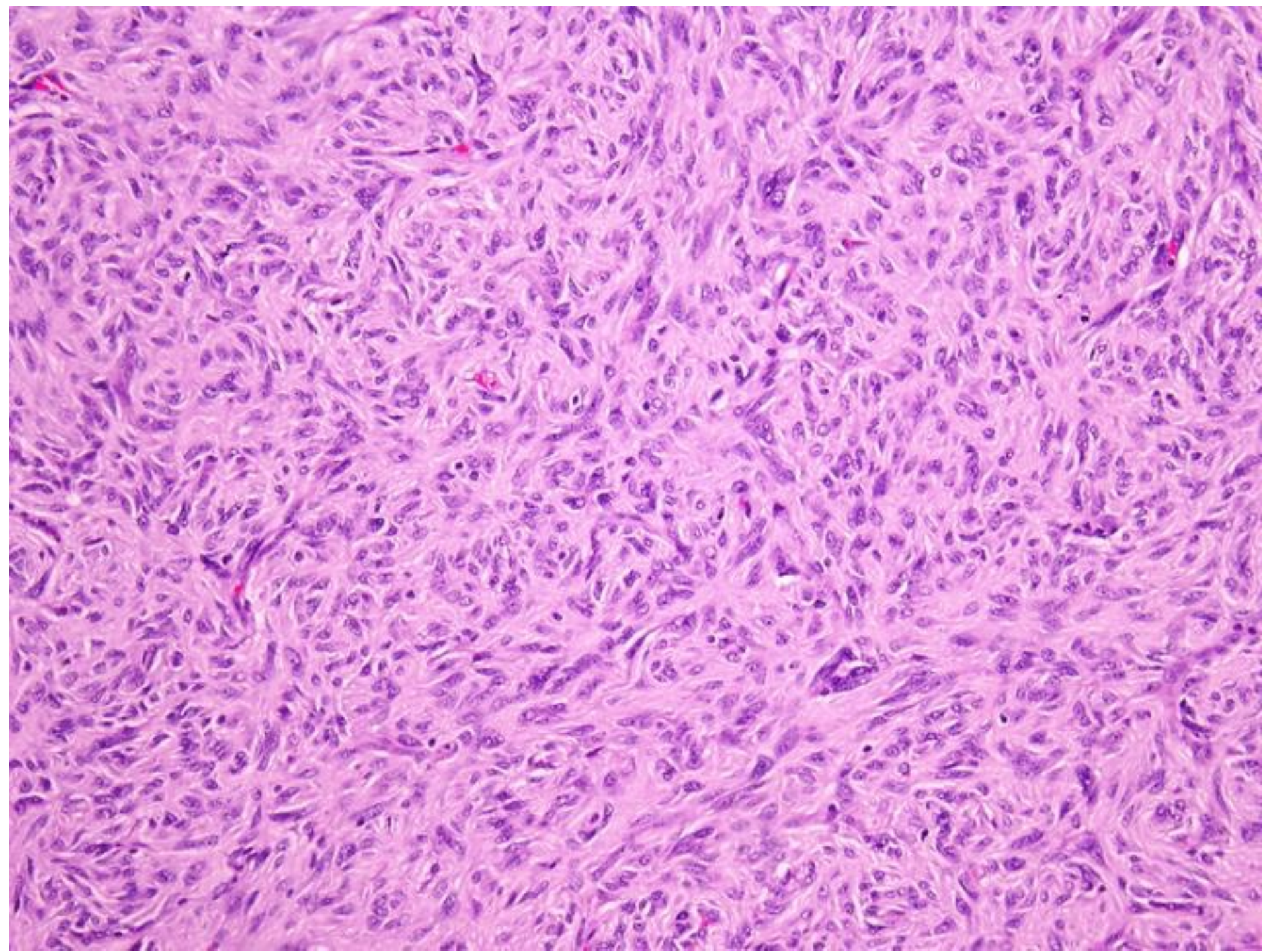
The many faces of GIST

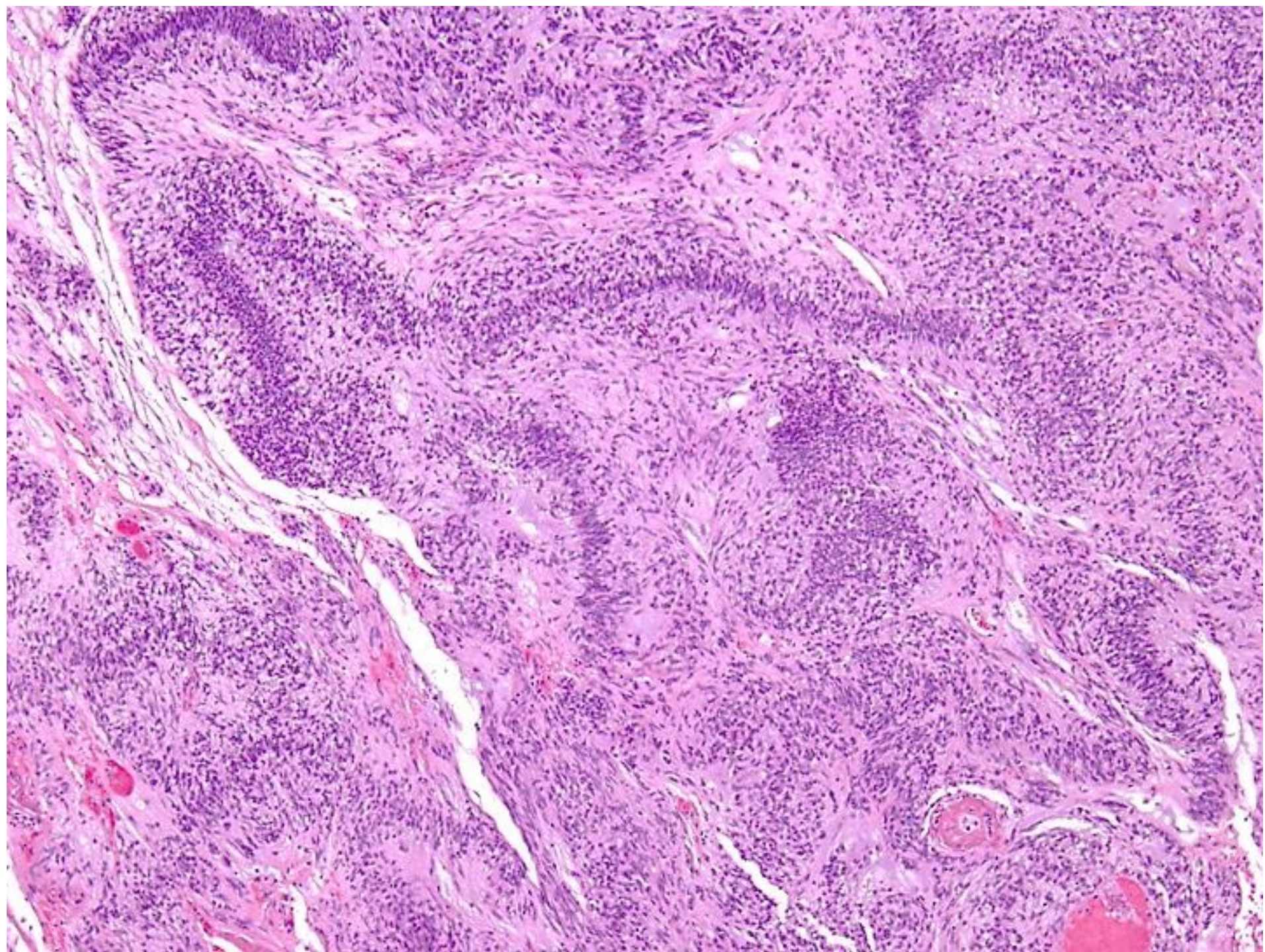


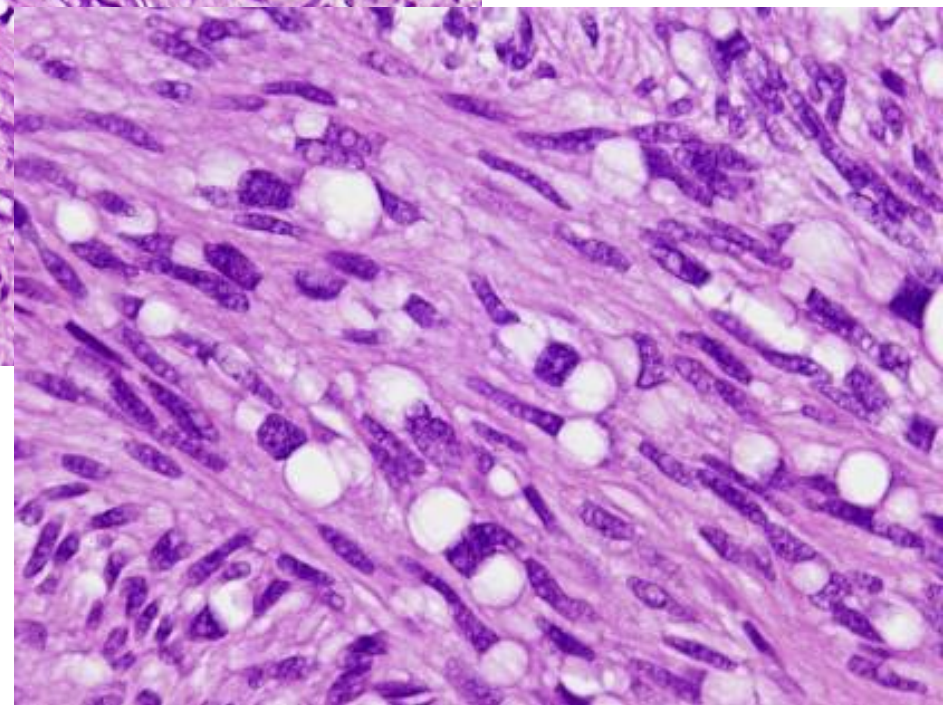
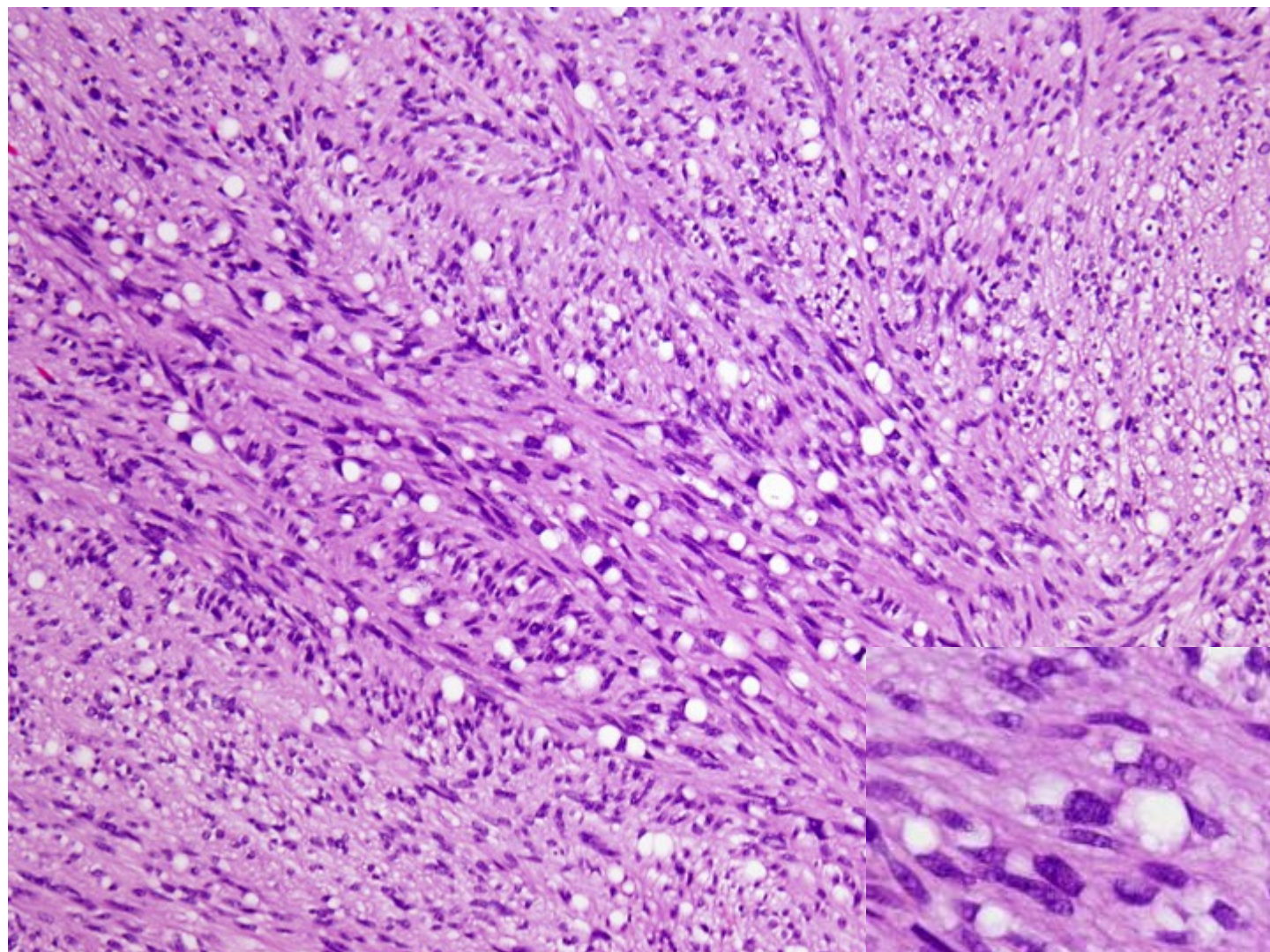


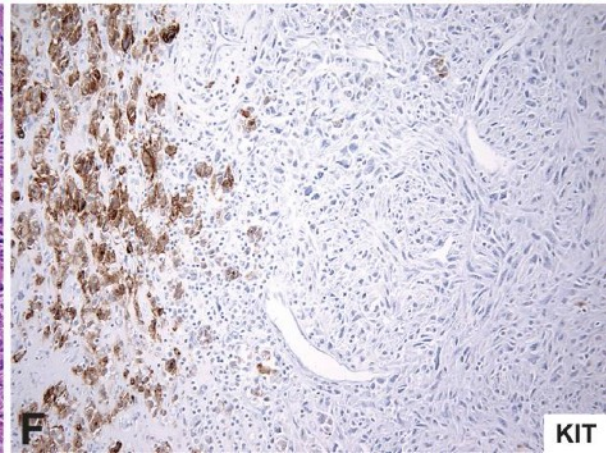
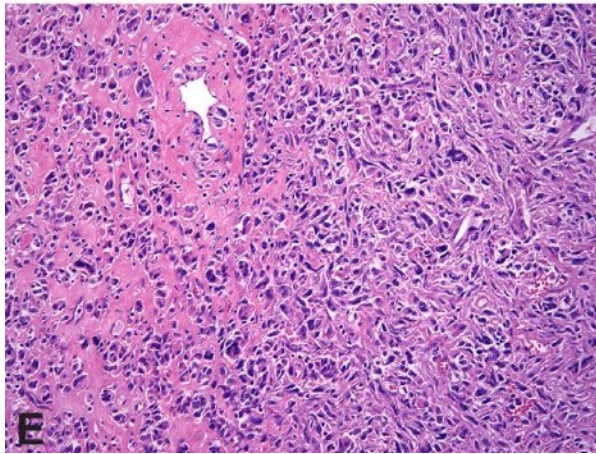
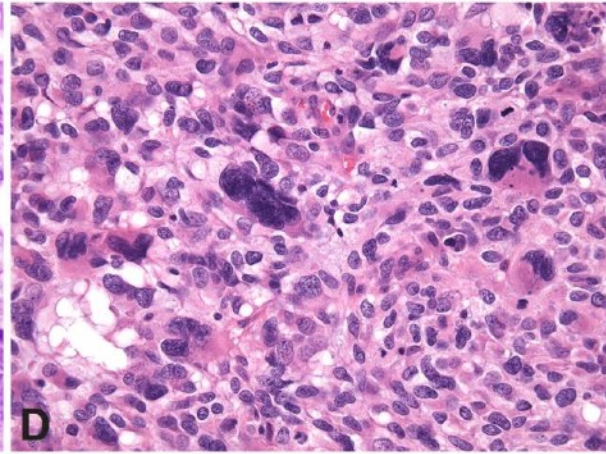
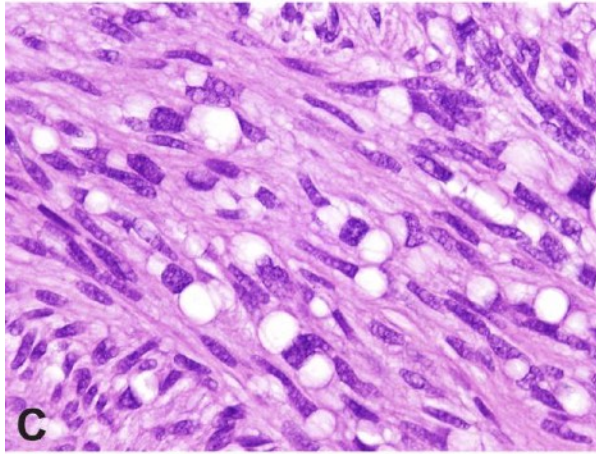
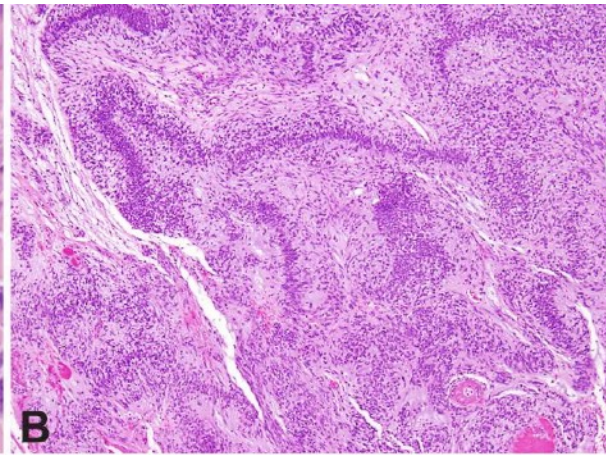
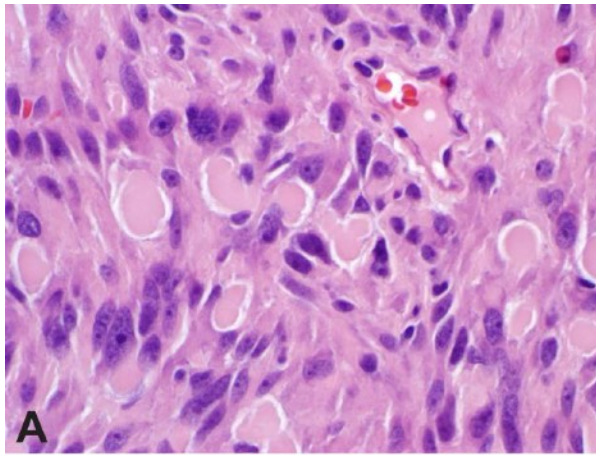


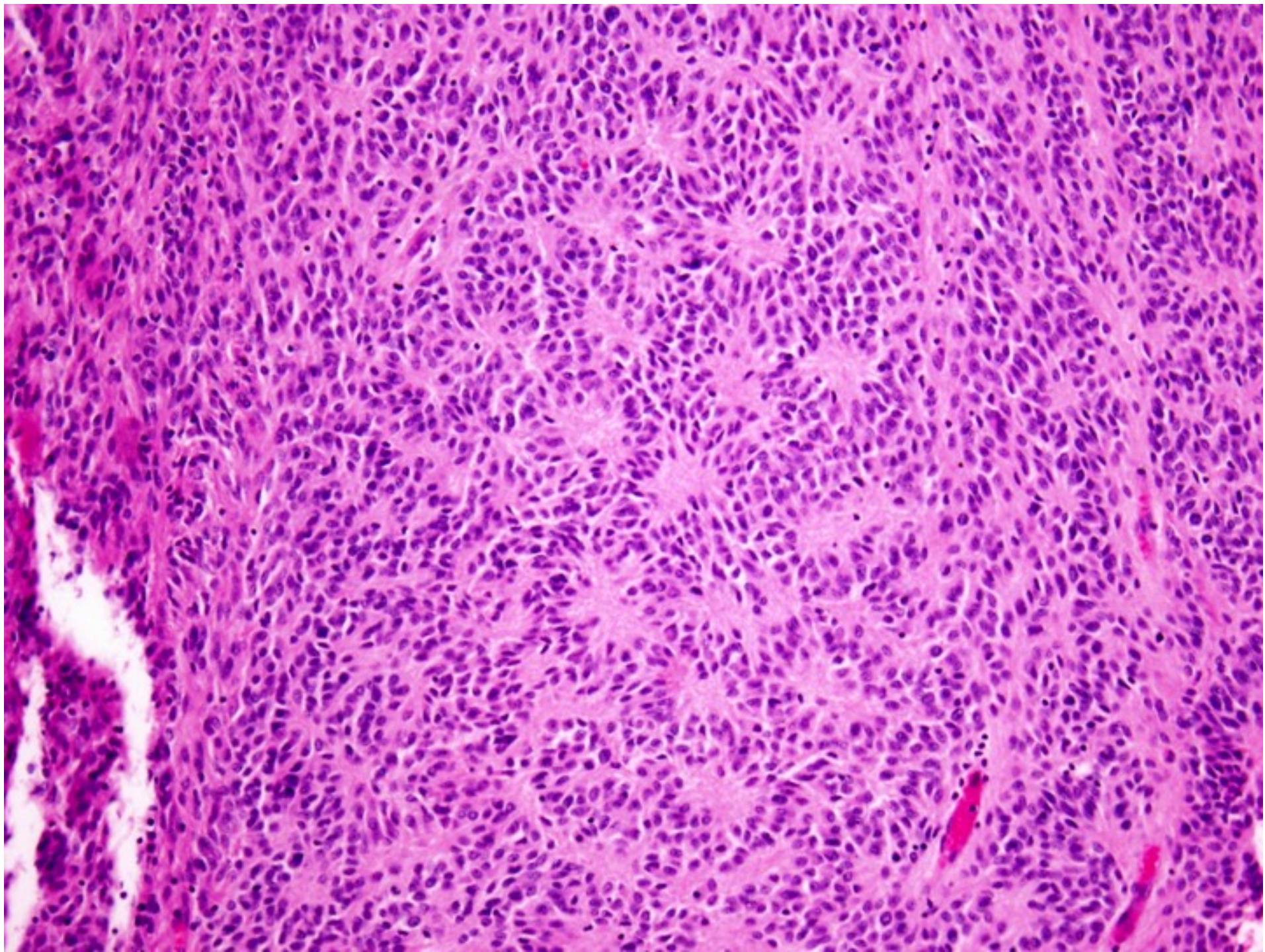












Clinical Characteristics of GIST

Wide age range – peak in 5th-7th decade

M = F

Small lesions = “incidentalomas”

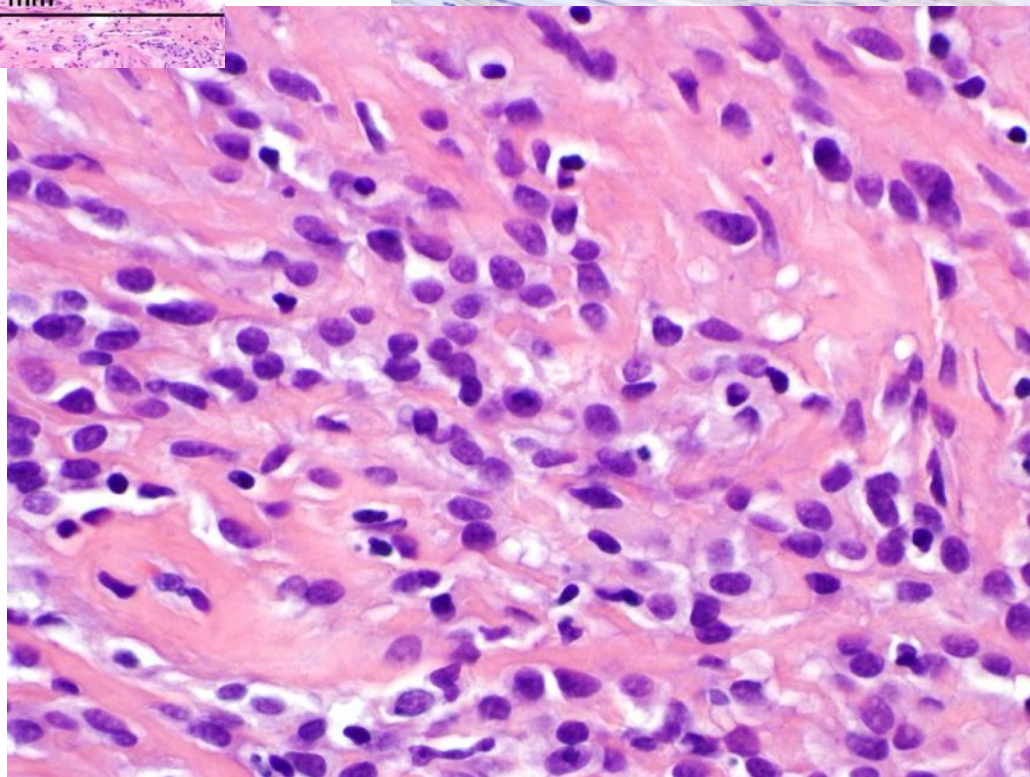
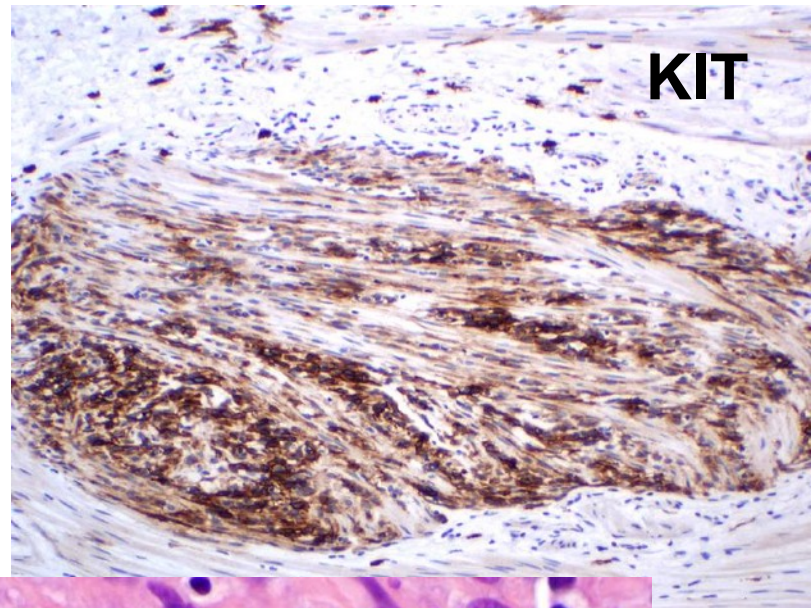
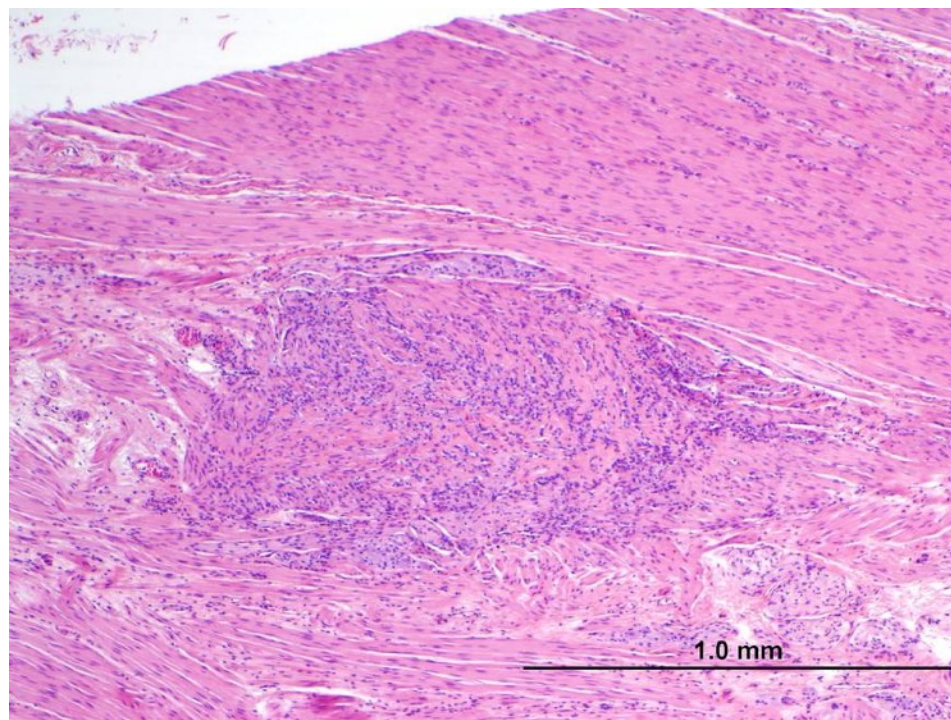
Presenting symptoms include:

abdominal pain,

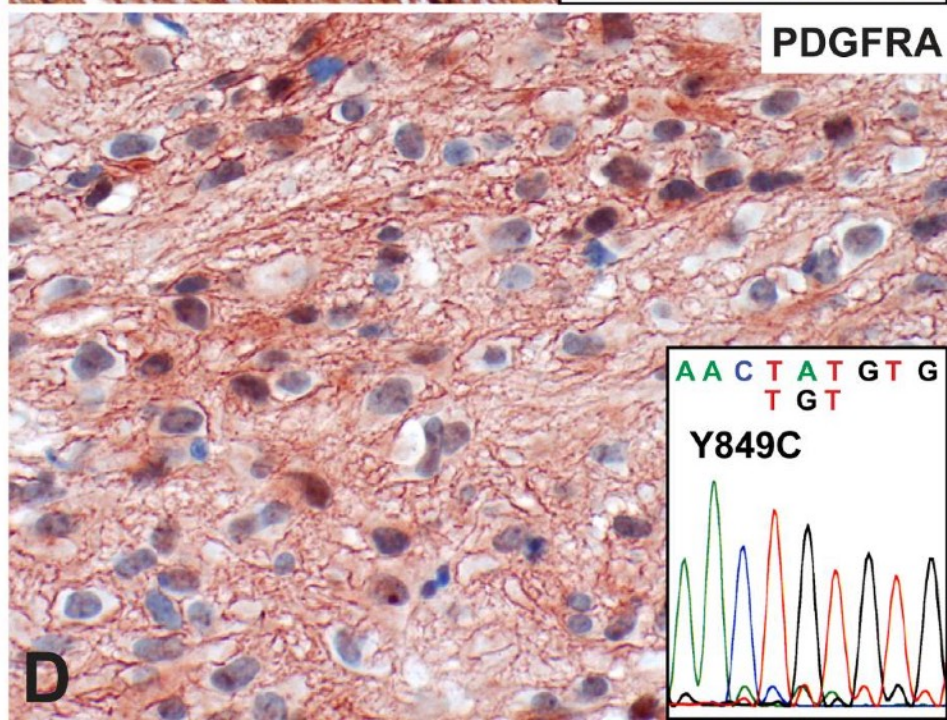
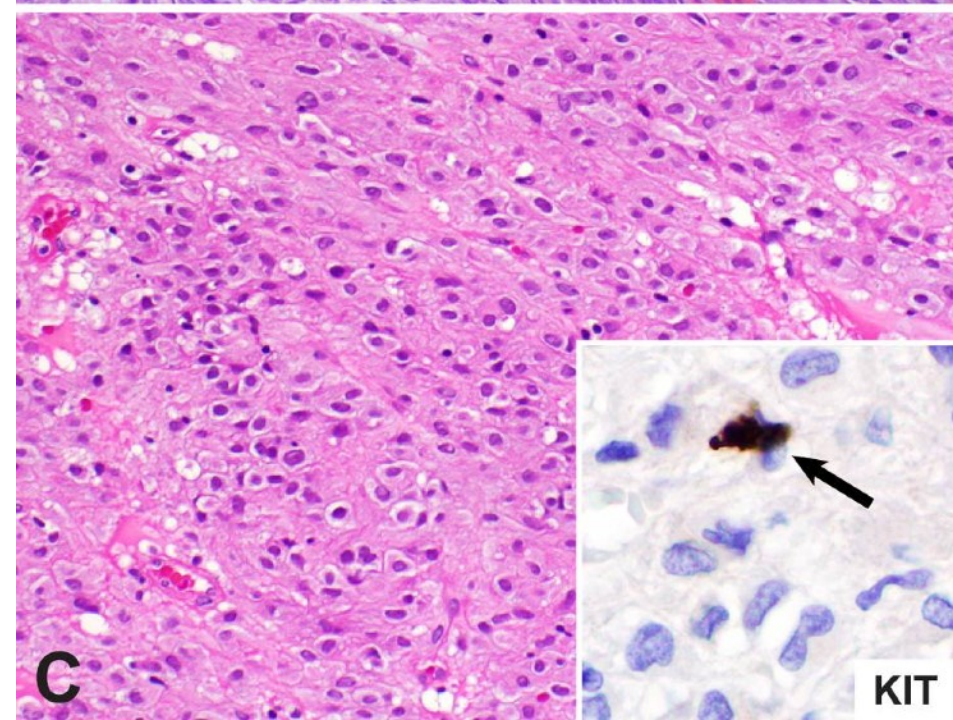
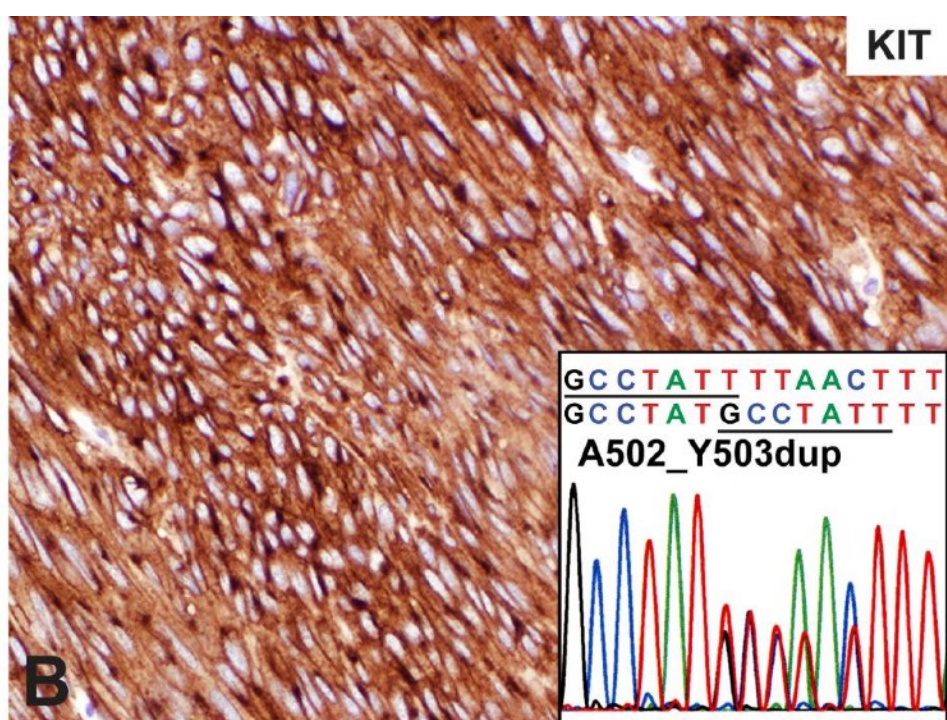
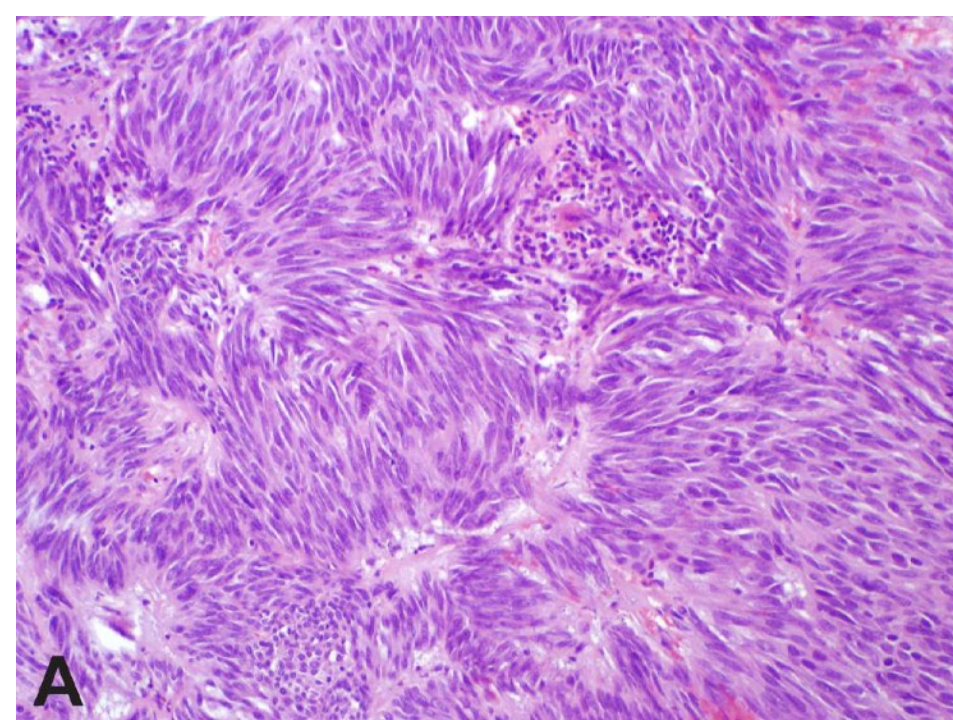
gastrointestinal bleeding,

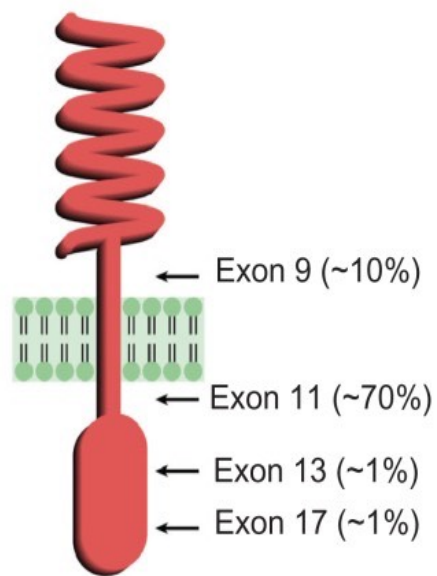
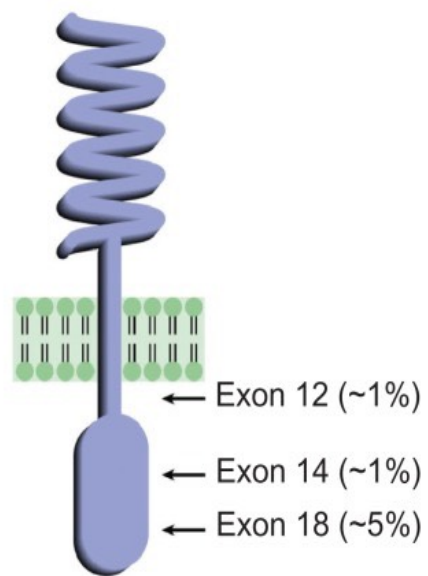
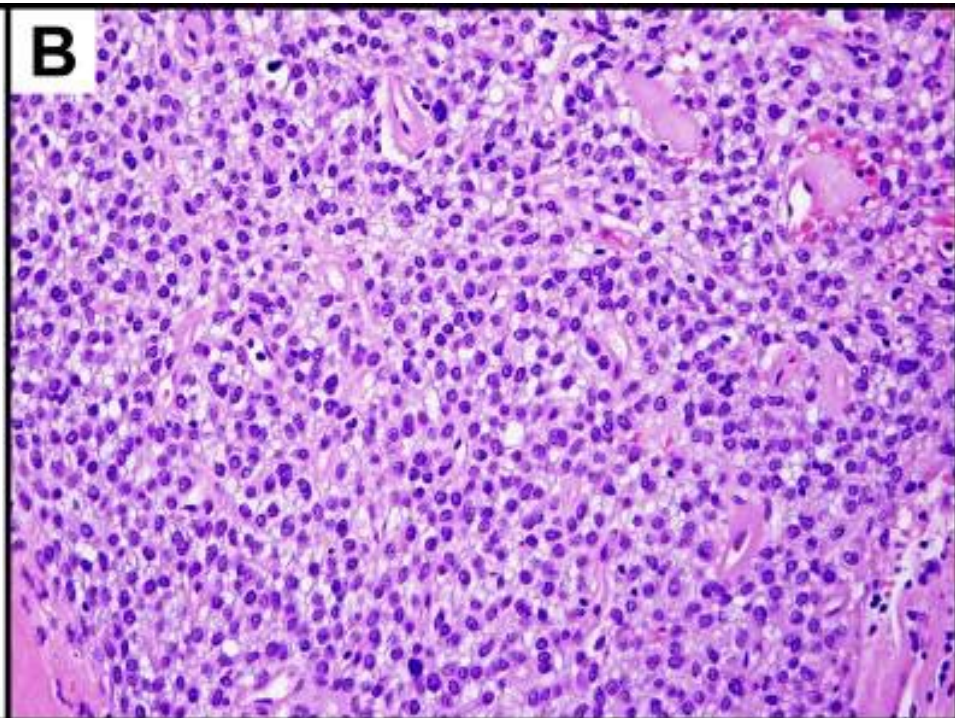
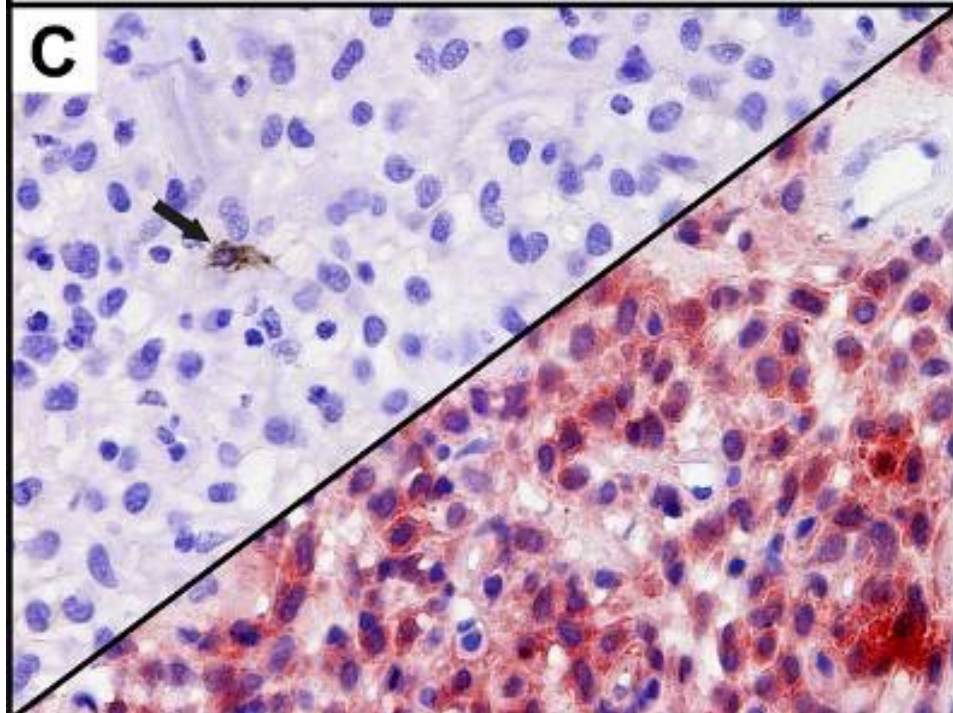
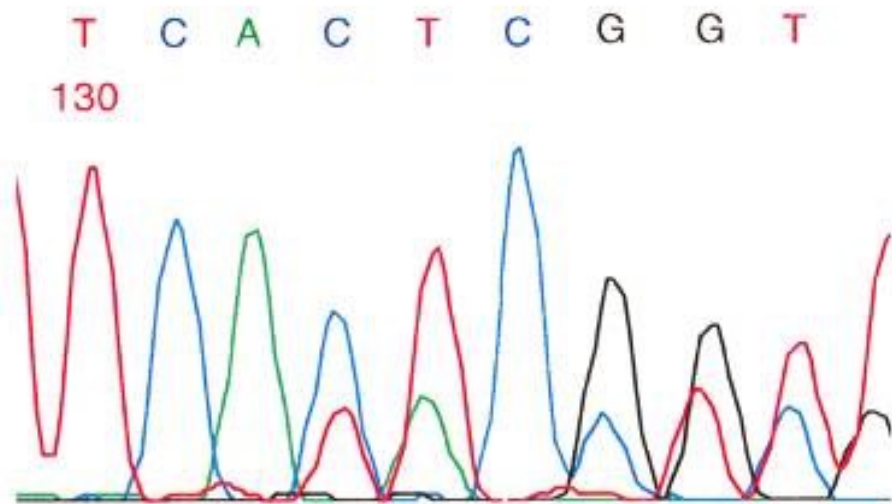
early satiety,

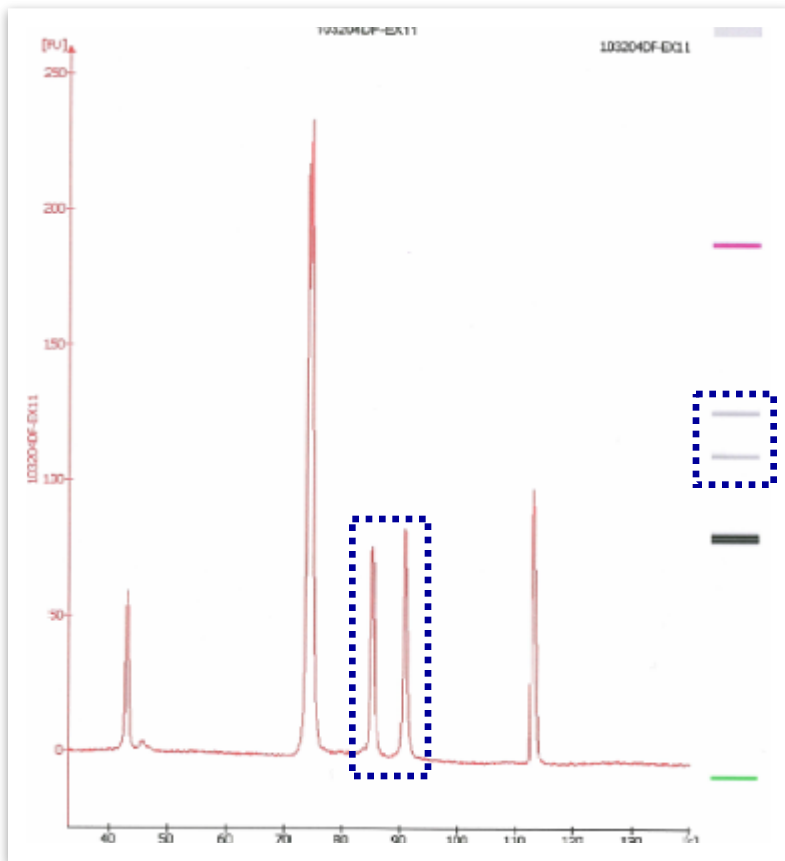
symptoms referable to a mass



courtesy of Susan Abraham,
UTMDACC, Houston, TX

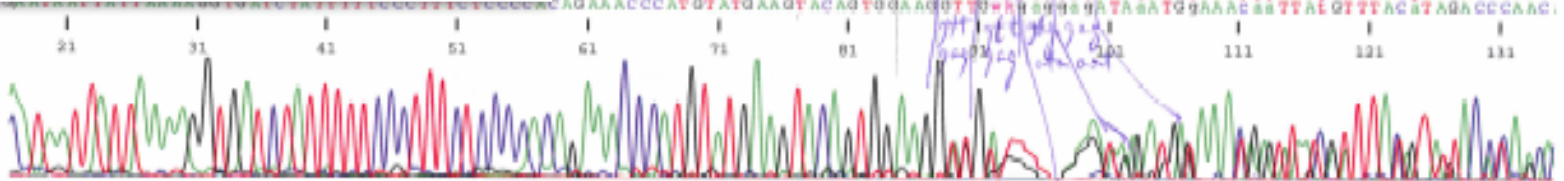
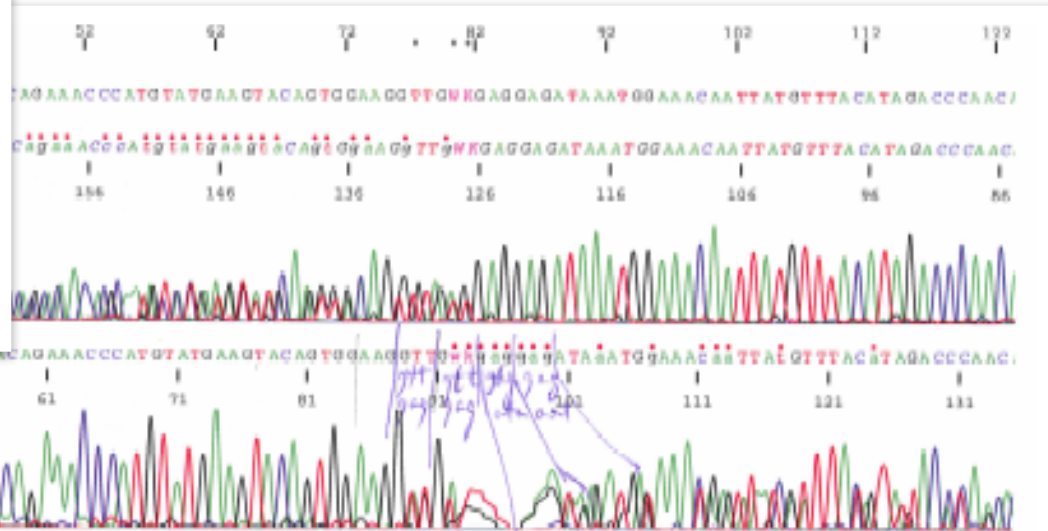


KIT**PDGFRA****B****C****D**



Exon 11

V559_V560del

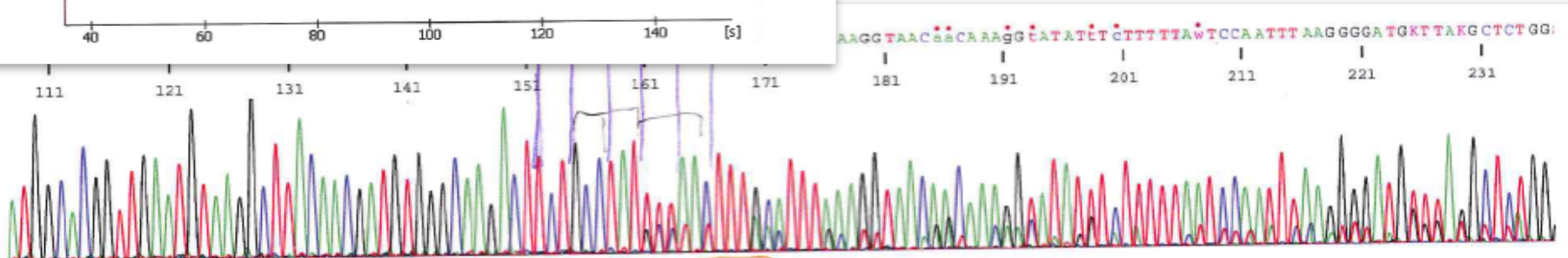
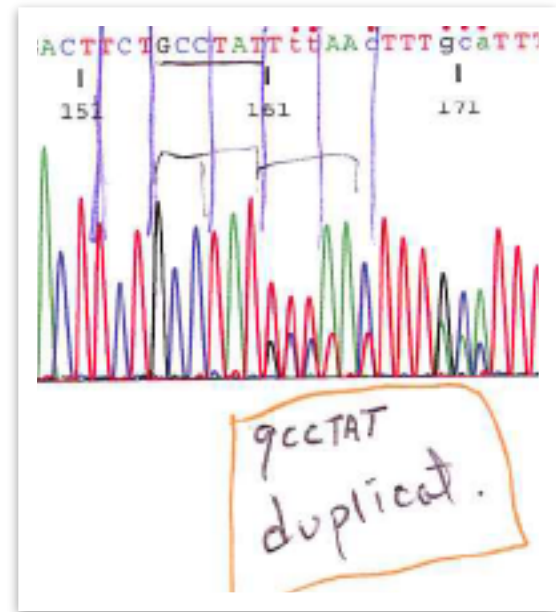
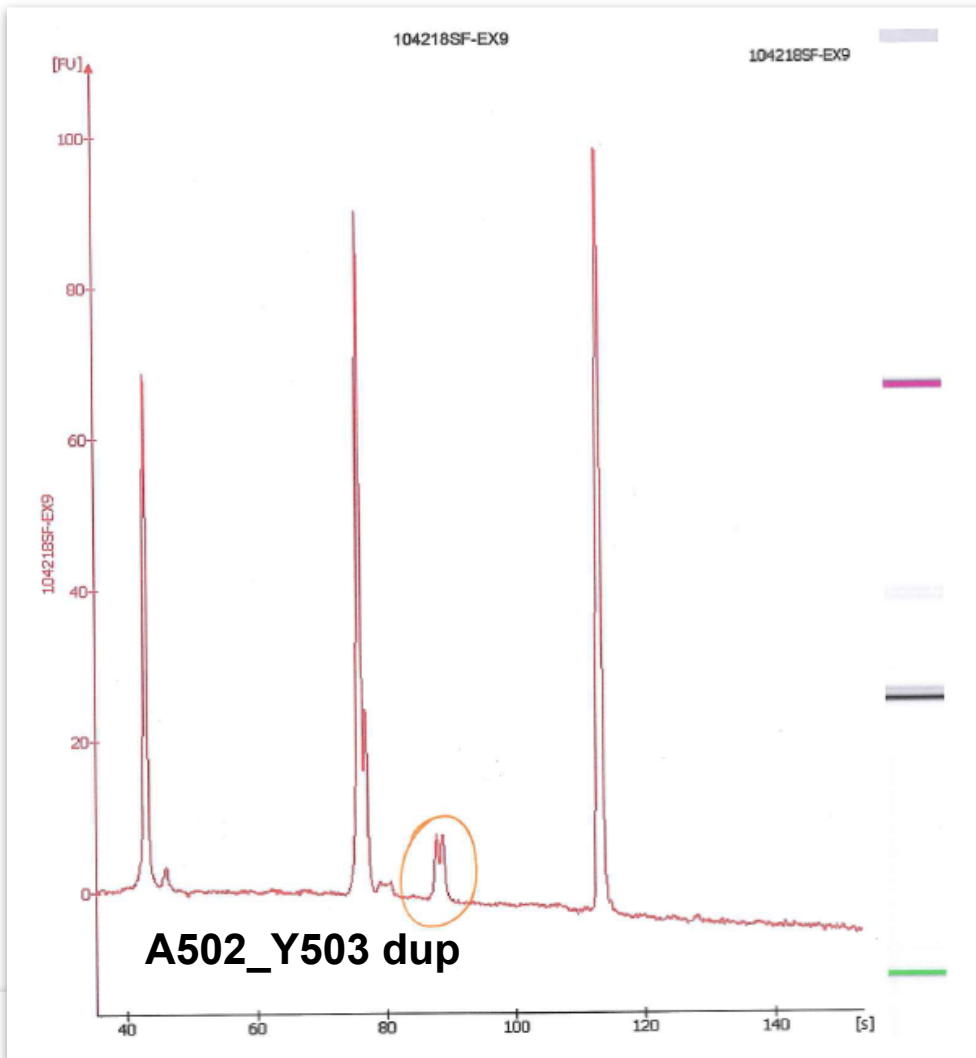


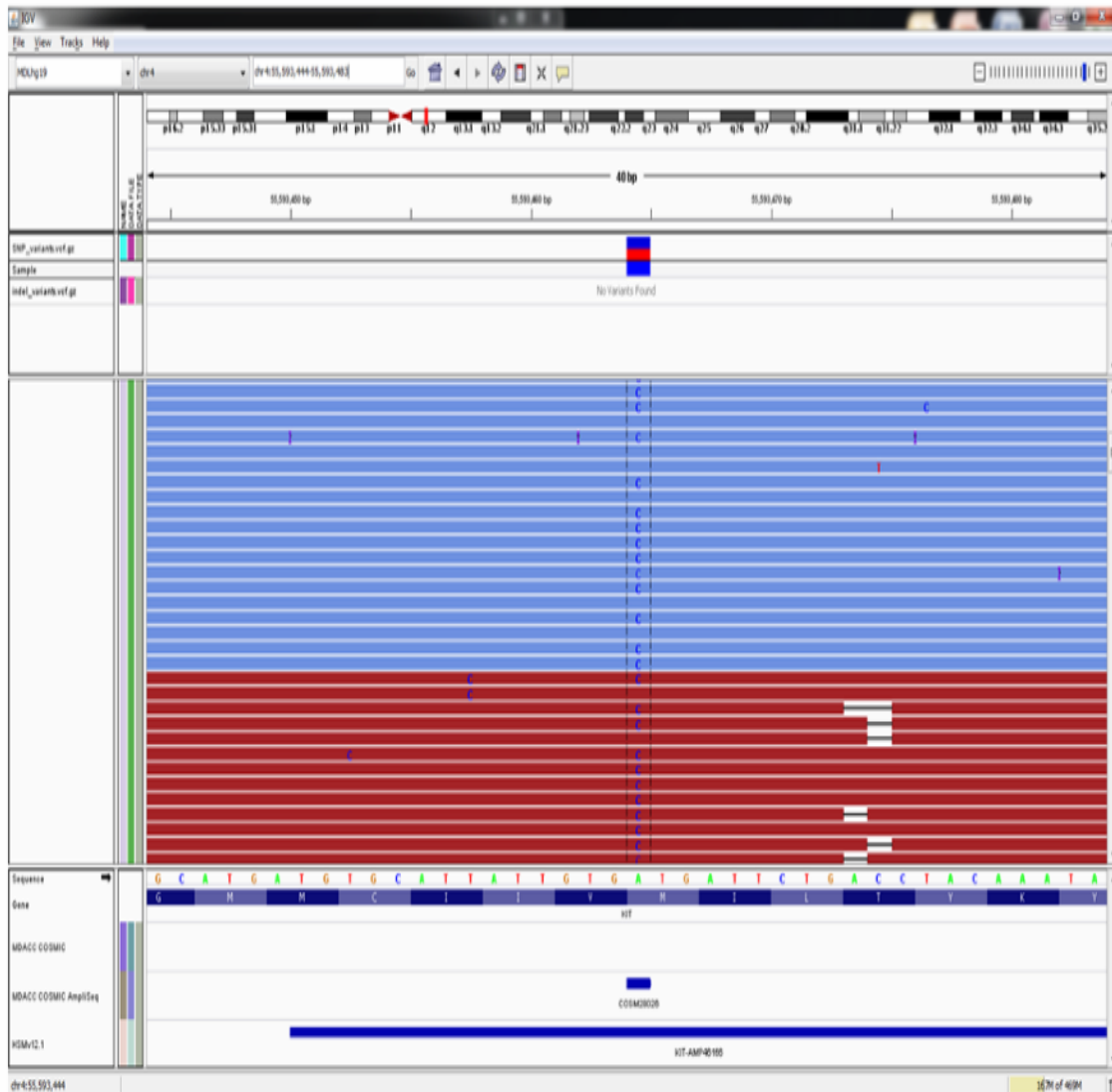
↑
 6 bp delct?
 TTG TTG
 gag gag ata aat

(V559-V560del)

Exon 9

A502_Y503dup





Detection of SNV in KIT Exon 10,

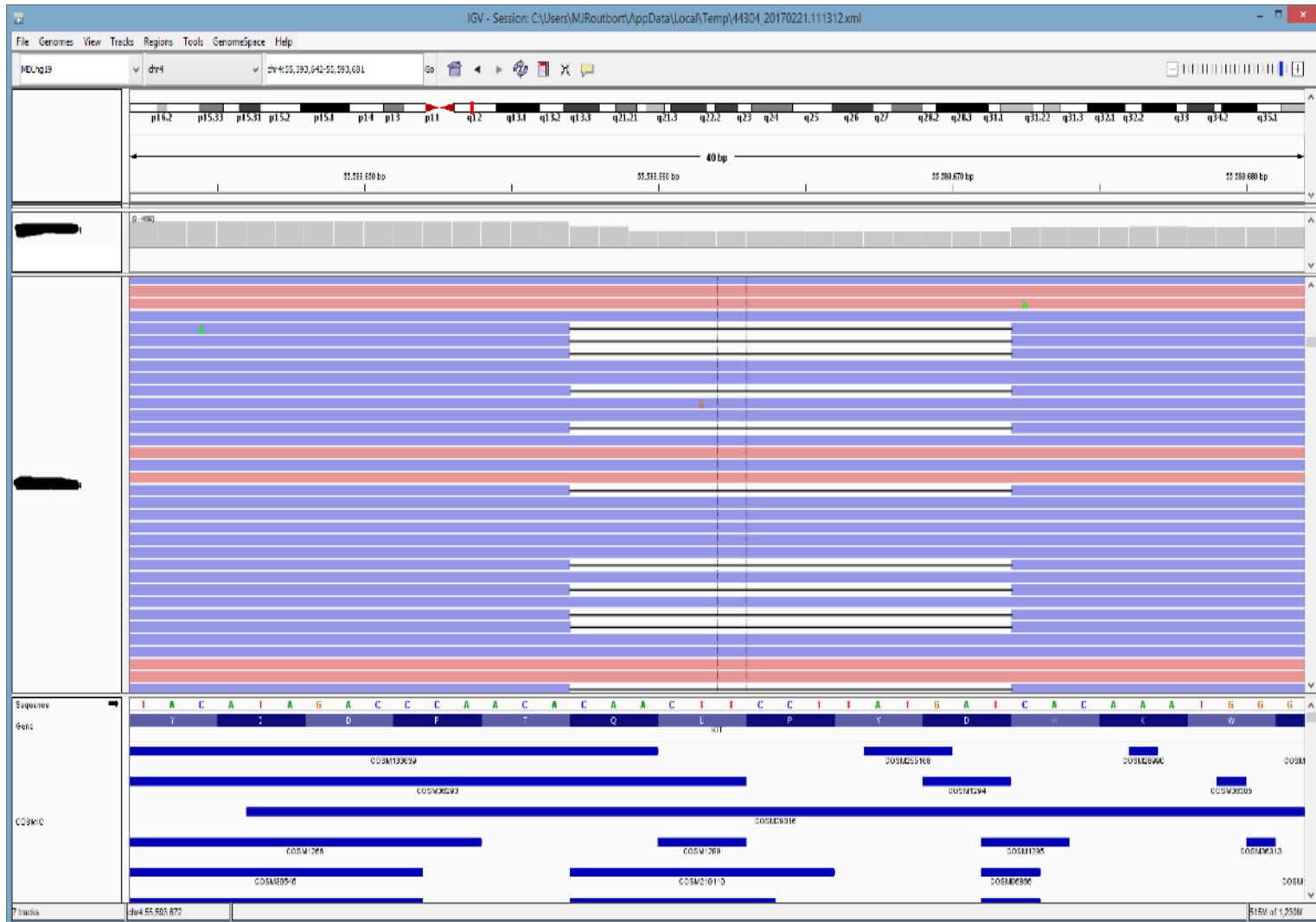


Patient Sample

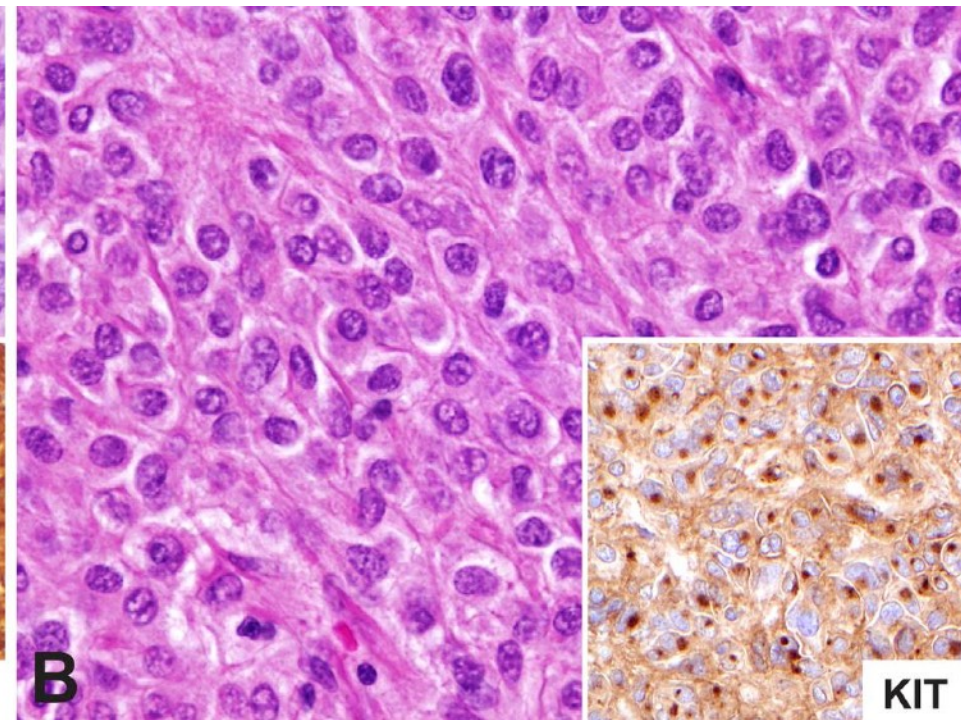
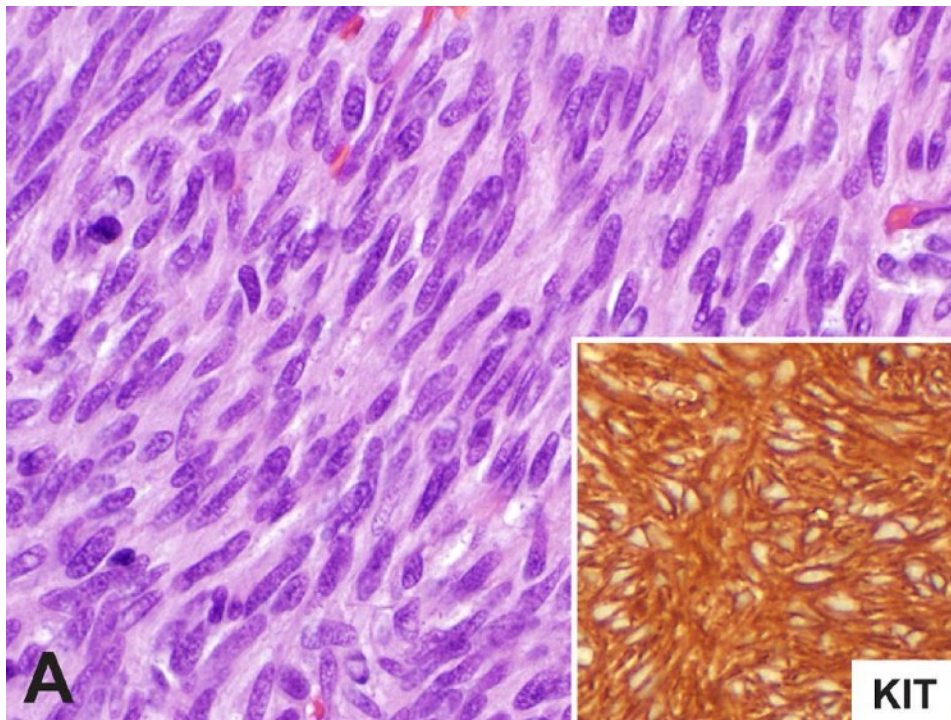
3346						
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NM_000222.2(KIT):c.1725_1739del p.Q575_D579del

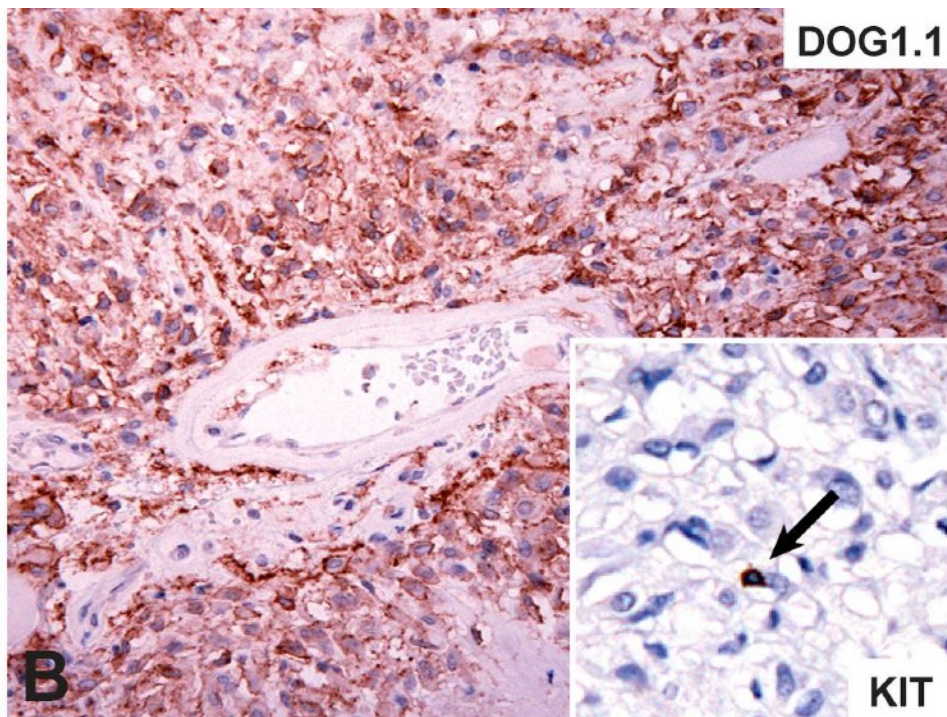
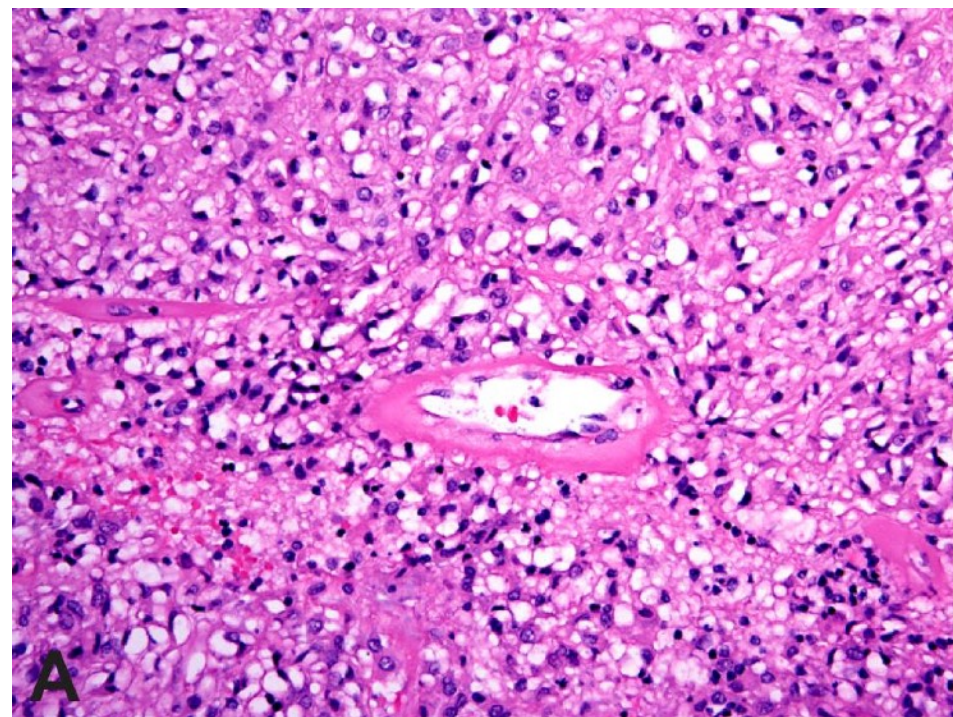
a 15-bp inframe deletion in exon 11 of KIT causing a loss of 5 amino acids.



KIT immunoreactivity in GIST



KIT-negative GIST



Gastric GISTs with Distinctive Histology (Multinodular/Plexiform)

- **Pediatric GISTs**

Female predominance (peak 2nd decade)

Indolent, but late metastases common

Molecular genetic basis unknown

Carney Triad

Gastric GIST, pulmonary chondroma, paraganglioma

Molecular genetic basis unknown

Carney-Stratakis Syndrome

Gastric GIST and paraganglioma

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

GIST with Distinctive Histology

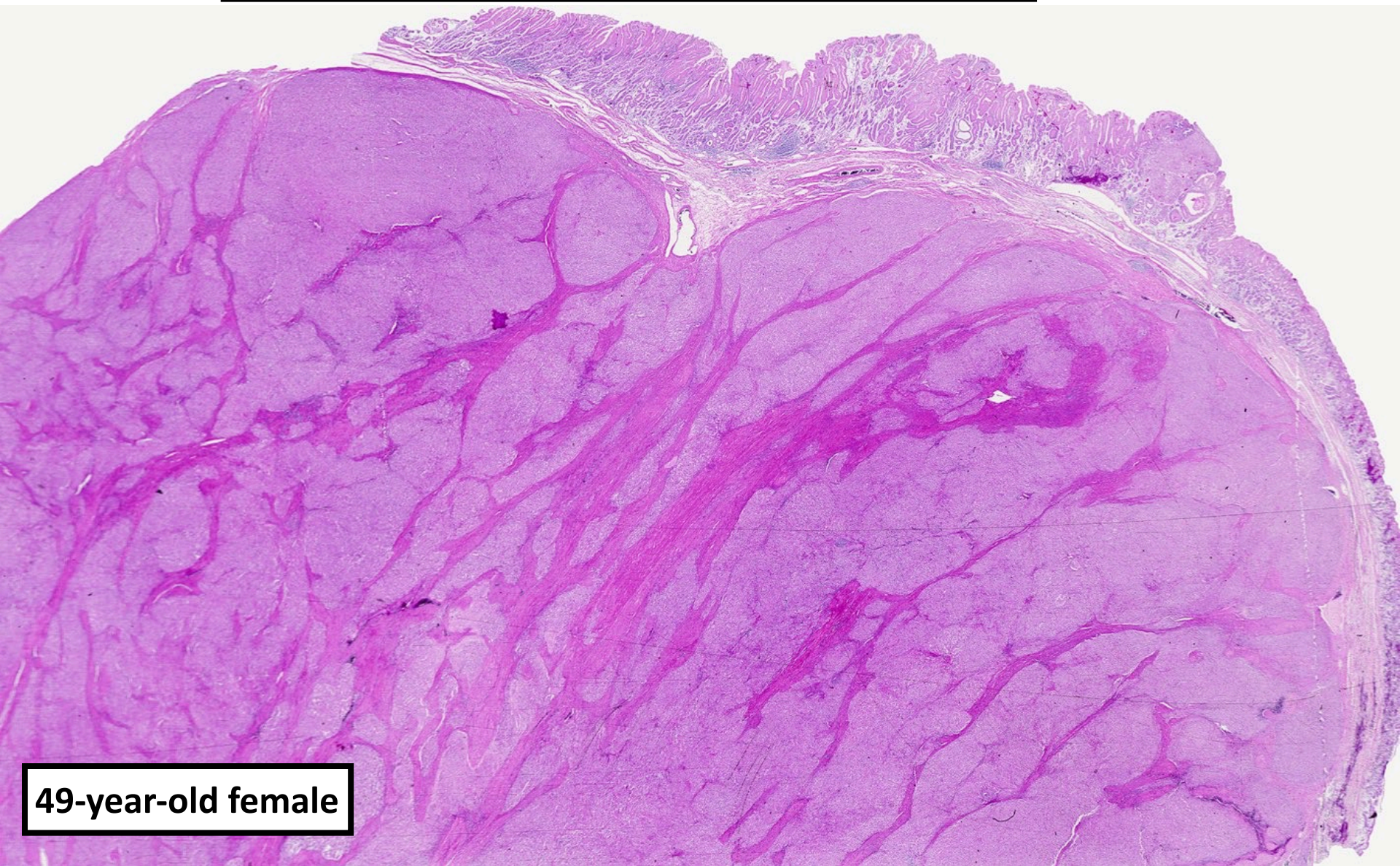
- **Multinodular/plexiform growth pattern**
- **Epithelioid or mixed morphology**
- **“Pediatric-type” or “type 2” GISTs**
- **Loss of SDHB staining by IHC**
- **Lymph node metastases common**
- **Distant metastases common – clinically indolent**
- **Current risk assessment criteria do not reliably predict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

11-year-old female



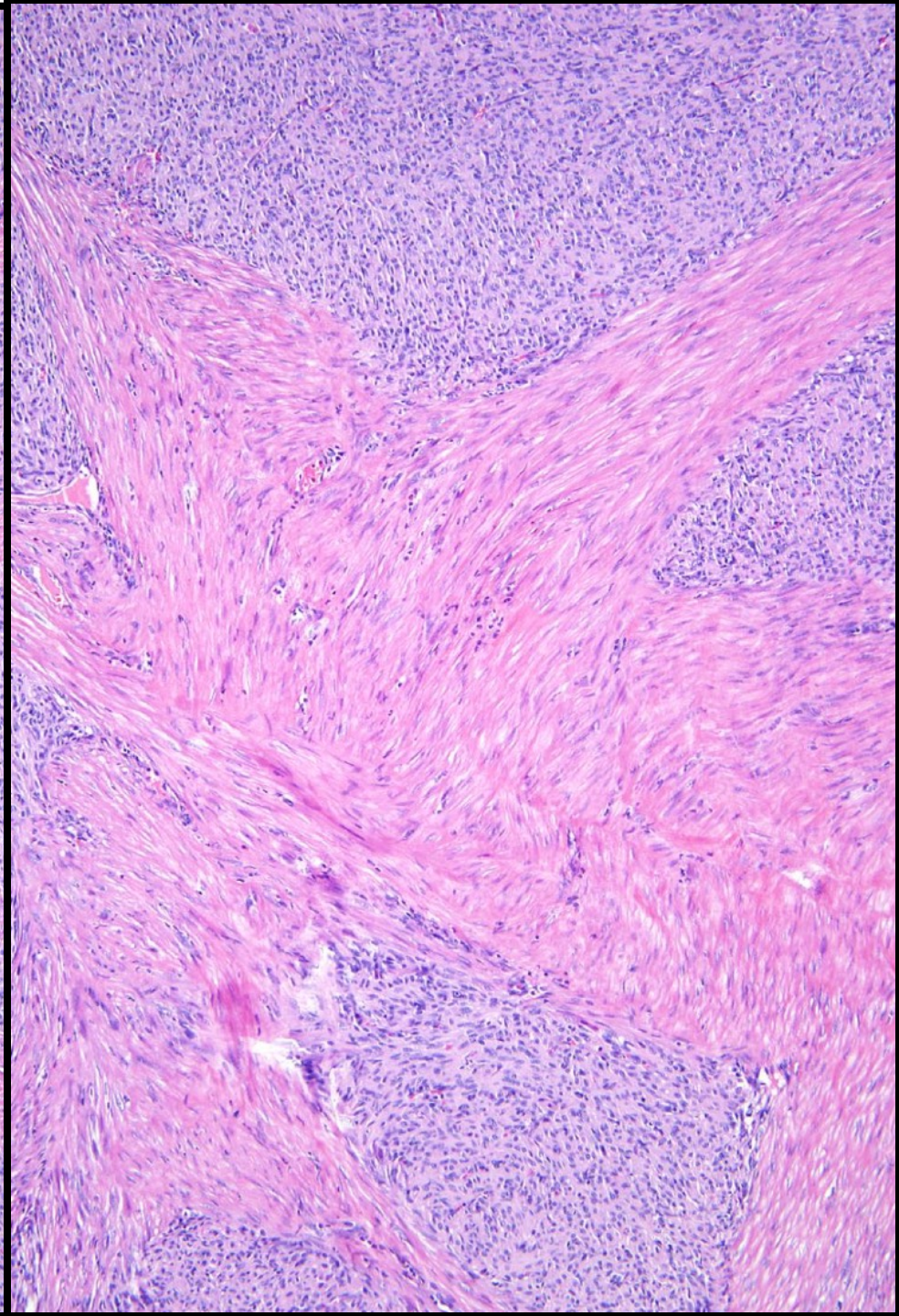
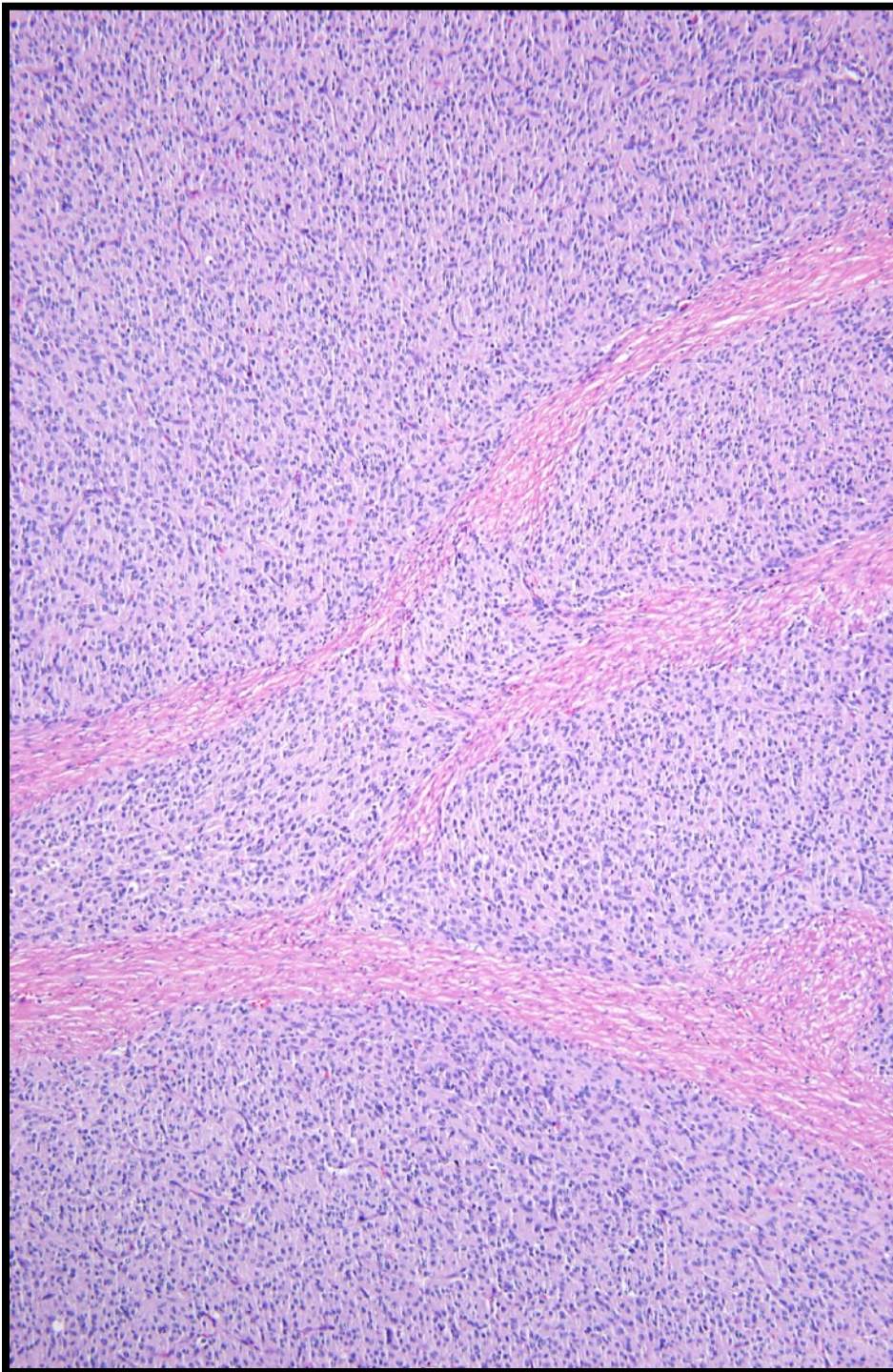
Courtesy of Jason Hornick, BWH/Harvard, Boston, MA

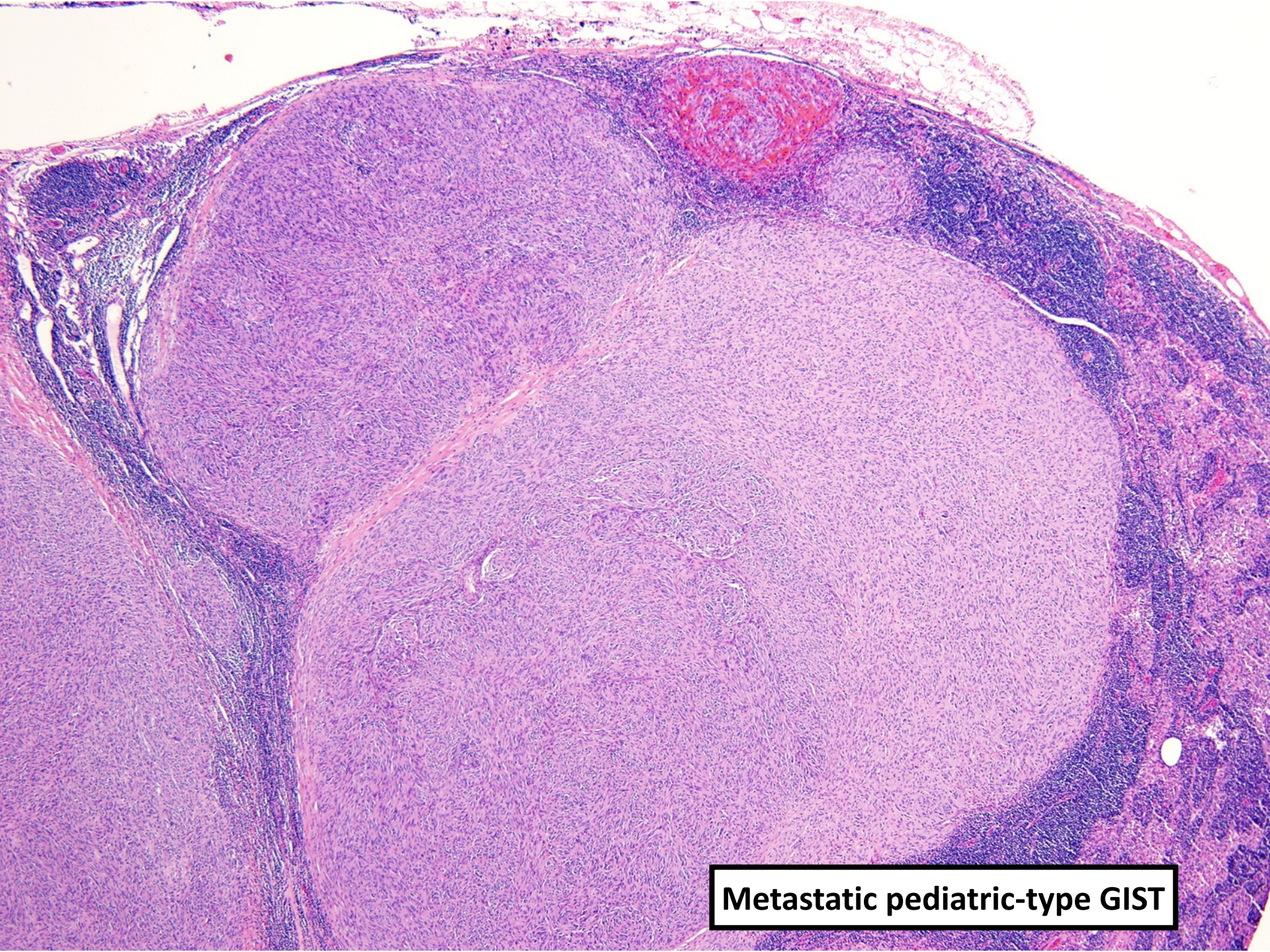
Pediatric-type GIST in an Adult



49-year-old female

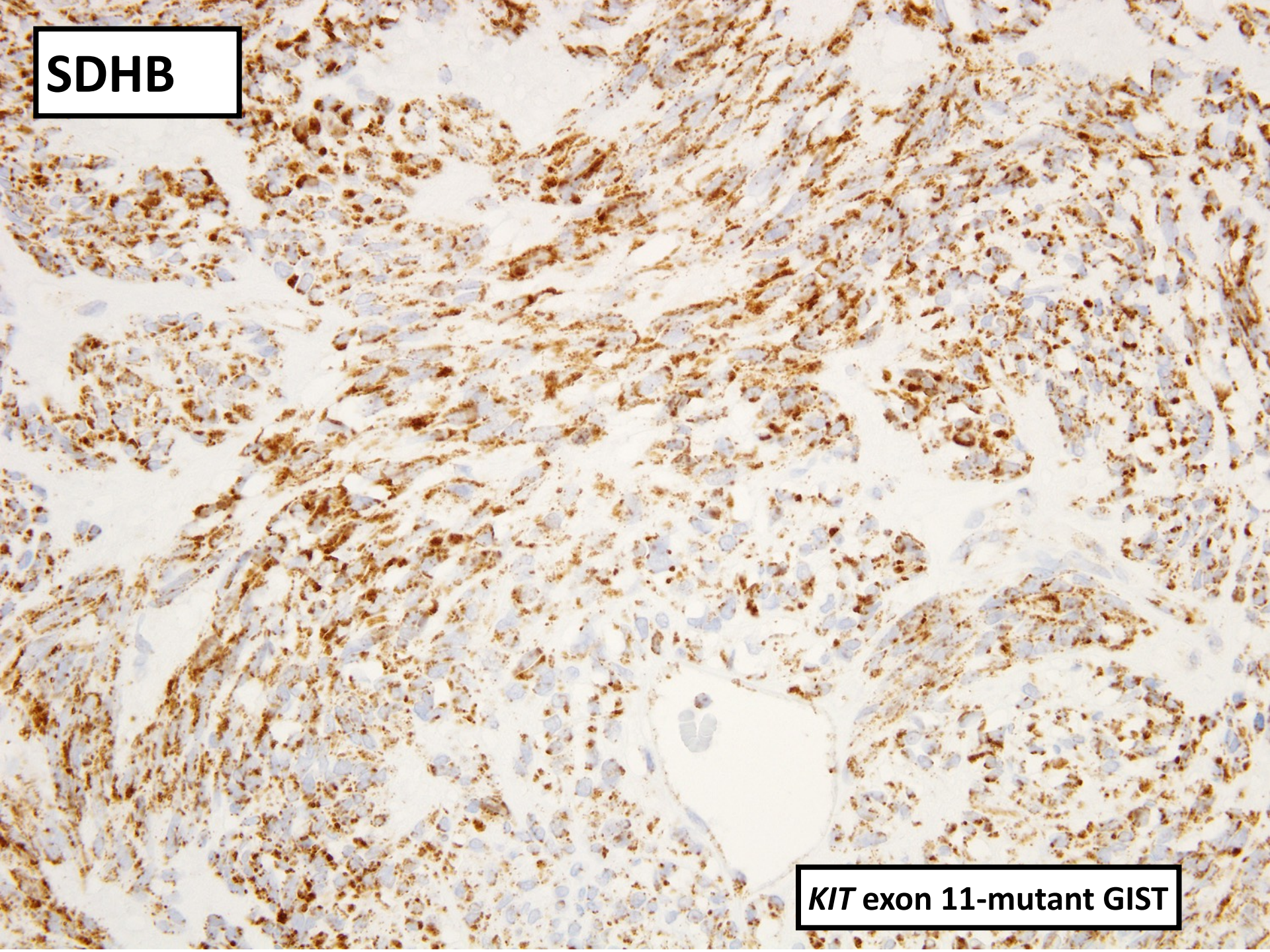
Courtesy of Jason Hornick, BWH/Harvard, Boston, MA





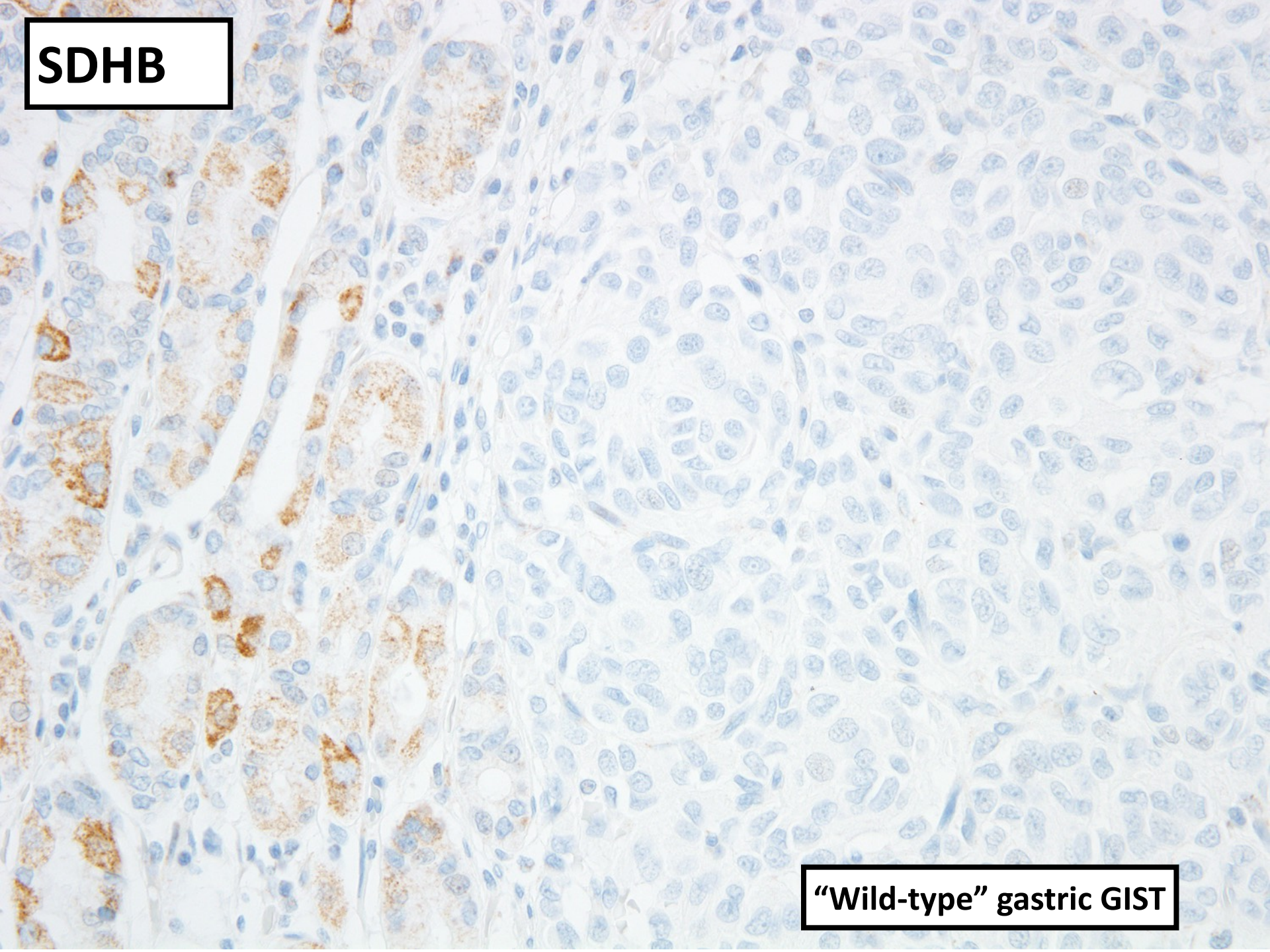
Metastatic pediatric-type GIST

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

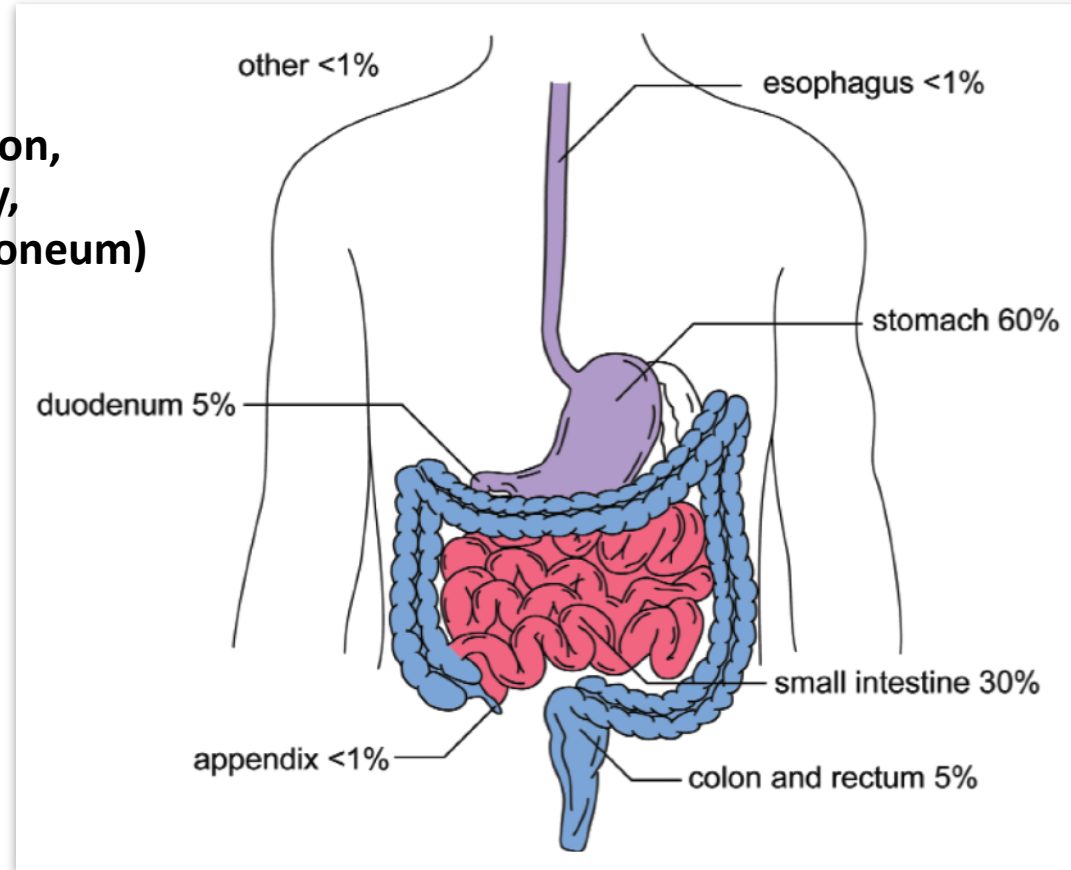
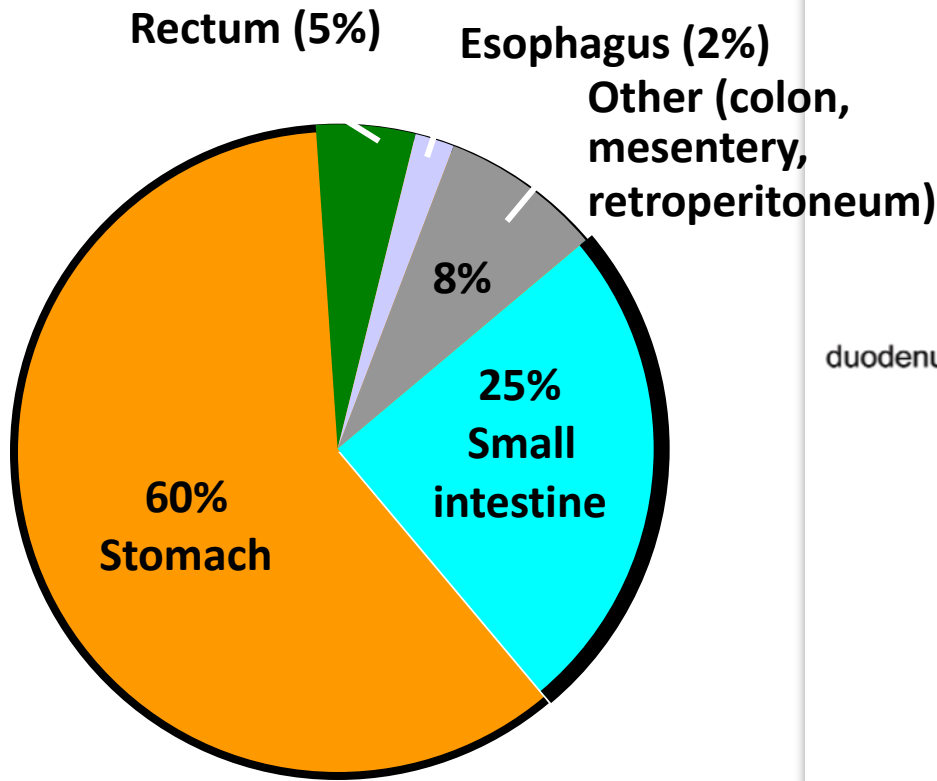
Nuclear Organizer Regions

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

NIH Consensus Risk Assessment

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

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

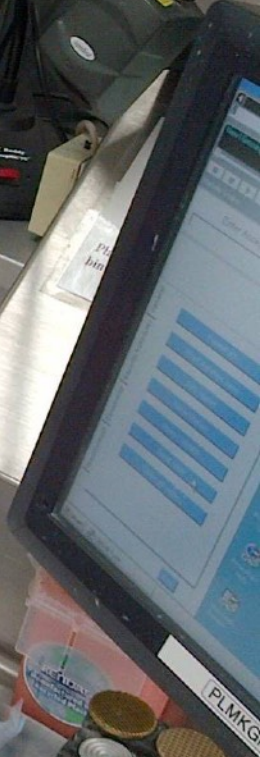


Courtesy of Brian Rubin, Cleveland Clinic



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



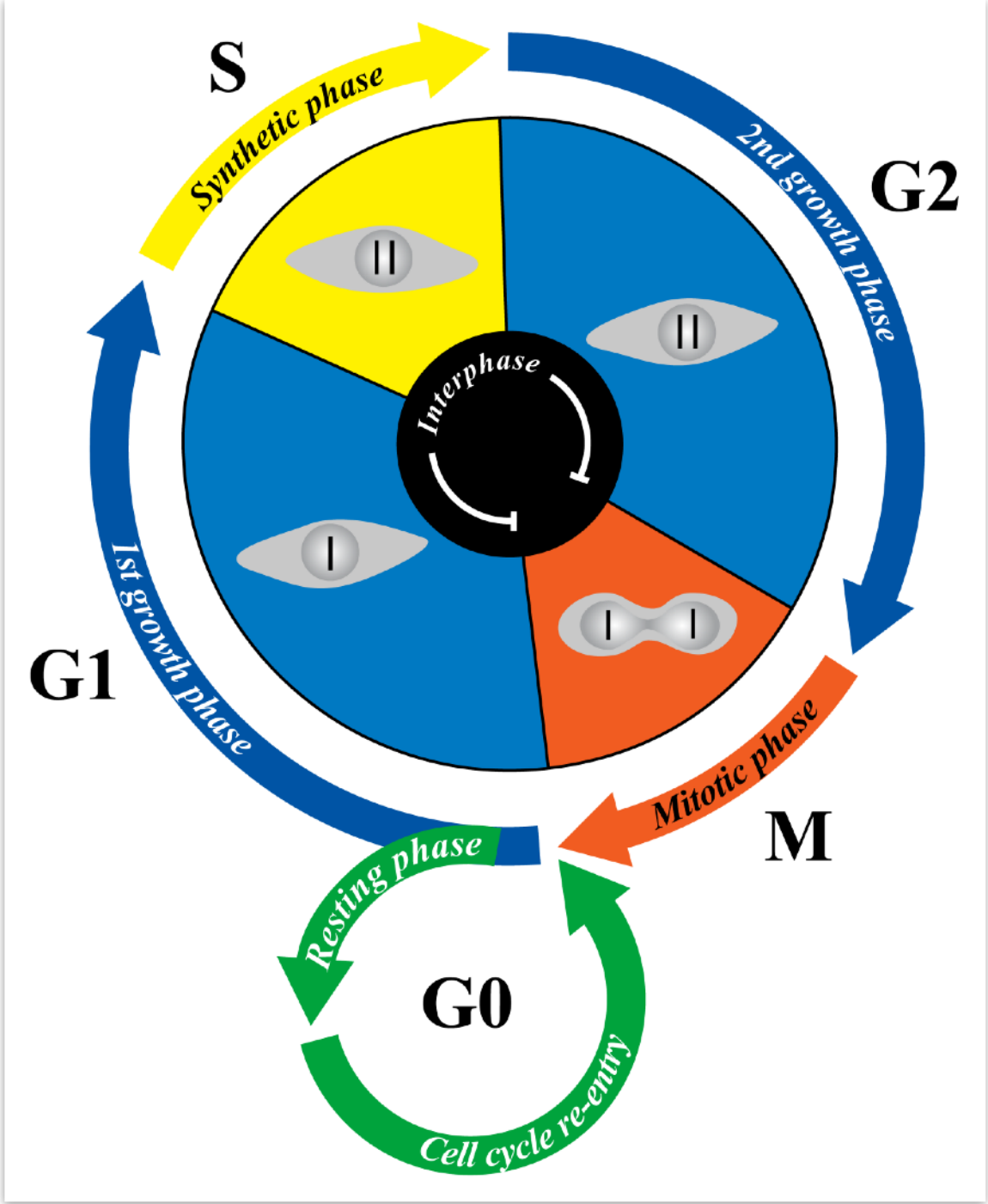


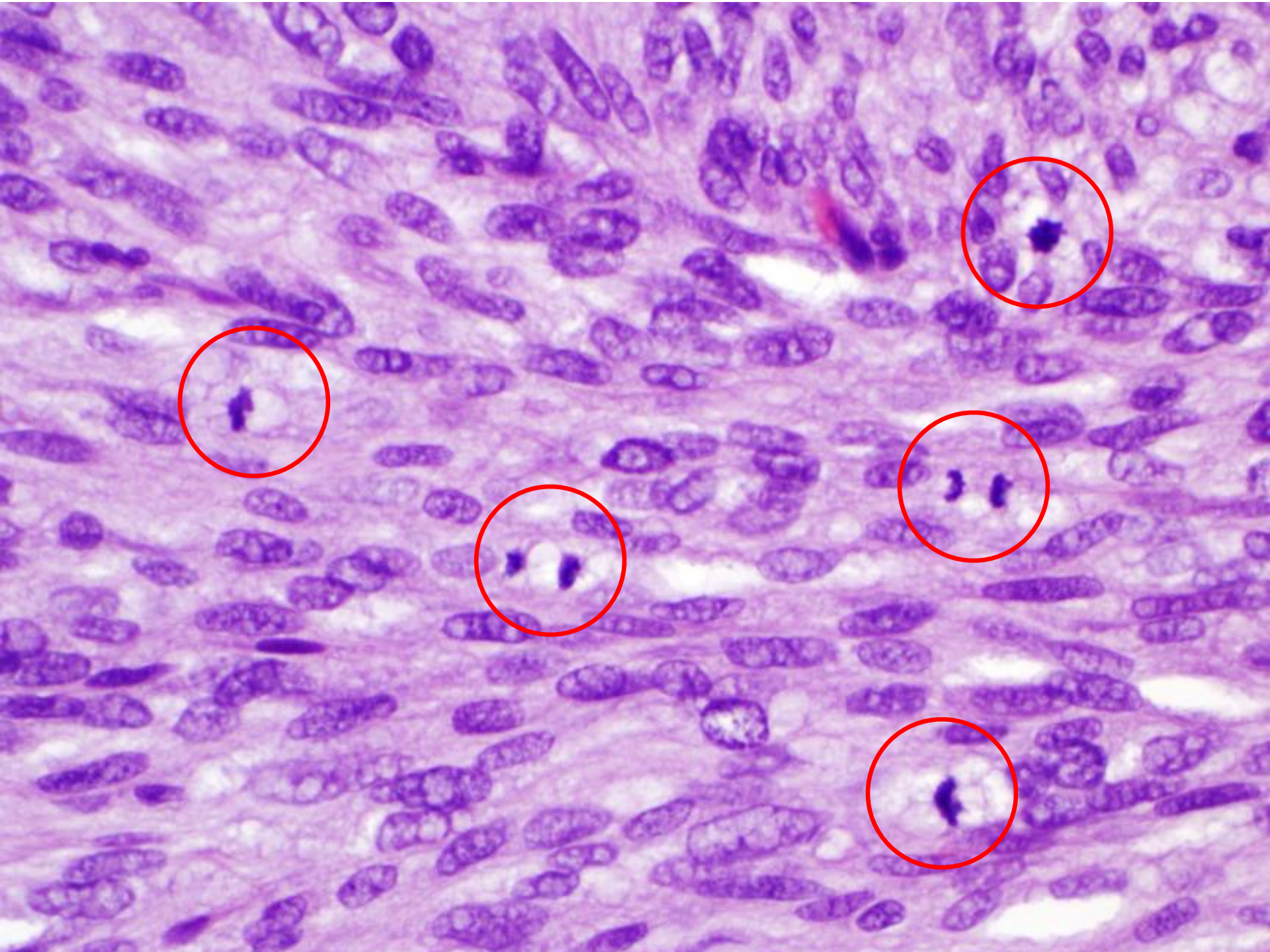
2007/2010/2014 NCCN GIST Risk Assessment Guidelines***

Tumor	Parameters	Risk of	Progressive	Disease# (%)	
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≤ 5 per 50 hpf	> 5 ≤ 10 cm	Low (3.6%)	(Insuff. data)	Moderate (24%)	(Insuff. data)
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	> 10 cm	High (86%)	High (86%)	High (90%)	High (71%)

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

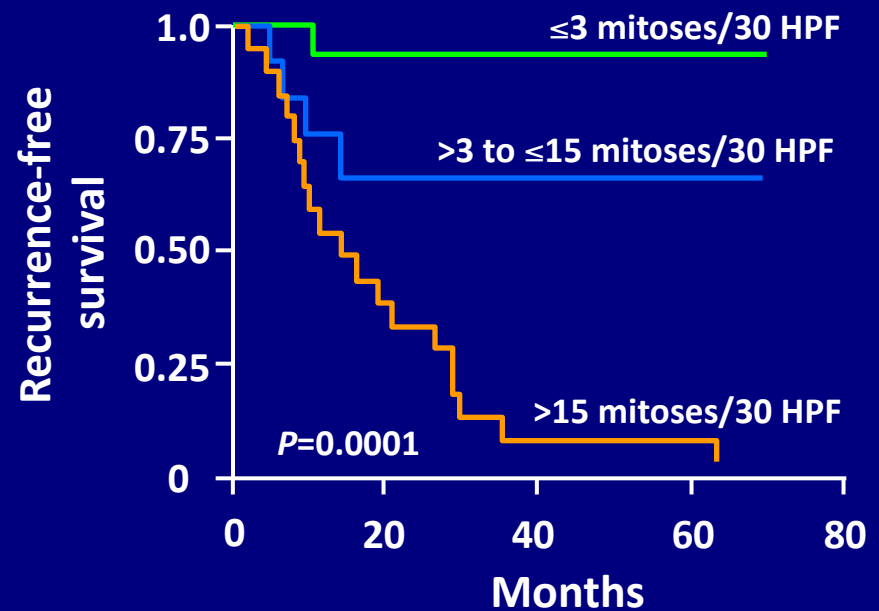
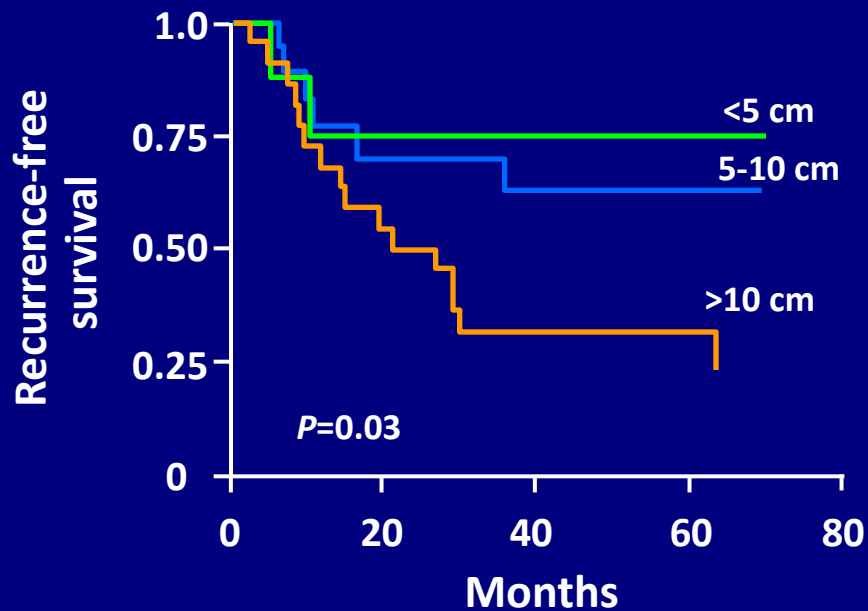
Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GIST





GIST - 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 mm²) using a 40x objective.

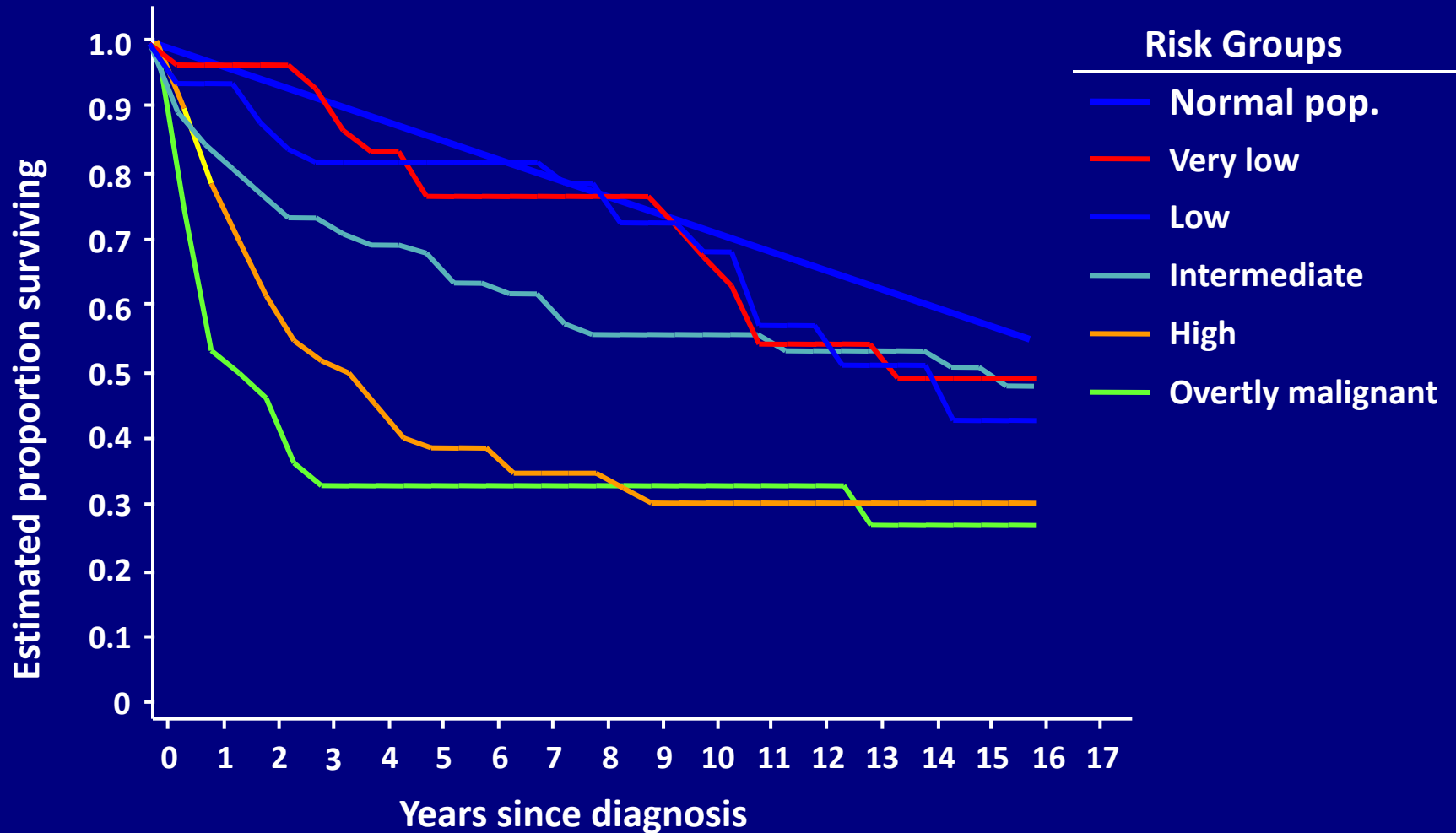
1. 0-9 mitoses per 10 HPFs
2. 10-19 mitoses per 10 HPFs
3. >20 mitoses per 10 HPFs

- **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

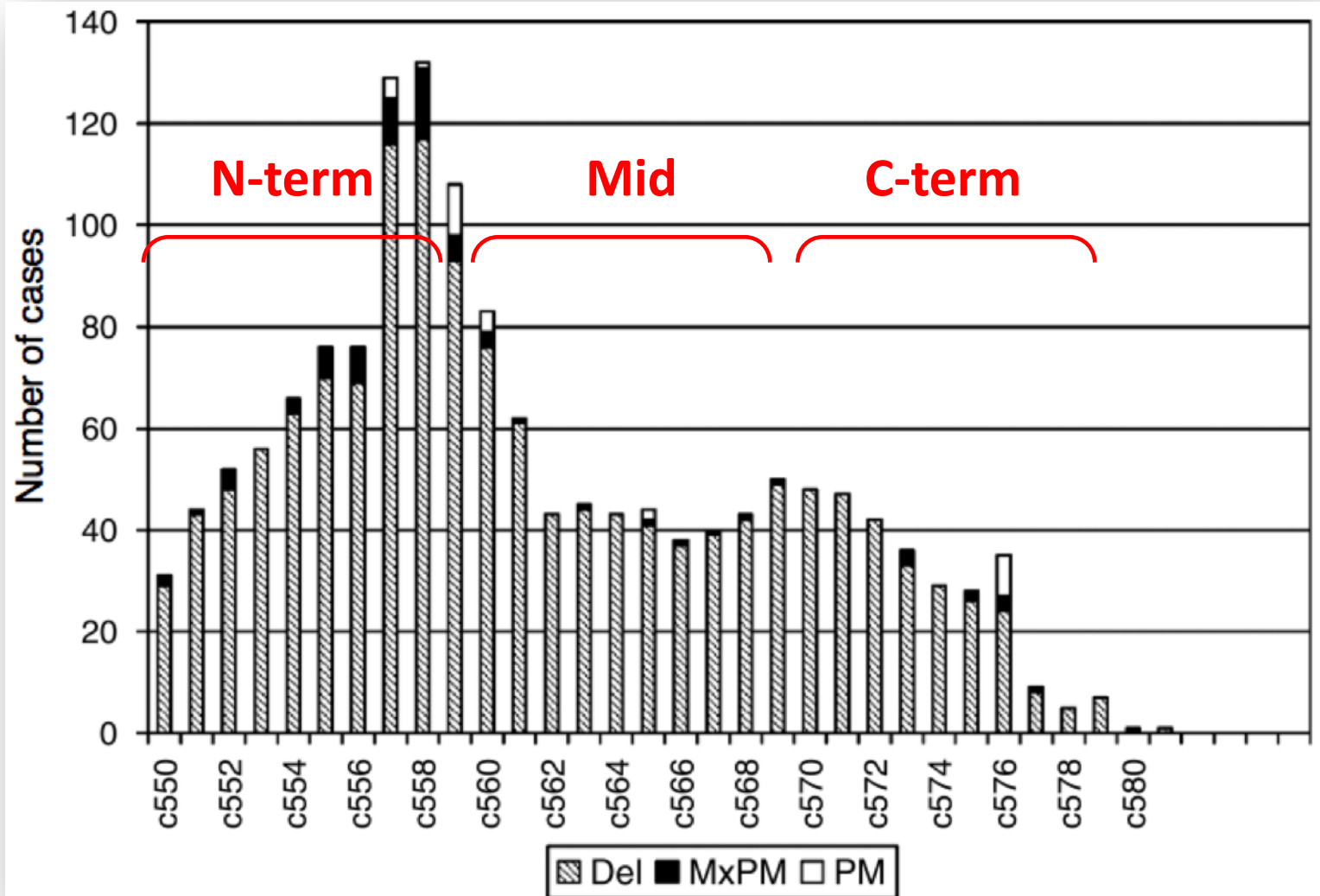


Genomic complexity and prognosis

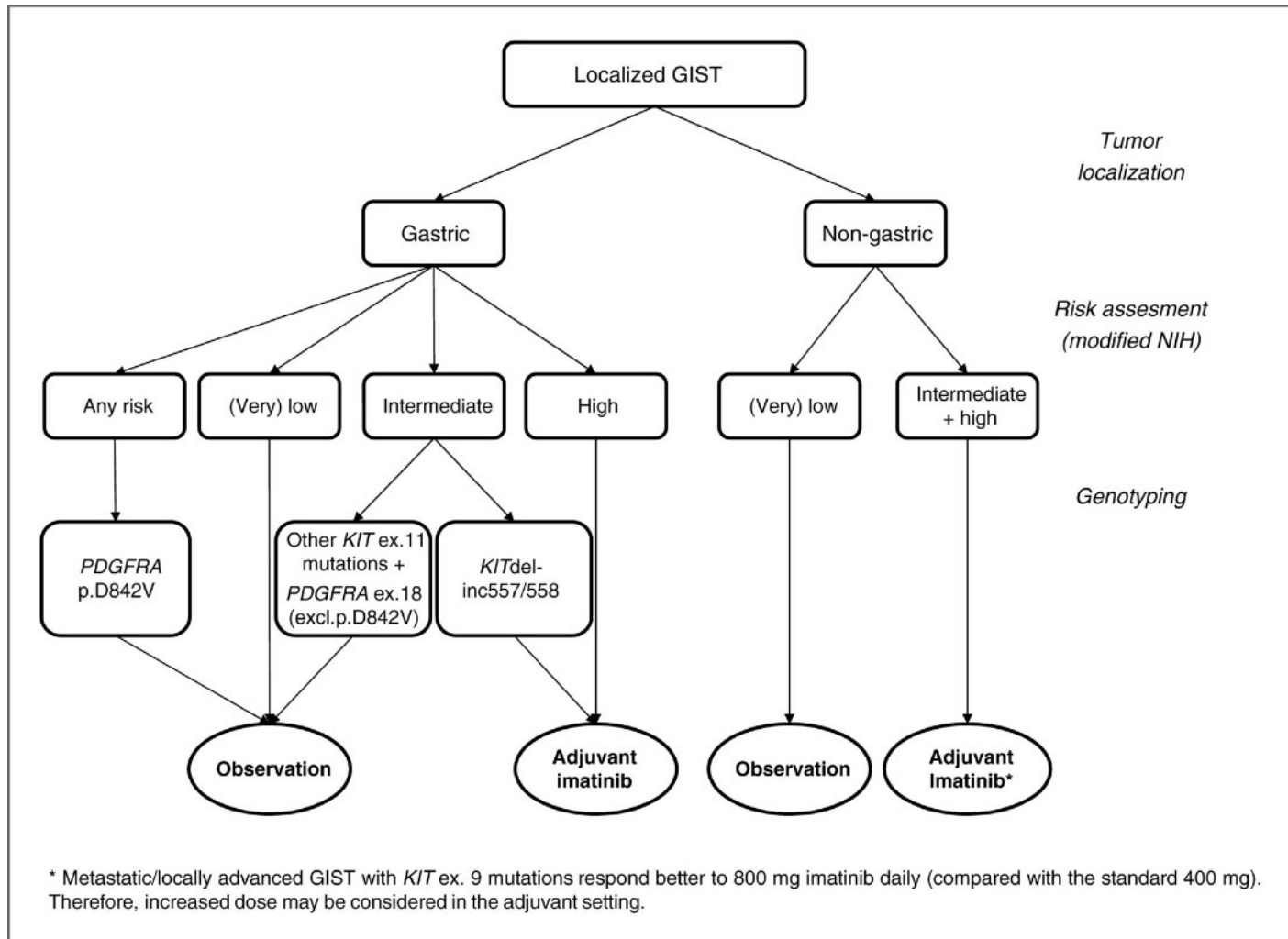
Possible approaches

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

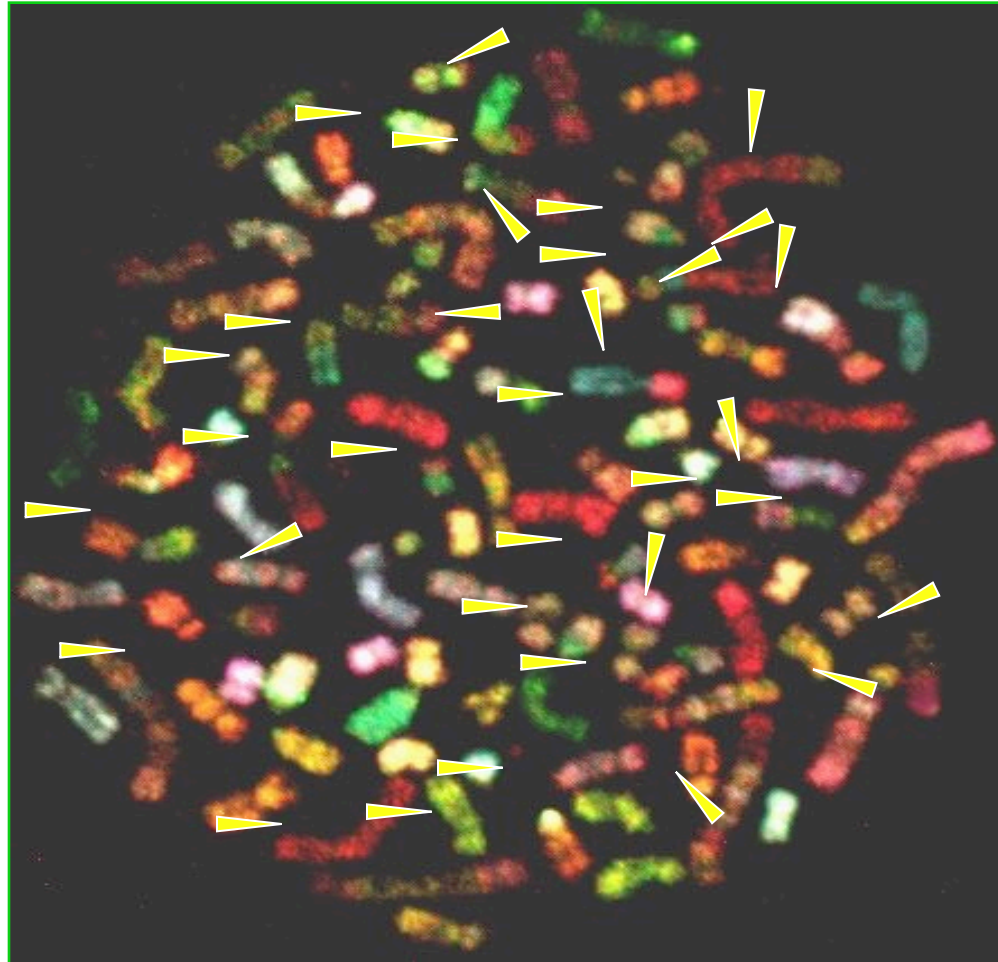
Spectrum of KIT Exon 11 Mutations



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 ...



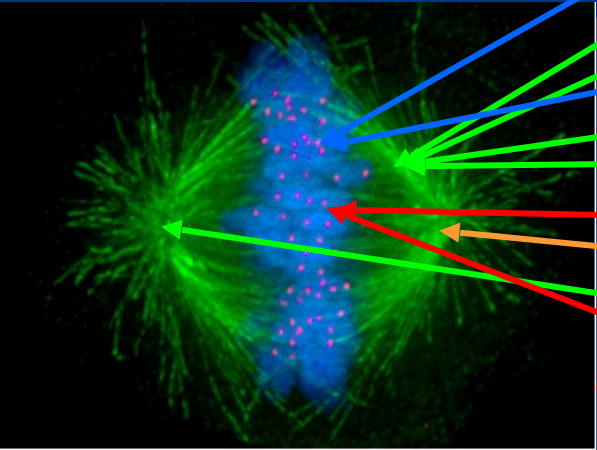
Chromosomal complexity and prognosis



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 instability signature

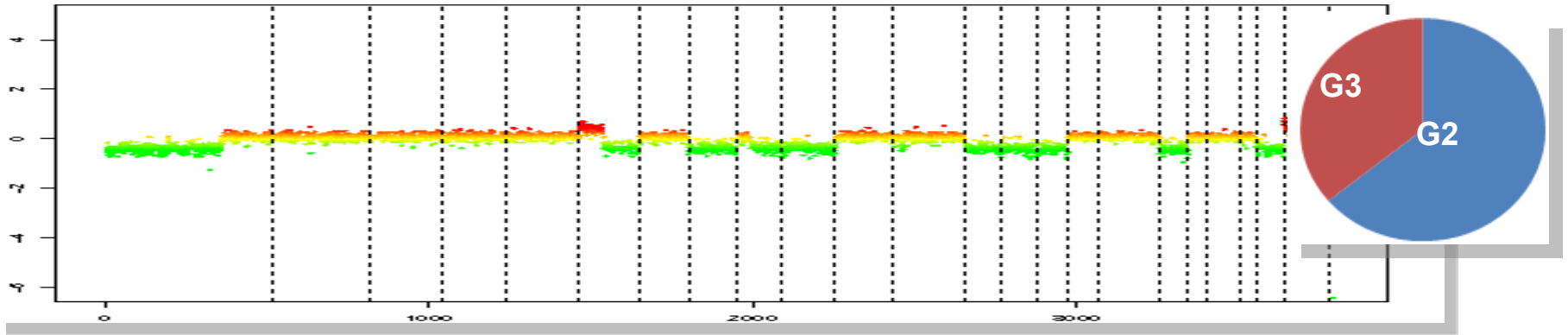
Carter et al *Nat Genet* 2002

- **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**

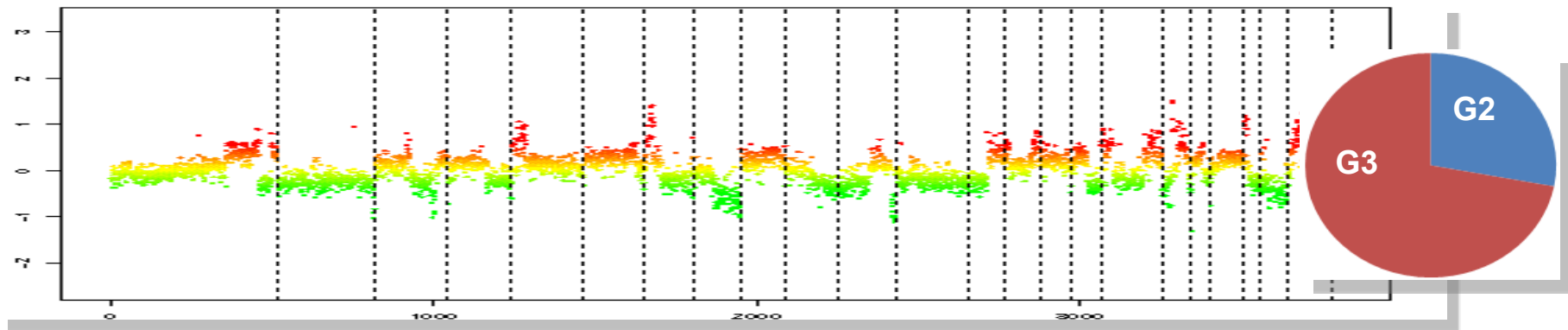
Courtesy of J-M Coindre & F Chibon,
Bordeaux, France (Fresch Sarcoma Group)

CINSARC : arrayCGH analysis and correlation with FNCLCC grading

« Arm » Profile



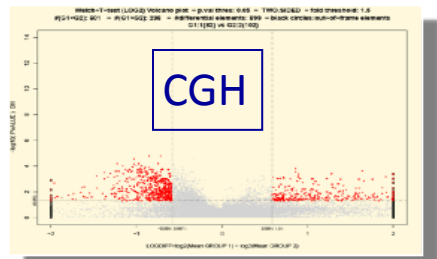
« Rearranged » Profile



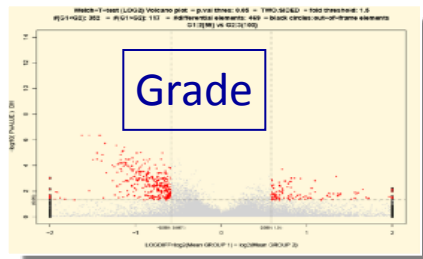
Courtesy of J-M Coindre & F Chibon,
Bordeaux, France (Fresch Sarcoma Group)

Molecular grading in sarcomas

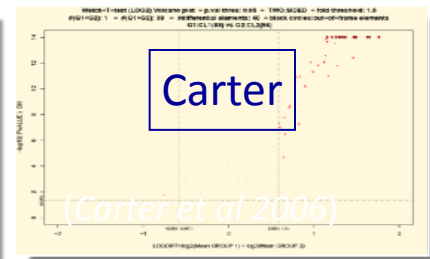
3 tests to compare the expression profiles of tumors classified according to:



86 genes



73 genes



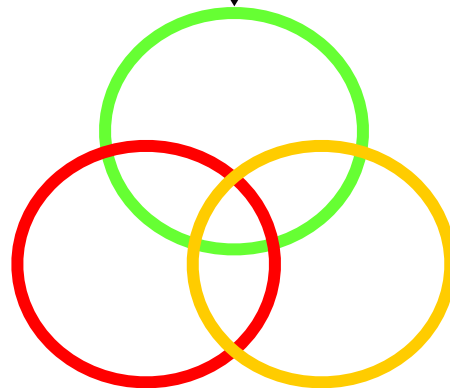
39 genes

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

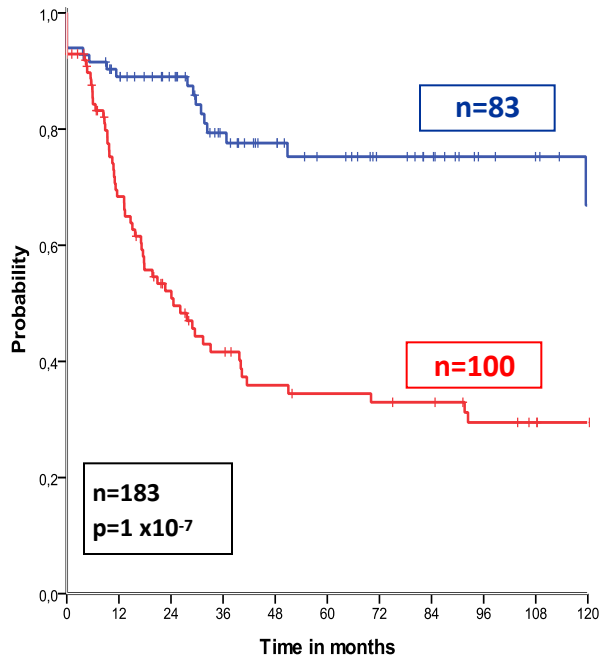


Complexity INdex
In SARComas
CINSARC

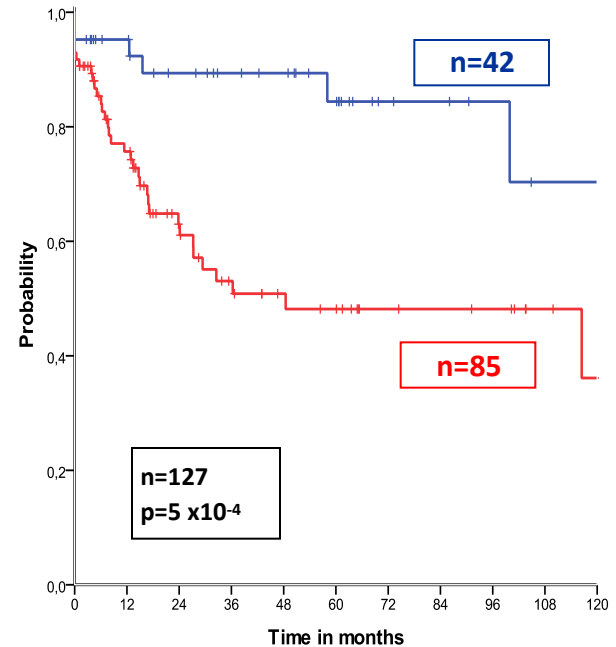
Courtesy of J-M Coindre & F Chibon,
Bordeaux, France (Fresch Sarcoma Group)

Prognostic value of CINSARC: Metastasis free survival

Cohort 1



Cohort 2



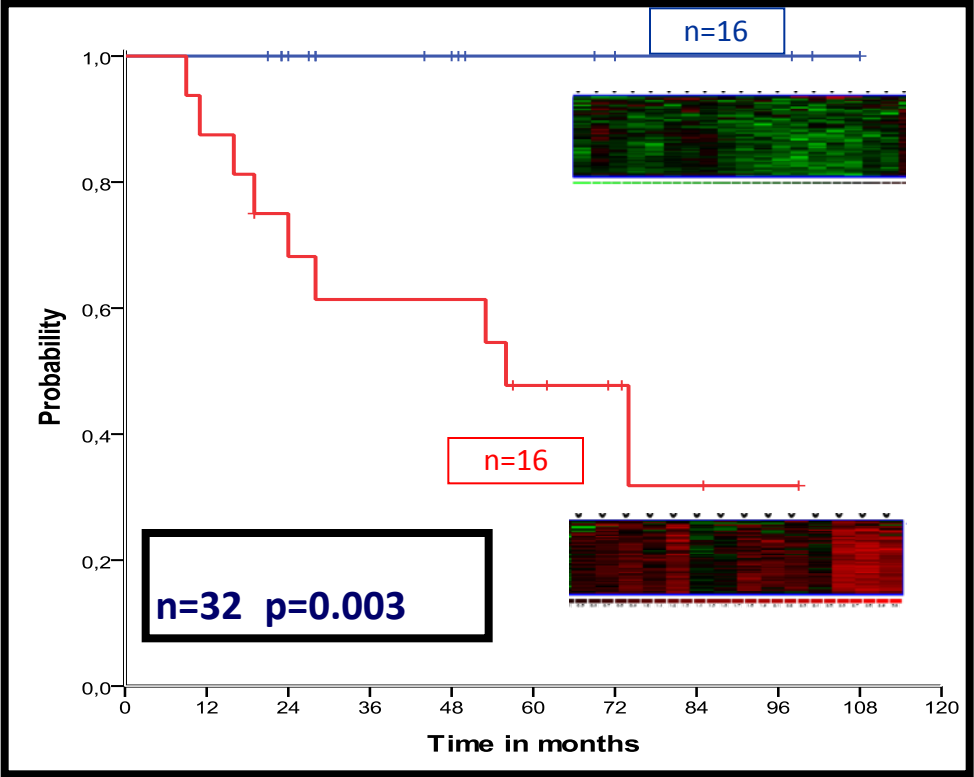
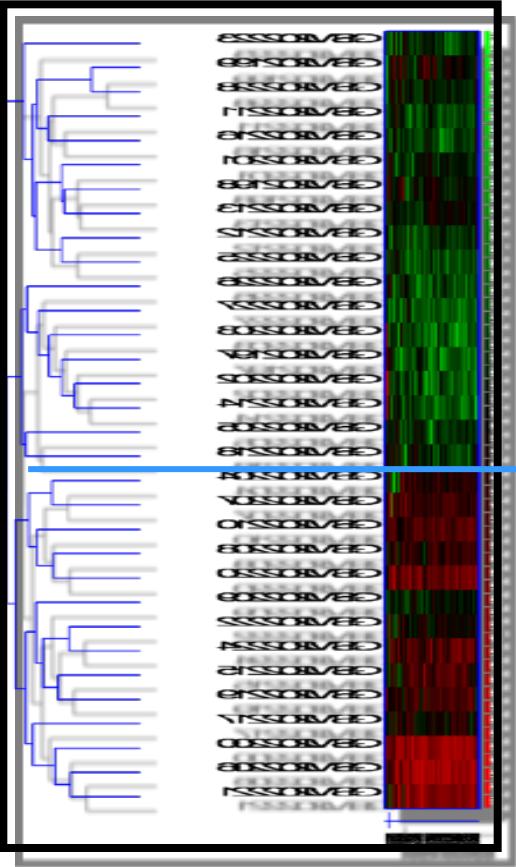
Multivariate analysis

CINSARC is an independent prognostic factor

CINSARC and GIST

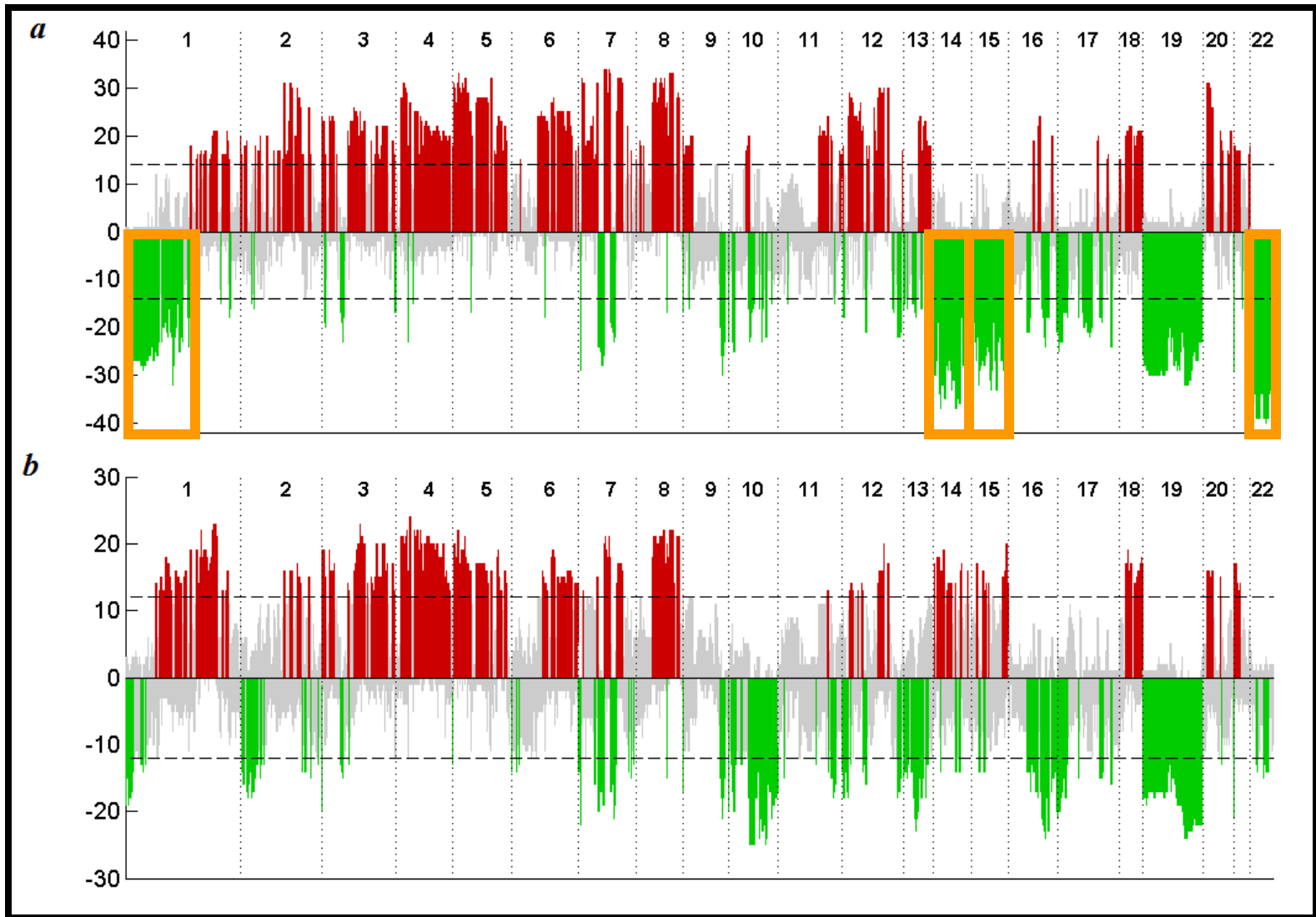
In-silico study of 32 GISTs

(Yamaguchi *et al* 2008)

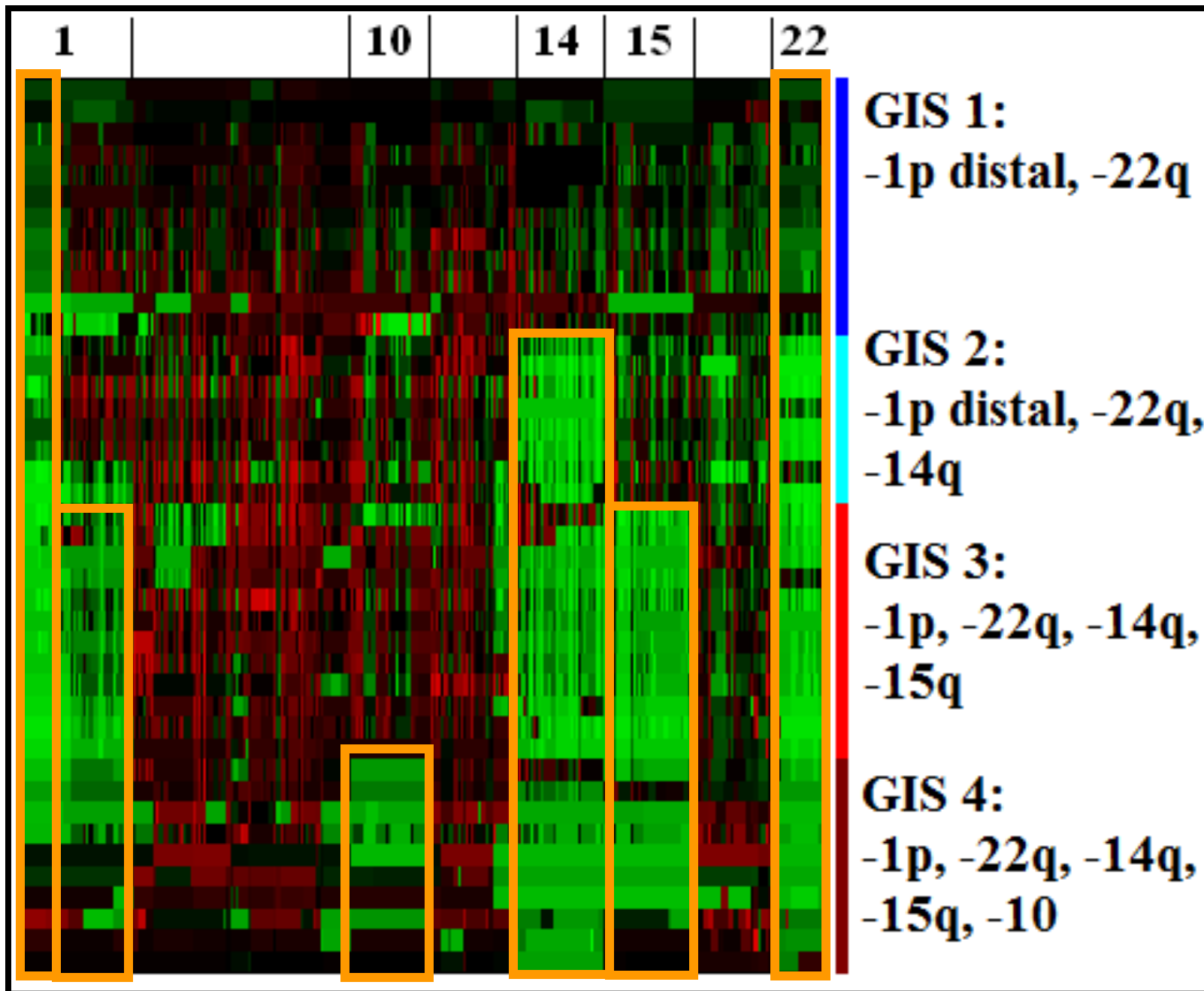


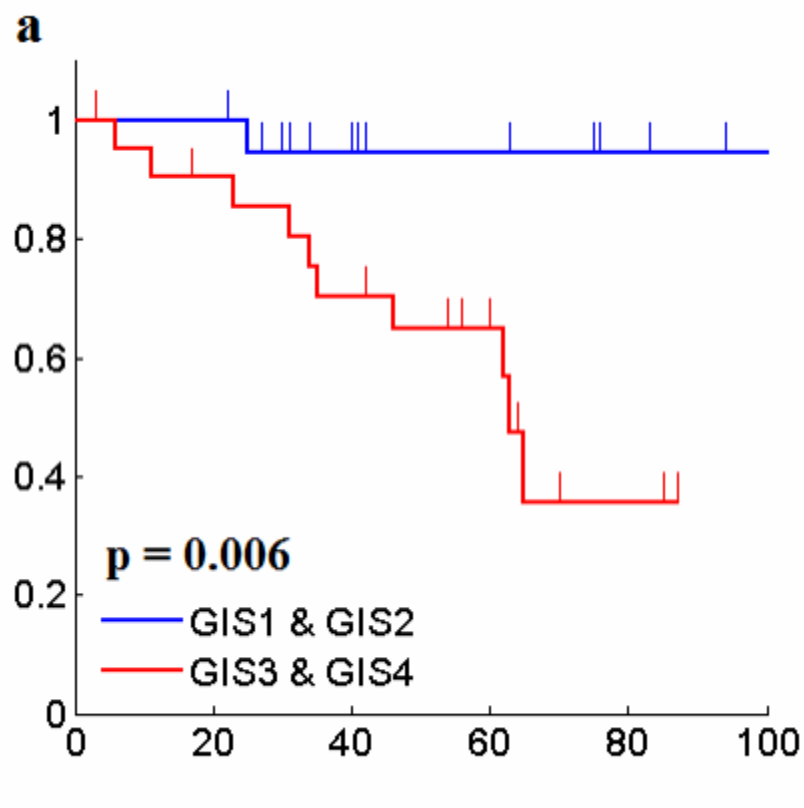
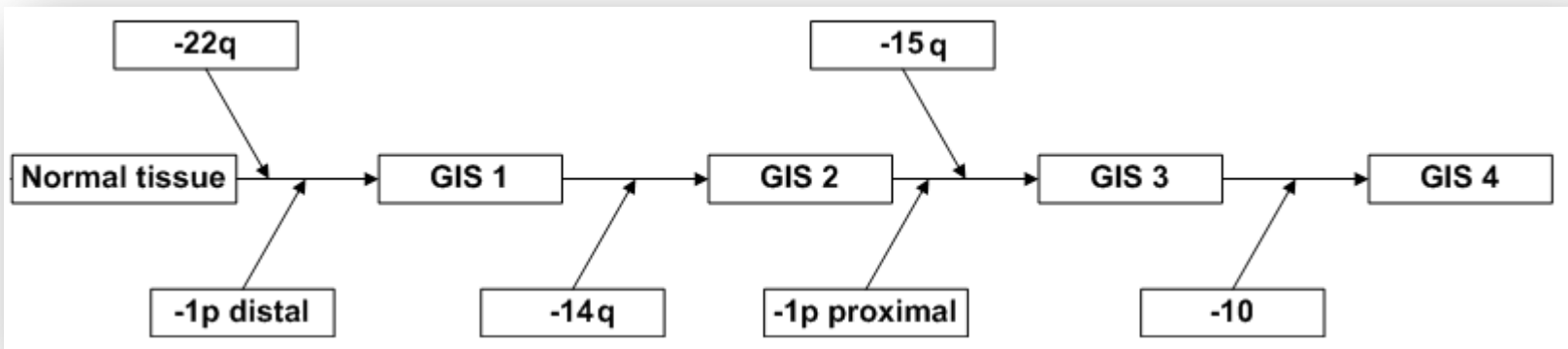
Courtesy of J-M Coindre & F Chibon, Bordeaux, France (Fresch Sarcoma Group)

GIST (n=42)

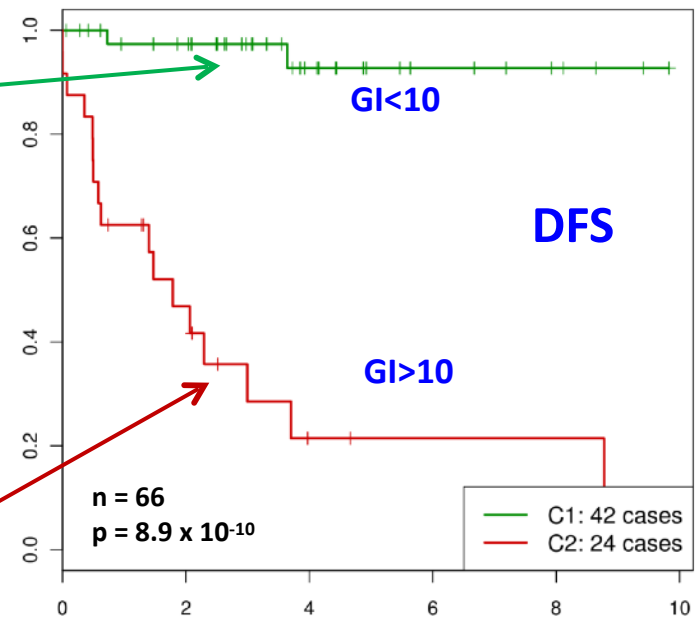
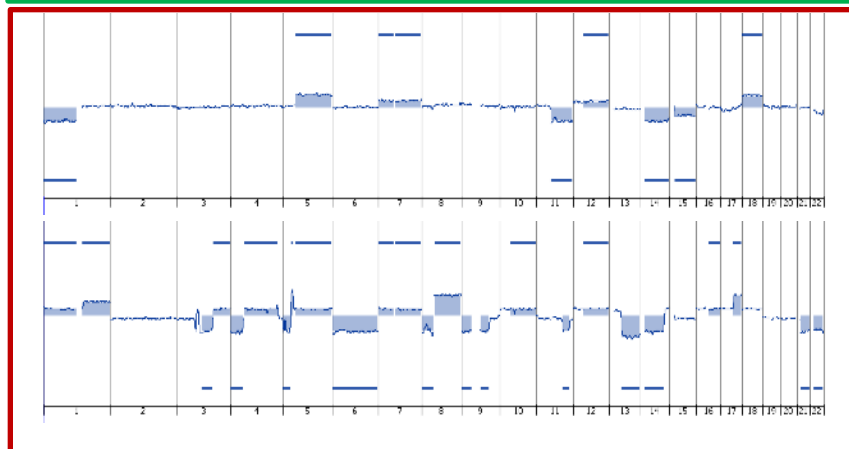
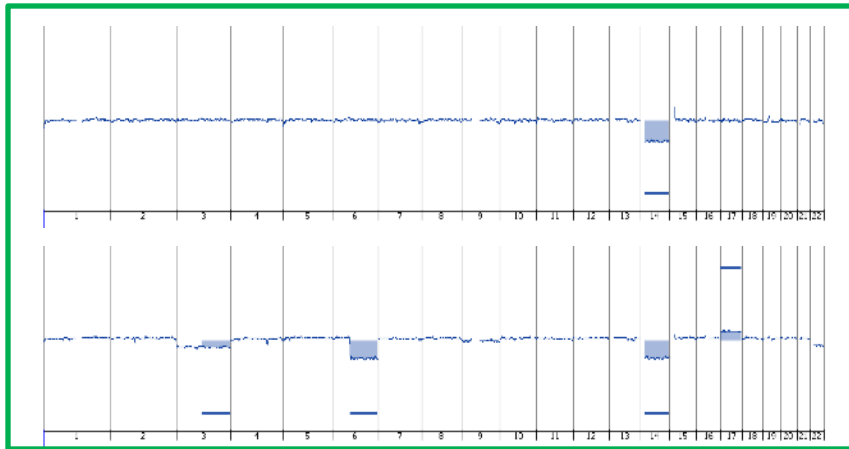


LMS (n=30)





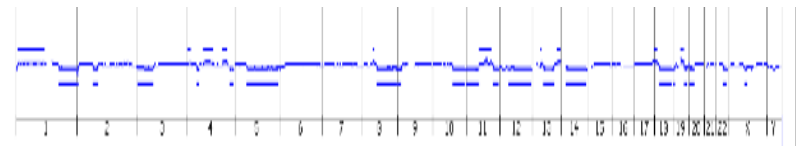
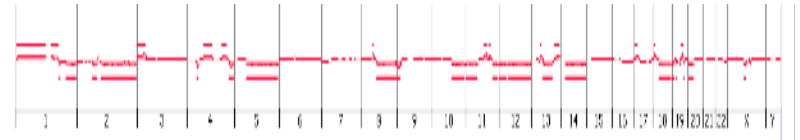
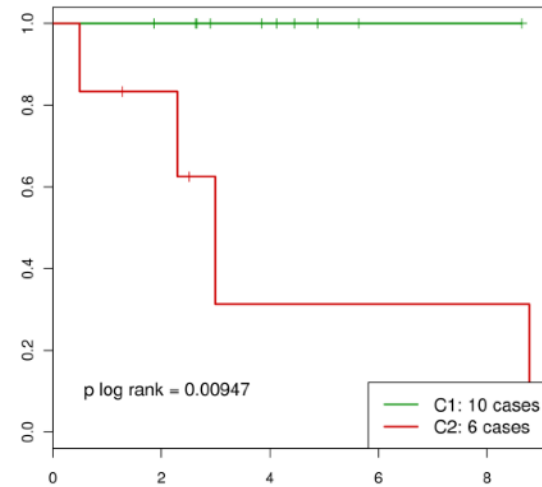
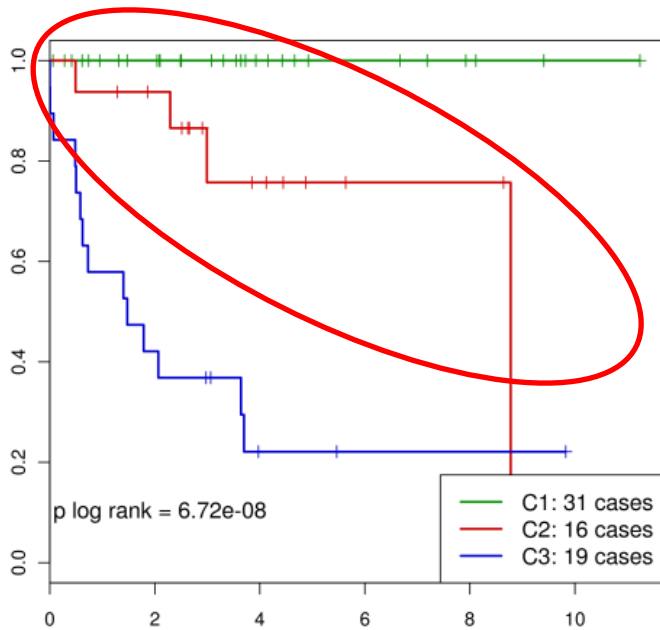
Genomic Index (GI) is a prognostic factor in GIST...



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)

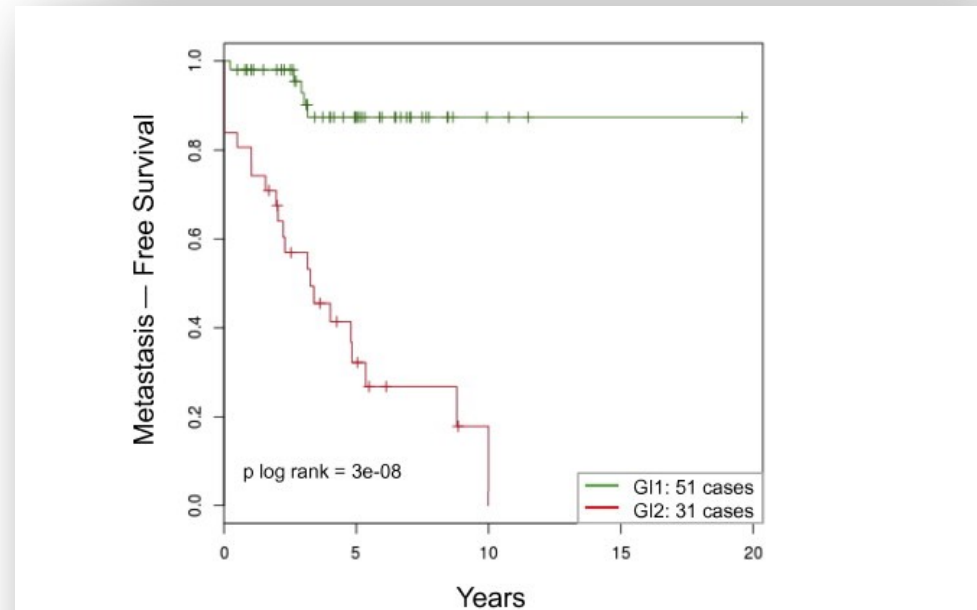
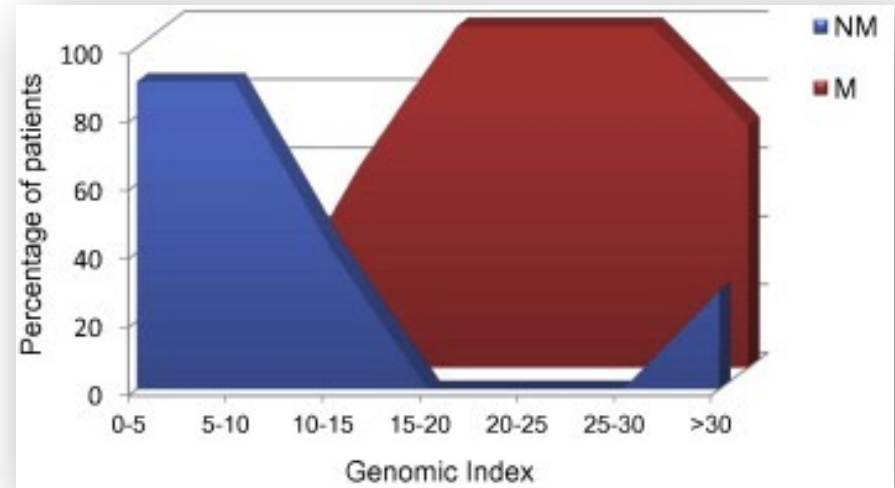


Courtesy of J-M Coindre & F Chibon,
Bordeaux, France (Fresch Sarcoma Group)

More 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

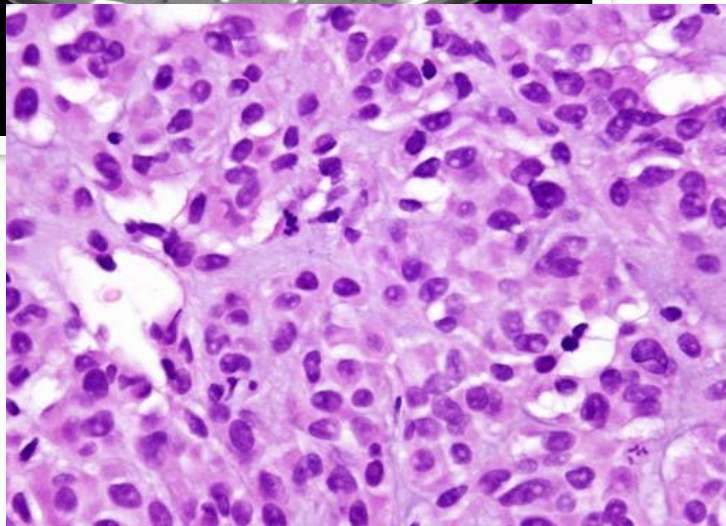
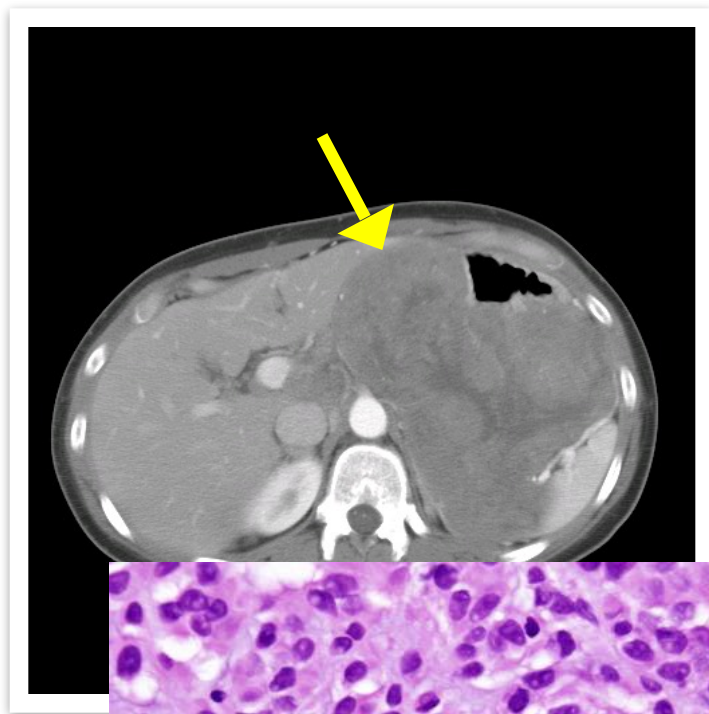


		0	1 y	2 y	3 y	4 y	5 y
GI1	Patients at risk	51	47	43	35	29	22
	Cumulated events	0	1	1	3	5	5
	Metastasis FS	1	0.98	0.98	0.93	0.87	0.87
GI2	Patients at risk	31	25	20	15	11	7
	Cumulated events	5	6	10	13	16	19
	Metastasis FS	0.84	0.81	0.68	0.57	0.45	0.32

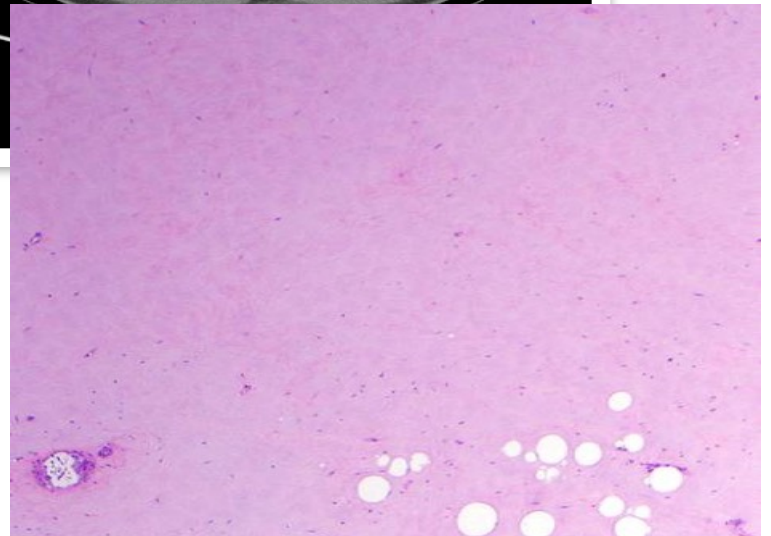
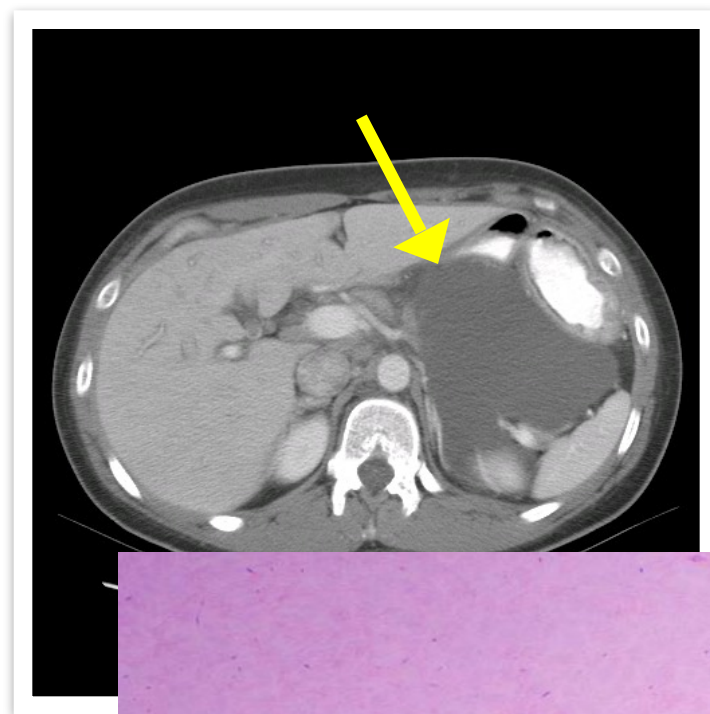
Chibon & Colleagues. Eur J Cancer 2014;
51(1):75-83.

Treatment can cause big changes.

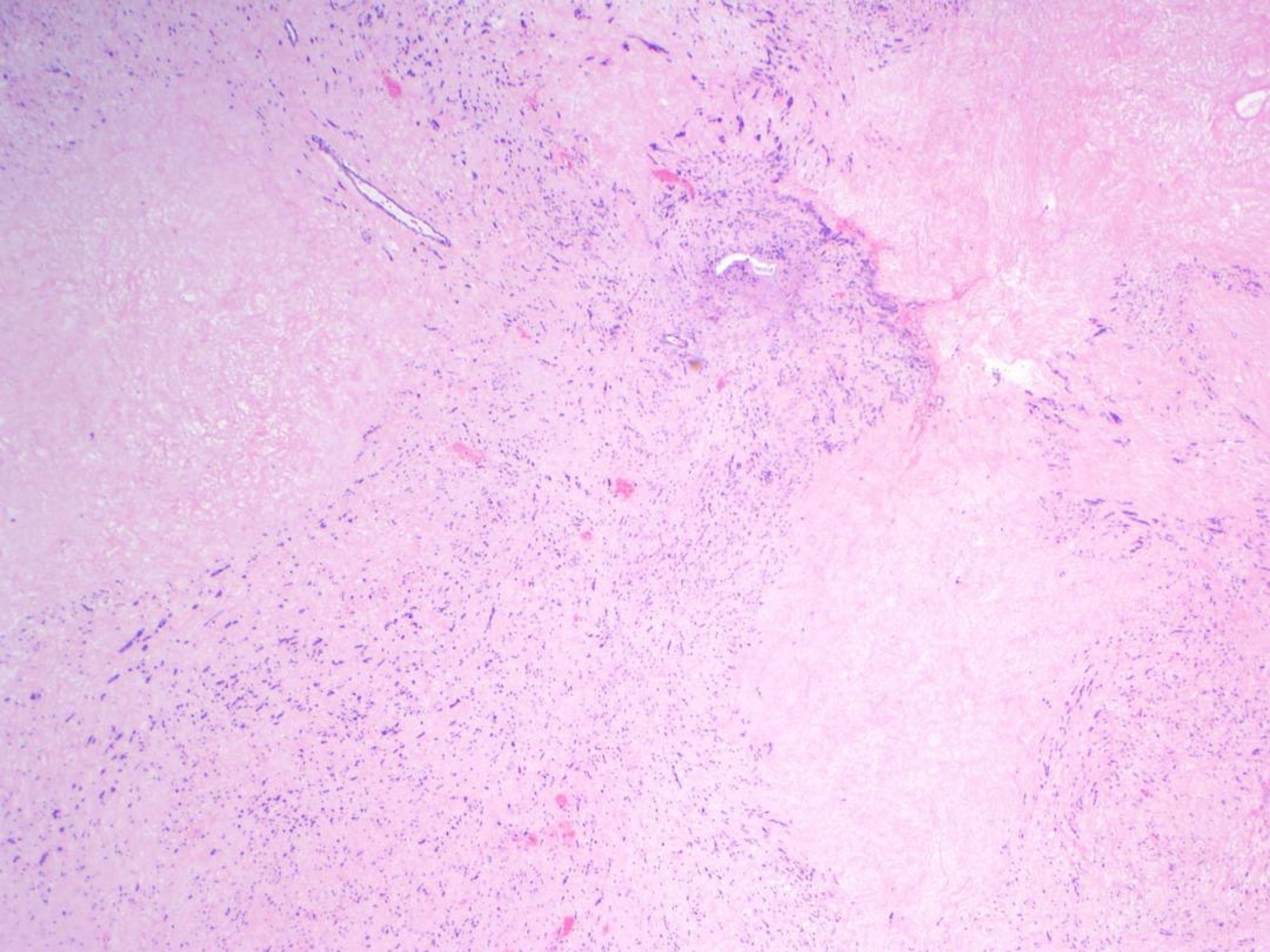
Treatment effect

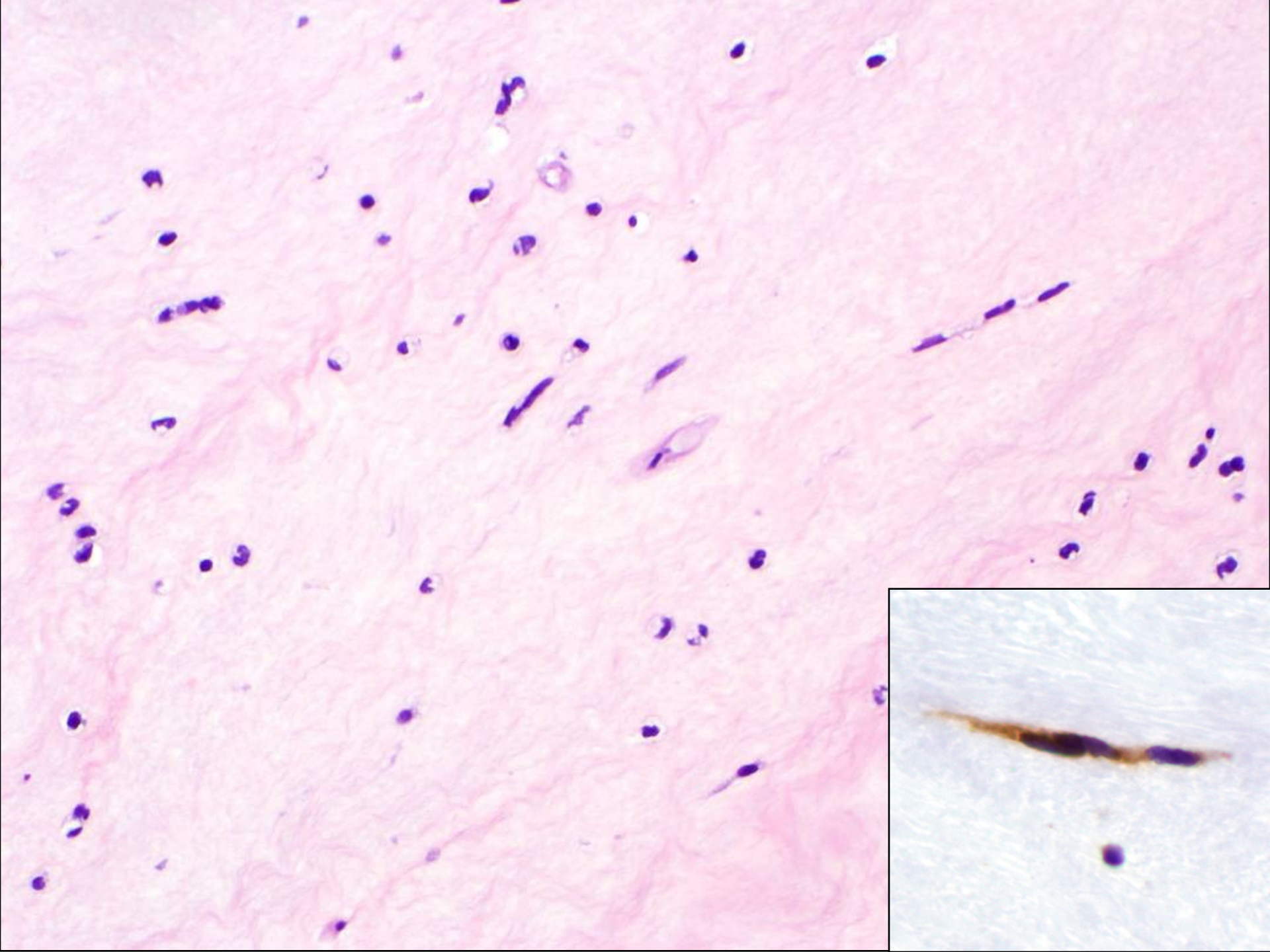


Pre-Imatinib

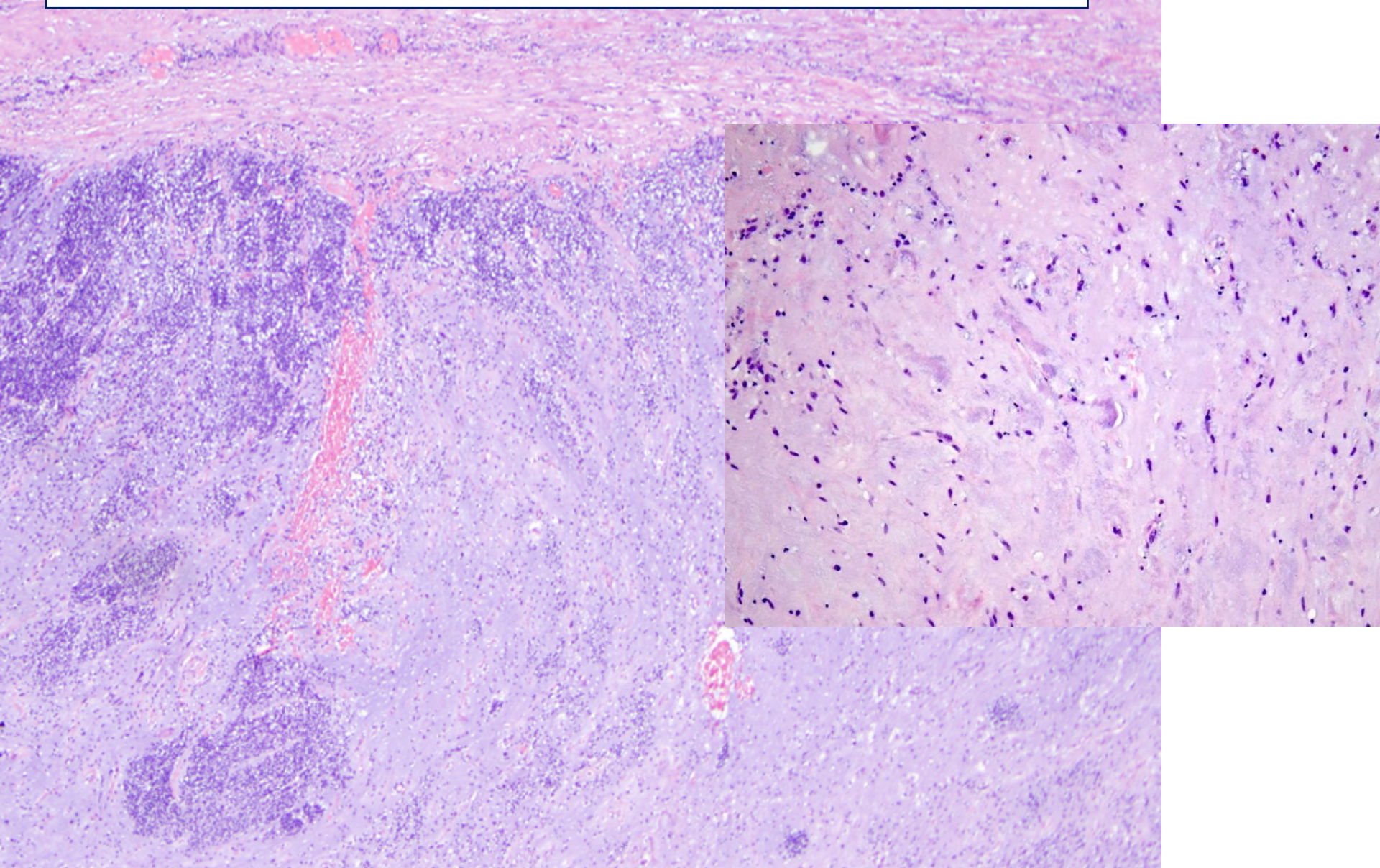


Post-Imatinib (8 weeks therapy)

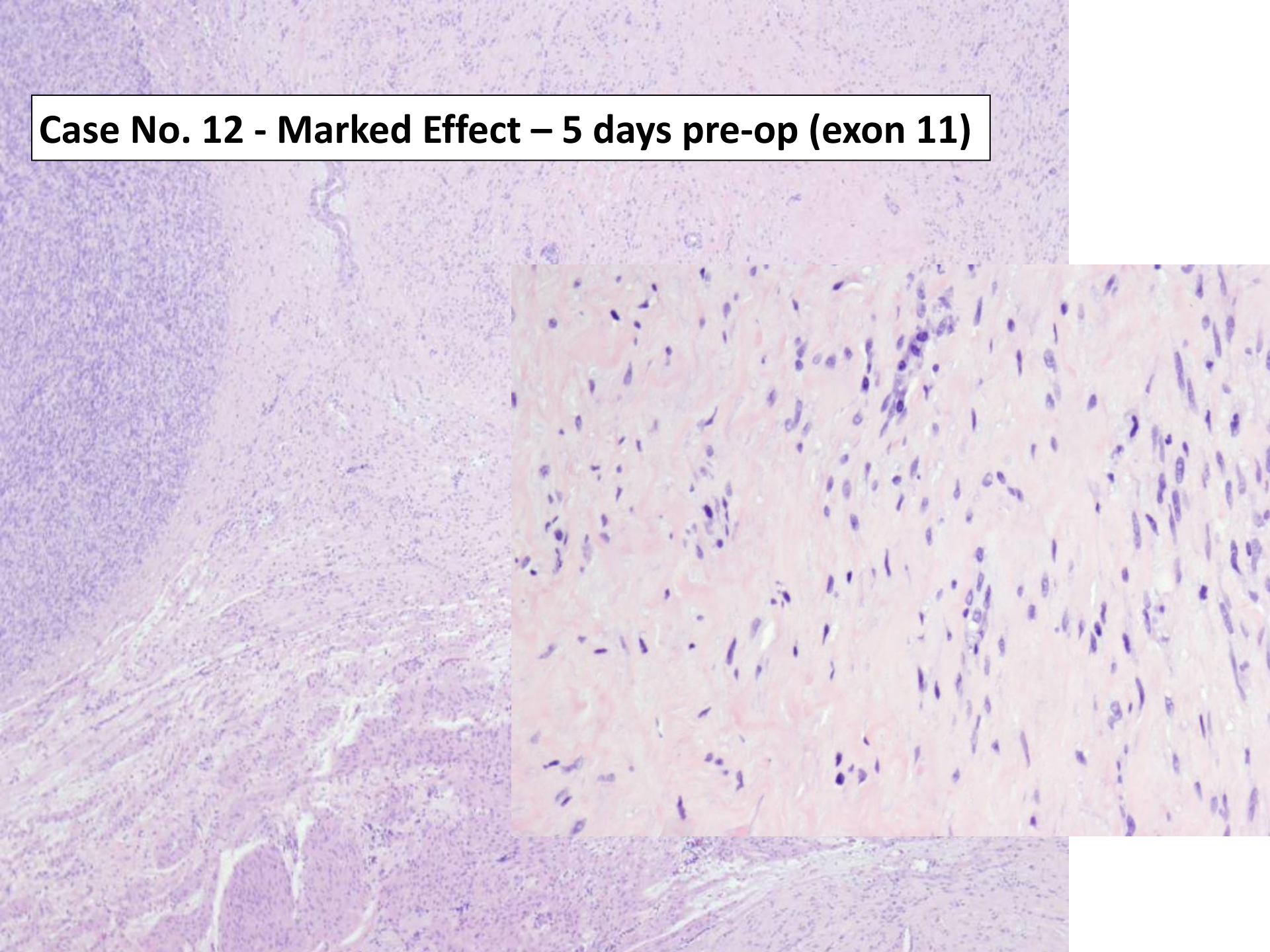




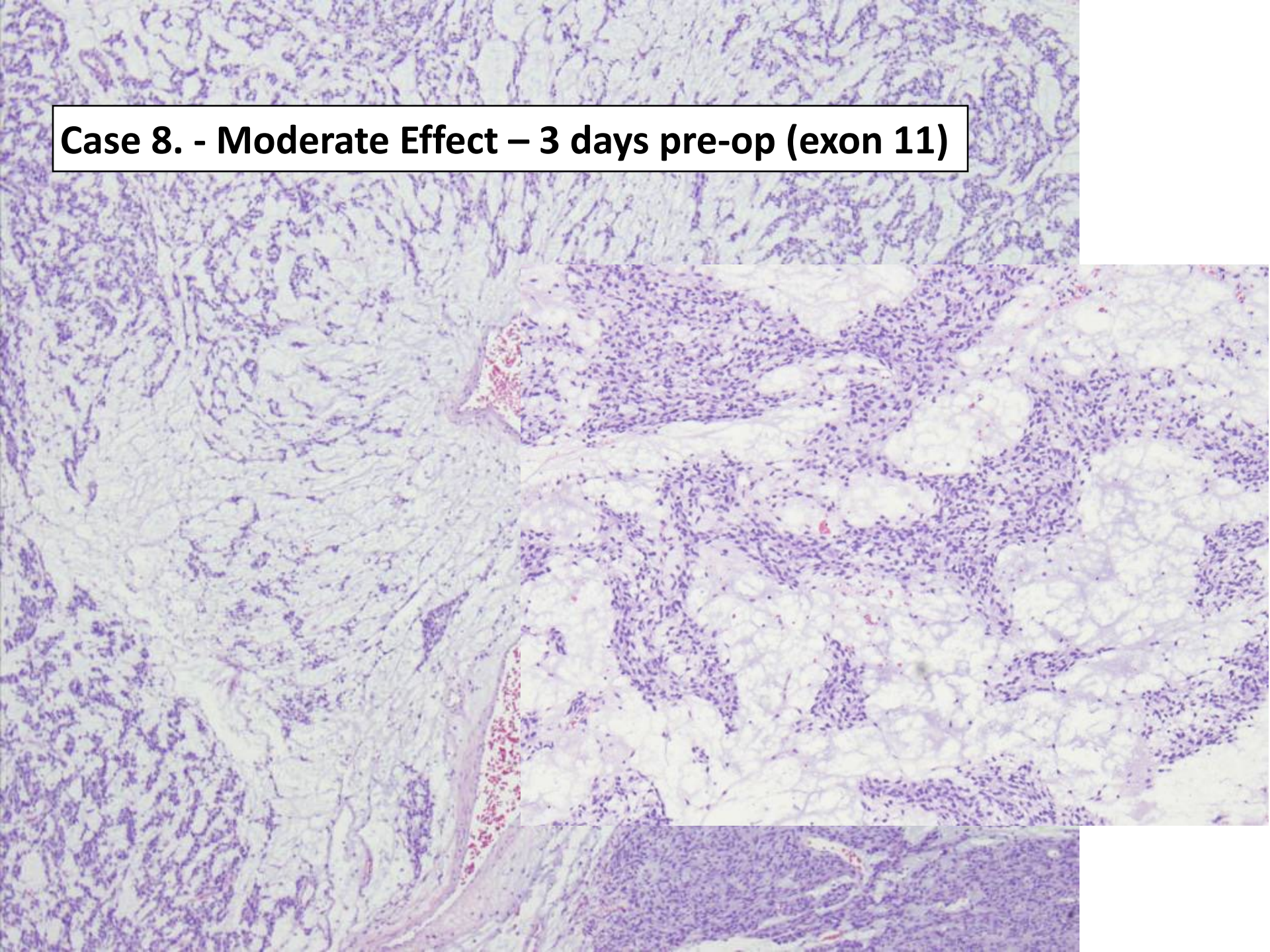
Case No. 22 - Marked Effect – 7 days pre-op (exon 11)



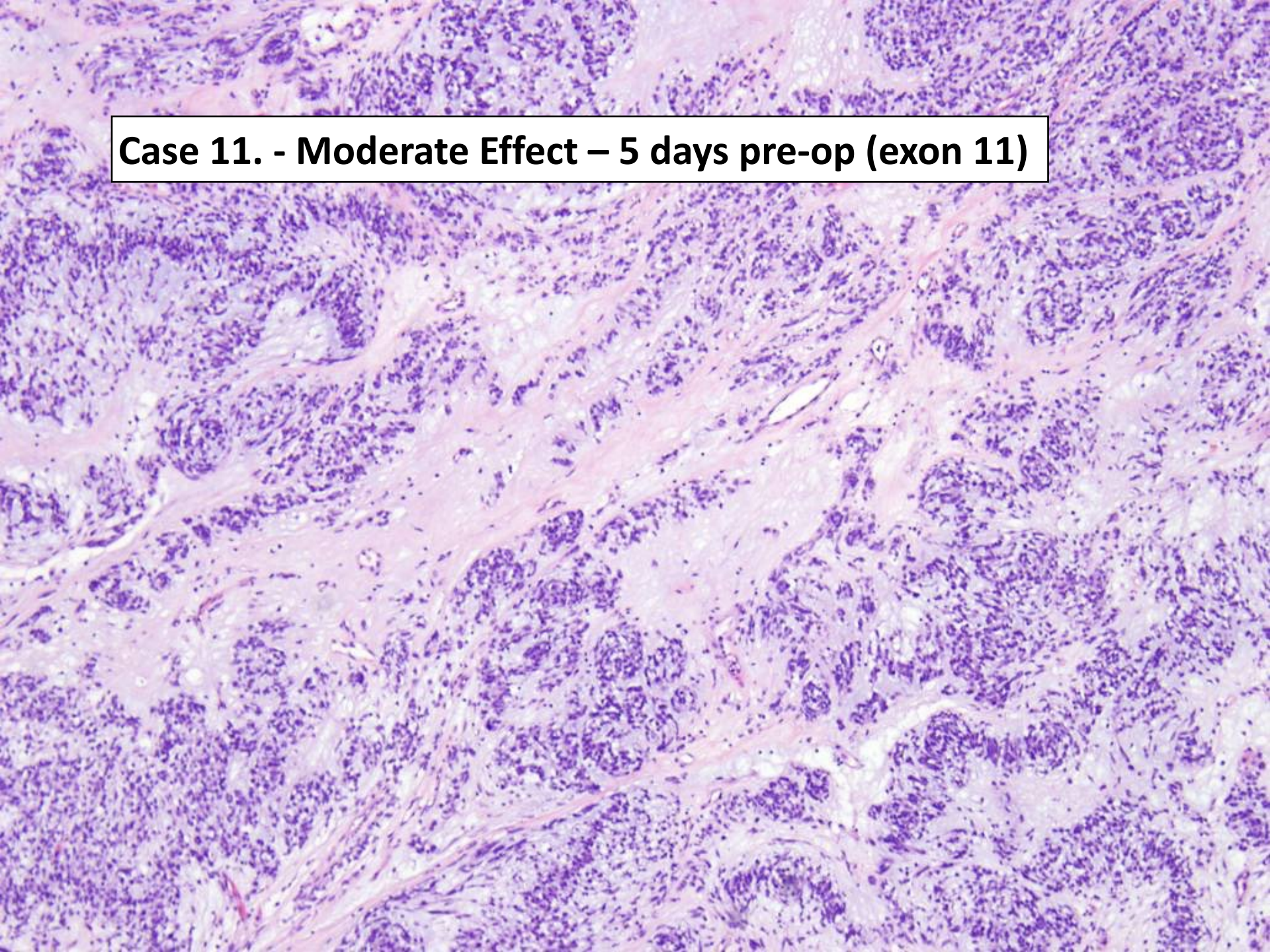
Case No. 12 - Marked Effect – 5 days pre-op (exon 11)



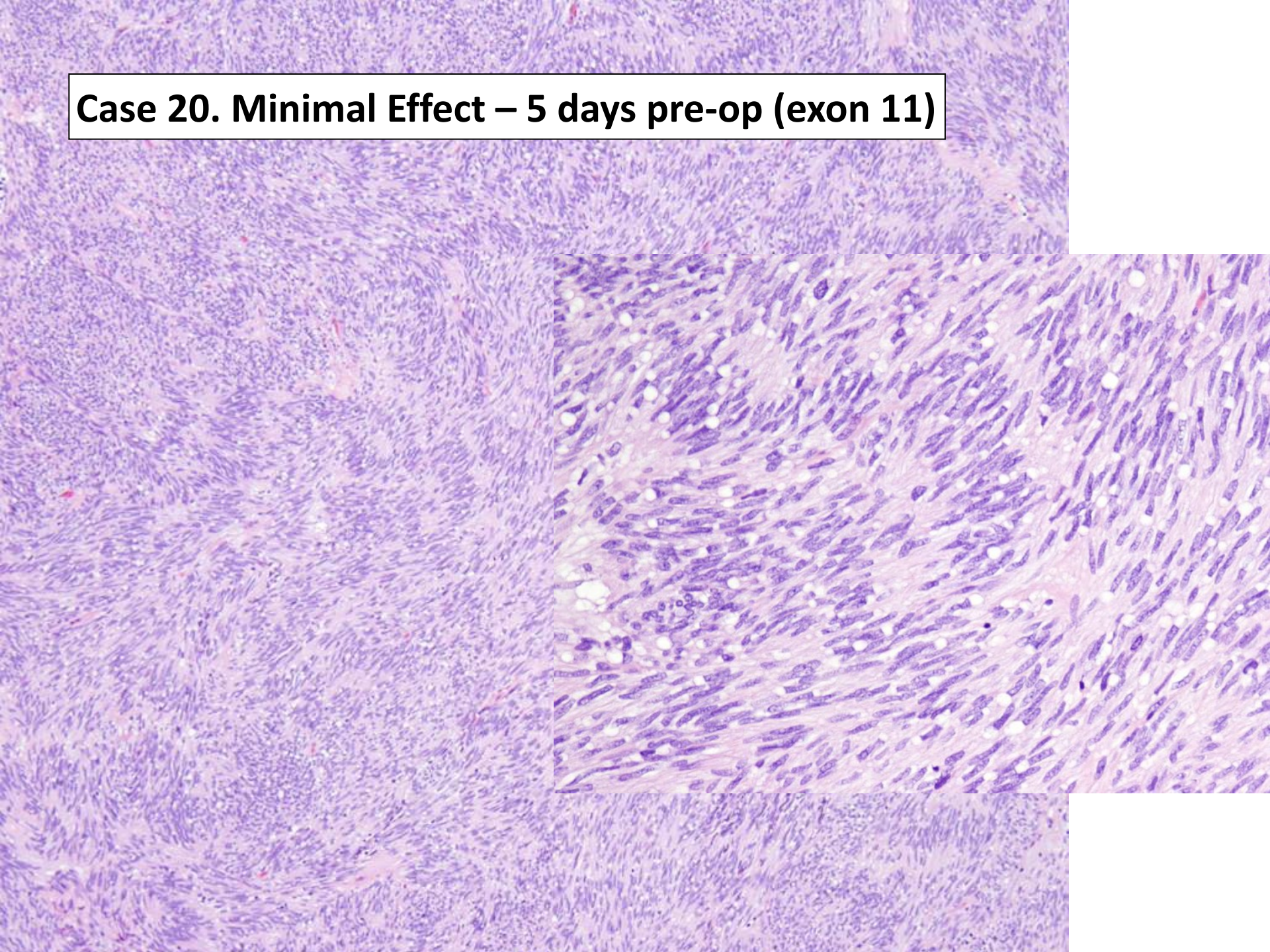
Case 8. - Moderate Effect – 3 days pre-op (exon 11)



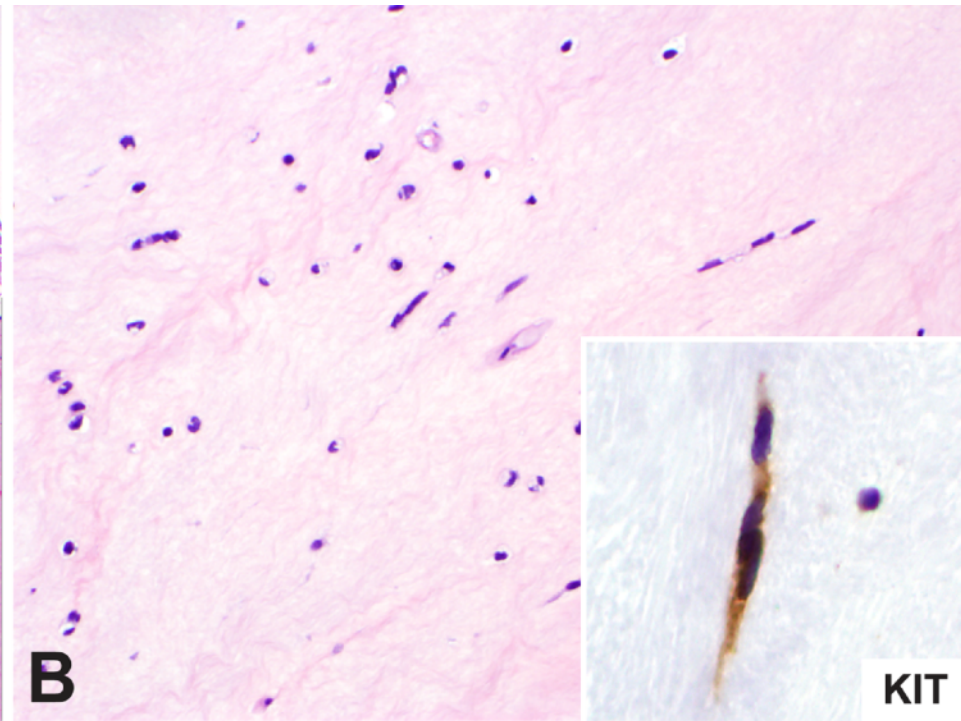
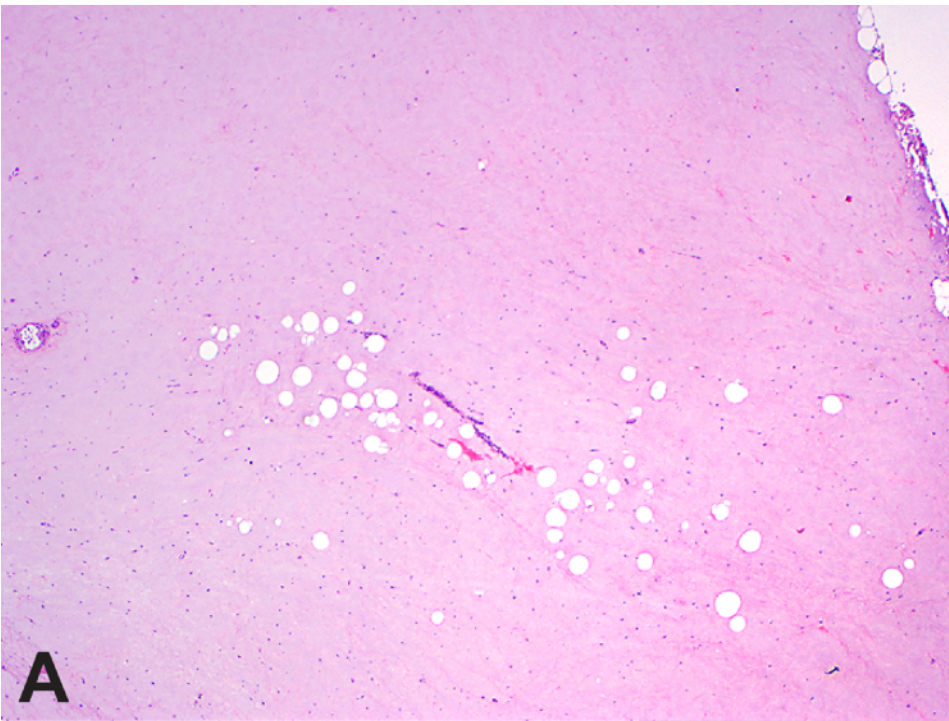
Case 11. - Moderate Effect – 5 days pre-op (exon 11)



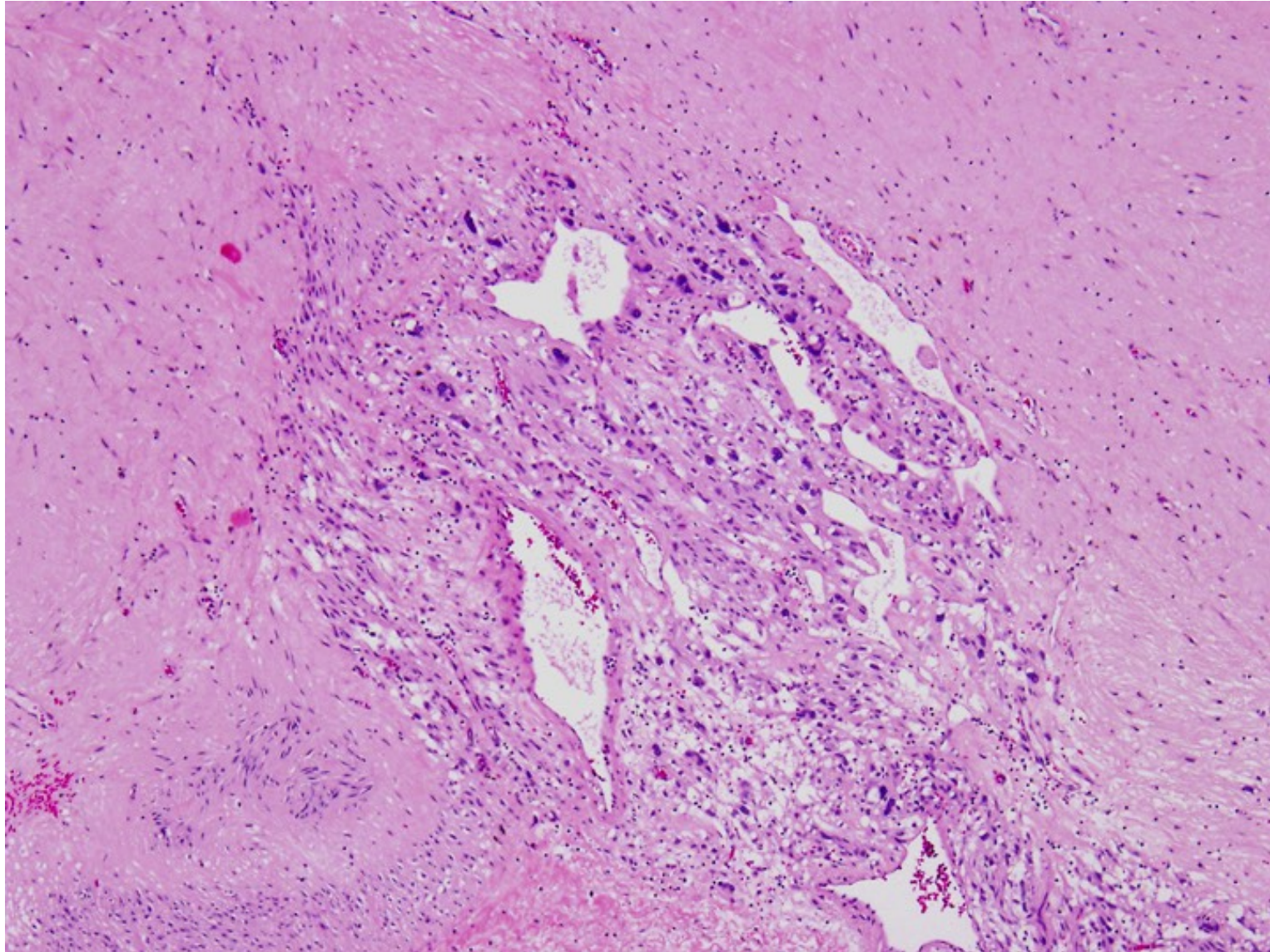
Case 20. Minimal Effect – 5 days pre-op (exon 11)

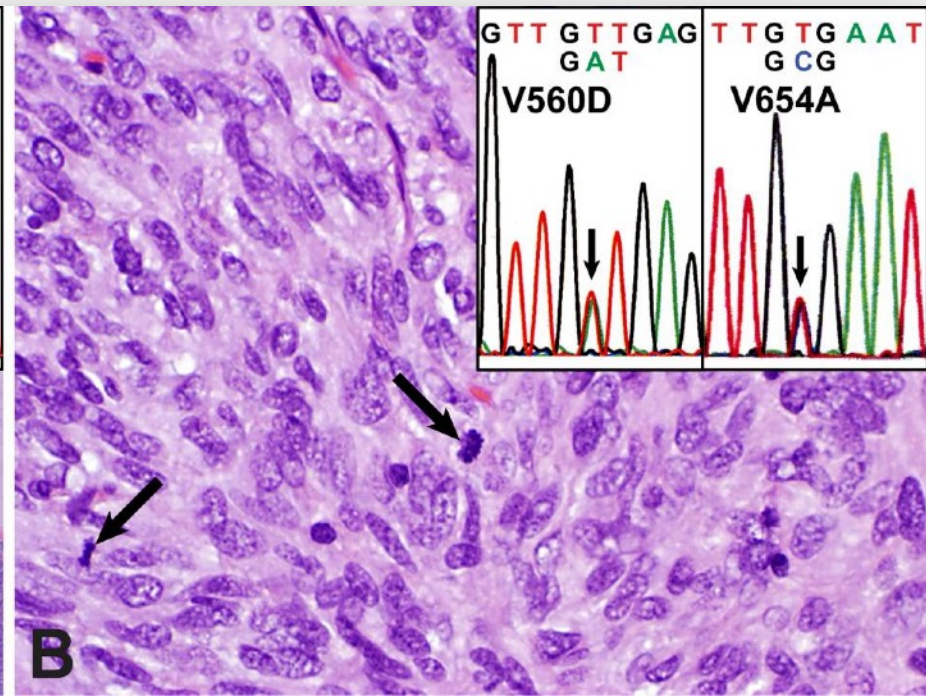
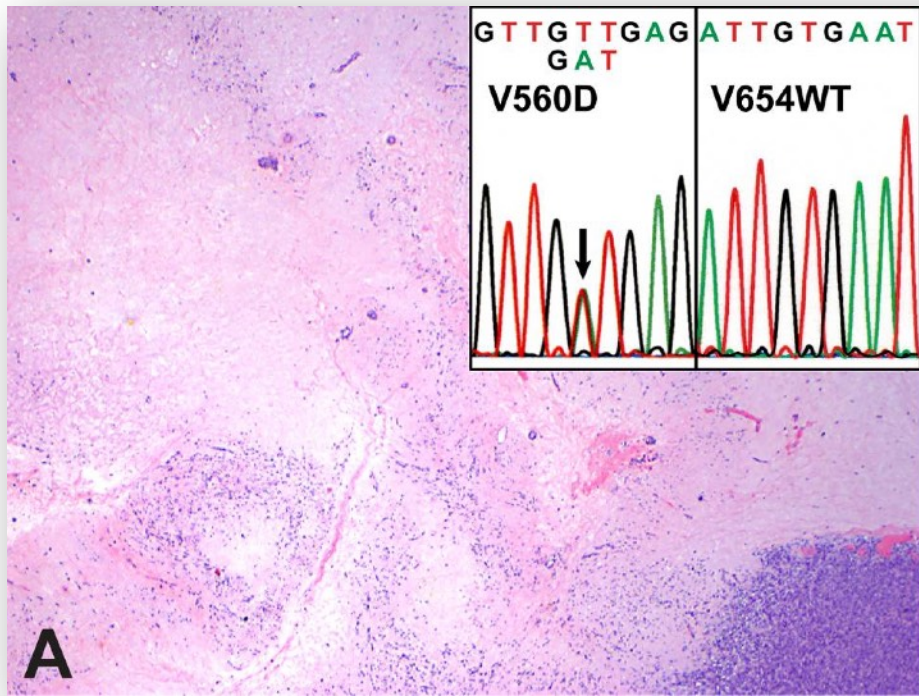


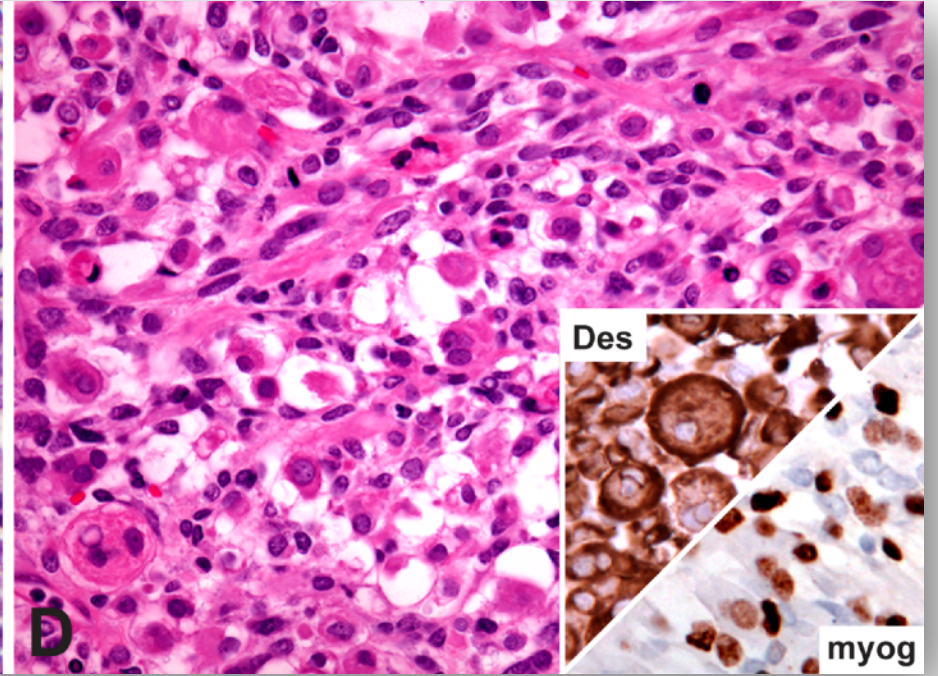
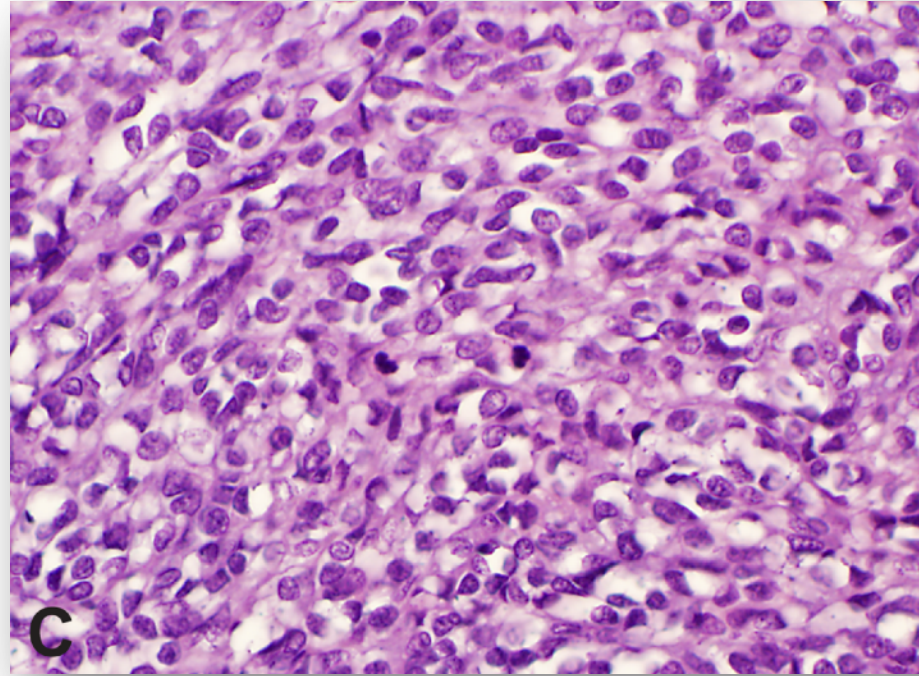
Long term Imatinib Tx



Long term Imatinib Tx







Thanks!

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- **Jon Trent, University of Miami.**
- **Many Fine Colleagues at UTMDACC.**

William O. Russell
Conference Room

