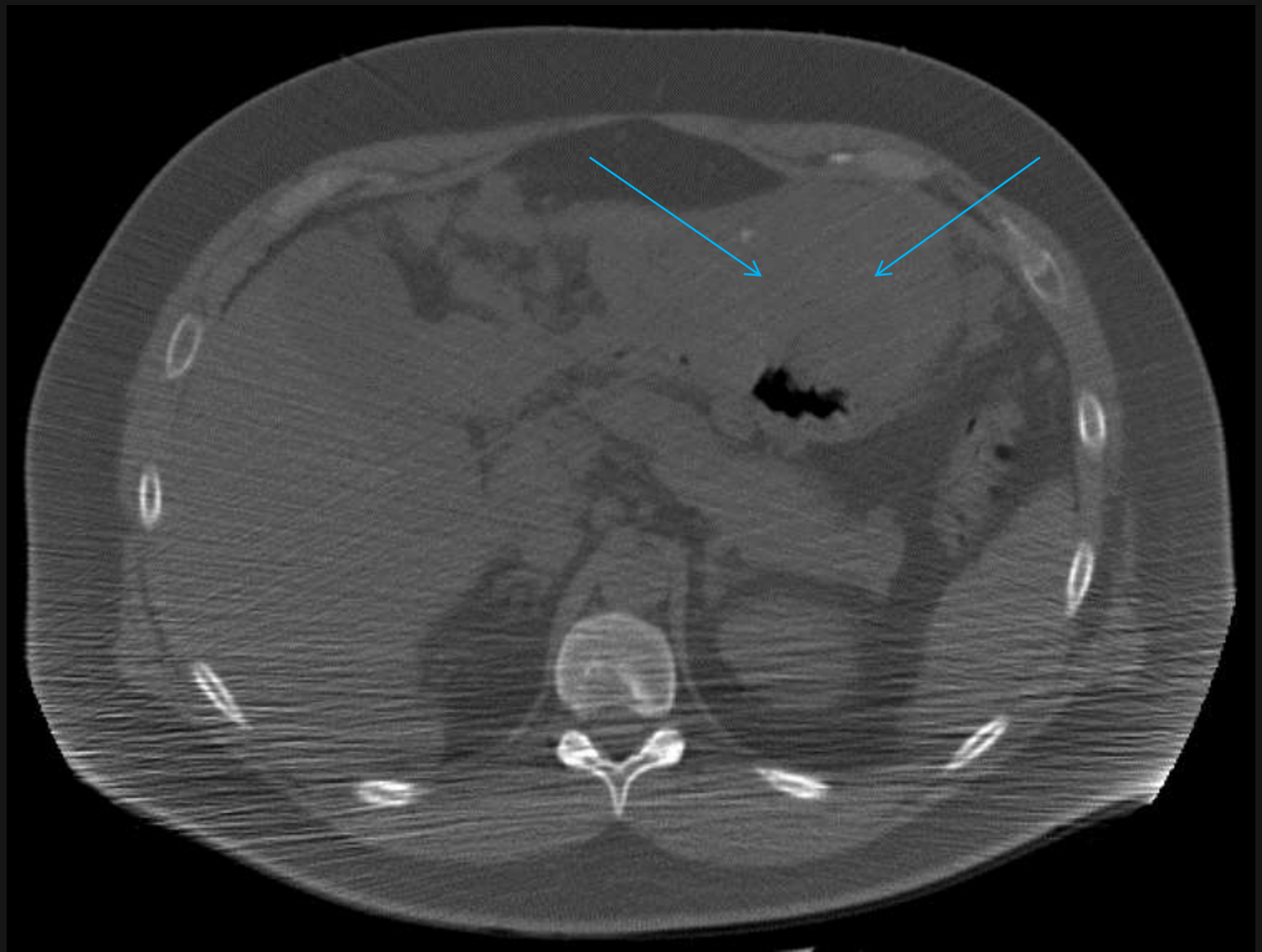
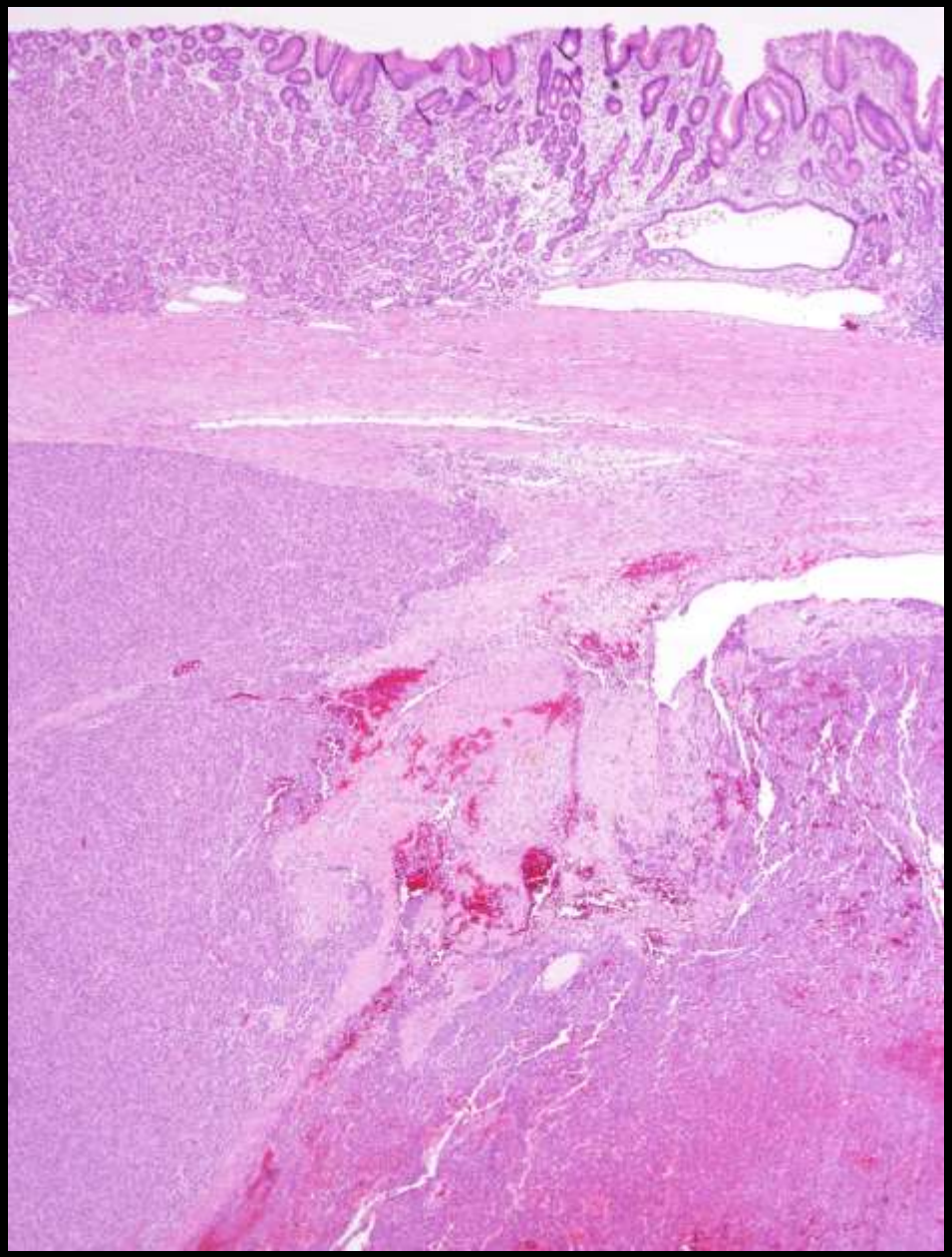
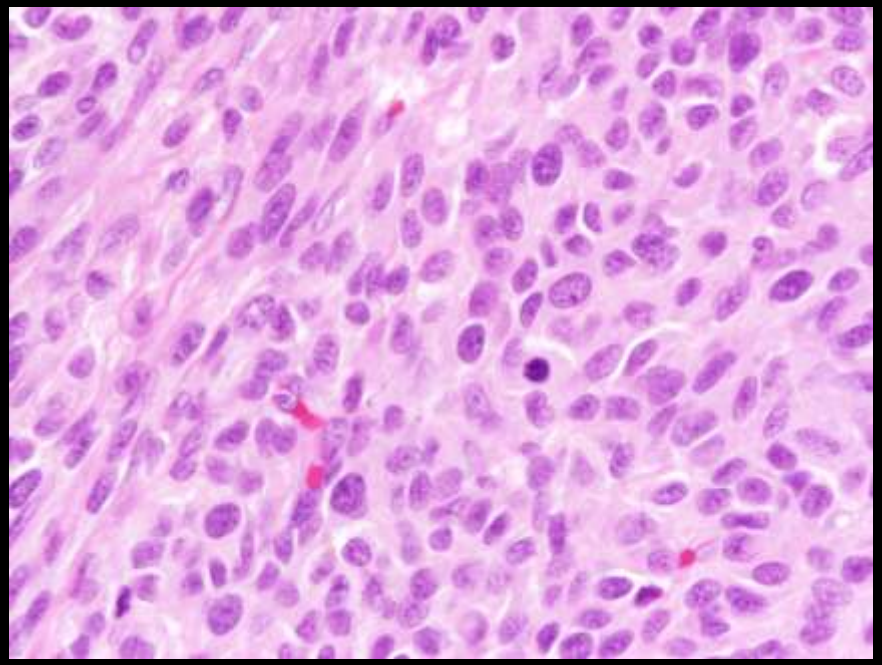
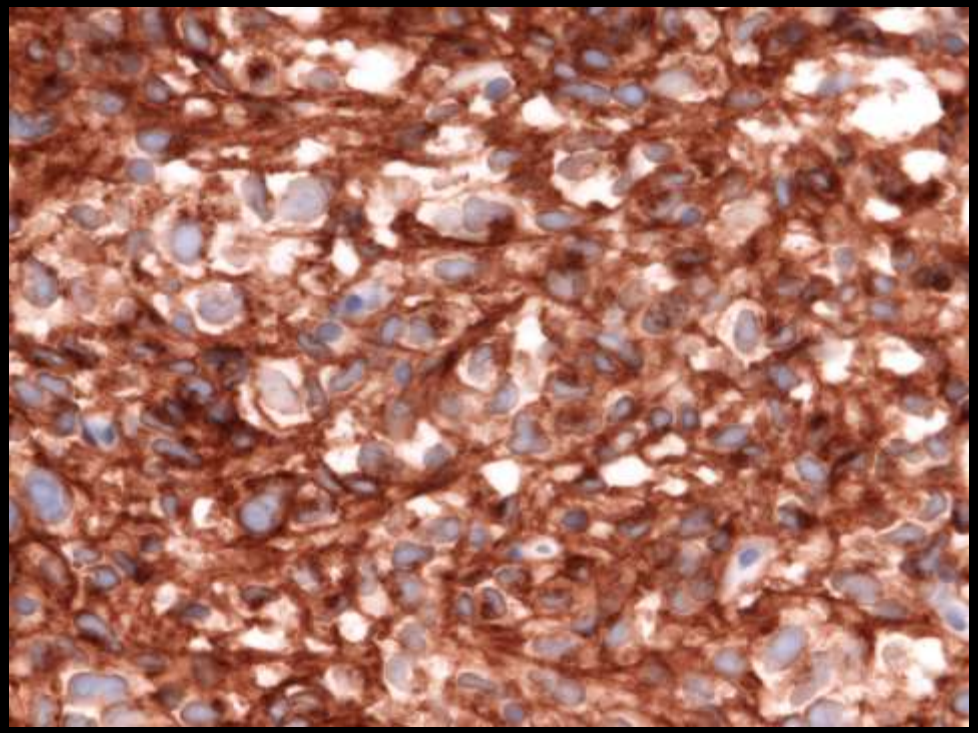
A 43 year old male presents with abdominal complaints. An axial CT reveals ….







Diagnosis: Gastrointestinal Stromal Tumor



C-kit

Location: stomach

Size: 12 cm

Mitotic count: 10 mitoses / 50 high power fields

Risk Assessment: High risk of aggressive behavior

Mutation status: ?

Gastrointestinal Stromal Tumors (GIST) Understanding Pathology and the Role of Mutations in Treatment

Gastrointestinal Stromal Tumors

Definition

Epidemiology

Pathology

Molecular pathology

oncogenic mutations

Prognostic Features

Cancer

A malignant tumor/neoplasm

- has the biological capacity to metastasize

Classified according to the normal tissues of the body

Epithelium – carcinoma

Melanocytes - melanoma

Immune cells – lymphoma/leukemia/myeloma

Connective tissue - sarcoma

Gastrointestinal Stromal Tumor

Definition: A mesenchymal neoplasm whose line of differentiation recapitulates the cells of Cajal and has a broad spectrum of biological behavior.

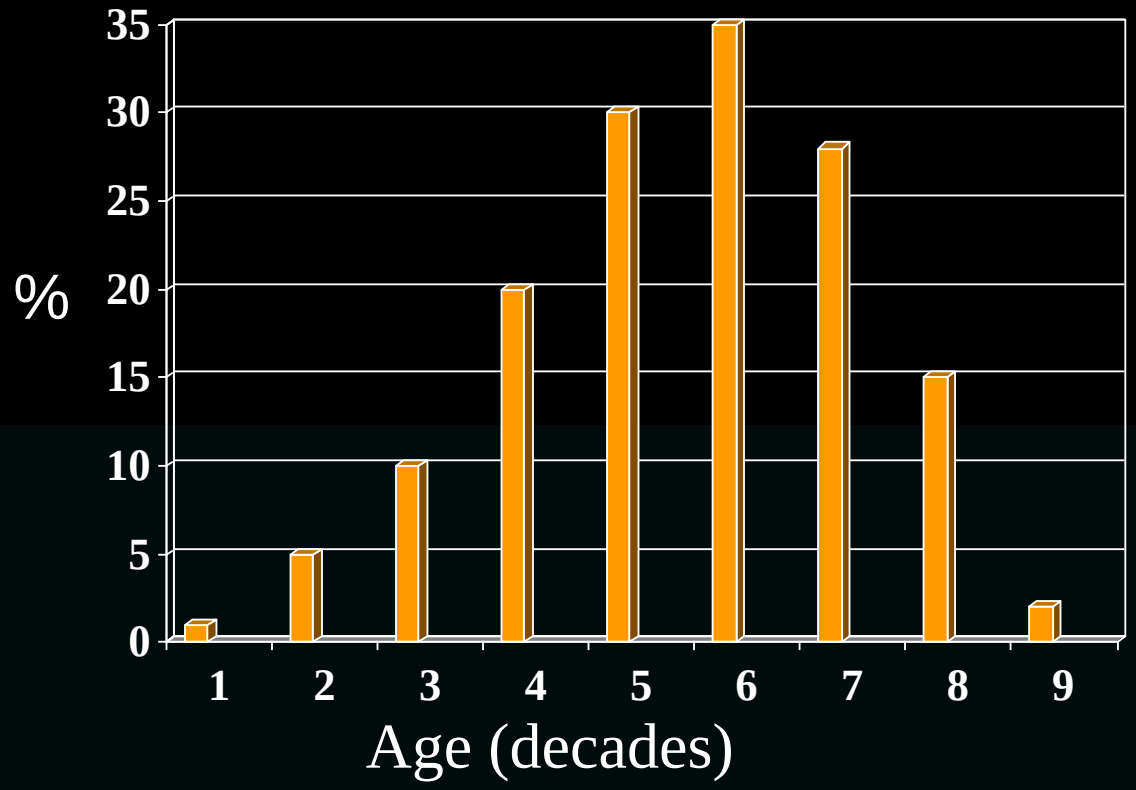
Benign Malignant

Gastrointestinal Stromal Tumors

Epidemiology

- 1% GI malignancies
- 3,300-6,000 new clinically significant cases/year in U.S.
- 11-20 per million persons
- 10-30% behave clinically malignant
- <1% familial

Gastrointestinal Stromal Tumors



Gender: M:F = 1:2

Gastrointestinal Stromal Tumors

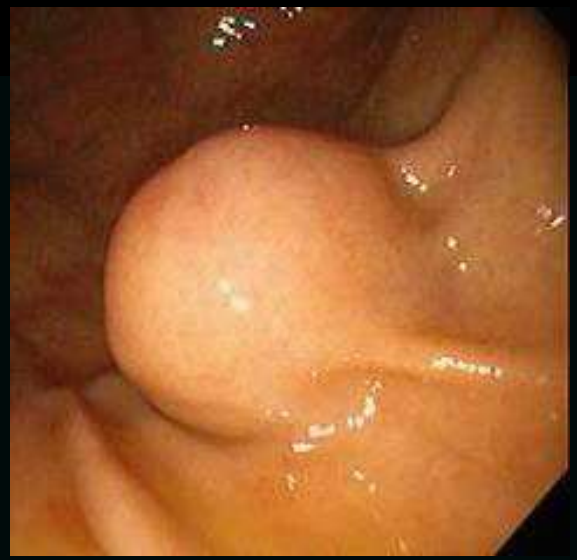
Clinical Findings

Depends on size, location and invasion of other organs

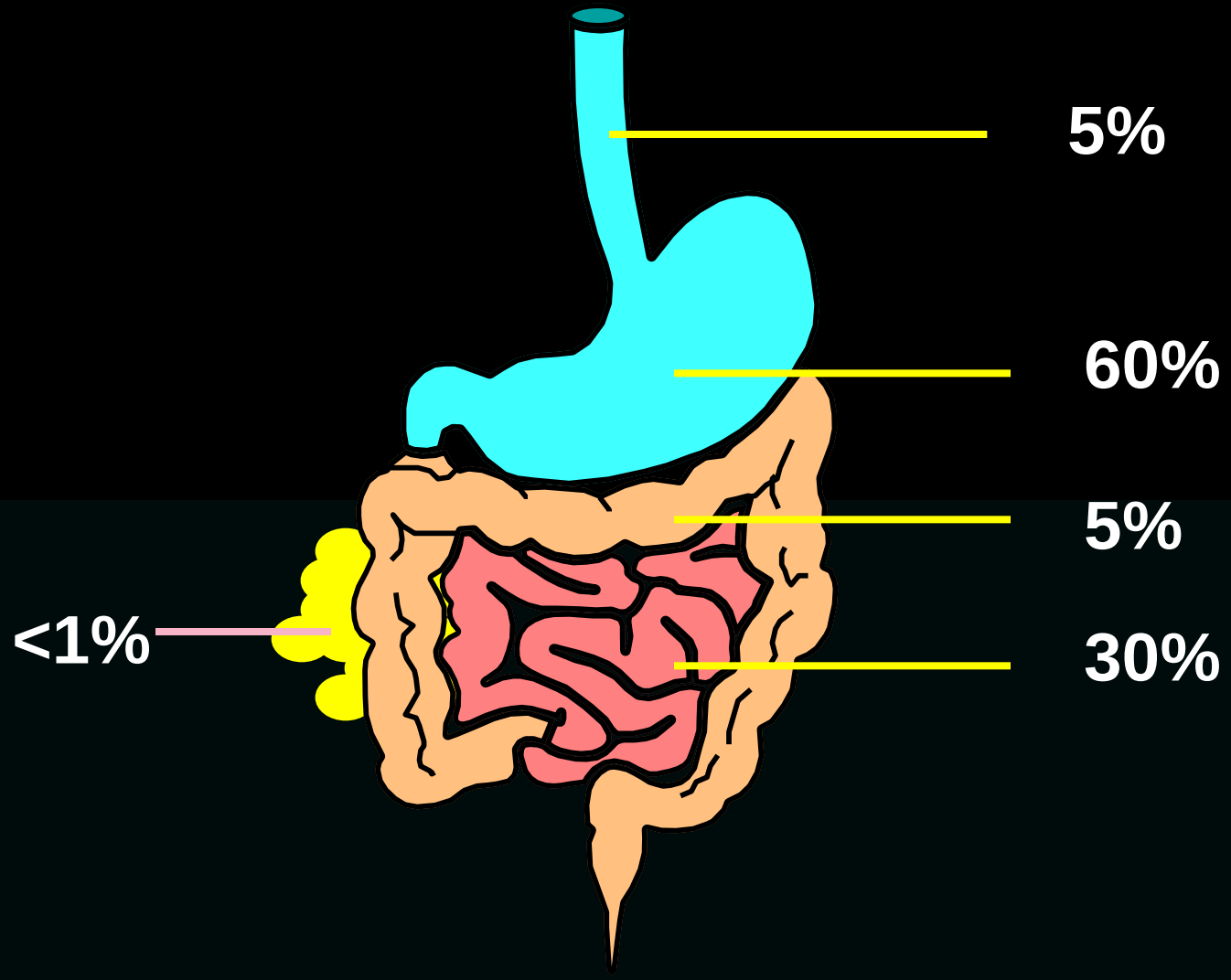
Abdominal mass, GI bleeding, pain, anorexia, perforation, fever

Site specific

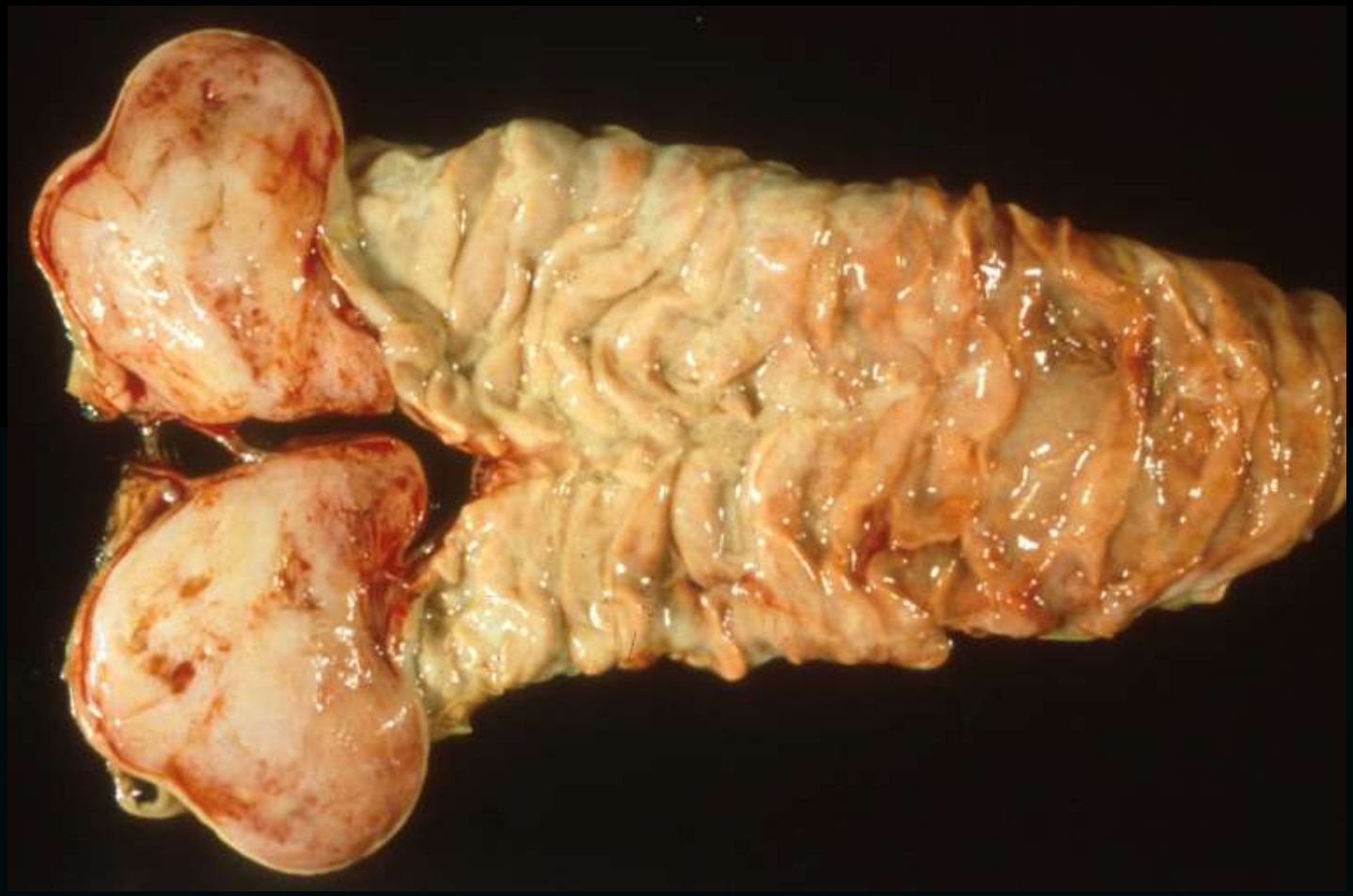
Incidental finding



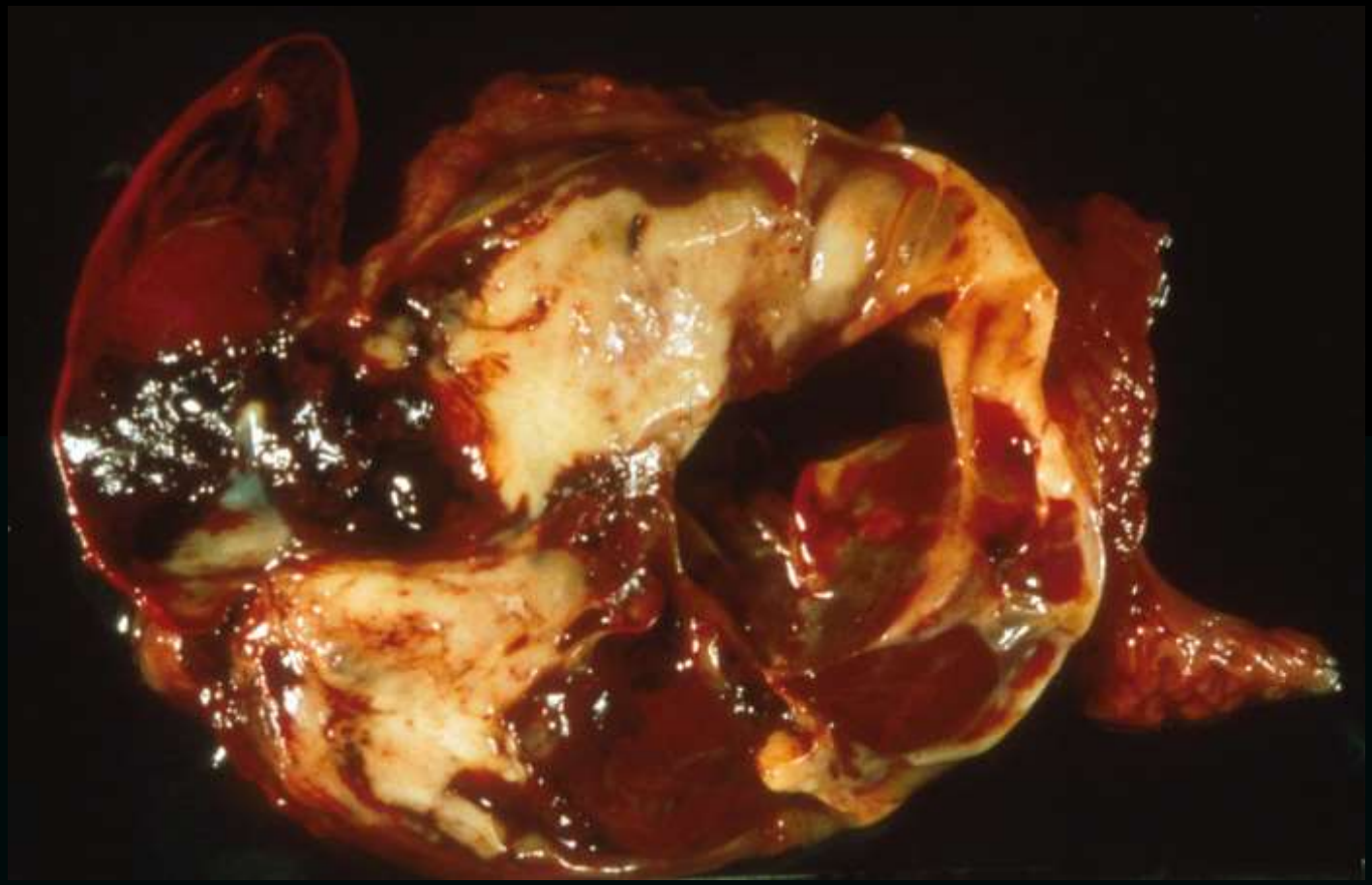
Gastrointestinal Stromal Tumors



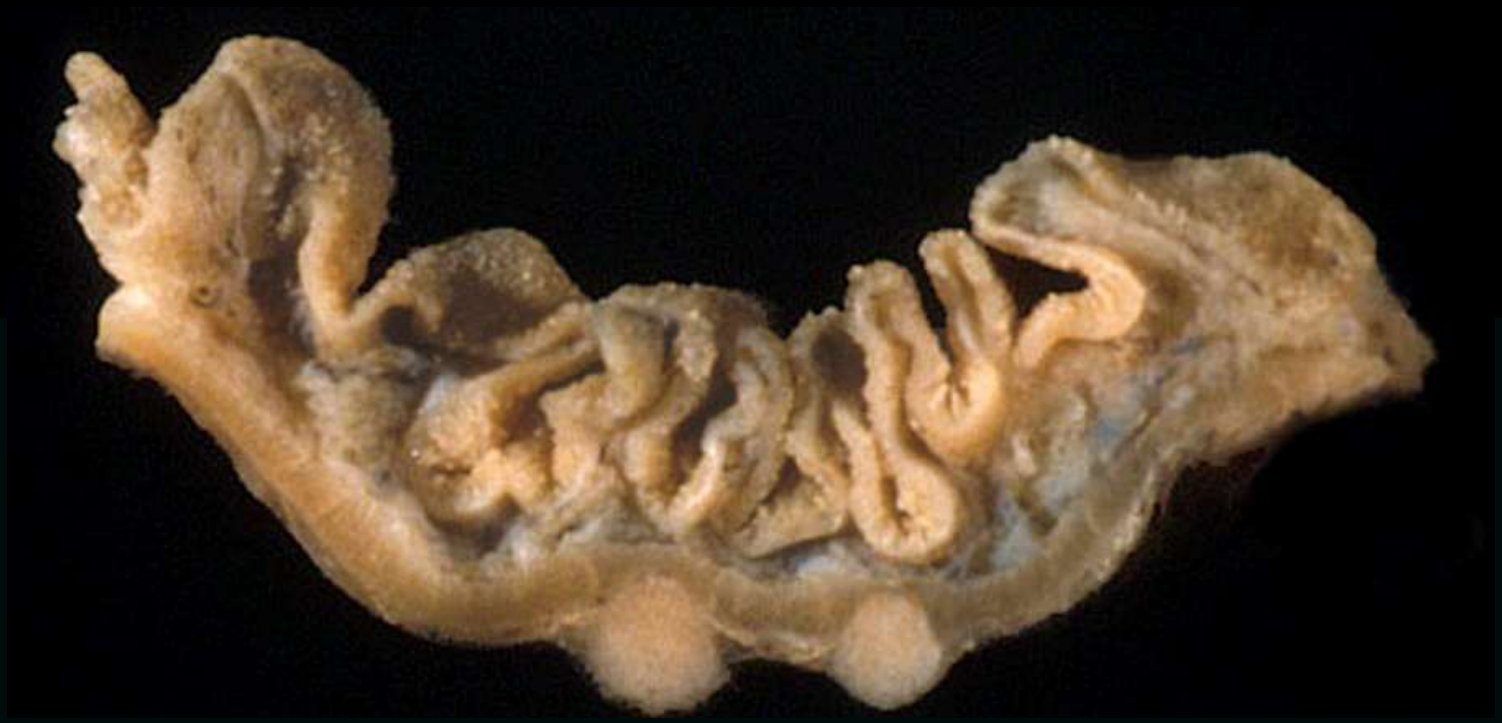
Gastrointestinal Stromal Tumors

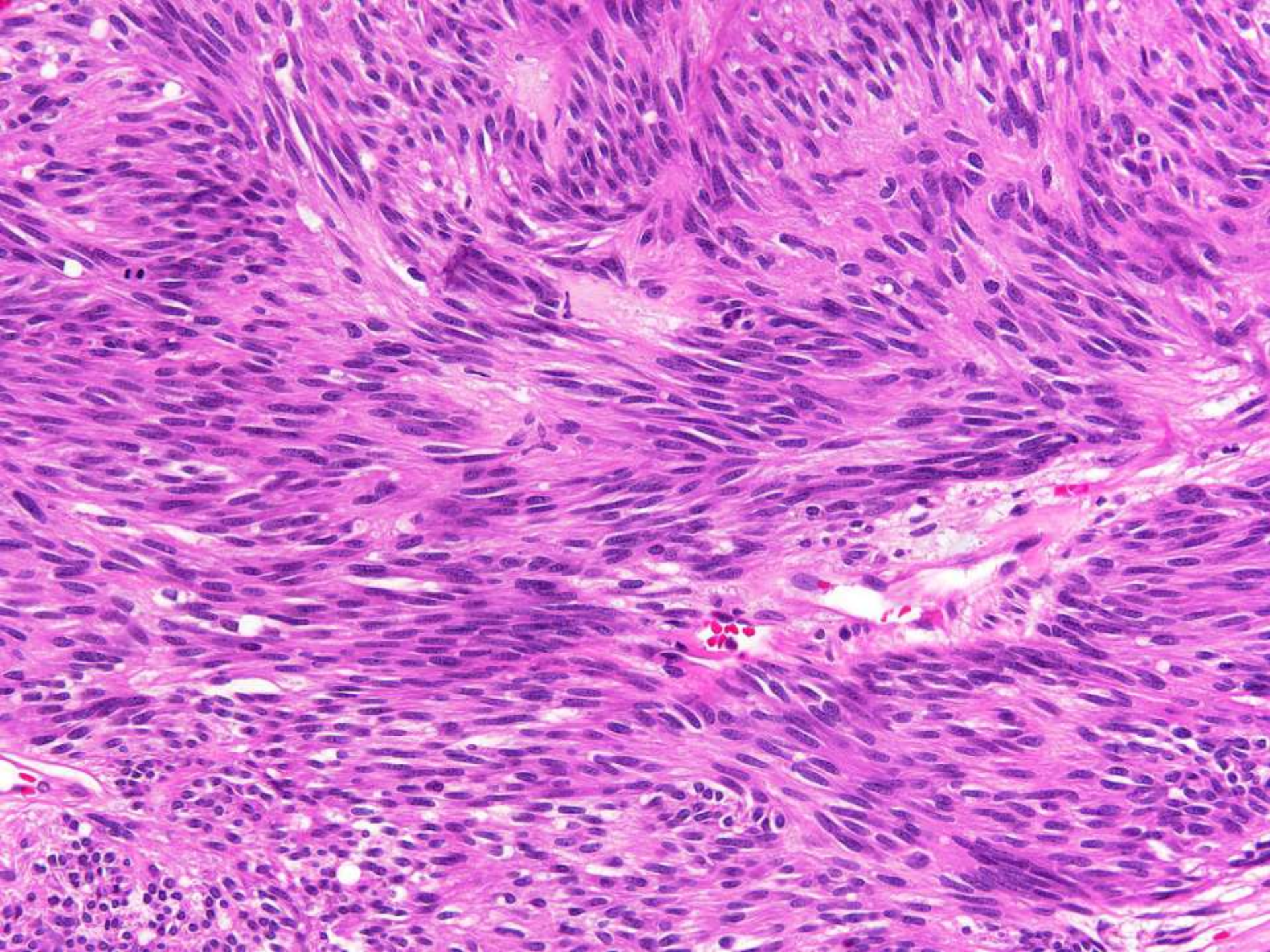


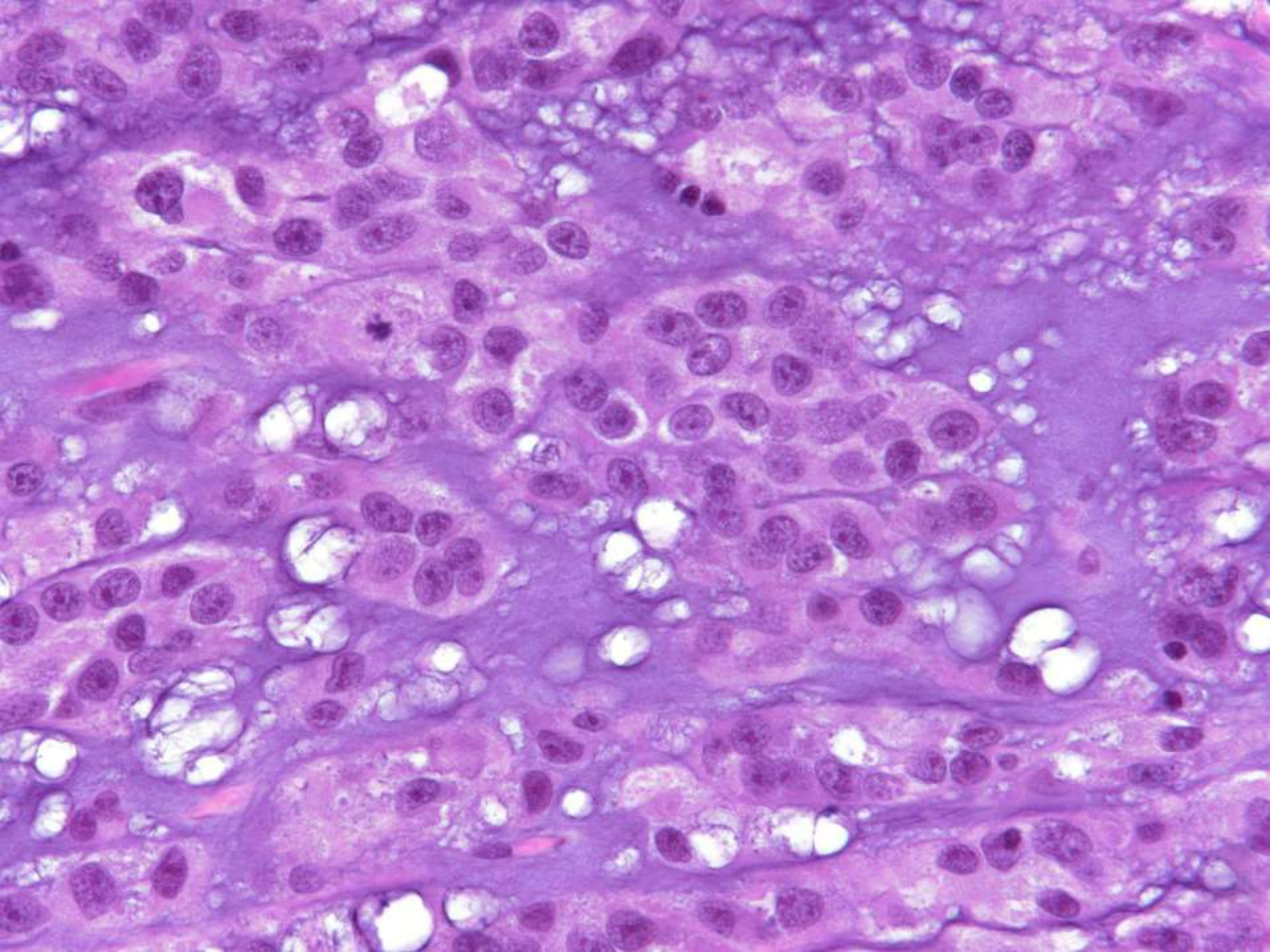
Gastrointestinal Stromal Tumors

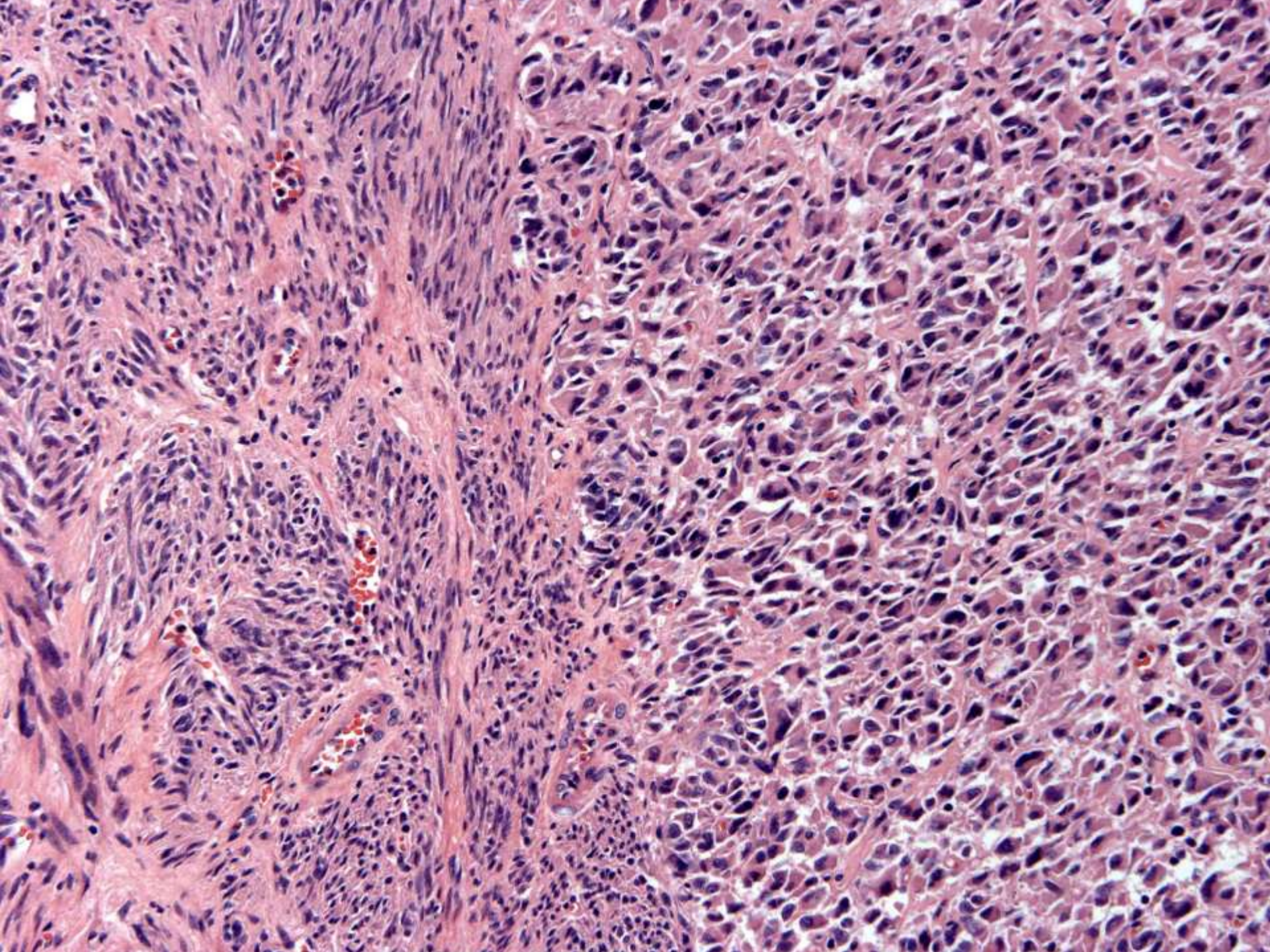


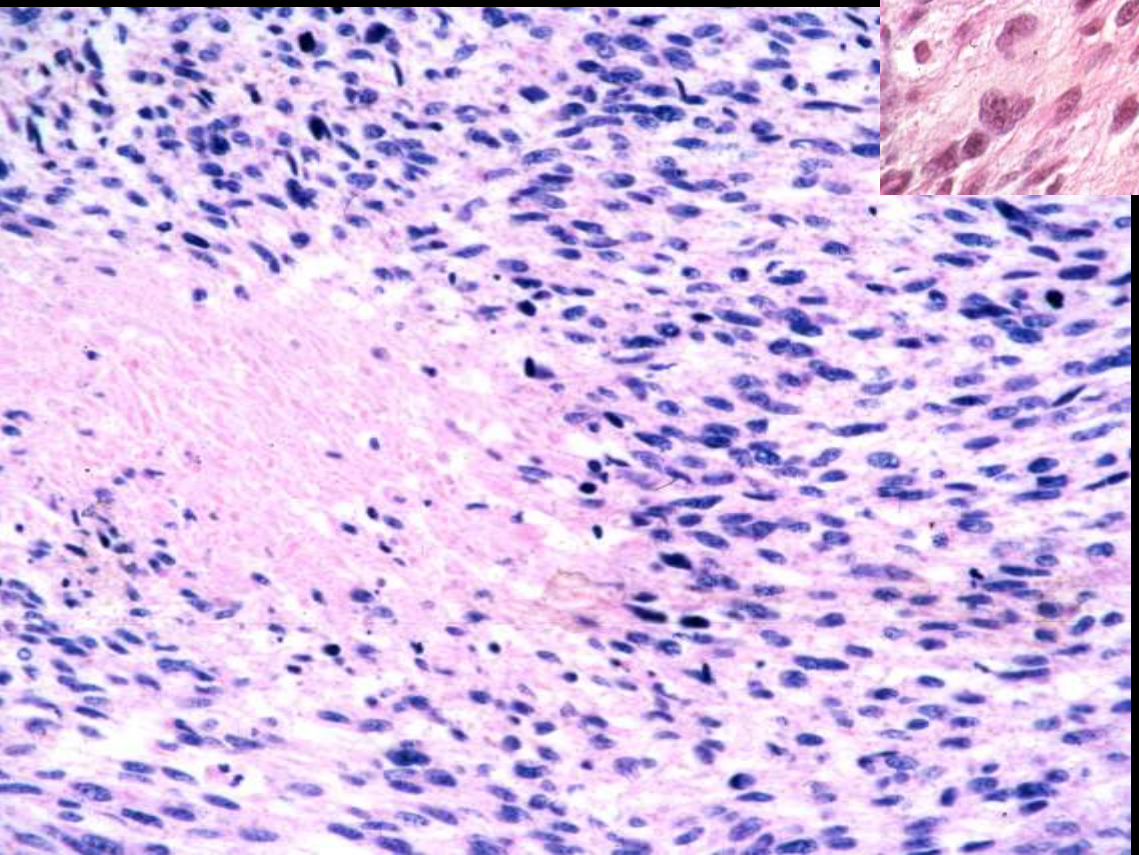
Gastrointestinal Stromal Tumors











Gastrointestinal Stromal Tumors

Risk Stratification

Tumor Feature		Risk of Progression			
Mitoses	Size (cm)	Stomach	Duod	Jej/Ileum	Rectum
<5/50 hpf	≤2	very low (0%)	very low (0%)	very low (0%)	very low (0%)
	>2≤5	very low (1.9%)	low (8.3%)	low (4.3%)	low (8.5%)
	>5≤10	low (3.6%)	high (34%)	mod (24%)	high (57%)
	>10	mod (12%)	high (52%)		
≥5/50 hpf	≤2	very low (0%)		high (50%)	high (54%)
	>2≤5	mod (16%)	high (50%)	high (73%)	high (52%)
	>5≤10	high (55%)	high (86%)	high (85%)	high (71%)
	>10	high (86%)		high (90%)	

J Surgical Oncology 2011;104:865-873

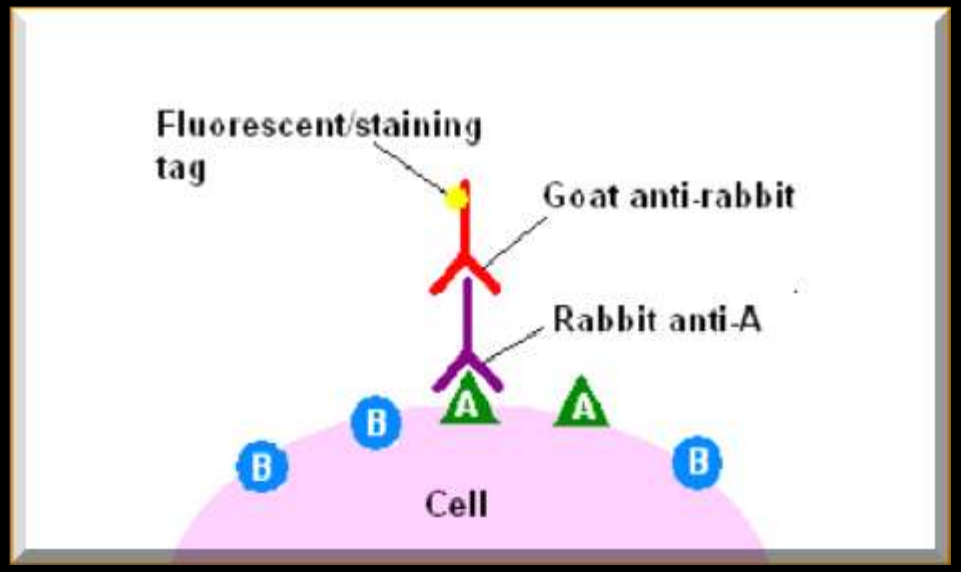
Gastrointestinal Stromal Tumors

Immunohistochemical profile

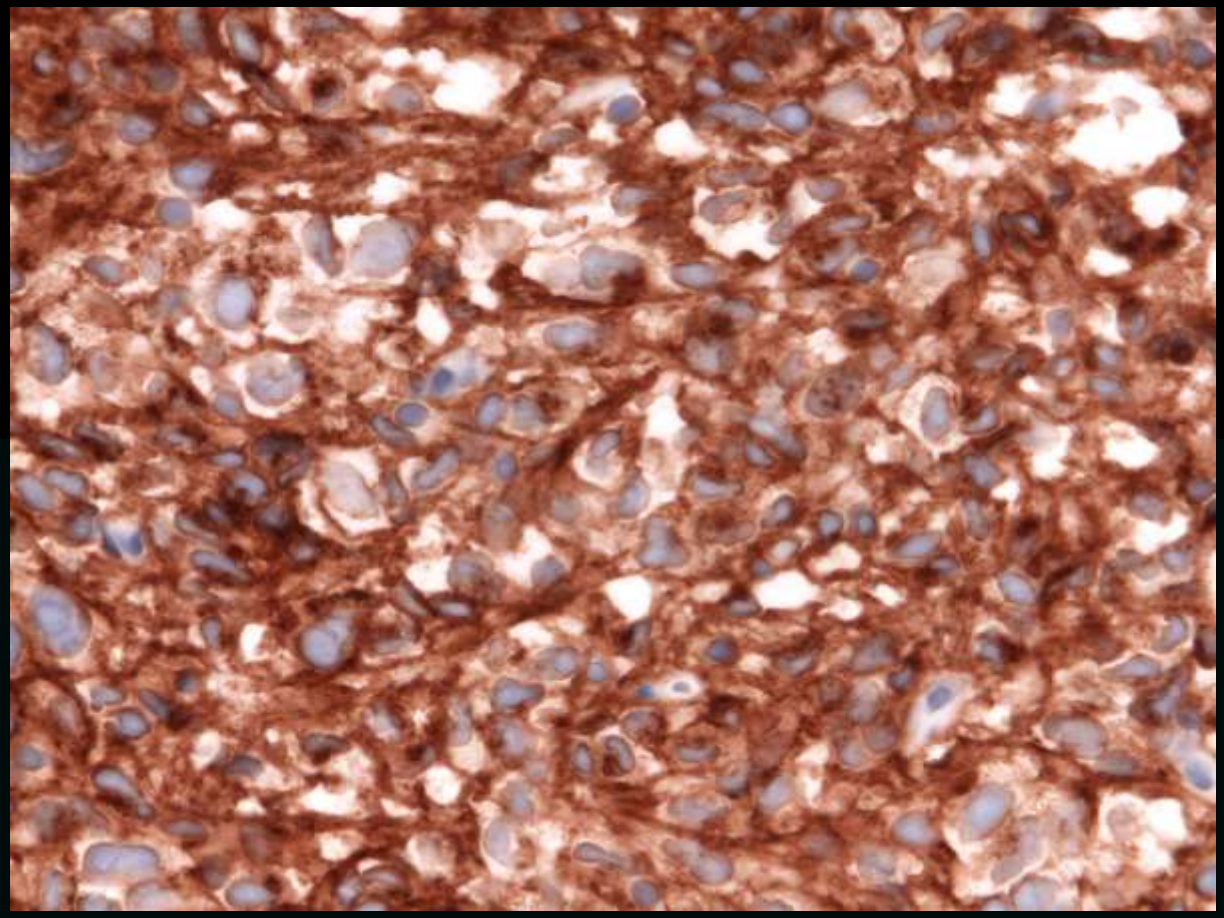
C-Kit: 85-100%

DOG-1: 85-100%

CD 34: 30-100%



Gastrointestinal Stromal Tumors



C-kit

Gastrointestinal Stromal Tumors

Terminology

Gastrointestinal stromal tumor;
Mazur 1983

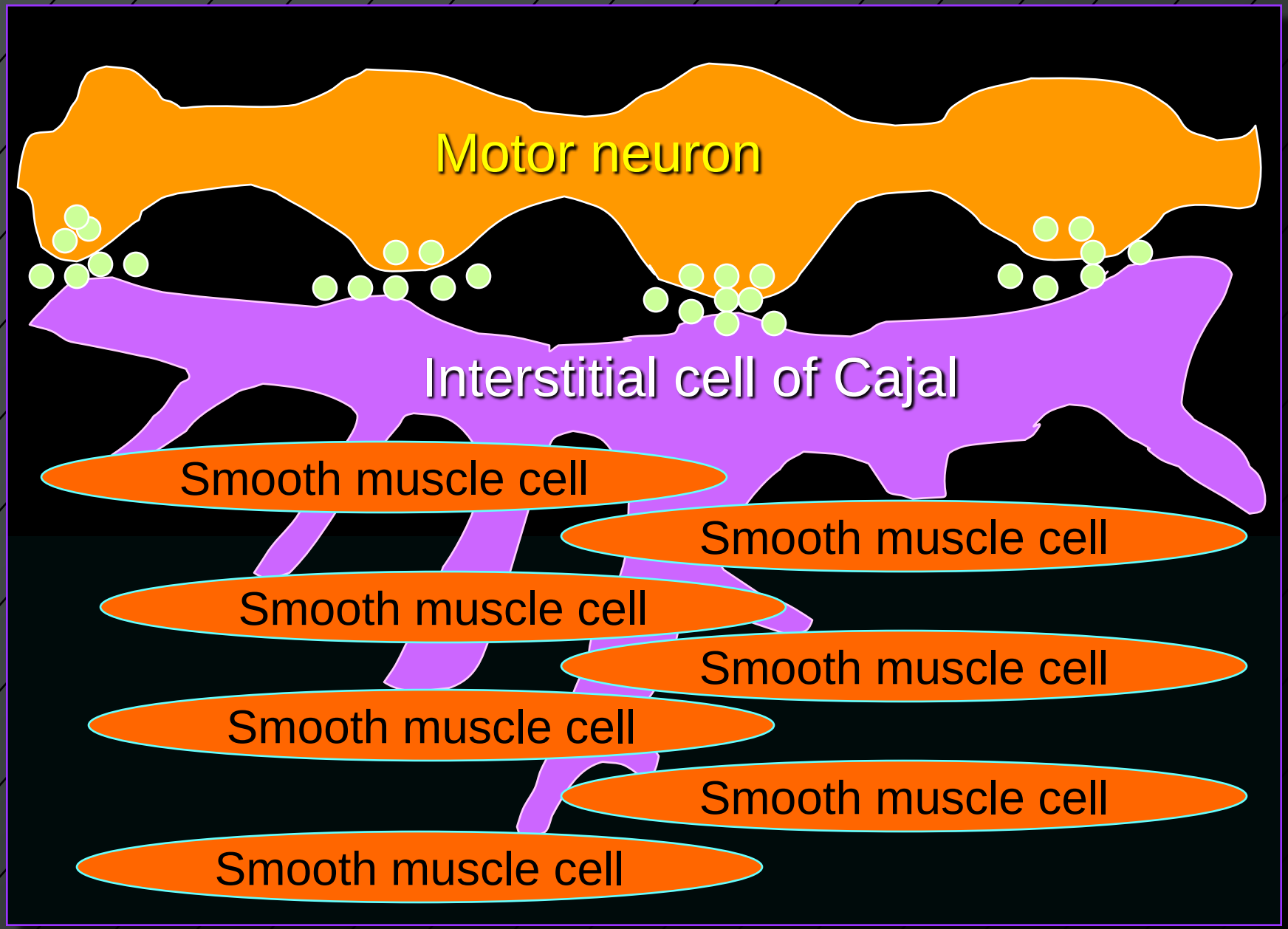
Interstitial Cells of Cajal

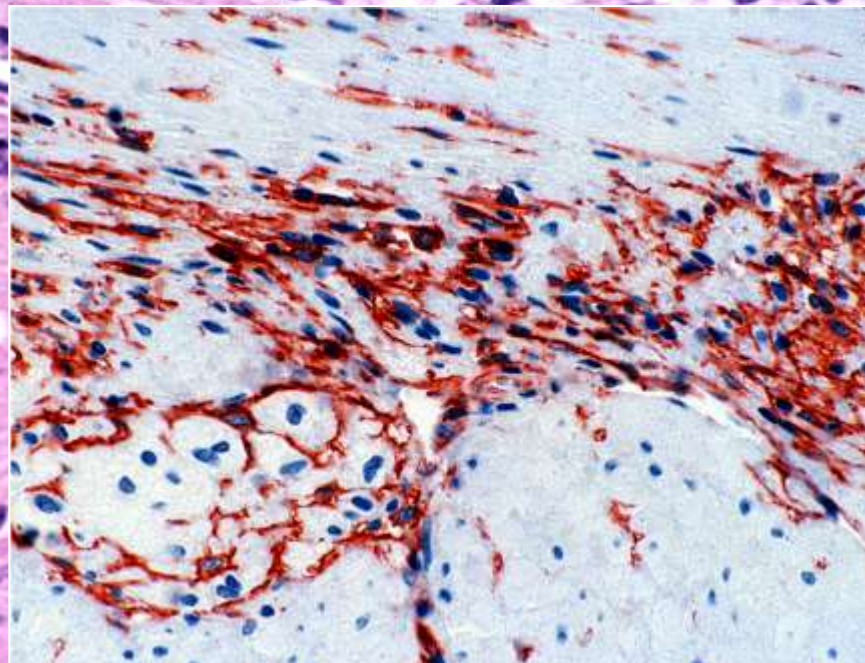
Described > 100 yrs ago

Located throughout GI tract

Function as ‘pacemaker’ and mediator of neuro transmission

C-Kit vital to development and function


Motor neuron
Interstitial cell of Cajal
Smooth muscle cell
Smooth muscle cell
Smooth muscle cell
Smooth muscle cell
Smooth muscle cell
Smooth muscle cell
Smooth muscle cell



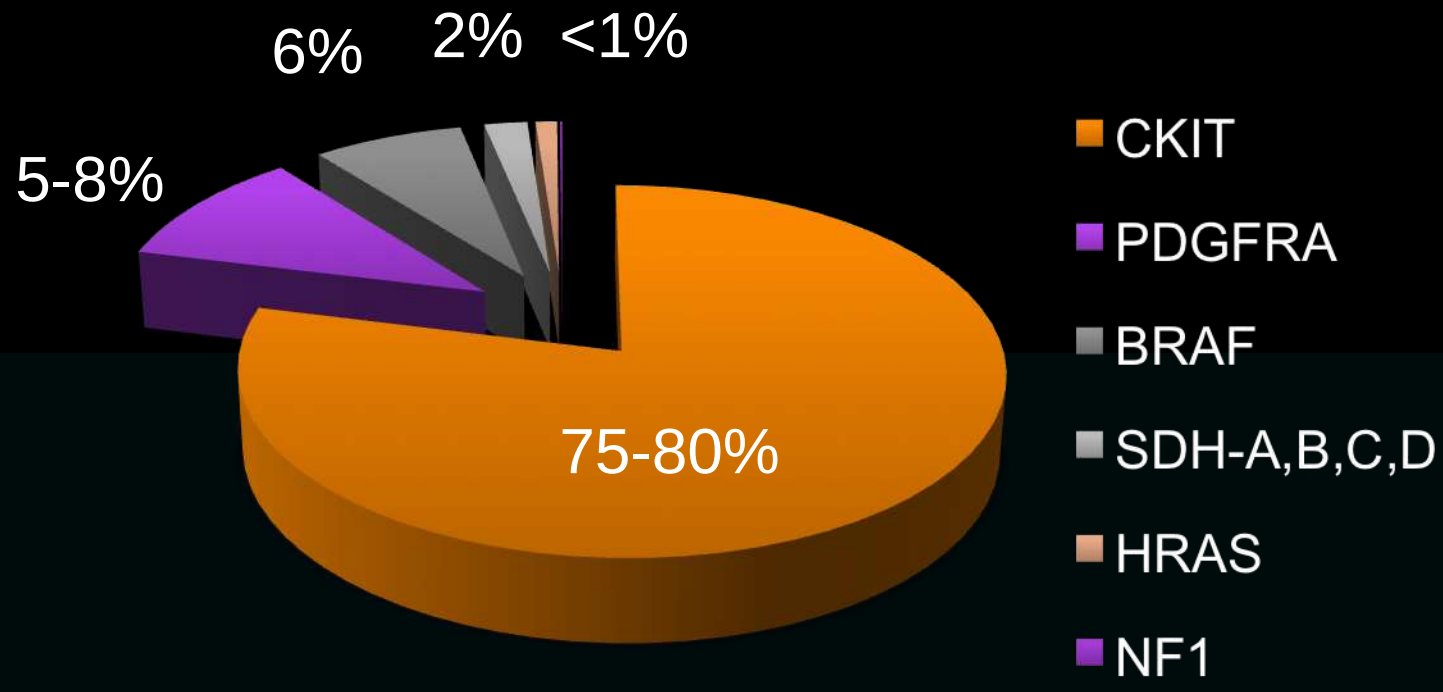
C-KIT

Protein – cell surface receptor - tyrosine kinase
Chromosome 4, Development of heme stem cells, germ cells, mast cells, melanocytes, interstitial cells of Cajal
Cell survival
Cell proliferation
Cell adhesion
Cell differentiation and maturation

Gastrointestinal Stromal Tumor

Genetic disease - caused by mutations

Molecular Classification of GIST



Gastrointestinal Stromal Tumors

C-Kit Mutations

Described 1998

Located on chromosome 4

Found in 75-80% of GIST

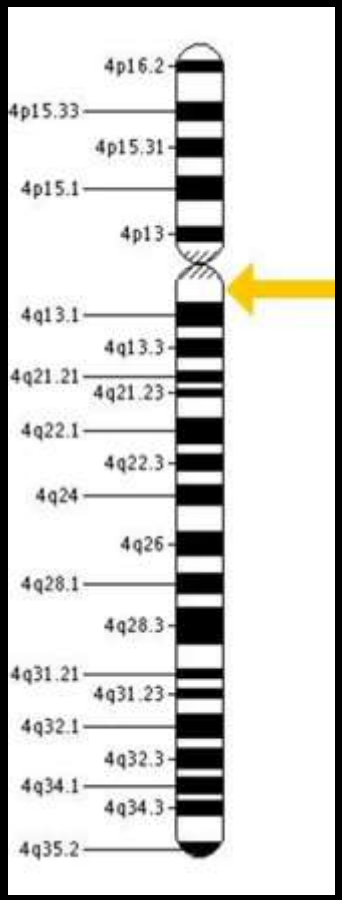
Mutations activate the tyrosine kinase receptor

PDGFRa Mutations

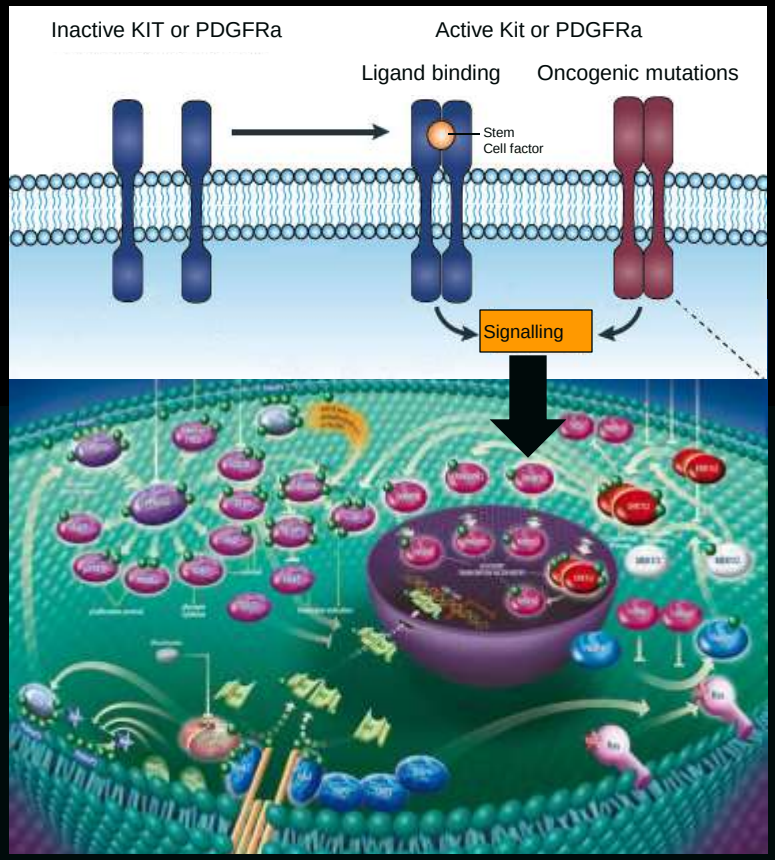
Located on chromosome 4

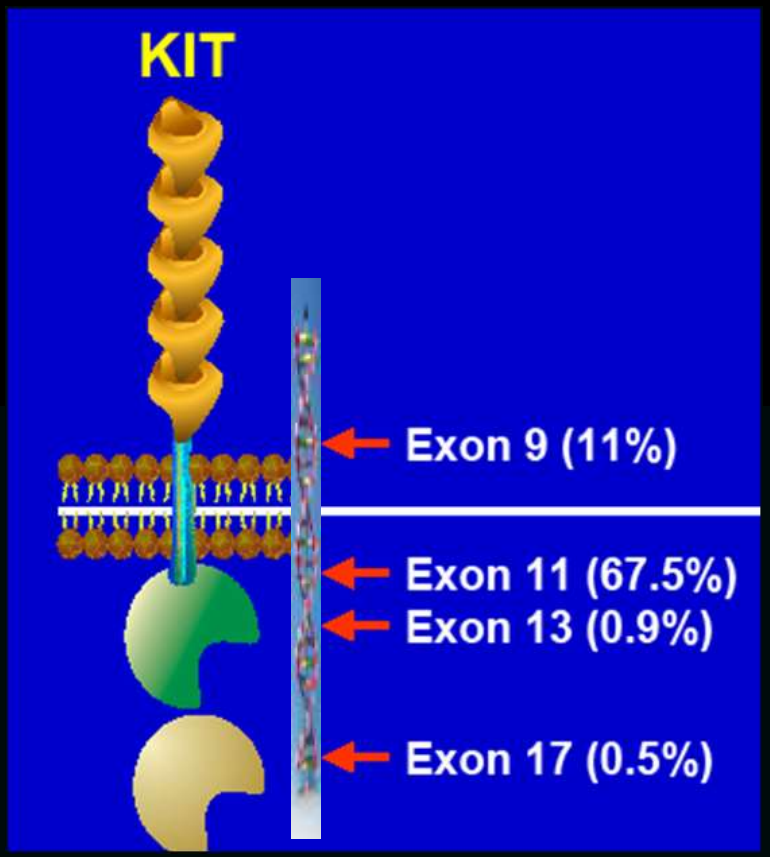
Found in 5-8% of GIST

Mutations activate tyrosine kinase receptor

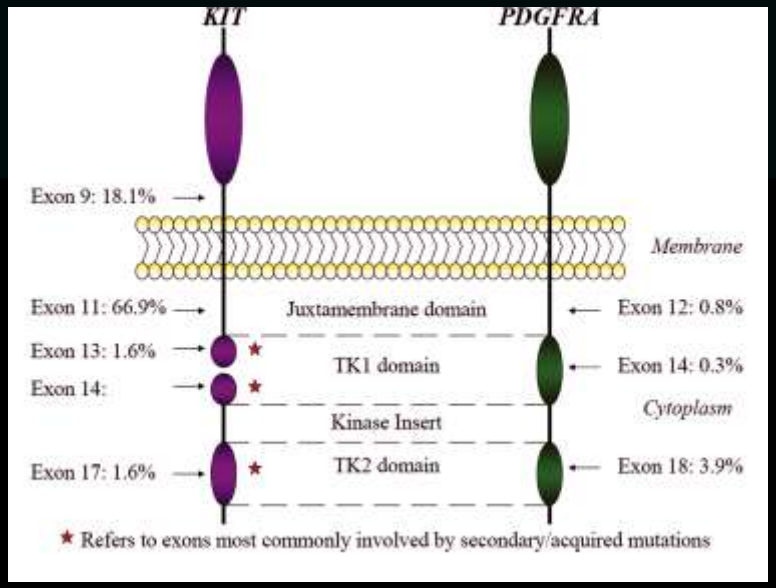


Gastrointestinal Stromal Tumors





Gastrointestinal Stromal Tumors



Arch Pathol 2011;135:1298-1310.

- Kit mutations -worse prognosis than PDGFRa mutations
  - deletions in exon 11 most aggressive
  - Exon 9 mutations associated with intestinal location and more aggressive course
- PDGFRa exon 14 and 18 mutations - gastric origin, epithelioid morphology and favorable outcome

C-Kit and PDGFRa Negative GIST

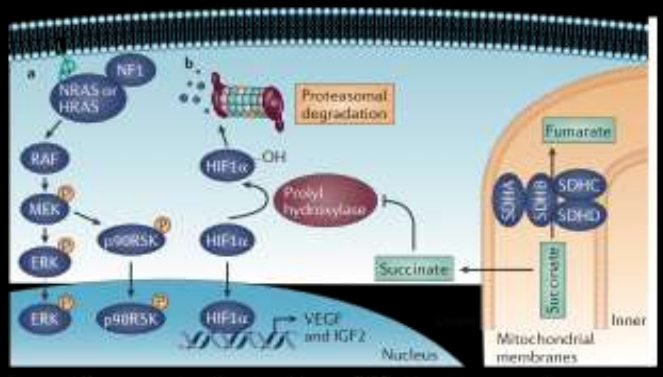
Account for 12% of GIST

epithelioid/stomach

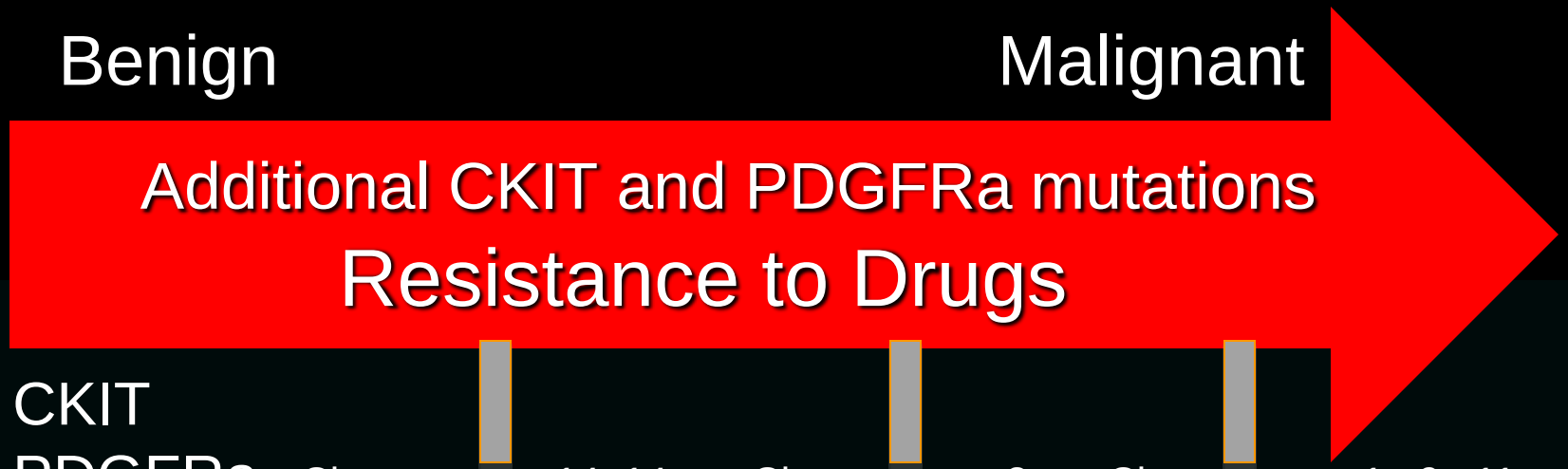
BRAF
NRAS
HRAS

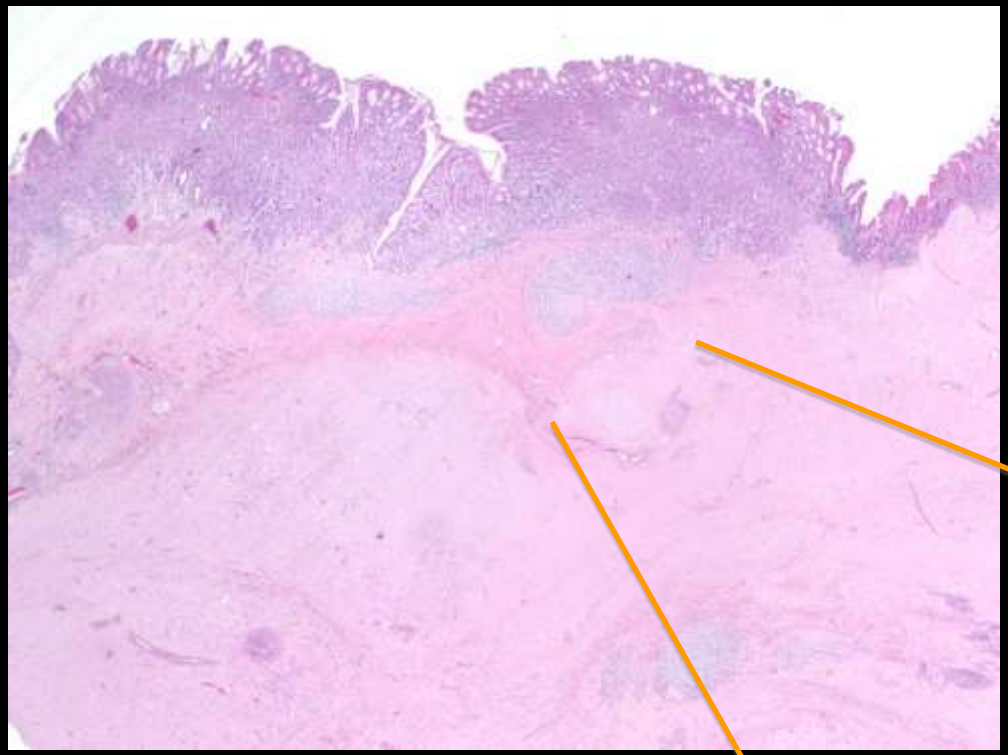
NF1

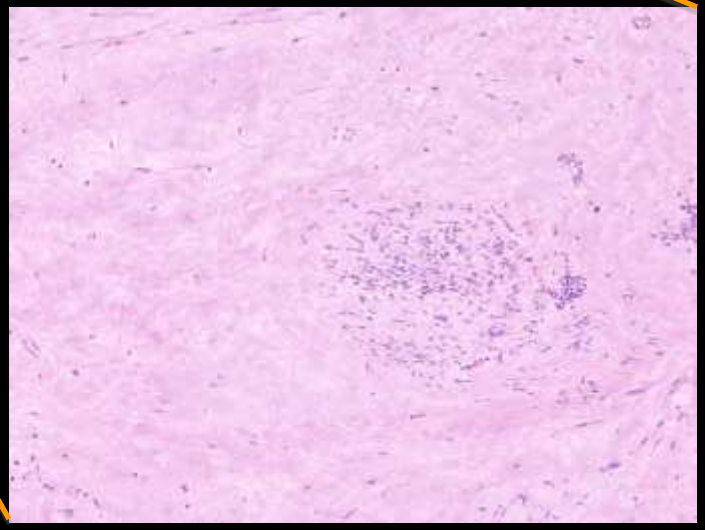
loss of function mutation
– succinate dehydrogenase &
IGFR amplification



Progression of Molecular Aberrations in GIST







GIST – Treatment Effect

Gastrointestinal Stromal Tumors

Outcome

Local recurrence 44-66%

spread along serosal sufaces

deposits in liver

5 yr survival 38-65%

60% develop metastases

(18% have metastases at presentation)

Gastrointestinal Stromal Tumors

Summary

GIST is the most common mesenchymal tumor of the bowel and recapitulates the cells of Cajal

GIST have the potential to be biologically aggressive – risk stratification based on size mitotic rate, and location

GIST is associated with mutations (KIT, PDGFRa, SDH, BRAF) and there is a relationship between mutation and biological behavior and response to therapy. Additional mutations are responsible for acquired resistance to therapy

Picasso at work

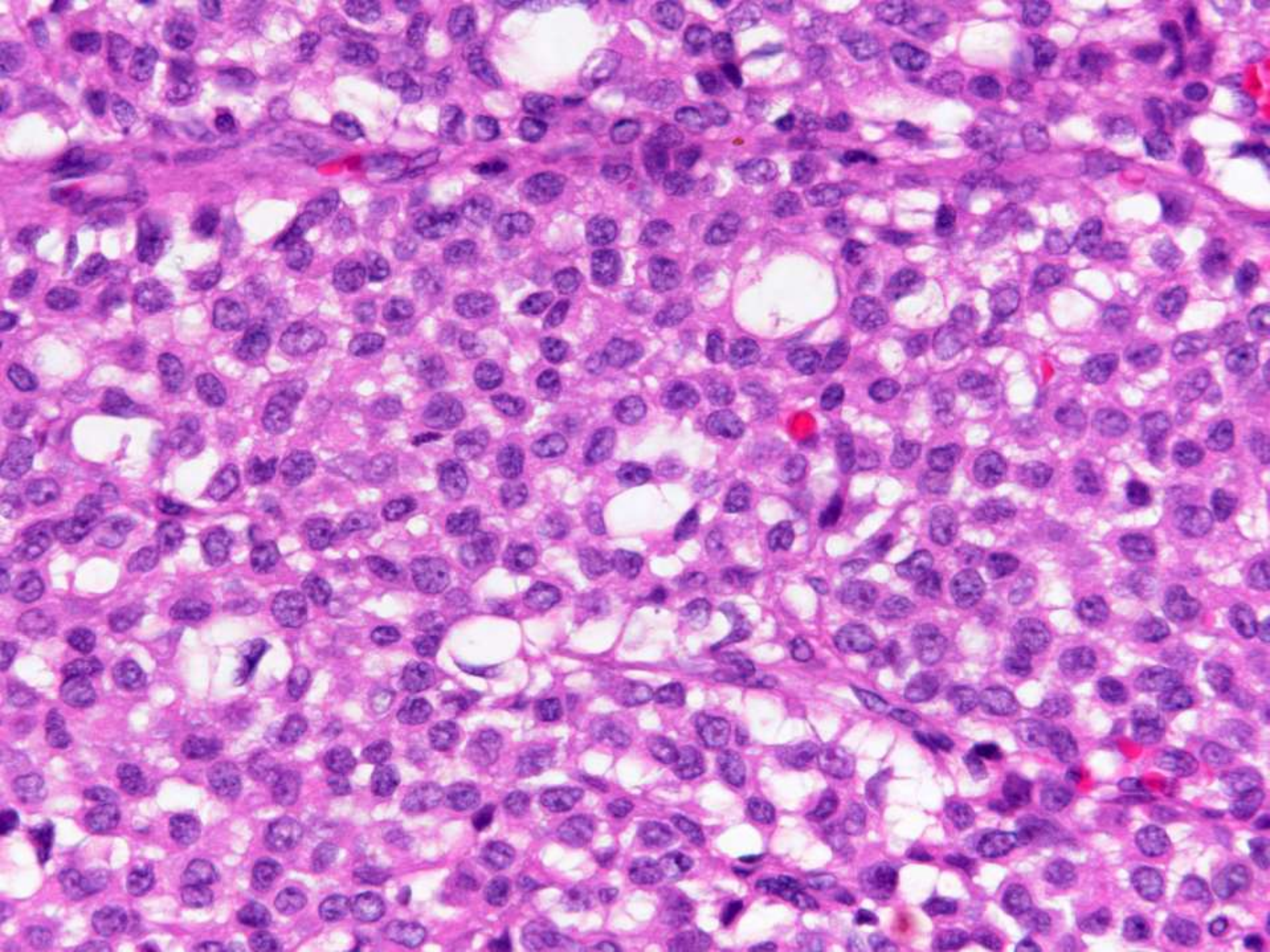
Gastrointestinal Stromal Tumors

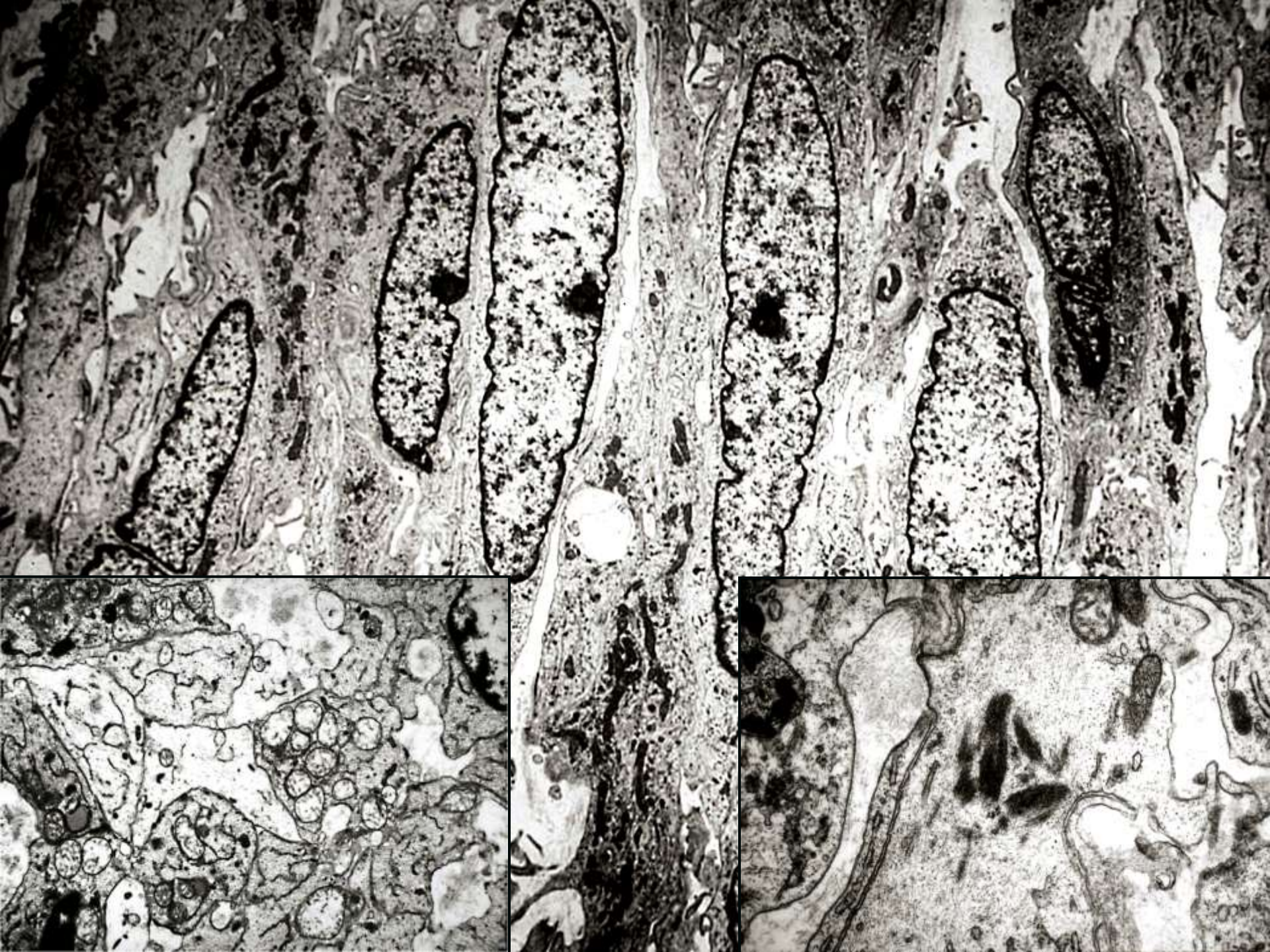
Etiology

Unknown – vast majority are sporadic; rarely a complication of prior radiation

Associated with syndromes: Carney's triad, Carney-Stratakis syndrome, von Recklinghausen's disease type 1

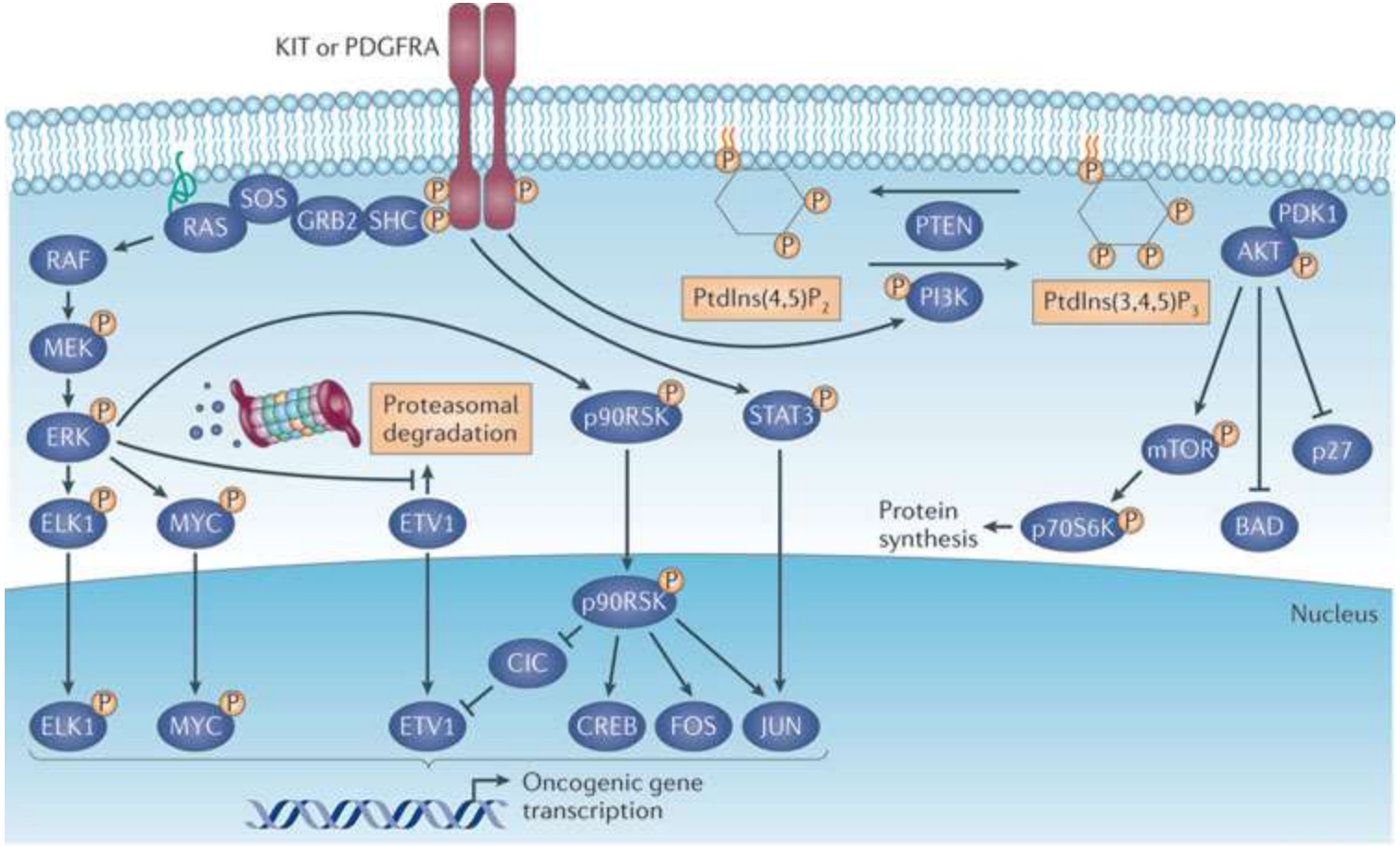
Familial forms





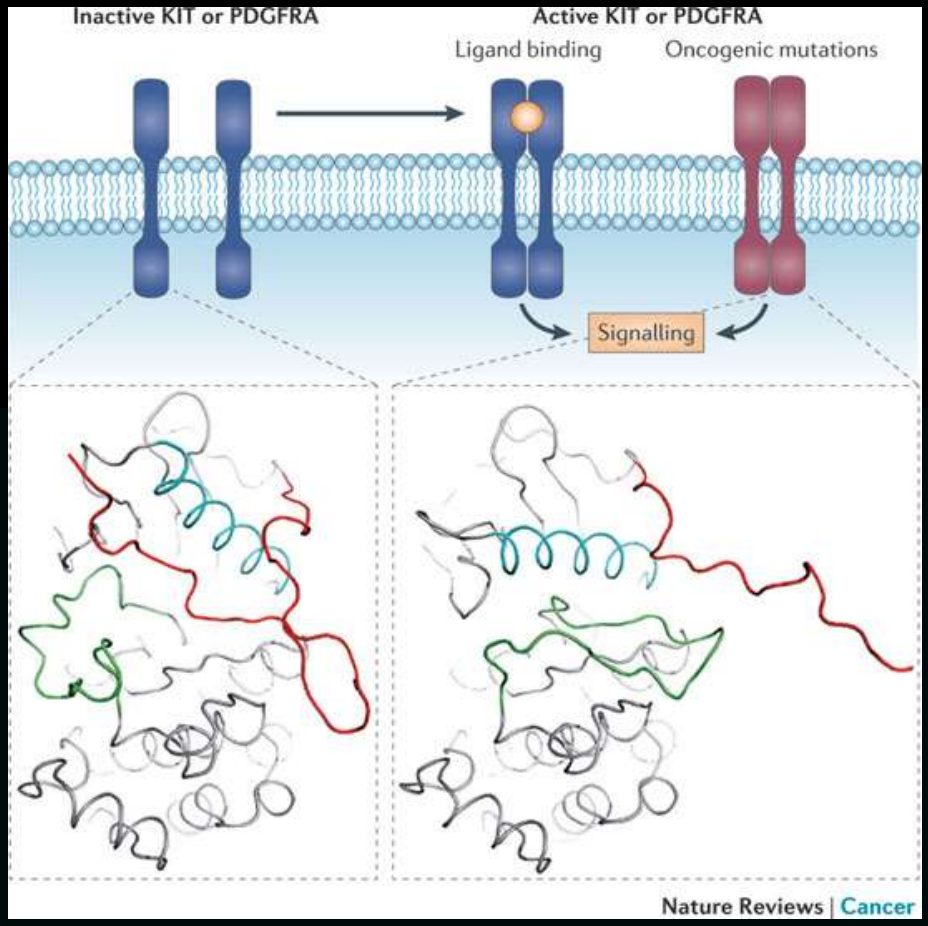
Genetic type	Relative frequency	Anatomic distribution	Germline examples
KIT mutation (relative frequency 75–80%)			
Exon 8	Rare	Small bowel	One kindred
Exon 9 insertion AY502-503	10%	Small bowel and colon	None
Exon 11 (deletions, single nucleotide substitutions and insertions)	67%	All sites	Several kindreds
Exon 13 K642E	1%	All sites	Two kindreds
Exon 17 D820Y, N822K and Y823D	1%	All sites	Five kindreds
PDGFRA mutation (relative frequency 5–8%)			
Exon 12 (such as V561D)	1%	All sites	Two kindreds
Exon 14 N659K	<1%	Stomach	None
Exon 18 D842V	5%	Stomach, mesentery and omentum	None
Exon 18 (such as deletion of amino acids IMHD 842–846)	1%	All sites	One kindred
KIT and PDGFRA wild-type (relative frequency 12–15%)			
BRAF V600E	~7–15%		
SDHA, *SDHB*, *SDHC* and *SDHD* mutations	~2%	Stomach and small bowel	Carney–Stratakis
HRAS and *NRAS* mutation	<1%		
Sporadic paediatric GISTs	~1%	Stomach	Not heritable
GISTs as part of the Carney triad	~1%	Stomach	Not heritable
NF1-related	Rare	Small bowel	Numerous

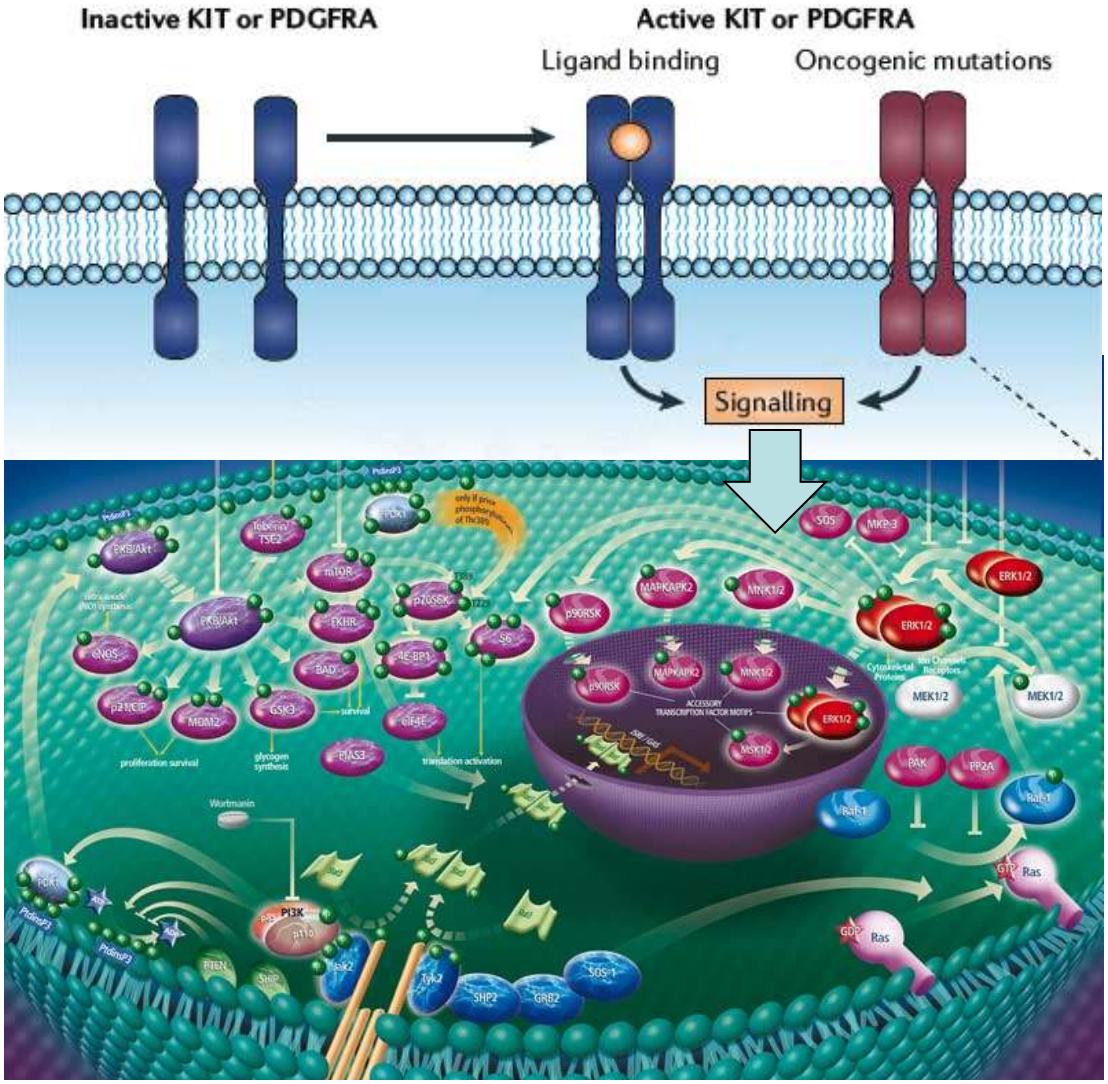
GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type I; *PDGFRA*, platelet-derived growth factor receptor-α; SDH, succinate dehydrogenase.

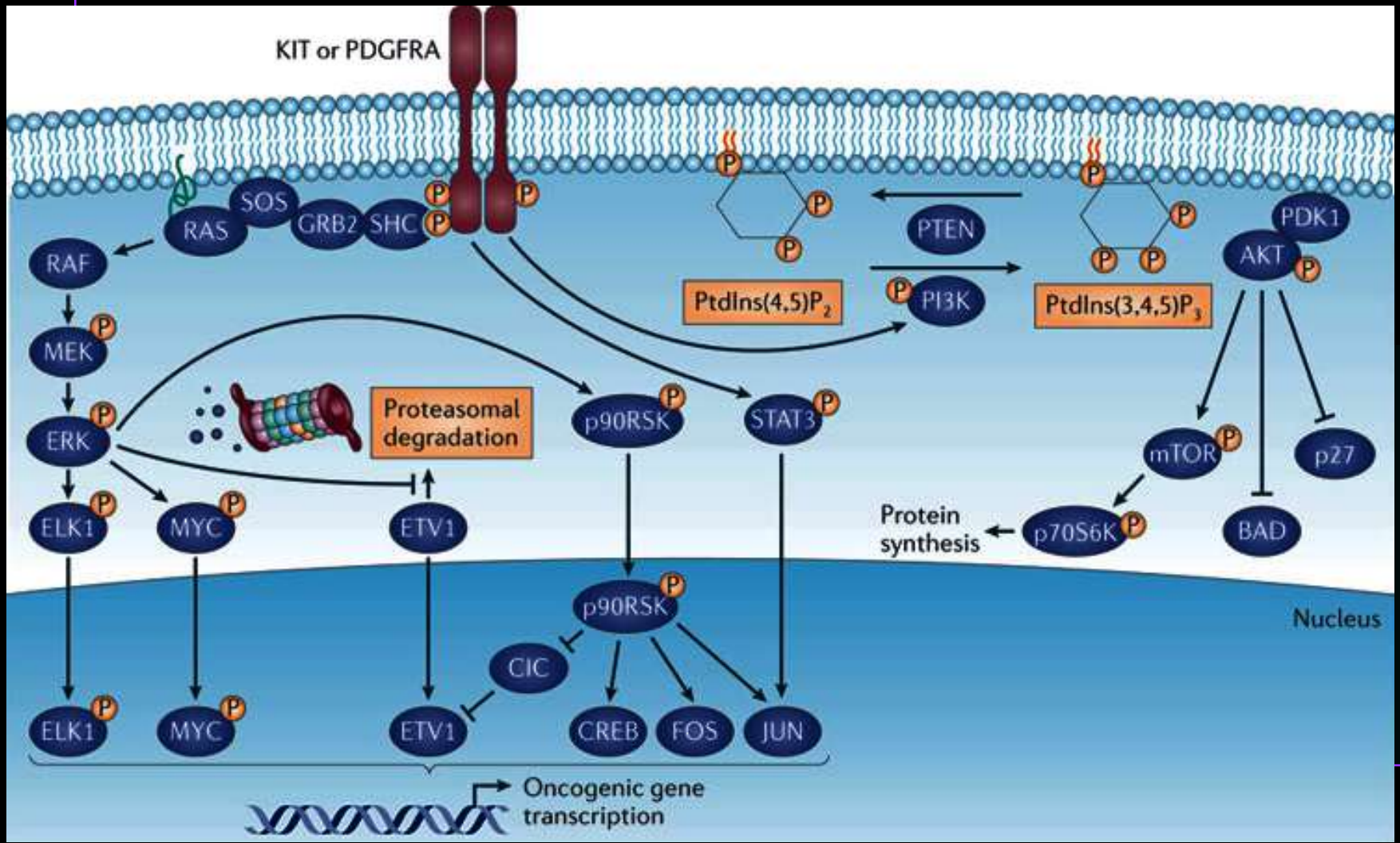


Nature Reviews | Cancer

C-Kit

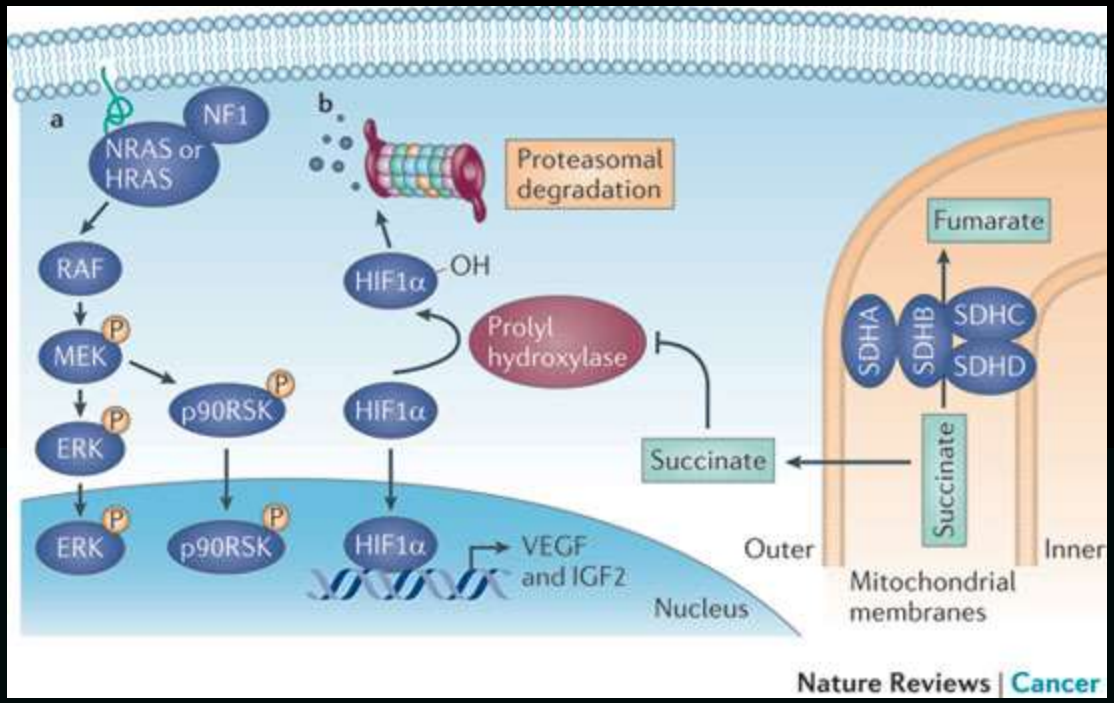

Inactive KIT or PDGFRA
Active KIT or PDGFRA
Ligand binding
Oncogenic mutations
Signalling
Nature Reviews | Cancer


Inactive KIT or PDGFRA
Active KIT or PDGFRA
Ligand binding
Oncogenic mutations
Signalling
PtdIns(3)P3
PDK1
Tuberin TSC2
mTOR
PKB/Akt
eNOS
p21/CIP
MDM2
GSK3
BAD
FKHR
4E-BP1
p70S6K
S6
eIF4E
PI3AS3
proliferation survival
glycogen synthesis
survival
translation activation
Wurtmanin
PI3K
p110
PTEN
SHP
Jak2
SHP2
GRB2
SOS-1
Ras
GTP
GDP
MAPKAPK2
p90RSK
MNK1/2
ERK1/2
MEK1/2
SOS
MKP-3
ACCESSORY TRANSCRIPTION FACTOR MOTIFS
SRF/ELK1
Cytoskeletal Proteins
Ion Channels Receptors
PAK
PP2A
Raf-1


KIT or PDGFRA
SOS
RAS
GRB2
SHC
RAF
MEK
ERK
ELK1
MYC
ETV1
Proteasomal degradation
p90RSK
STAT3
PTEN
PI3K
PtdIns(4,5)P2
PtdIns(3,4,5)P3
PDK1
AKT
mTOR
p27
p70S6K
BAD
Protein synthesis
Nucleus
p90RSK
CIC
ELK1
MYC
ETV1
CREB
FOS
JUN
Oncogenic gene transcription

GI Stromal Tumors

Genotype	% cases	Imat. Resp
KIT exon 11	70%	85%
KIT exon 9	15%	45%
KIT exon 13	<5%	few
KIT exon 17	<5%	few
PDGRA d842	4%	none
PDGFRA other	1%	few
No KIT/ PDGFRA	5-10%	little


a
NF1
NRAS or
HRAS
RAF
MEK
P
ERK
P
p90RSK
P
ERK
P
p90RSK
P
b
Proteasomal
degradation
HIF1α
OH
Prolyl
hydroxylase
HIF1α
HIF1α
VEGF
and IGF2
Nucleus
Succinate
Fumarate
SDHA
SDHB
SDHC
SDHD
Succinate
Outer
Inner
Mitochondrial
membranes
Nature Reviews | Cancer

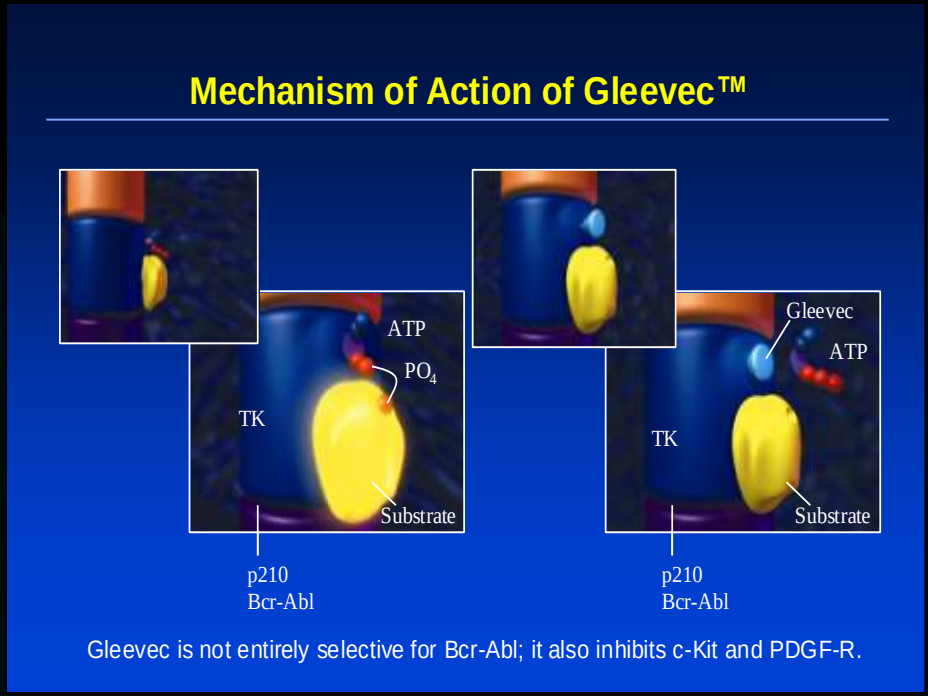
GI Stromal Tumors

Treatment

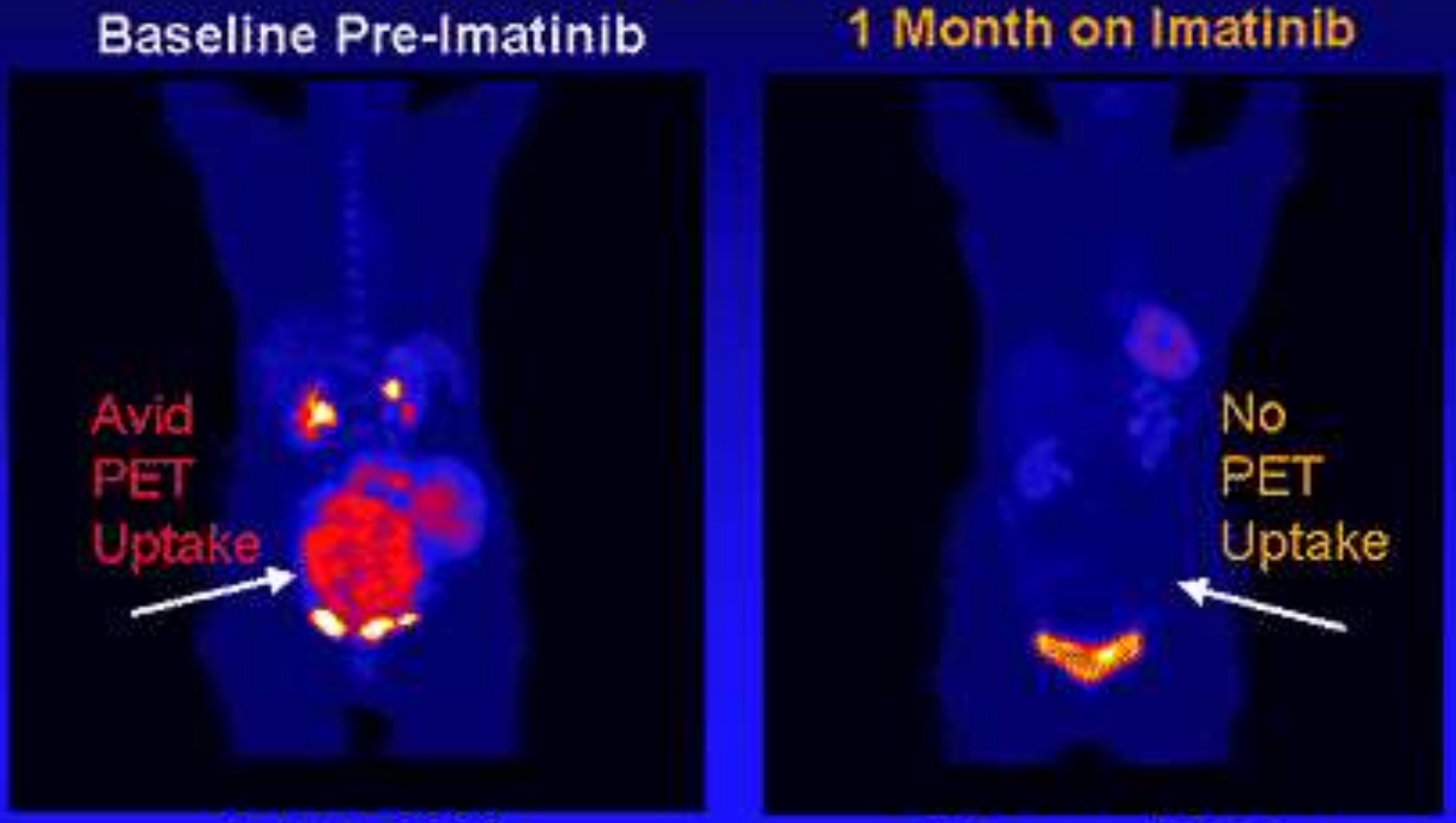
Complete resection; Conventional chemotherapy fails

Imatinib - inhibitor of c-Kit

most effective



Metastatic GIST Before and After Imatinib



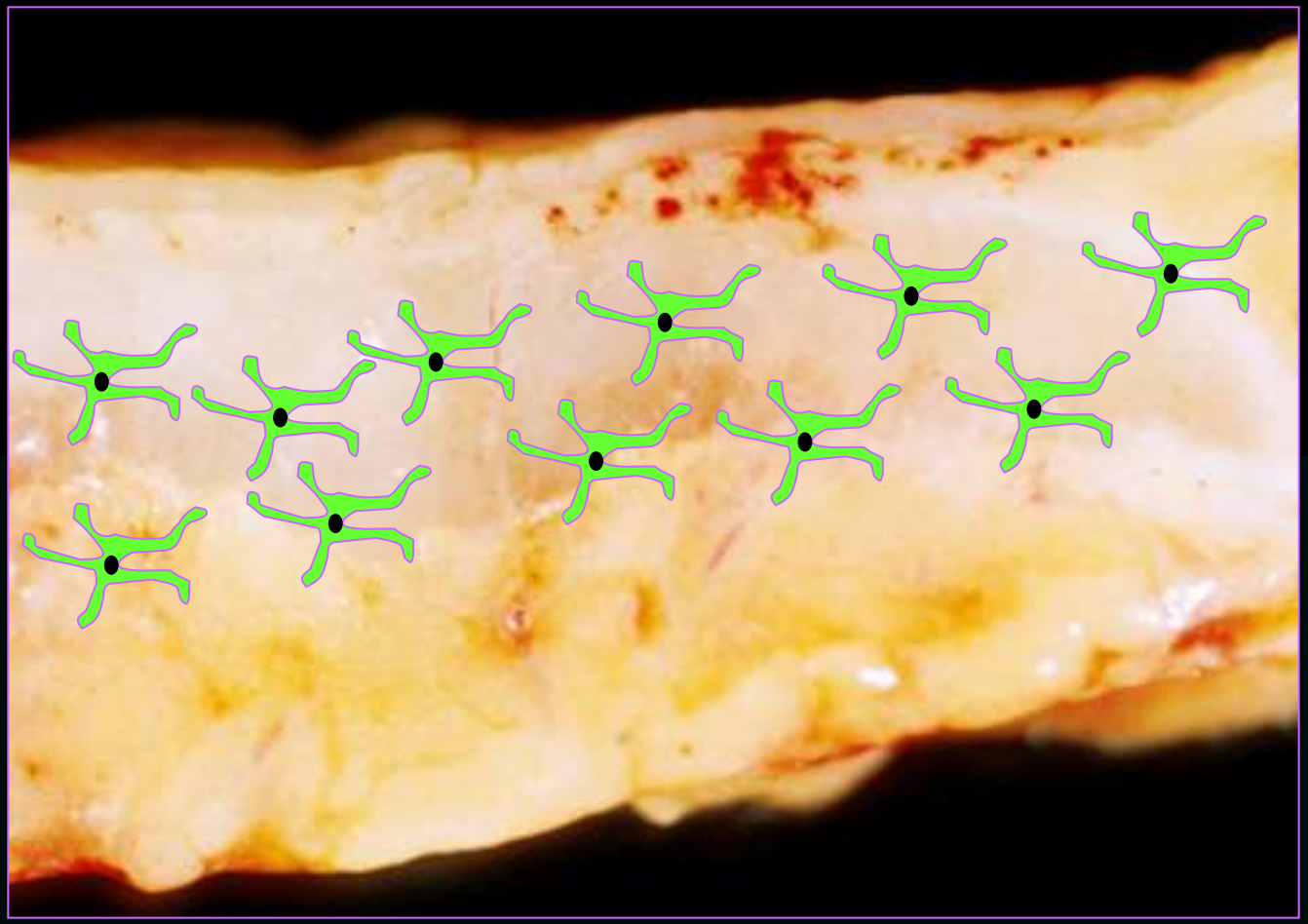
Courtesy of George D. Demetri, MD.

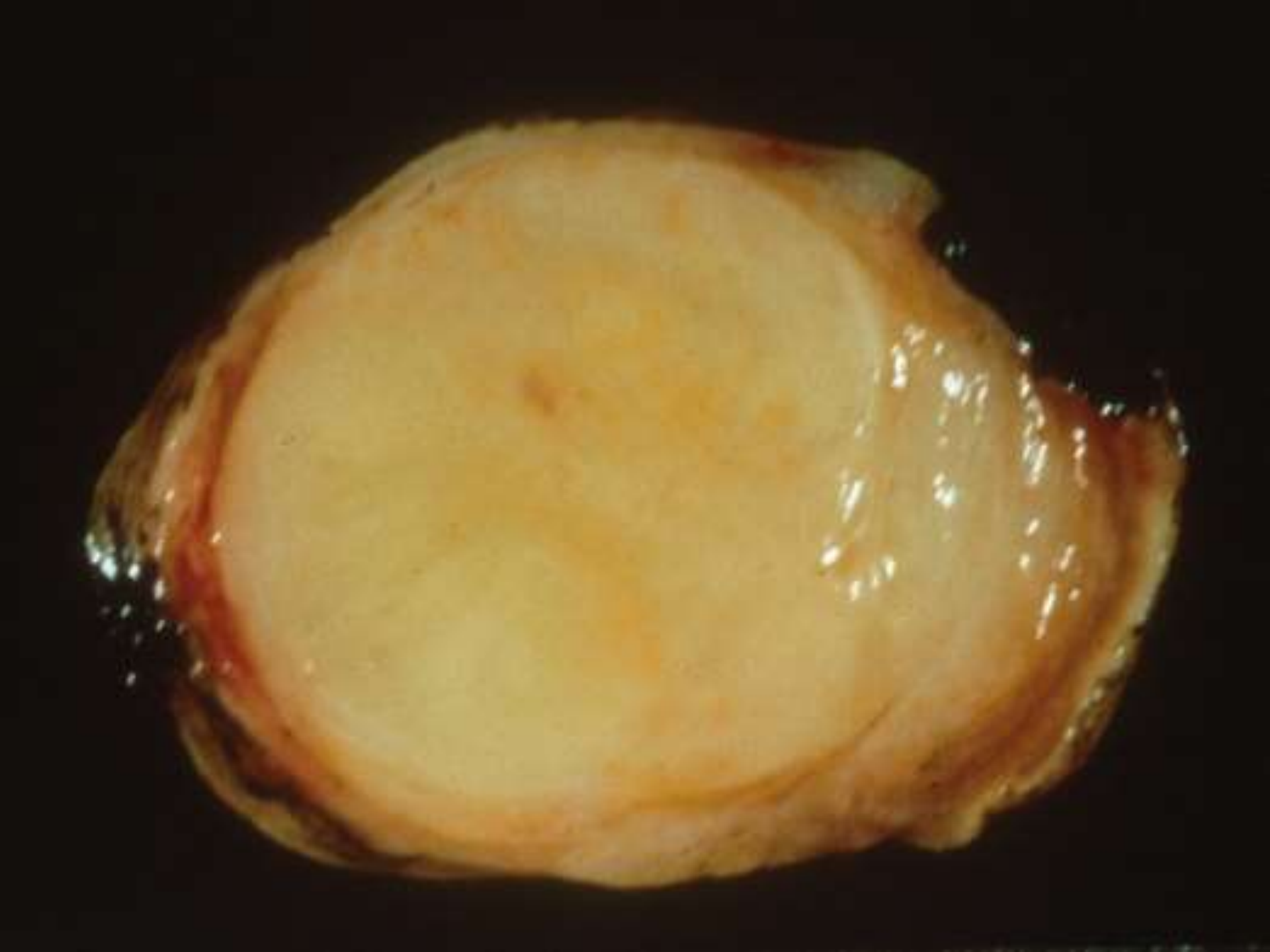
GI Stromal Tumors

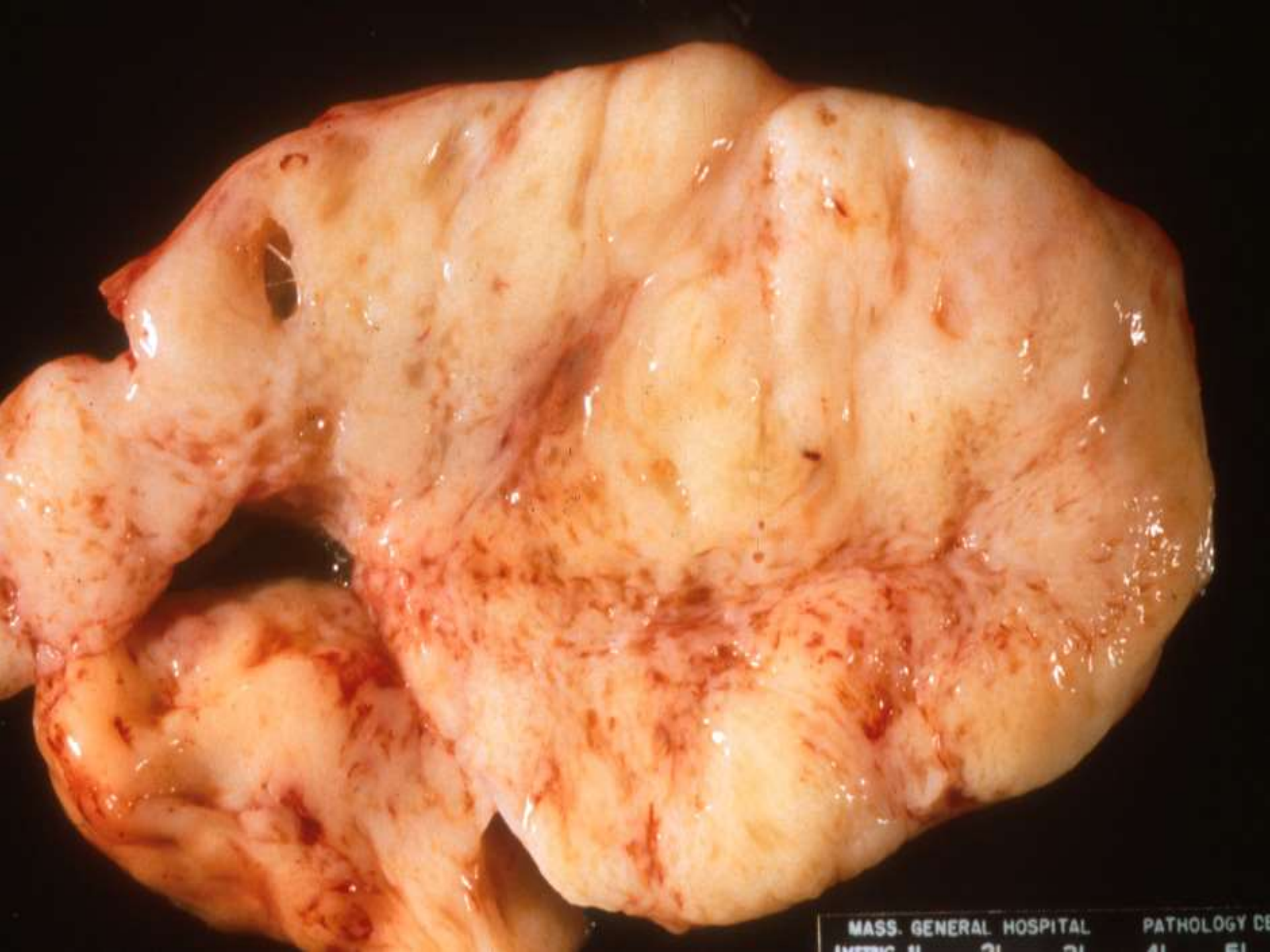
Differential Diagnosis

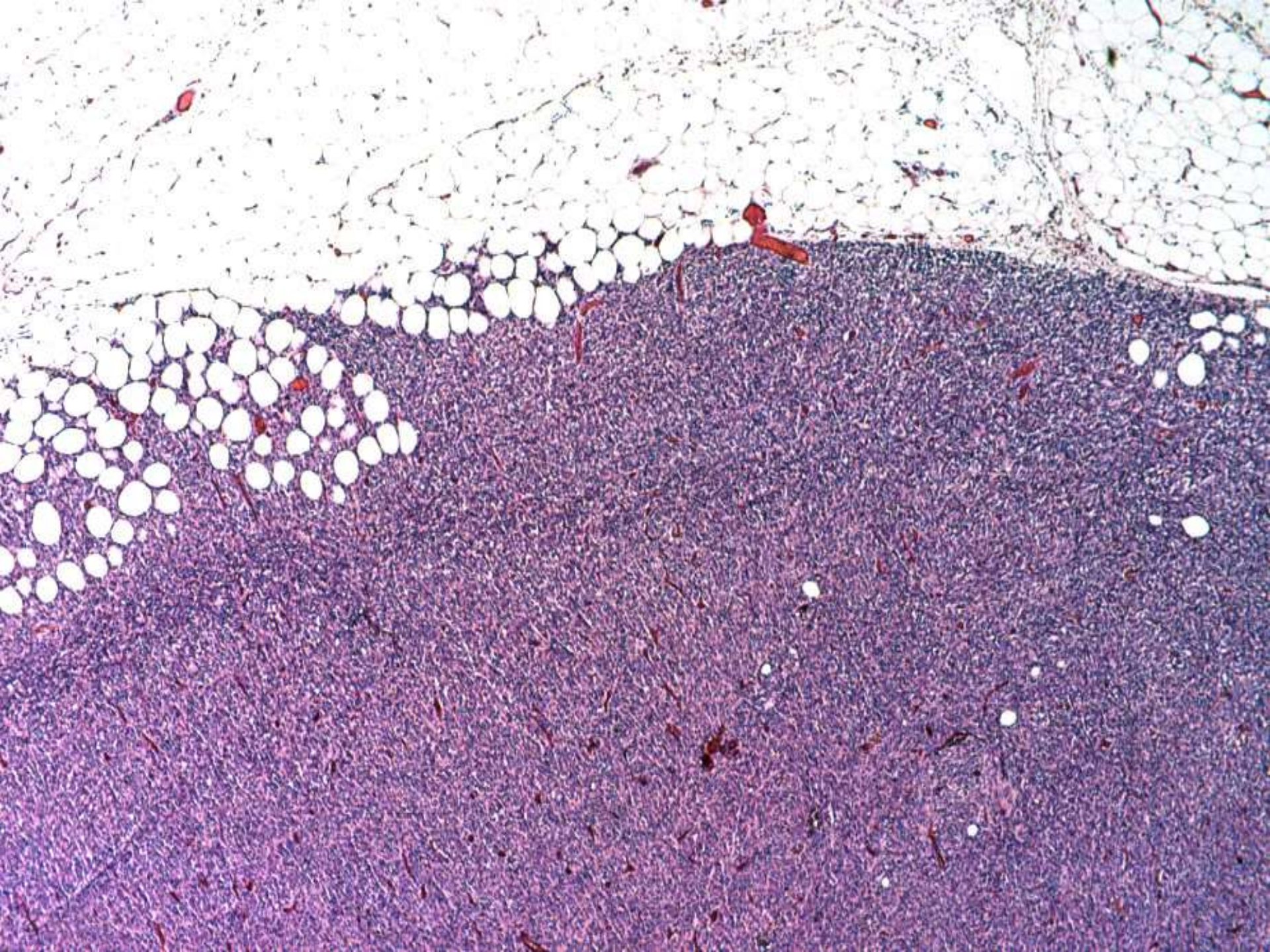
- Fibromatosis
- Leiomyoma, leiomyosarcoma
- Schwannoma
- Inflammatory fibroid polyp

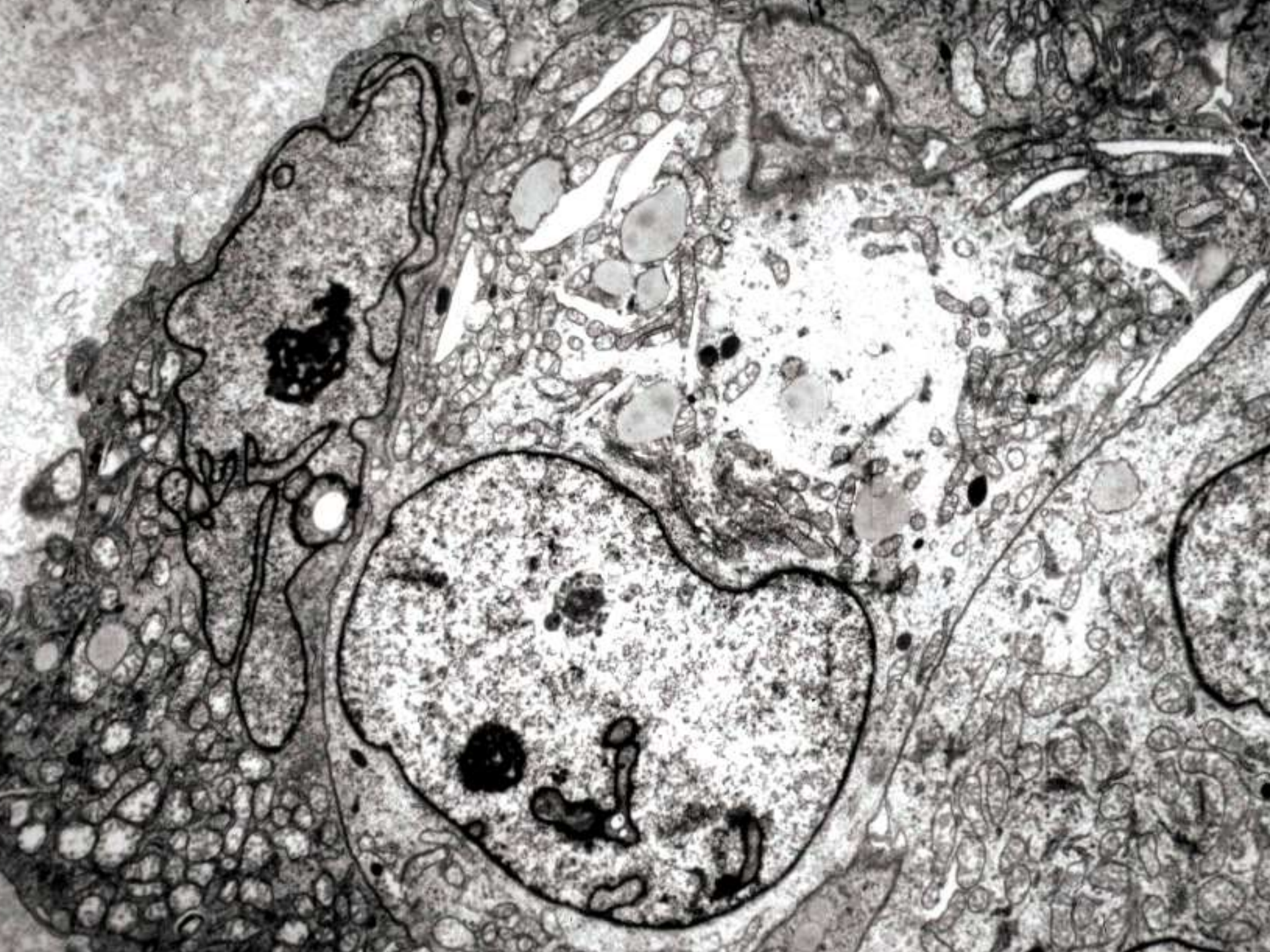
Interstitial Cells of Cajal






MASS. GENERAL HOSPITAL
PATHOLOGY





GI Stromal Tumors

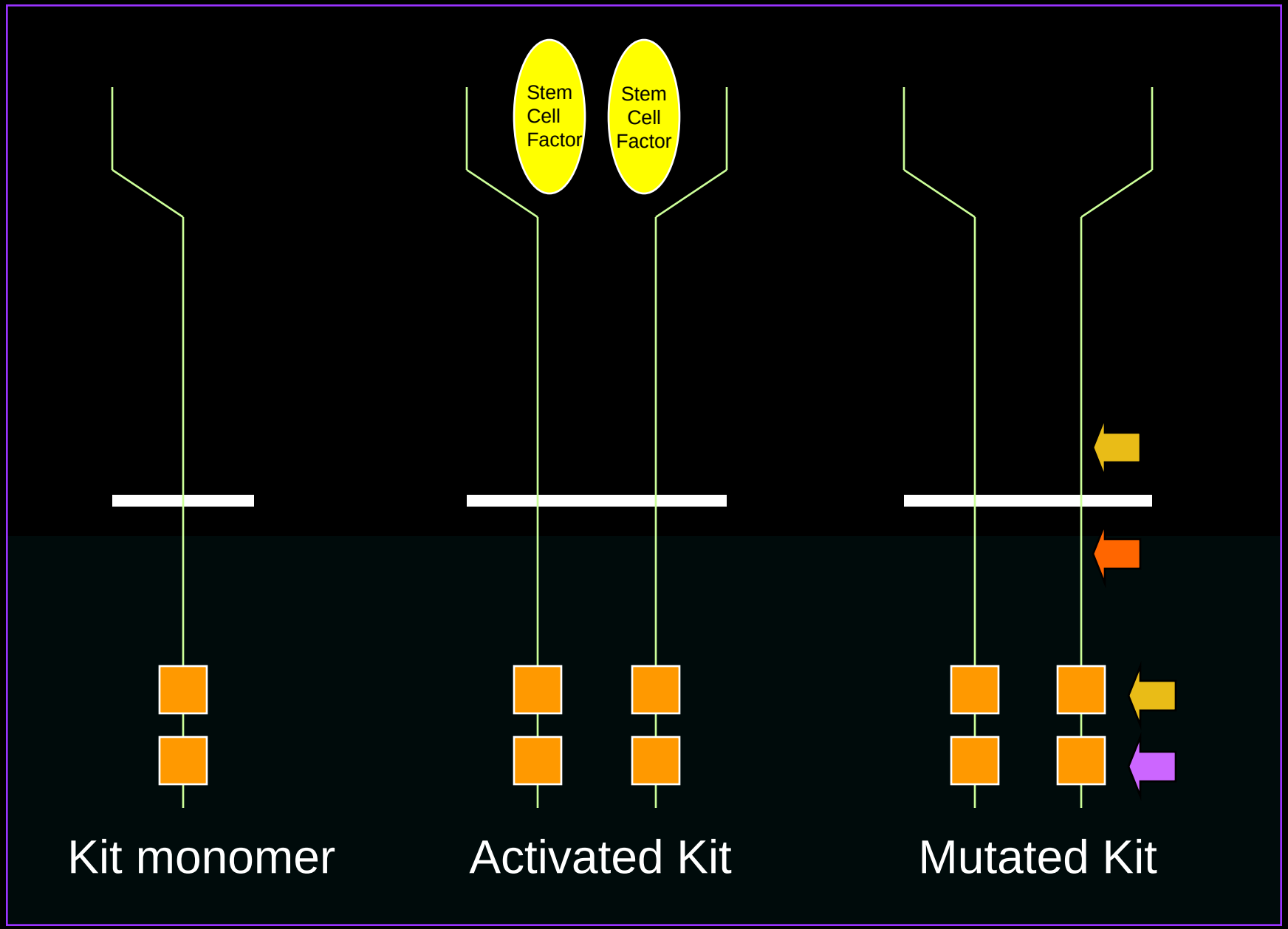
GIST recapitulates cells of Cajal

- Similar ultrastructural features and immunophenoype as cells of Cajal
- Similar distribution as cells of Cajal
- Both express c-Kit

GI Stromal Tumors

Other Prognostic Features

- Proliferation markers
  - Ki-67, PCNA
- Flow Cytometry
  - aneuploidy


Stem Cell Factor
Stem Cell Factor
Kit monomer
Activated Kit
Mutated Kit

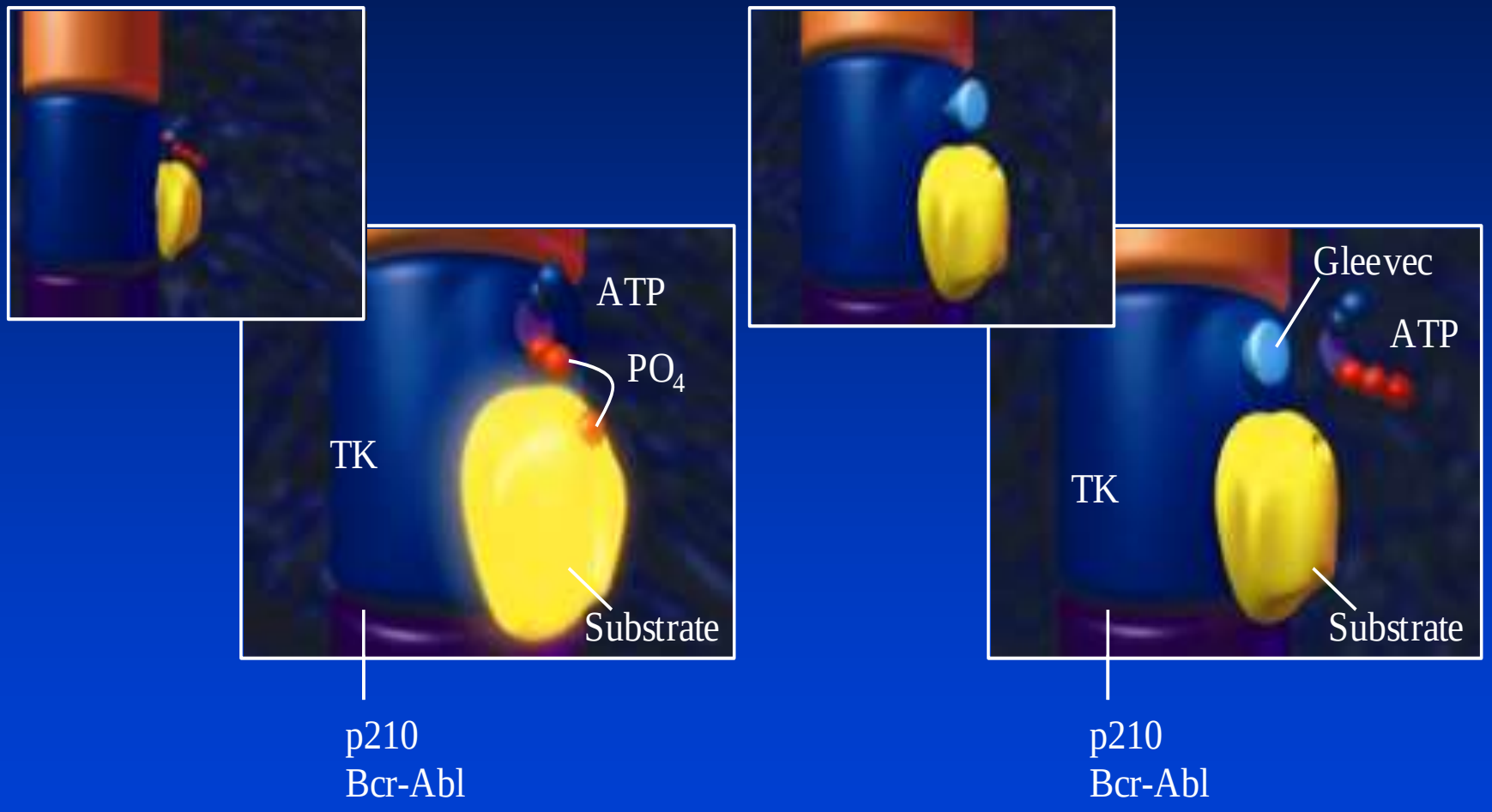
GI Stromal Tumors

Morphologic Prognostic Features

Location, size, mitotic activity and invasion of other organs

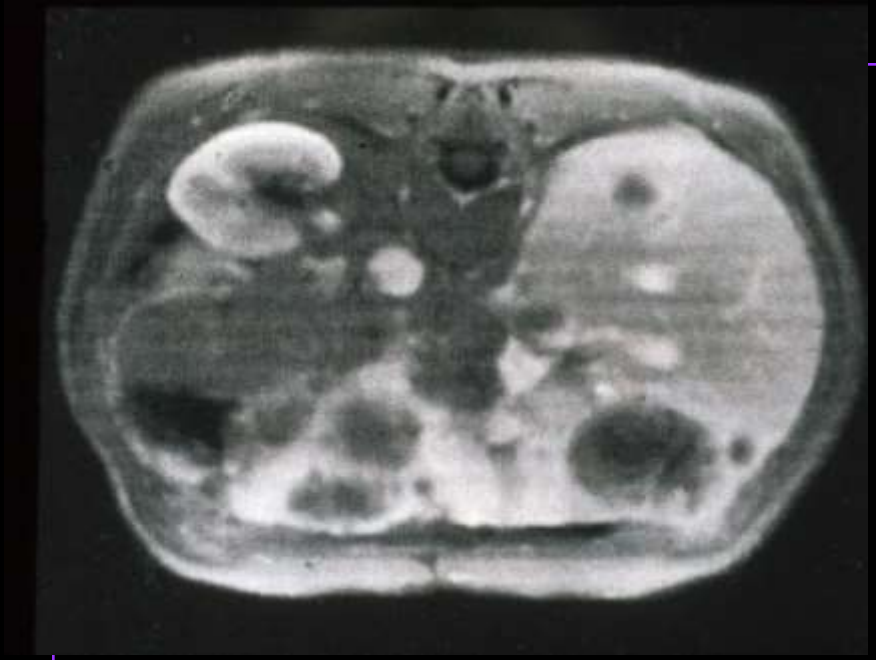
Good features: stomach, $\leq$ 5cm, $\leq$ 1 mitosis/50 hpf, non-invasive

Mechanism of Action of Gleevec™

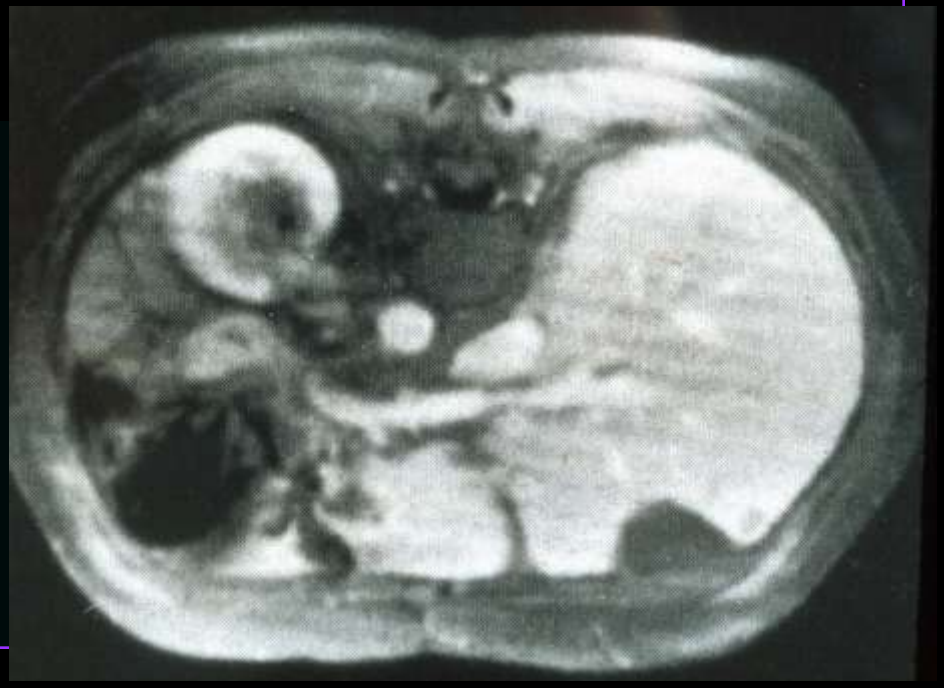


Gleevec is not entirely selective for Bcr-Abl; it also inhibits c-Kit and PDGF-R.

GIST Treated with Imatinib



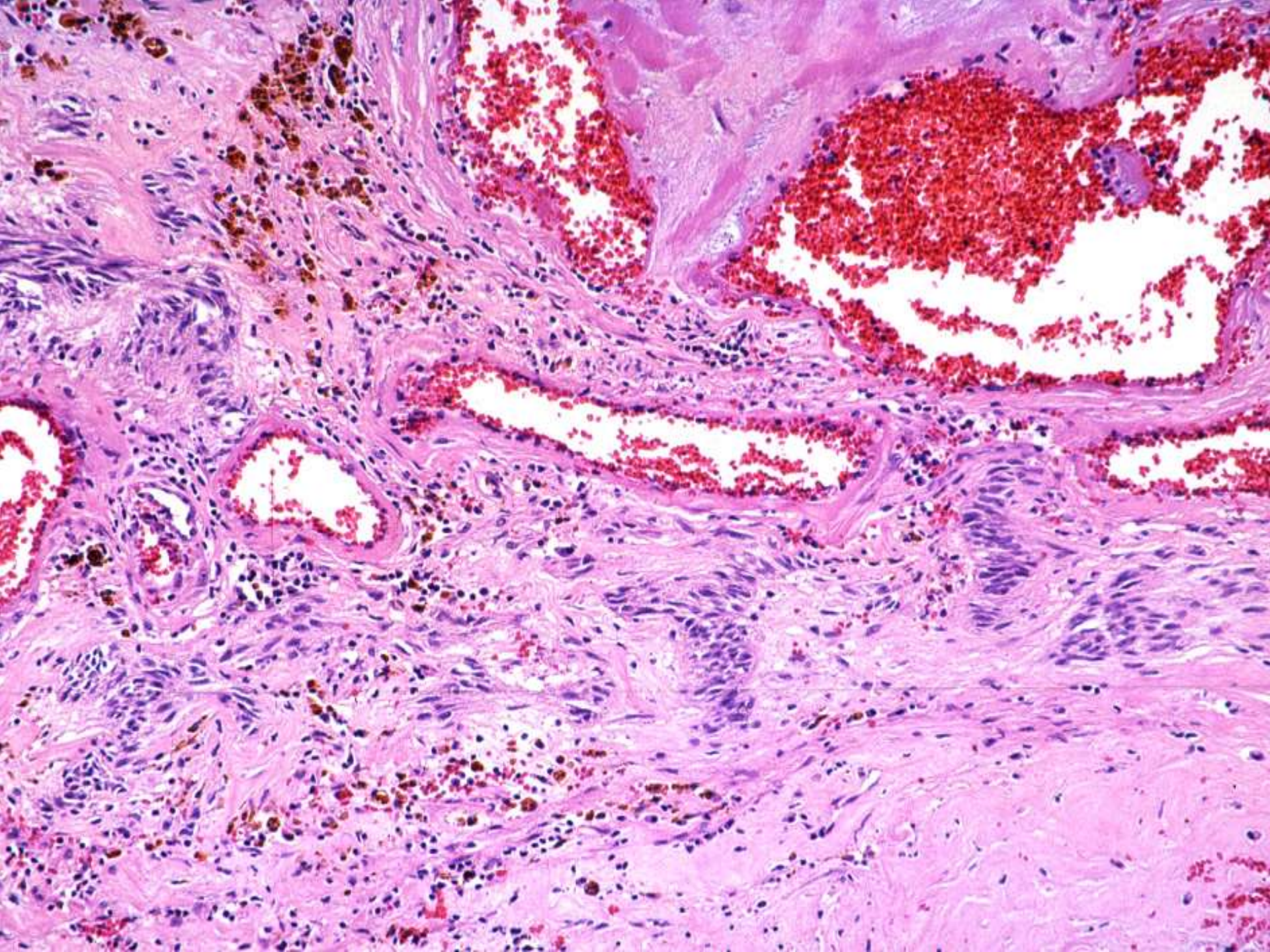
Pre-treatment

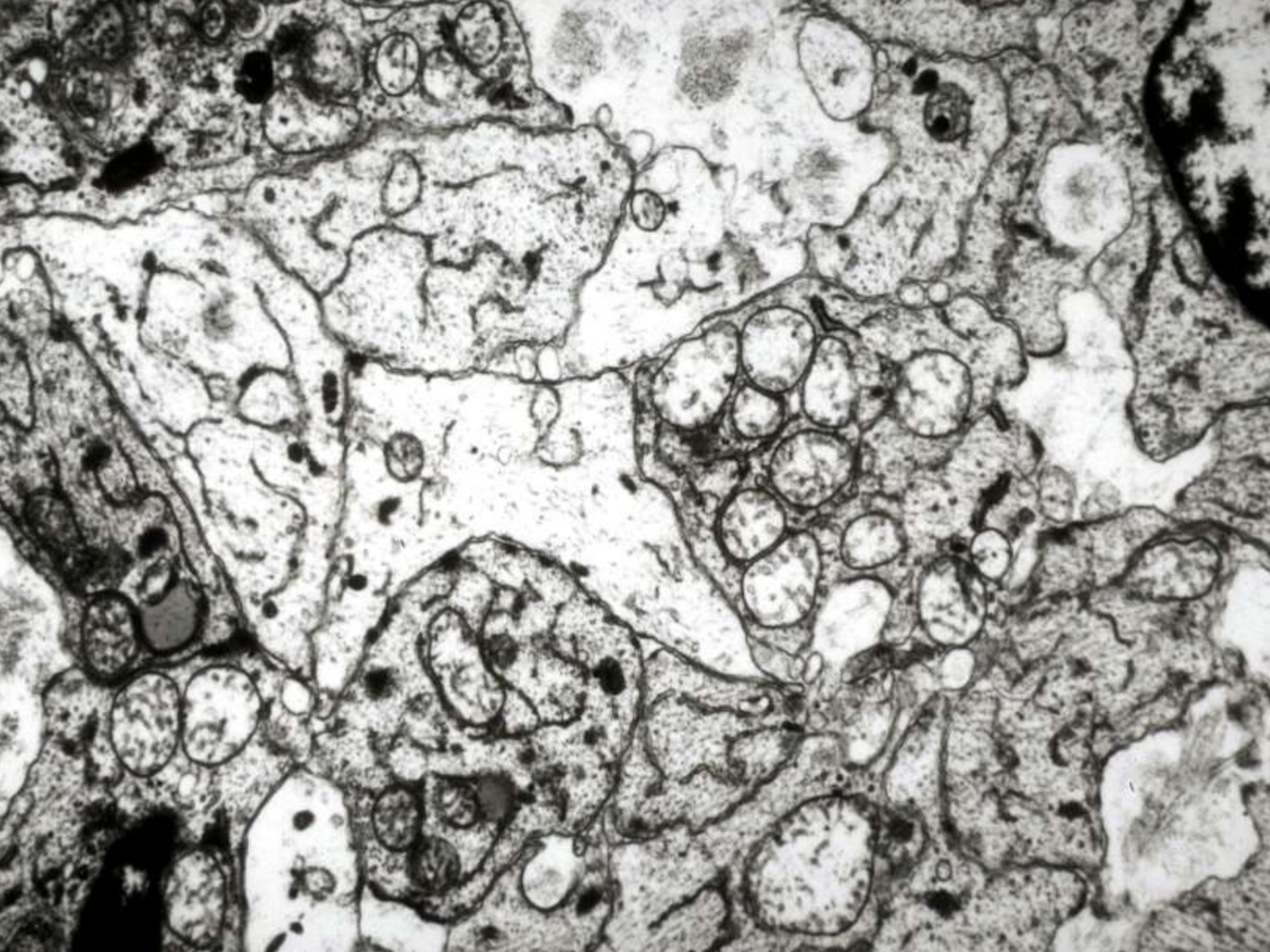


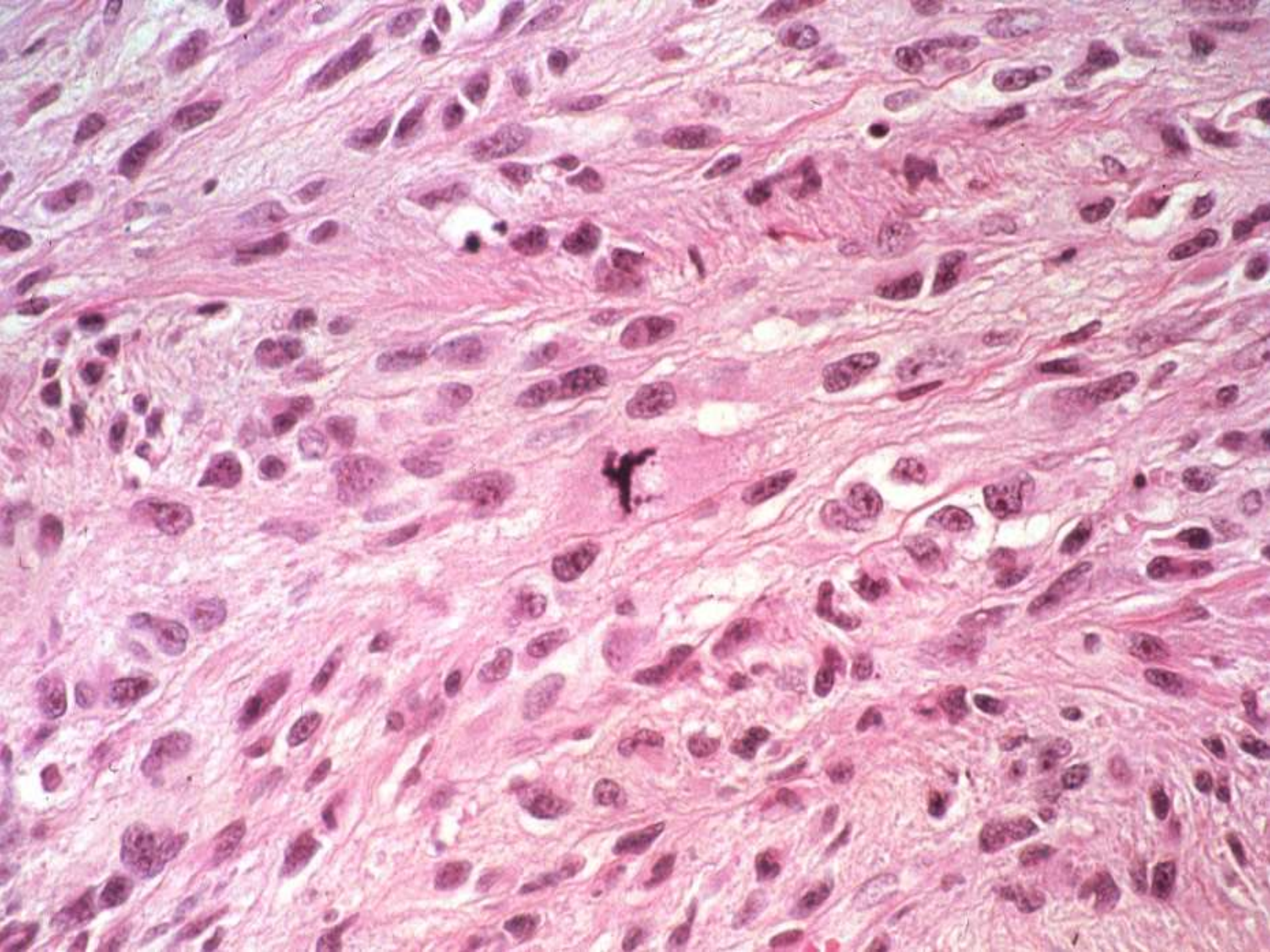
Post -treatment

Gleevec Trials

- Partial response 59%
- Stabilization 28%
- Progression 13%
- If no ckit mutation, 8x more likely to have progression (44%) vs Exon 11 mutation (5%)







Special Groups of GIST

Children

usually female, usually have epithelioid morphology

Familial GIST- inherited mutation in exon 11 Kit gene

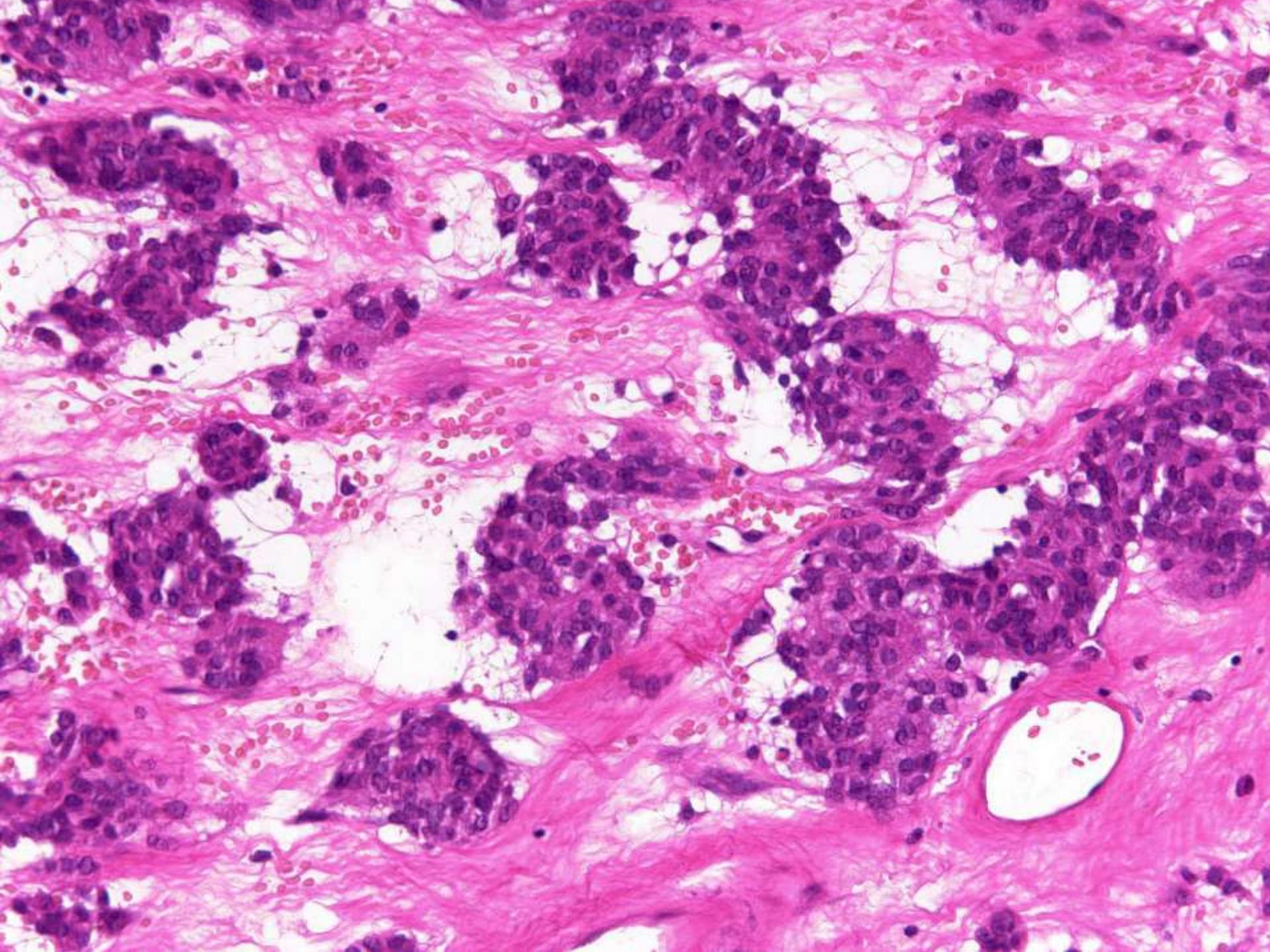
ICC hyperplasia & multiple GIST, hyperpigmentation

Type 1 von Recklinghausen's Disease

arise in background of diffuse hyperplasia of ICC, multiple, lack mutation in KIT + PDGFA

have inactivating mutation of NF1 gene producing dysfunctional protein neurofibromin

Carny's triad – gastric GIST, pulmonary chondroma, paraganglioma, no Kit or PDGF mutations



GI Stromal Tumors

Etiology

- unknown
- rare complication of radiation
- associated with Carney's triad,

  von Reckinghausens disease, type 1, and intestinal neuronal dysplasia

C-Kit Negative GIST

Epithelioid morphology

PDGFR-alpha mutations

Originate in omentum/peritoneum

Many are responsive to Imatinib

Imatinib mesylate (Gleevac)

MECHANISM:

Binds to ATP binding pocket of C-KIT kinase domain and inhibits receptor phosphorylation

TOXICITY:

Mild anemia, nausea, diarrhea, muscle cramps hepatorenal failure (rare)