Gastrointestinal Stromal Tumors(GIST)

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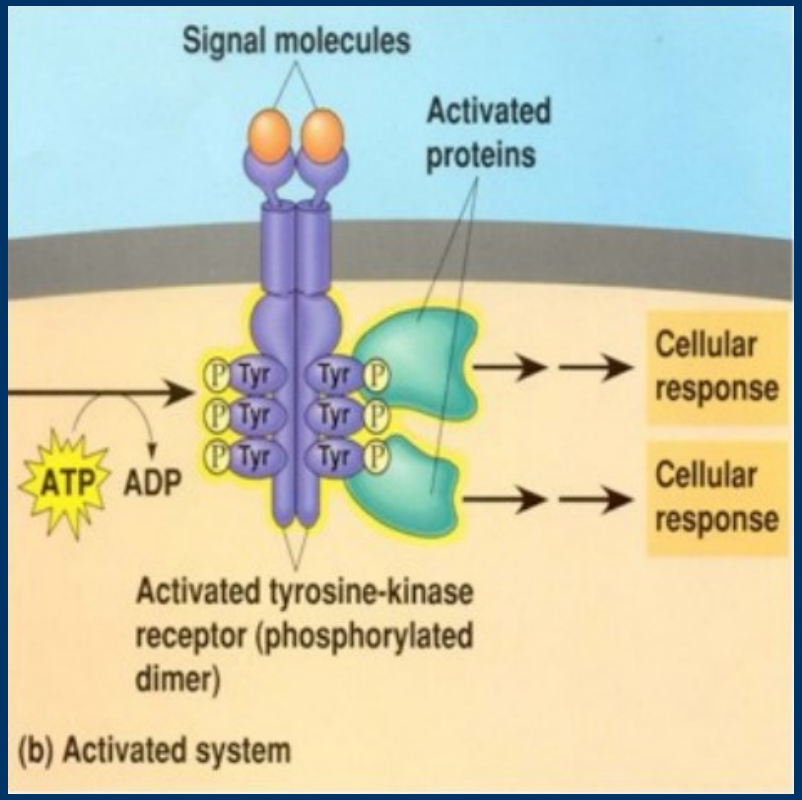
Are GISTs derived from ICCs?

- Interstitial cells of Cajal (ICCs/Pacemaker cells) form the interface between the autonomic innervation of the bowel wall and the smooth muscle of muscularis propria.
- The KIT RTK plays essential roles in the development and maintenance of normal ICCs .
- It is postulated that GISTs originate from CD34 positive stem cells within the wall of the gut and differentiate toward the pacemaker cell phenotype (ICC)

Membrane ReceptorTyrosine Kinases(RTK)



- RTKs are involved in cellular signaling pathways and regulate key cell functions such as proliferation, differentiation, anti-apoptotic signaling and neurite outgrowth.
- Unregulated activation of these enzymes can lead to various forms of cancer as well as benign proliferative conditions.

•Nishida T, Hirota S, Taniguchi M, et al: Familial gastrointestinal stromal tumours with germline mutation of the KIT gene

GIST and C-kit

- The c-kit receptor is one of many membrane tyrosine kinase receptors involved in cellular signaling pathways.
- CD117 molecule (or antigen) is part of the c-kit receptor, a membrane tyrosine kinase.
- The c-kit receptor is a product of the c-kit or KIT protooncogene.
- The CD117 antigen is expressed by almost all GISTs in contrast to other spindle-cell tumors of the GI tract.

UNCONTROLLED KINASE ACTIVATION (THE MOLECULAR ETIOLOGY)

- In normal cells activation of the of the c-kit tyrosine kinase requires the presence of an endogenous ligand (KIT ligand, c-kit ligand, or stem cell factor)
- Approx 80 % of GISTs have KIT protooncogene mutations that lead to activation of the c-kit receptor resulting in spontaneous receptor activation not requiring a ligand.

- Observed both in sporadic and hereditary cases
- A subset of GISTs lacking c-kit mutations have activating mutations in the **PGFRa** gene (platelet derived growth factor receptor alpha), another tyrosine kinase.

GISTs are identified by:

- either c-kit immunoreactivity (detection of the CD117 antigen) or
- the presence of activating mutations in KIT or PDGFRa

LOCATION :

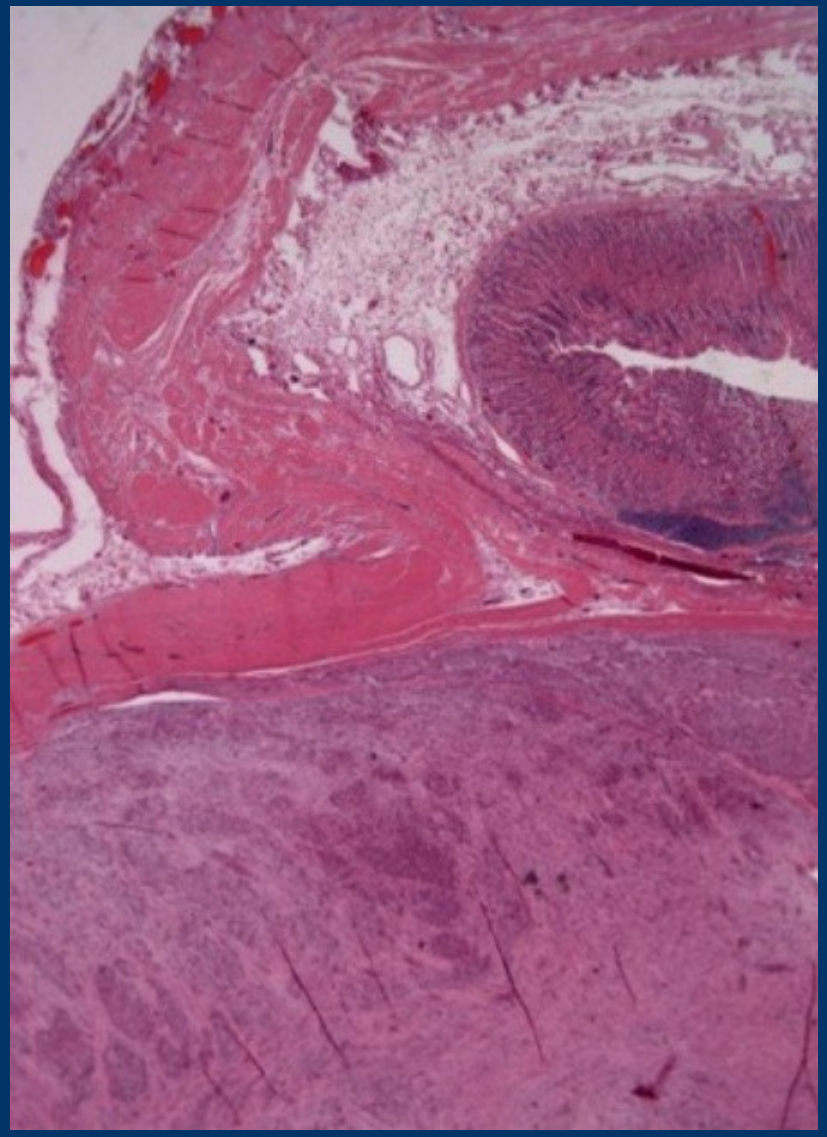
- Stomach – 50 percent
- Small bowel – 25 percent
- Colon/ Rectum– 10 percent
- Omentum/mesentery 7 – percent
- Esophagus – 5 percent

CELLULAR MORPHOLOGY

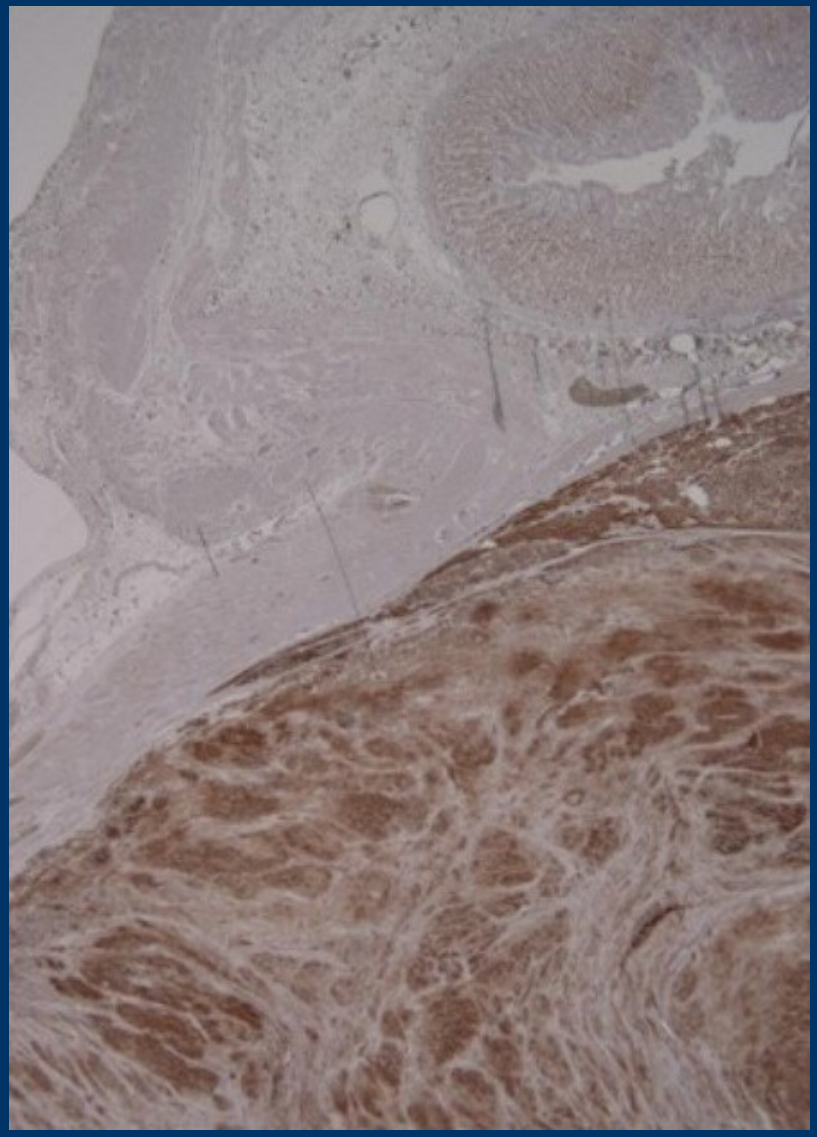
- Three relatively distinctive types
  - **Spindle cell type** – 70 percent
  - **Epithelioid type** – 20 percent, more commonly c-kit negative and found in omentum and mesentery
  - **Mixed type** – 10 percent Histologic type may be of prognostic significance, worse with epitheloid

HISTOPATHOLOGY

- Differential Diagnosis
  - H&E stain: Melanoma, leiomyoma/sarcoma, peripheral nerve sheath tumor, desmoid
  - Histology difficult
  - Immunophenotyping crucial
    - 95 % are positive for C-kit (CD117)
    - 60-70 % positive for CD34
    - Negative for alpha-smooth muscle actin (SMA) (leiomyoma)
    - Negative for S100 protein (Schwannoma)
    - Negative for Desmin (desmoids)



H&E stain



C-kit(CD 117)

Determinants of Malignant Behavior

- Size: More than 3 cm in diameter(most malignant GISTs are larger than 10 cm at diagnosis)
- Mitotic rate: > 25 mitoses per 50 high power fields
- Warning: Even very small lesions (< 2 cm) with a low mitotic rate occasionally metastasize

Approach for defining Risk of Aggressive Behavior in Gastrointestinal Stromal Tumors

	Size, mm	Mitotic index, per 50 HPF
Very low risk	<20	<5
Low risk	20–50	≤5
Intermediate risk	≤50	6–10
	50–100m	≤5
High risk	>50	>5
	>100	Any mitotic rate
	Any size	>10

HPF, High-power field.

Metastasis

- GISTs behave differently than other soft tissue sarcomas:
  - GISTs frequently metastasize to the liver and rarely to regional lymph nodes.
  - GISTs virtually never metastasize to lungs whereas this is the most common site of metastasis for leiomyosarcomas.

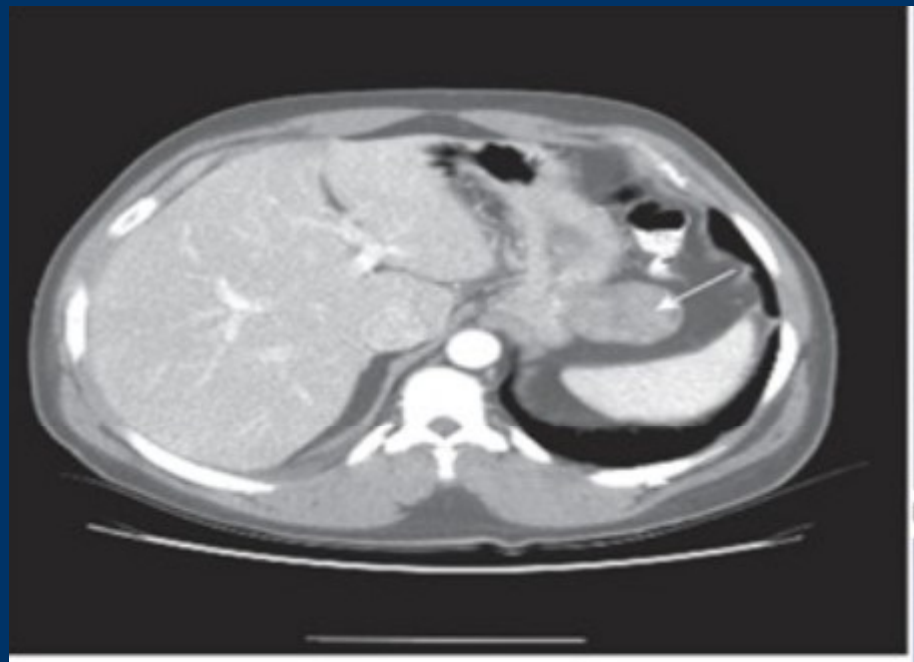
CLINICAL MANIFESTATIONS

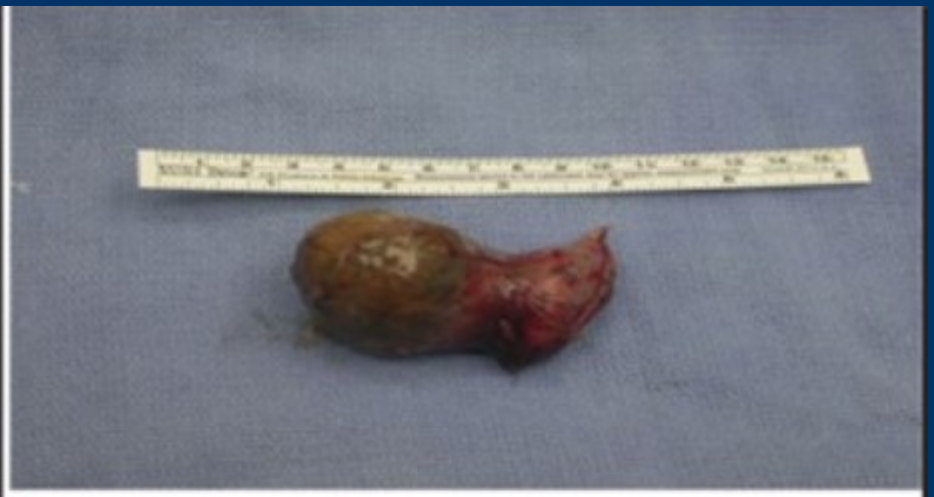
- Mesenchymal tumors of the GI tract are often asymptomatic and discovered incidentally during endoscopic or barium studies.
- Overt GI bleeding — 40 percent
- Abdominal mass — 40 percent
- Abdominal pain — 20 percent
  - The vast majority of GIST metastases at presentation are intra-abdominal, either with metastases to the liver, omentum, or peritoneal cavity .

Diagnosis :

- CT scan
  - Leiomyomas: solid hypodense lesions
  - GISTs: typically enhance with IV contrast
- Endoscopy
  - Smoothly contoured submucosal mass, possible central umbilication
- EUS
  - Hypoechoic mass arising from muscularis propria

CT scan





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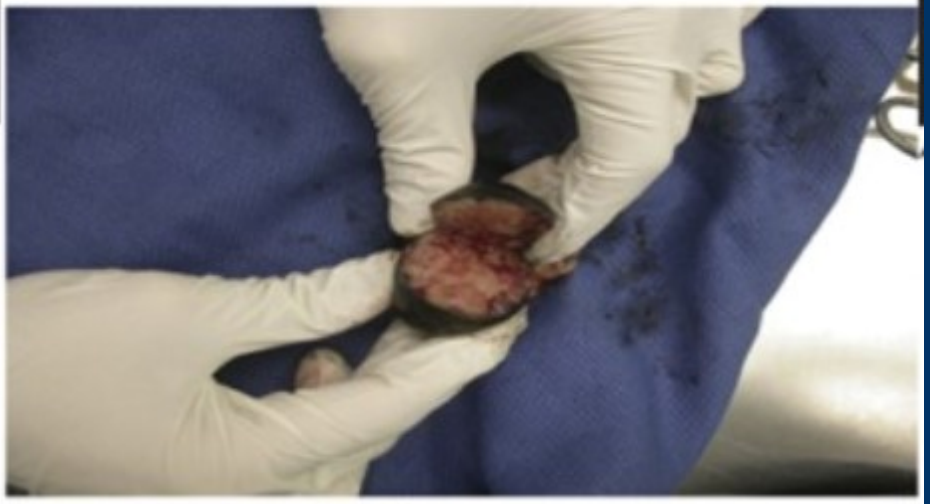

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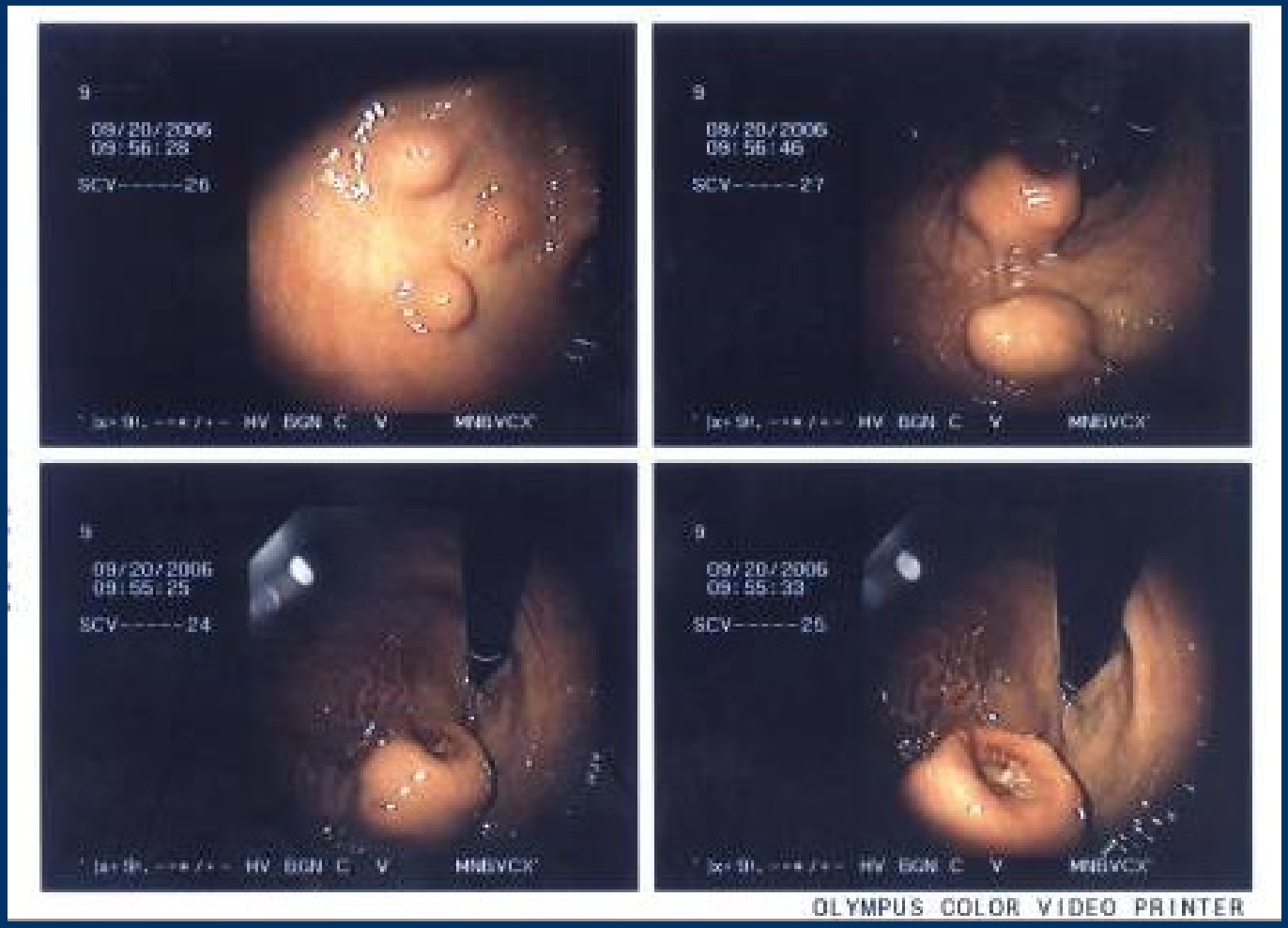
Endoscopy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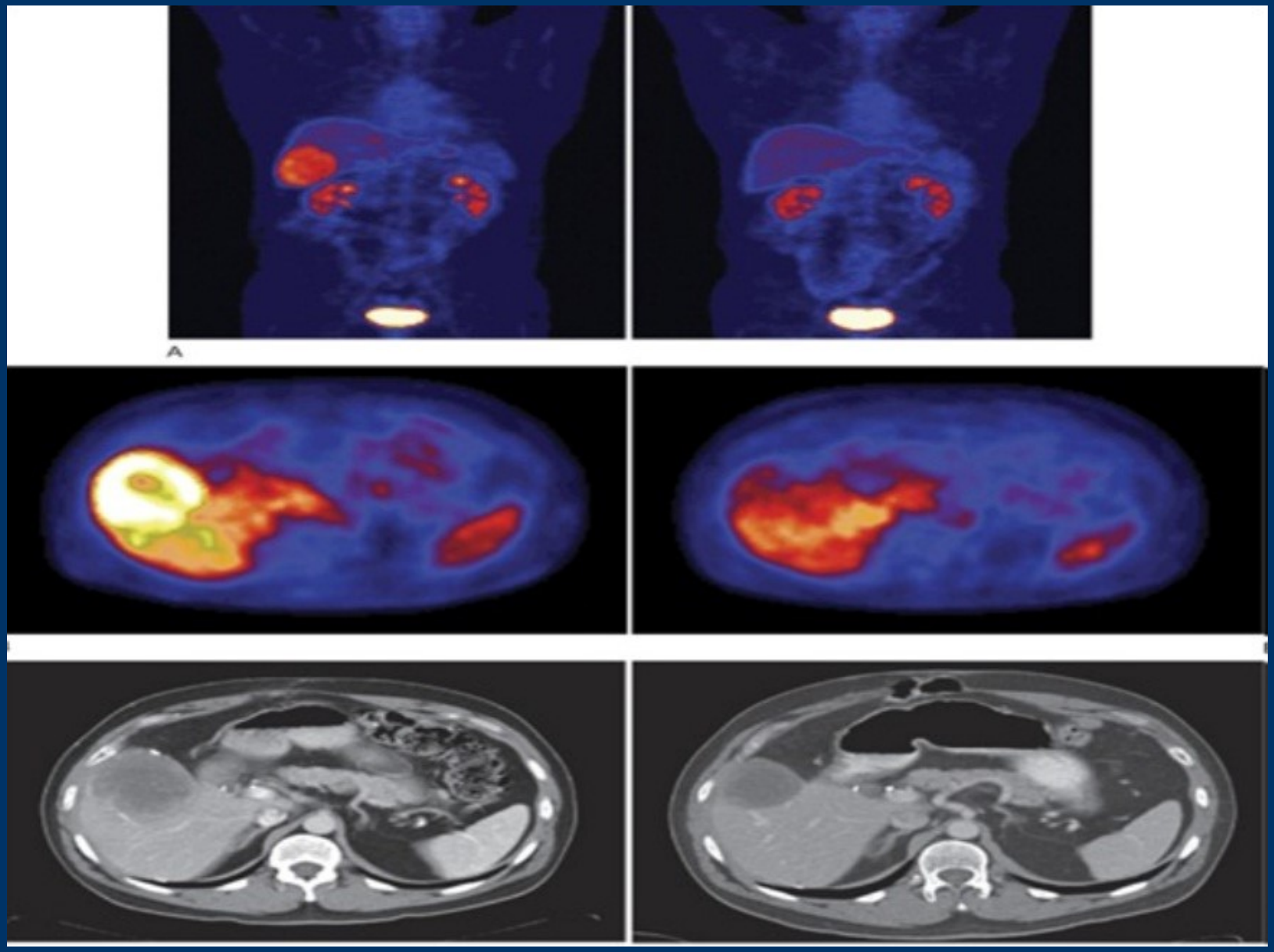

- PET scan and CT scans in a patient with a GIST metastatic to the liver, before (left) and after treatment with imatinib mesylate

Imatinib (Gleevec) a Tyrosine Kinase Inhibitor

- Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase.
- Imatinib is also an inhibitor PDGF and c-kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in (GIST) cells, which express an activating c-kit mutation

Imatinib (Gleevec) a Tyrosine Kinase Inhibitor

- Imatinib (Gleevec) is very effective for CD117 positive GISTs .
- It also has antitumor effficacy in tumors that lack KIT mutations but have alterations in the PDGFRa pathway.
- Some PDGFRa mutations are imatinib-sensitive, others not therefore, patients with advanced tumors that are histologically c/w GIST should not be denied a trial of imatinib if they are c-kit negative.

Management

PRIMARY, LOCALIZED DISEASE (EARLY-STAGE GIST)

- Surgery remains the mainstay of treatment for patients with primary localized GIST
- GIST lesions are highly vascularized and often exhibit a fragile pseudocapsule; therefore, surgeons should be careful to minimize the risk of tumor rupture.
- GIST rarely involves the locoregional lymph nodes.
- Adjuvant Therapy :At present, it is unclear whether the administration of imatinib in the postresection adjuvant setting would confer significant clinical benefits on patients.