HOSPITAL BEATRIZ ÂNGELO

When to think on GIST?

A review of CT and MRI features with pathologic correlation

ESGAR 2019

Primitivo, Ana; Oliveira, Helena; Loureiro, Ana; Branco, José Castelo; Cruz, Rita.

Learning Objectives

- Review the key radiologic features of gastrointestinal tumor in CT and MR imaging, with pathological correlation.
- Discuss some of the most common complication associated with these tumors and main differential diagnosis.
- To serve as a learning tool for radiology trainees.

Background

- Gastrointestinal stromal tumor (GIST) are the most common nonepithelial tumor of the gastrointestinal tract, and account for 90% of mesenteric tumors. The esophagus is the only exception where leiomyomas are more frequent than GIST.

- 1% of all GI tract neoplasms

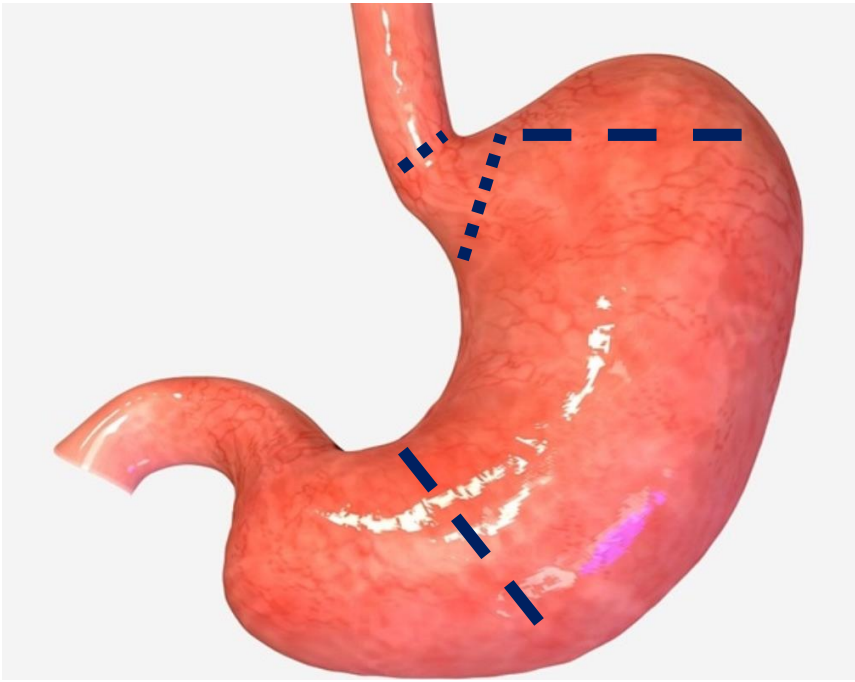
- **Median age:** 60-65 years

Background

- Most (70-80%) GISTs are nonmalignant.

Locations:

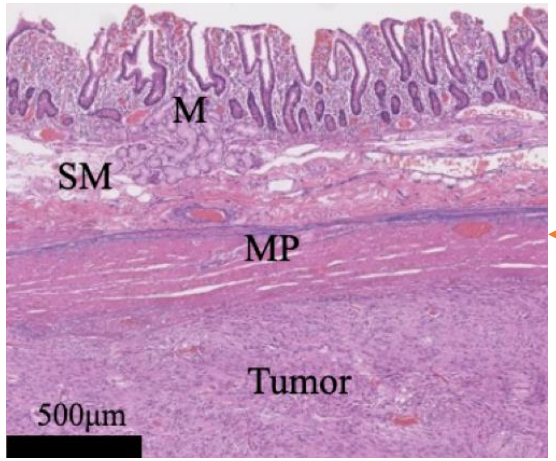
- **Stomach (60-70%)**
- Jejunum and ileum (30%)
- Duodenum (5%)
- Rectum (4%)
- Esophagus (1%)
- Extravisceral locations (mesentery, omentum, or retroperitoneum)



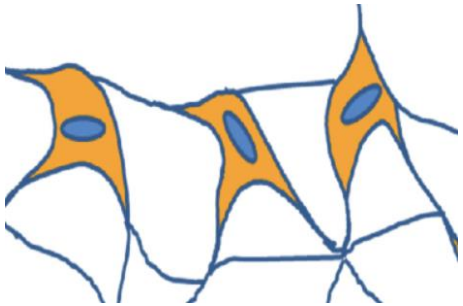
Within the stomach, the BODY is a more common location than the antrum.

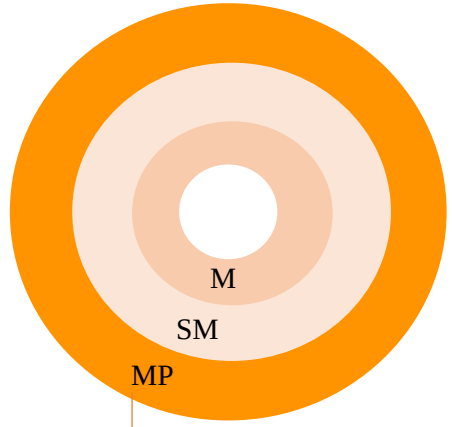
The rate of malignancy correlates with the location. Lesions in the CARDIA or FUNDUS → more likely to be malignant

Background



M – Mucosa
SM – Submucosa
MP – Muscular Propria

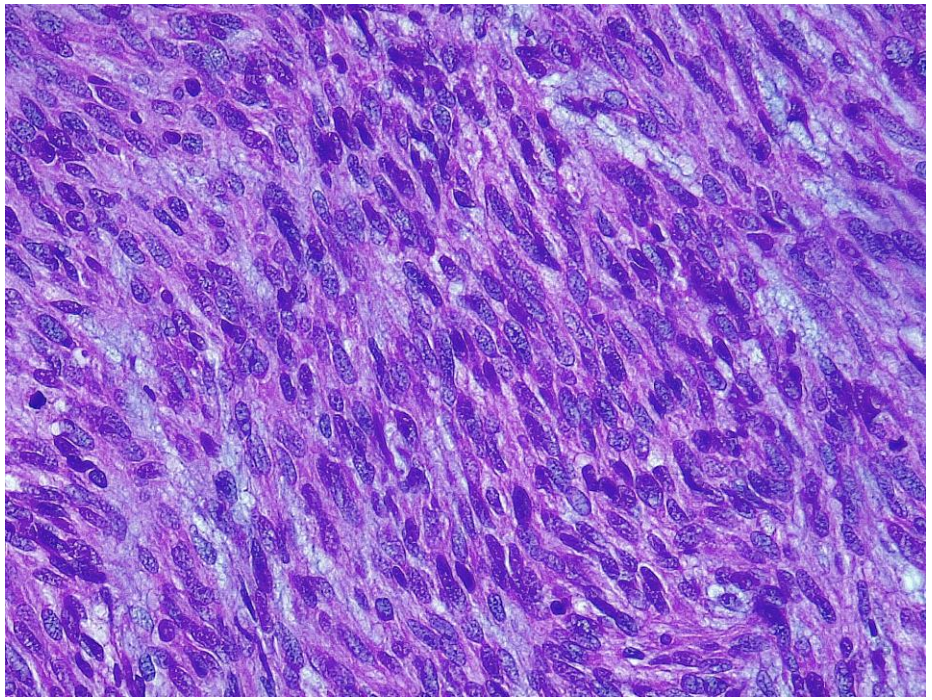




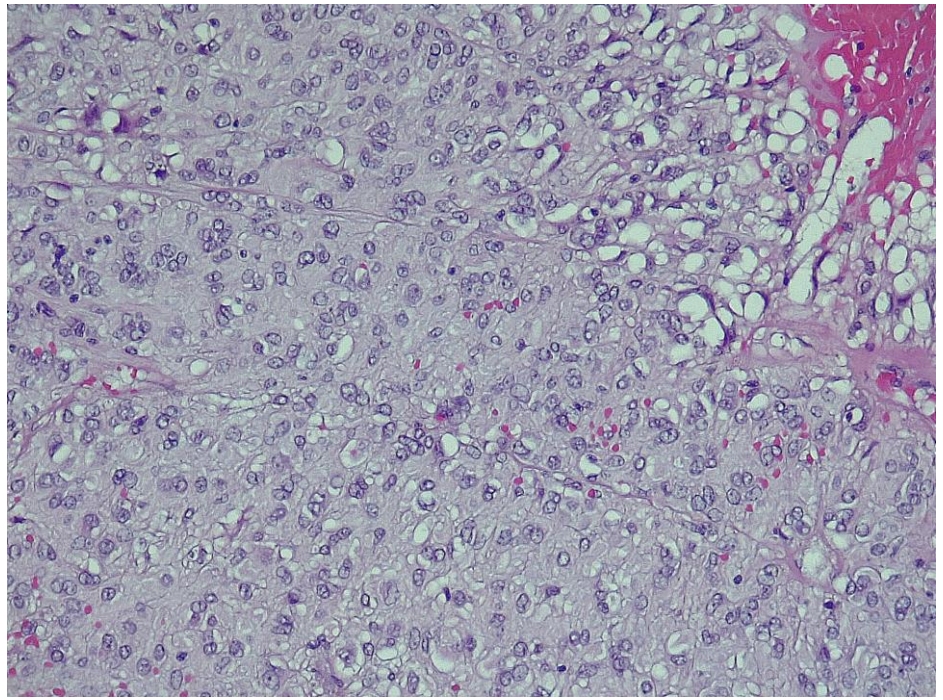
GISTs most commonly arise from **intestitial cells of Cajal (ICC) or related stem cell-like precursors**. Interstitial cells of Cajal are the pacemaker cell in the Auerbach's plexus of the gastrointestinal tract. They present as submucosal tumors arising from the **muscularis propria**, because Auerbach's plexus is located between the inner circular muscular layer and outer longitudinal muscle layer.

- **GISTs** are classified into **3 main** histological subtypes:
  - **Spindle cell type** (70%) - Fascicles of uniform spindle cells, arranged in short fascicles and whorls.
  - **Epitheliod type** (20%) - Round to oval nuclei, arranged in nests or sheets, with variably eosinophilic to clear cytoplasm and vesicular nuclei.
  - **Mixed type GISTs** (10%) - Both spindle cell and epithelioid componente are present.

  - ***Desdifferentiated GISTs*** - Rare exemples of GISTs which show abrupt transformation from conventional KIT-positive tumor cells to KIT-negative cells with marked anaplasia.



Spindle cell type (70%)
Fascicles of uniform spindle cells with eosinophilic cytoplasm



Epithelioid type (20%)
Round to oval nuclei and eosinophilic cytoplasm

Pathologic and Immunohistochemical features (ICH)

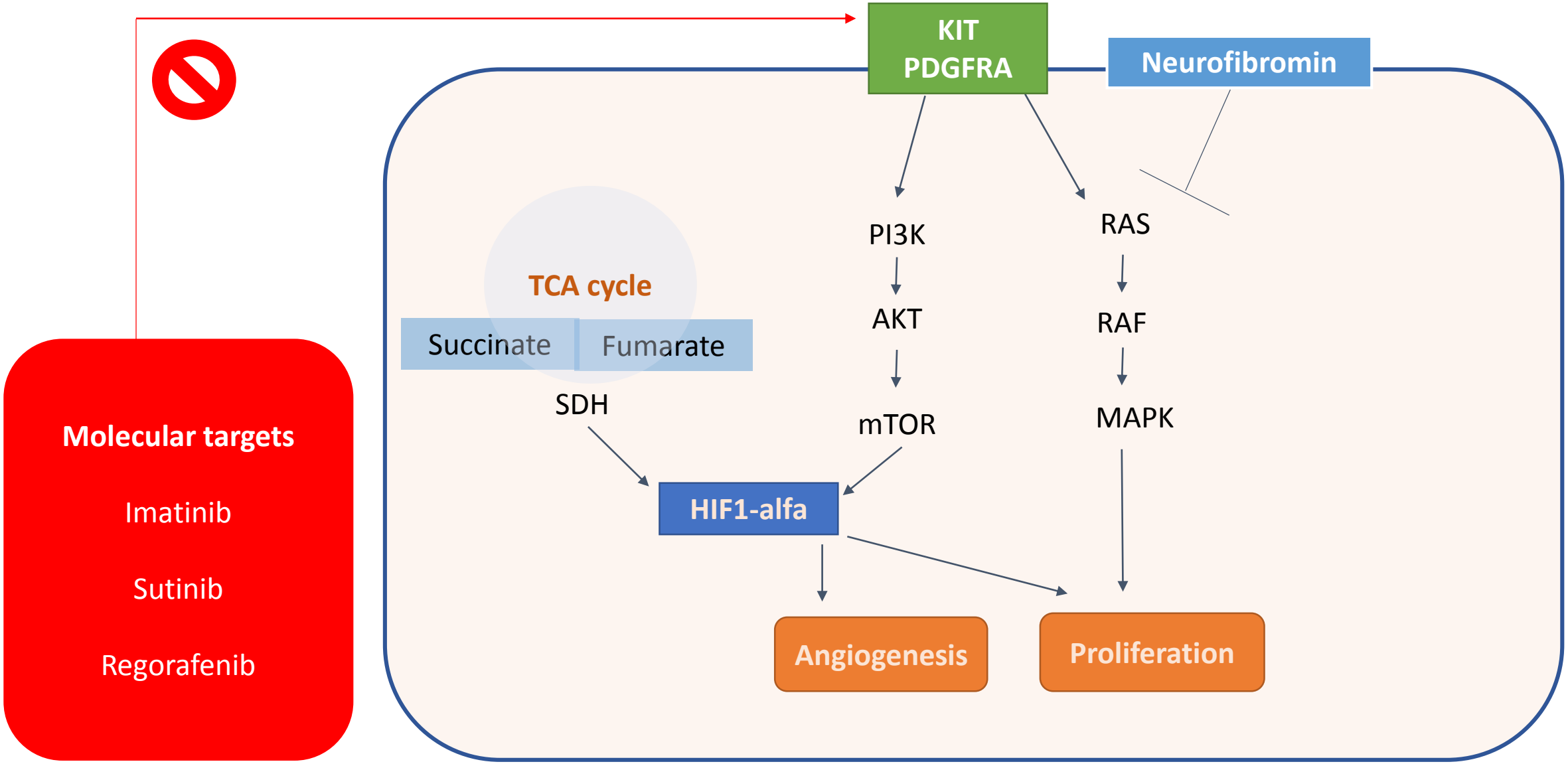
- **85-90%** of cases - activating mutations **in C-KIT (CD-117)** or platelet-derived growth factor receptor alpha **(PDGFRA)**
  - Constitutive activation of the thyrosine kinase activity of these receptors, and consequently activation of downstream signaling pathways
  - Interstitial cells of Cajal can normally express CD 117, indicating c-kit (tyrosine kinase) receptors.

- **10-15%** of GISTS there are **NO mutations** in either KIT or PDGFRA, are classified as “wild type”, and **resistant to imatinib therapy.**

The “GIST Syndromes”

- **Succinate dehydrogenase mutation syndromes**
  - **Carney triad**
    - Gastric GISTs + extra-adrenal paraganglioma + pulmonary chondromas
    - Young women
  - **Carney-Stratakis syndrome**
    - GIST and paraganglioma
    - Very rare
- **Neurofibromatosis type 1**
  - Often multicentric GIST, predominatly located in the small bowel.

Brief molecular biology of GIST



- In most GISTs **c-KIT (CD117)** and **CD34** are **positive** by immunohistochemical staining (IHC).
  - ***c-KIT*** – growth factor receptor tyrsoine kinase that is normally expressed on hematopoietic stem cells, mast cells, melanocytes, and the myenteric plexus of gastrointestinal tract.
- Most KIT-negative GISTs are epithelioid cell morphology in the stomach.

- **DOG1** is an excelente IHC marker, because it is constantly positive in GISTs, regardless of the c-KIT and CD 34 expression.

- **Desmin** and **S-100** are negative in GISTs, and help to differentiate from other mesenchymal tumors such as leiomyoma and schwannoma (traditionally regarded as GIST in the past).

IHC	GIST	Leiomyoma	Schwannomas
KIT	+	-	-
CD34	+	-	-
DOG1	+	-	-
Desmin	-	+	-
S-100	-	-	+

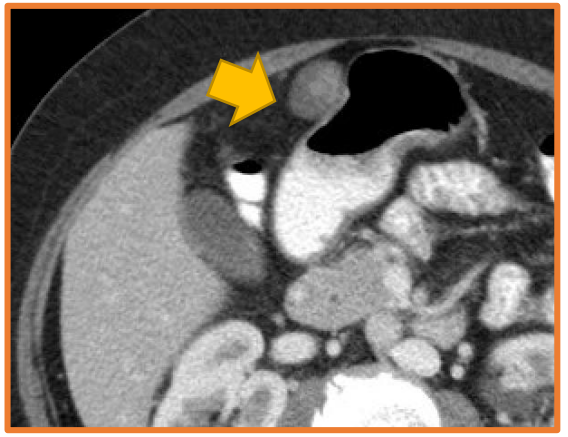
Clinical features

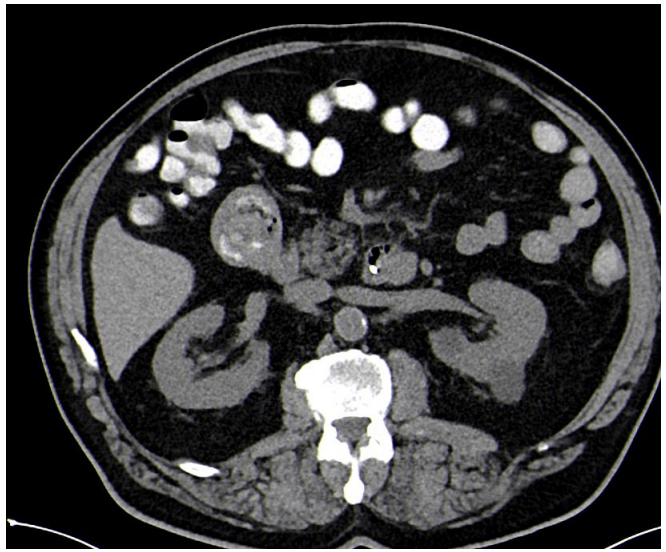
- Dependent on **size** and **location** of tumor.

- *Asymptomatic: Small GISTs*
- *Dysphagia: Esophageal GIST*
- ***Complications:***
  - *Gastrointestinal bleeding* — Large tumors can develop ulceration resulting in **rupture and hemorrhage**
  - Bowel obstruction is rare
  - *Perforation*

Imaging features

Often well defined, exophytic, rounded soft tissues, arising from the wall of a hollow viscus (yellow arrow).



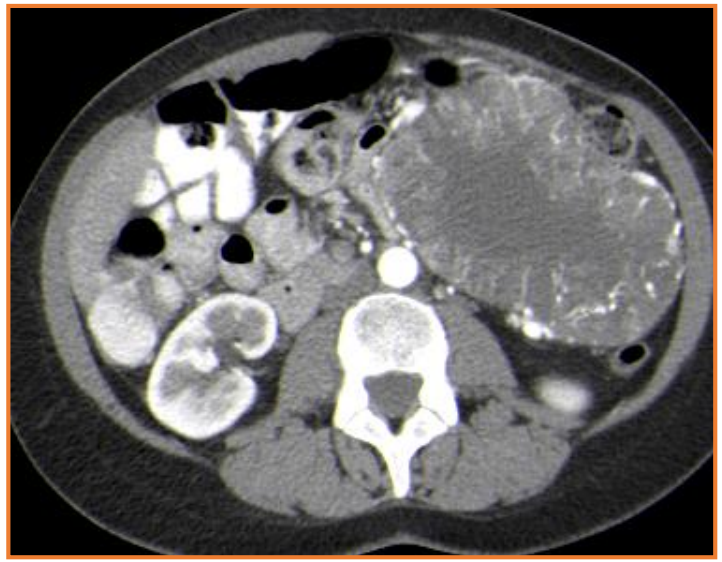


Duodenal GIST

An intraluminal growing mass, with irregular margins. CT number attenuation is around 80 HU (portal venous phase).

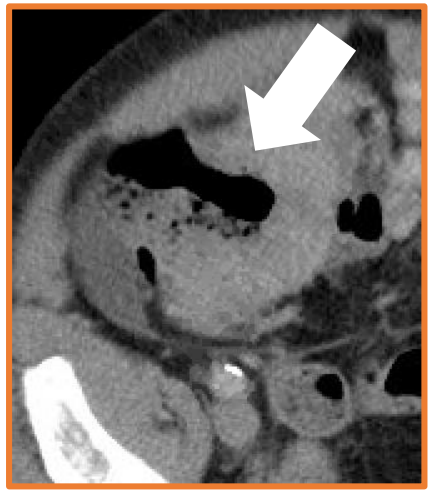
The mean CT attenuation is usually higher in GISTs and neuroendocrine tumors than in adenocarcinomas, lymphomas and metastasis.

Imaging features



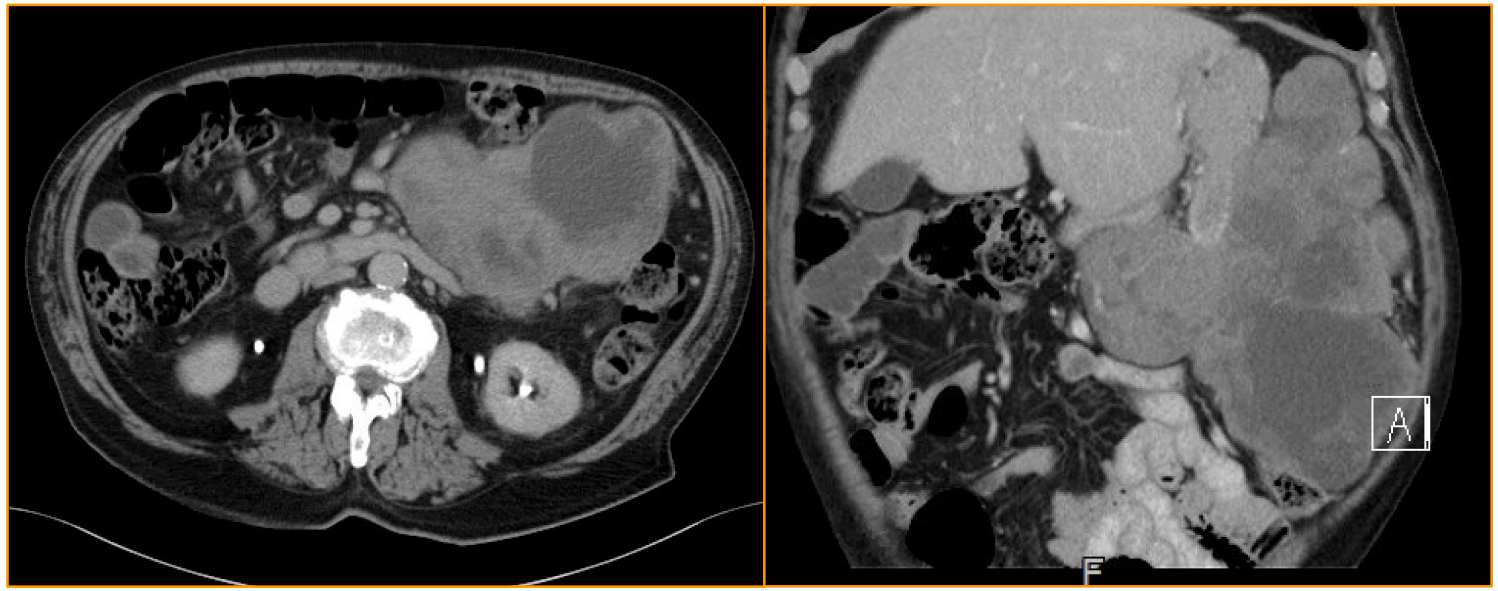
Enhancement is typical peripheral (due to central necrosis).

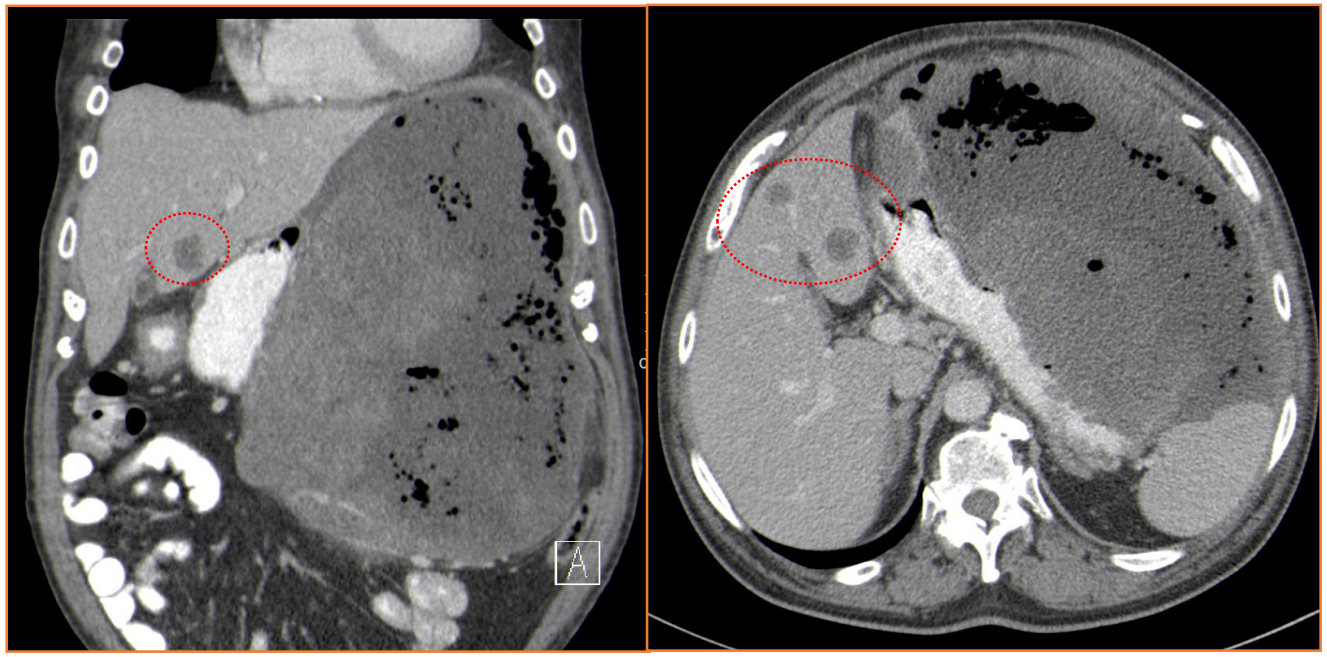
A deep crescent-shaped ulceration demonstrating an internal air-fluid level may also been seen, suggesting an ulcerating neoplasm — *Torricelli-Bernoulli sign (white arrow).*



Imaging features

Mucosal ulceration is present in **50%** of cases with large cavities, resulting from extensive hemorrhage or necrosis comunicating with the lumen.



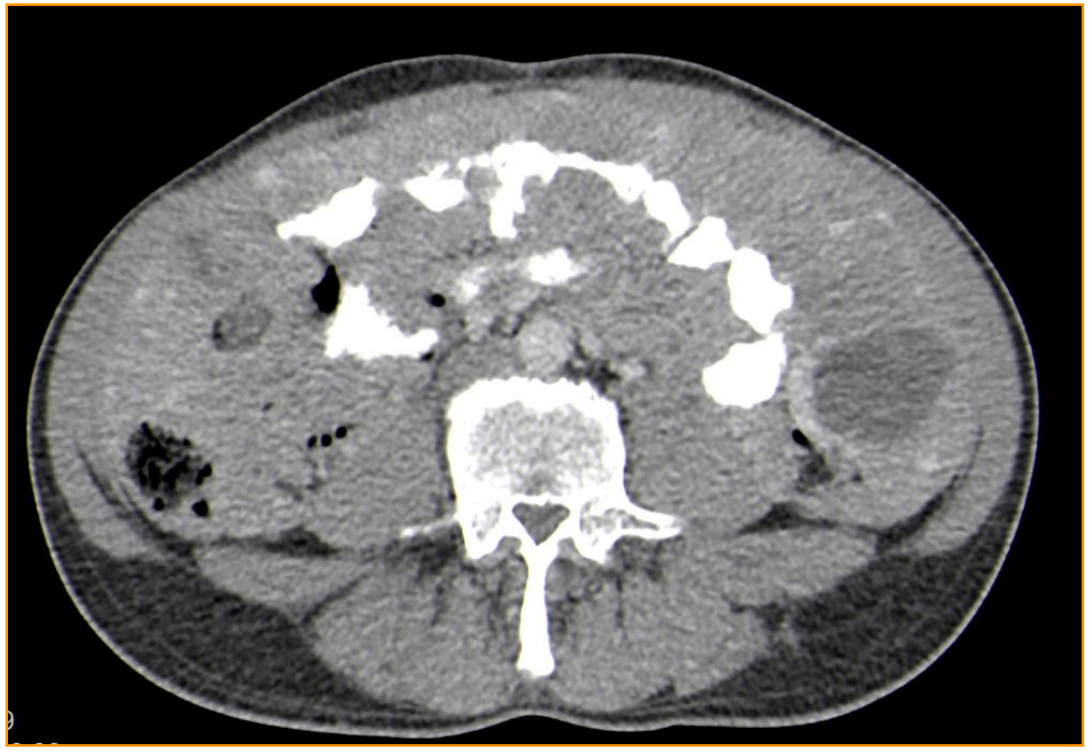


GISTs range in size from several milimeters to greater than 30 cm.

A large mass arising from the stomach wall, with large areas of cavitation and necrosis, compressing adjacent tissue.

Also note the liver metastasis found at the initial presentation in this patient (red circle).

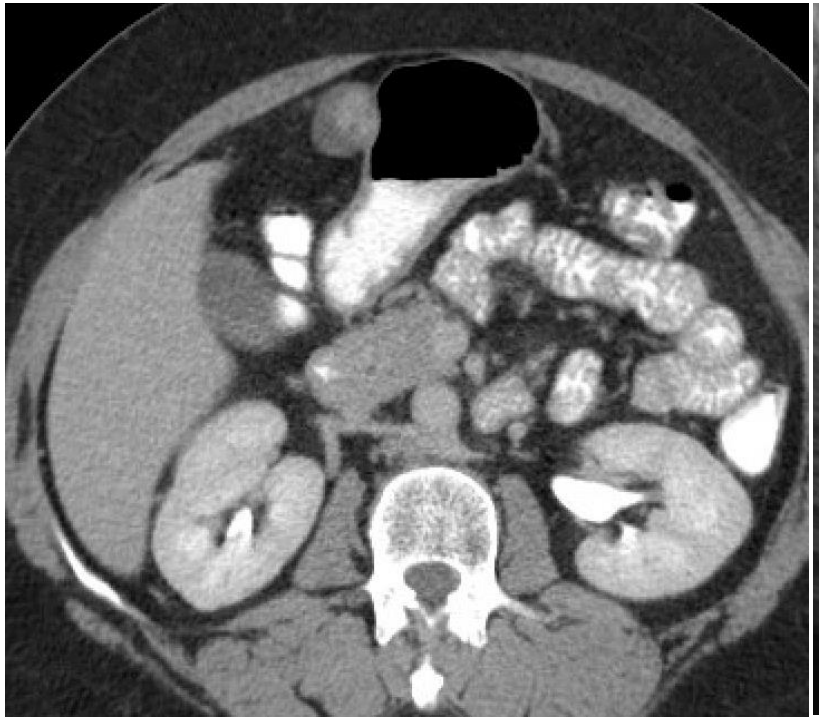
Imaging features

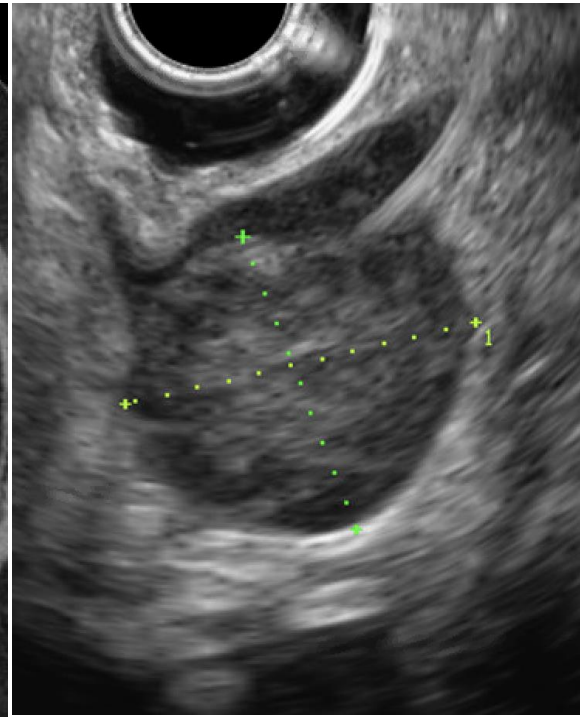


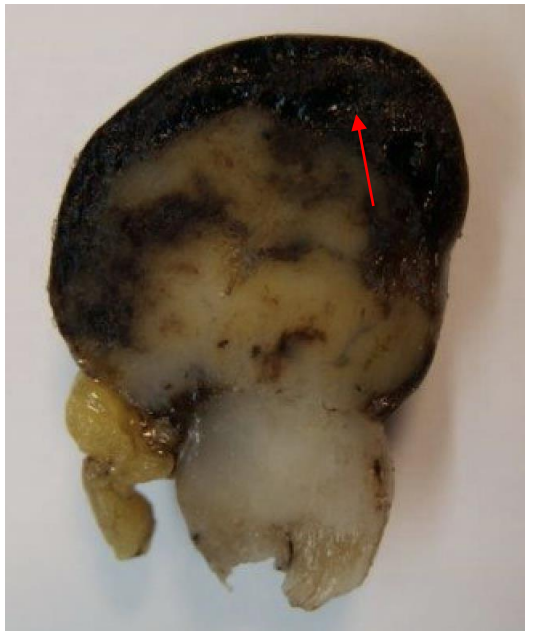
GIST can also appear on extravisceral location as in this very rare form, in the peritoneum.

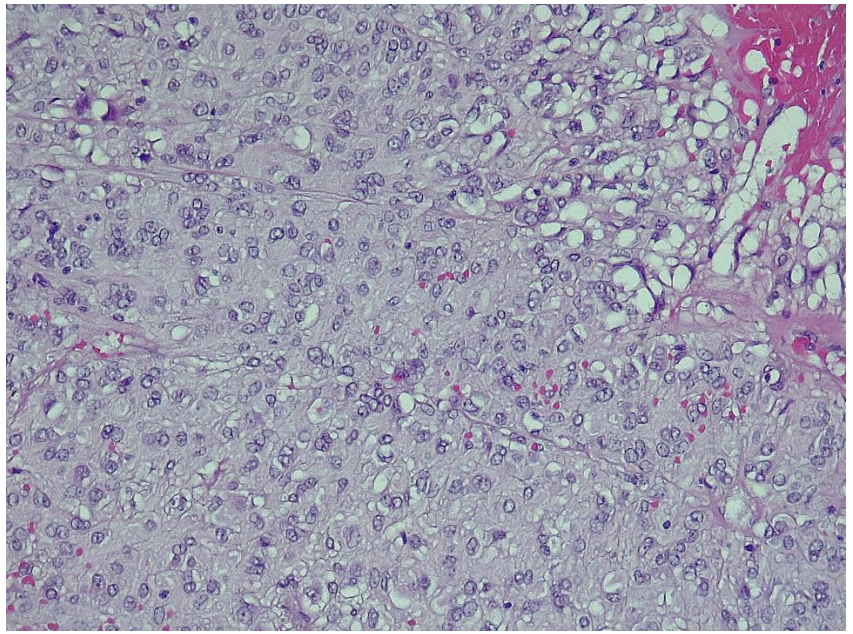
A 57 year old woman with abdominal pain

- **Abdominal CT:** mural based mass covered by enhancing layer (mucosa)
- **Endoscopic ultrasonography (EUS):** a 25 mm hypoechogenic mass, well-defined, arising from the 4th low-echoic layer representing the muscularis propria, suggesting a submucosal tumor. It also had low echogenic areas (not shown) suggesting necrosis/hemorrhage
- **Gross specimen:** Yellow tumor in the gastric wall, exophytic and heterogeneous, with hemorrhagic areas at periphery (arrow)
- **Microscopic (H&E):** epitheliod pattern; 0 mitosis/5mm^2

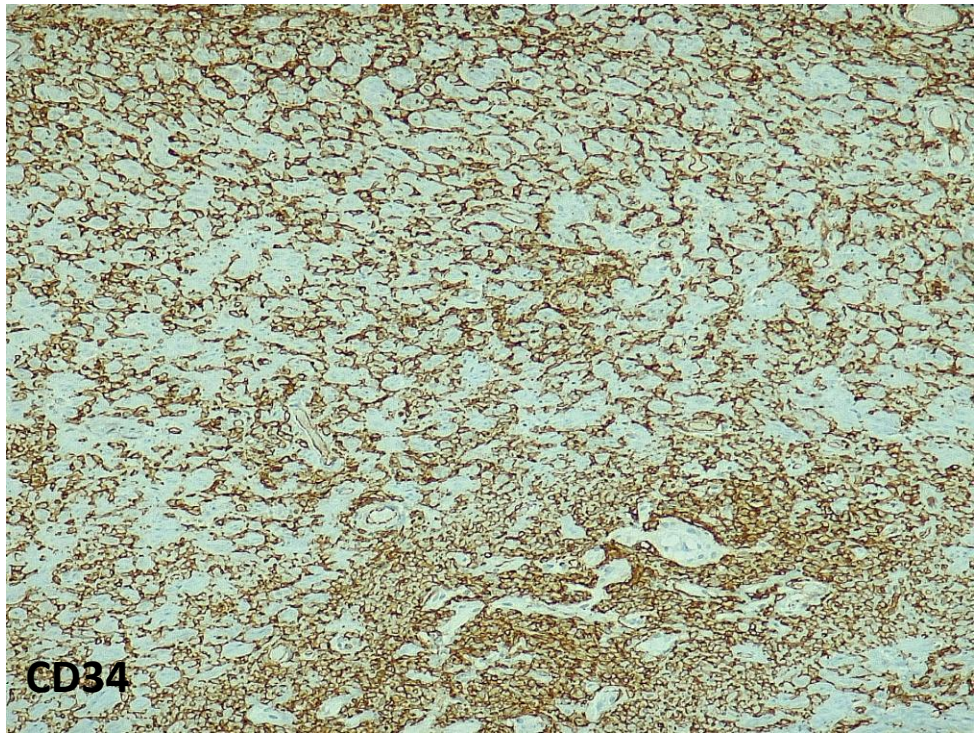


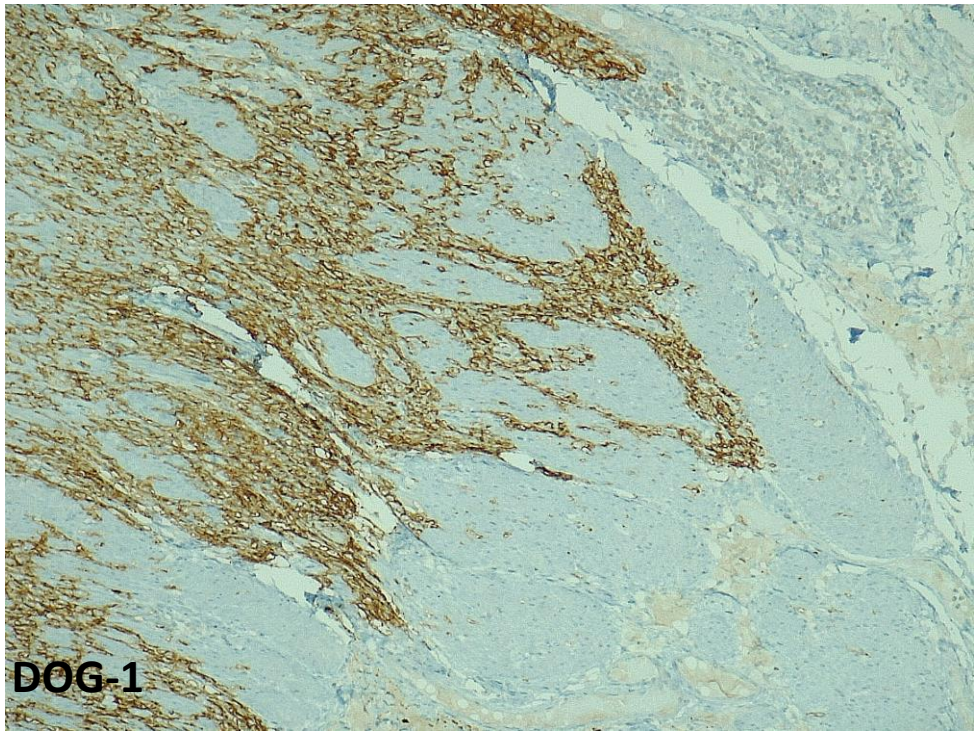






- **ICH:**
  - <u>CD34 and DOG1 – Strongly positive</u>
  - CD 117 and desmin – Weakly positive
  - S100 and actin - Negative





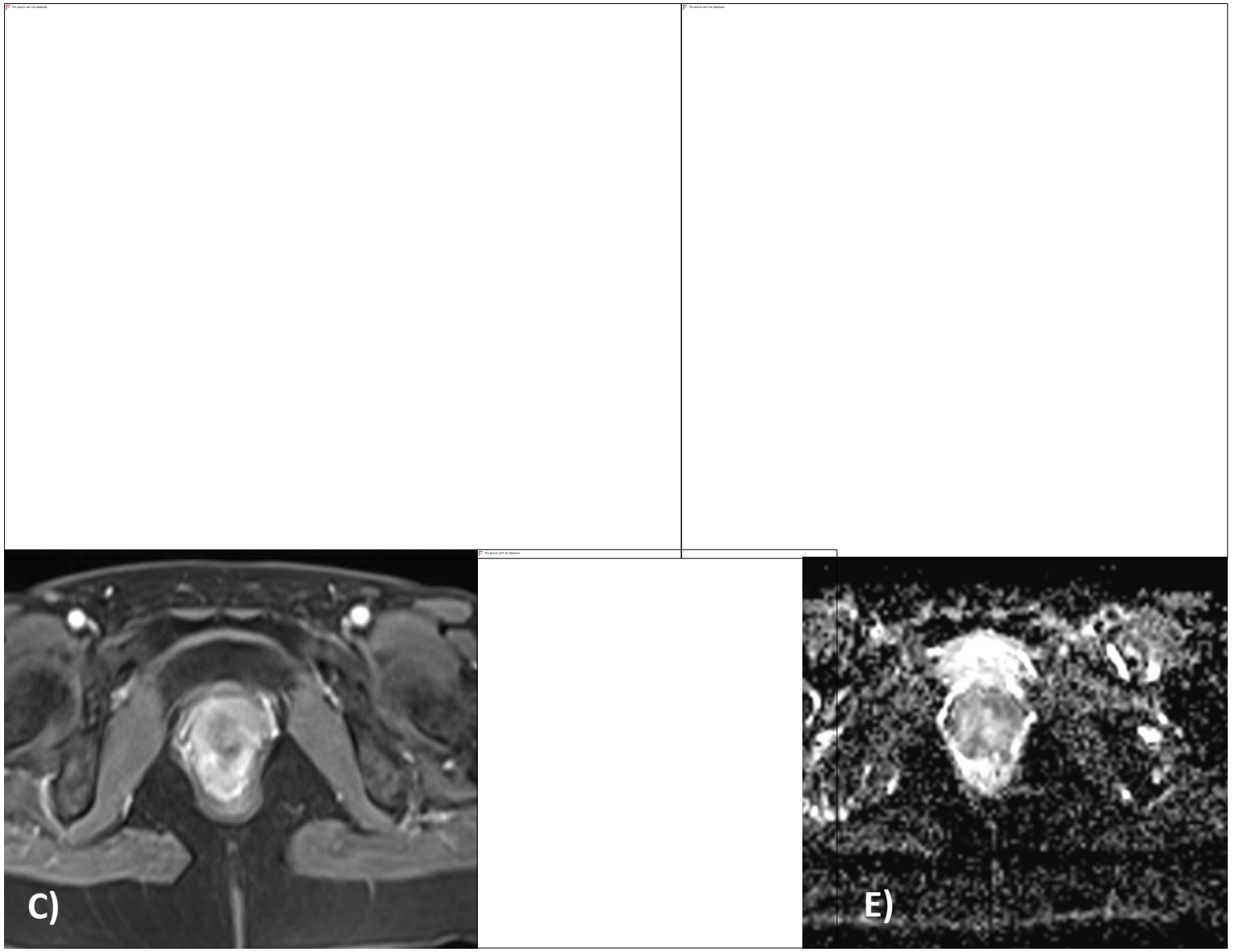
GASTRIC GIST

RECTAL GIST

- A rectal lesion with 3 cm, showing intermediate signal intensity on T2 WI (axial and sagital views – **A)** and **B),** and avid contrast enhancement after gadolinium – **C).** Also presenting restricted diffusion – **D)** and **E).**

At histology the diagnosis was **rectal GIST**, and the patient underwent **neoadjuvant treatment with Imatinib.** After that, **transvaginal resection** was performed.

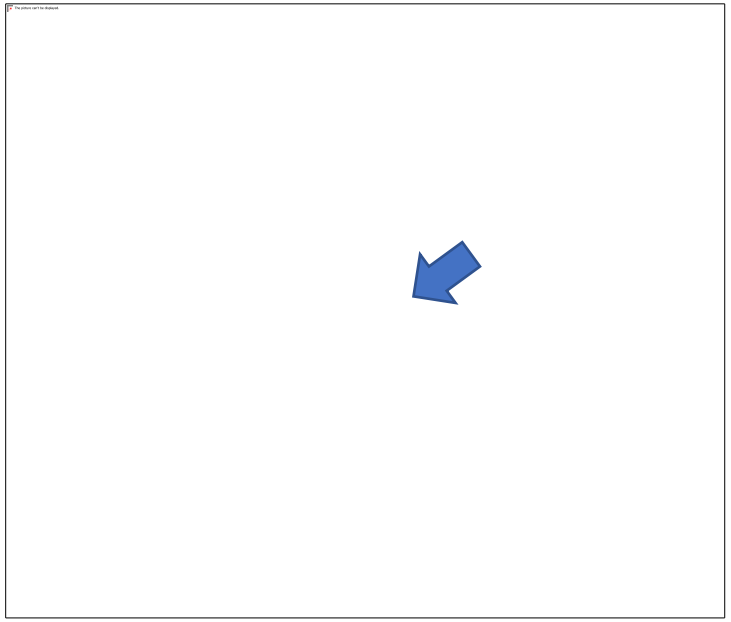
After 2 years, a small nodule was detected on rectal examination, and transanal surgery was performed.

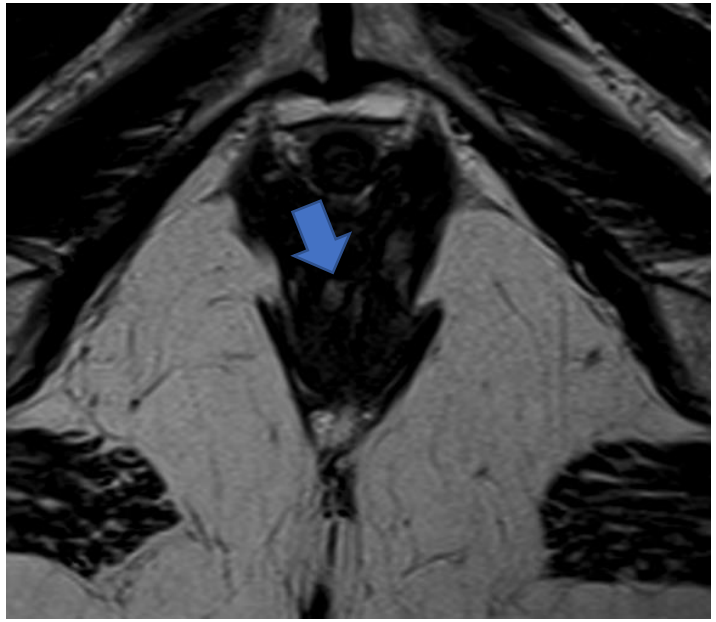


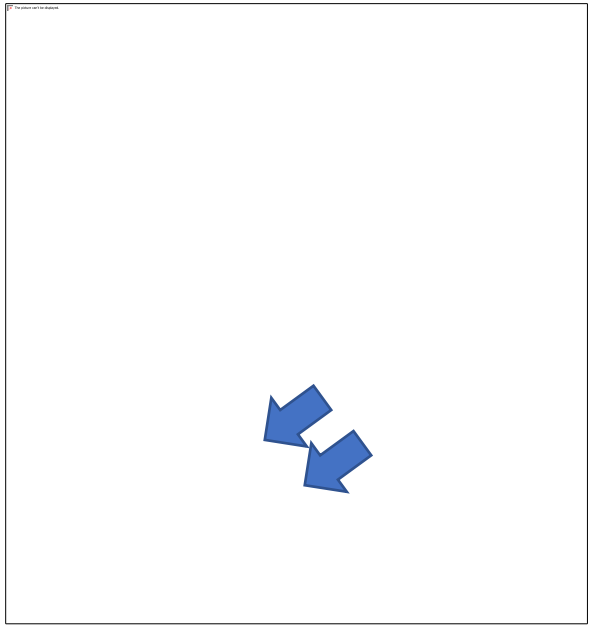
RECTAL GIST

- New lesions appear on MRI after 3 years of follow up (blue arrows).
  - Abdomino-perineal resection was than performed.

- **At histology**: well defined submucosal nodules suggesting **relapse**, with high grade histology (56 mitosis per 5 mm^2).



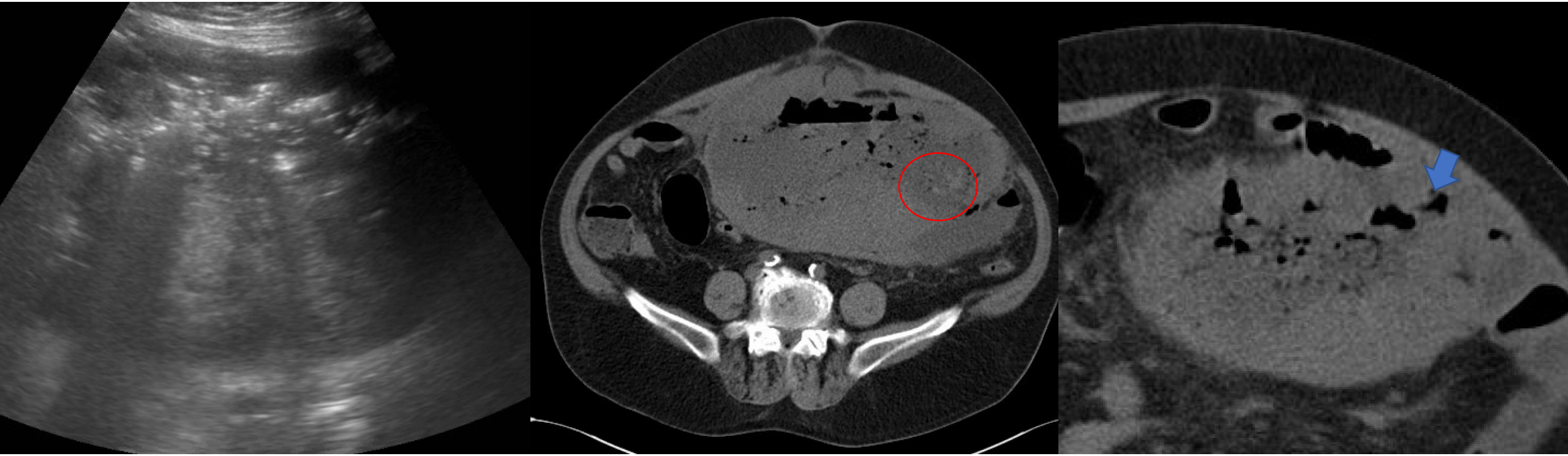




Complicated GIST

A 59 year old man presented at the emergency department with weight loss and melenas 10 days long.

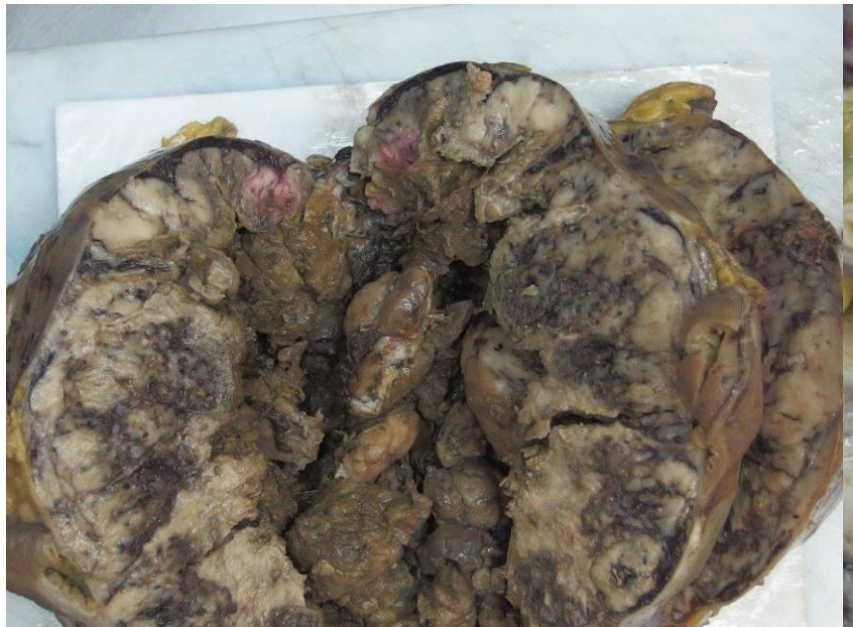
- **Ultrassonography:** large hypoechoic mass with echogenic foci.
- **Abdominal CT:** large mass, with liquid-air levels, and central areas of necrosis. It involves several bowel loops, presumably with areas of mucosal ulceration associated (blue arrow). Also note the hyperdense areas at unhenchanced CT, in relation to hemorrhagic content (red circle).

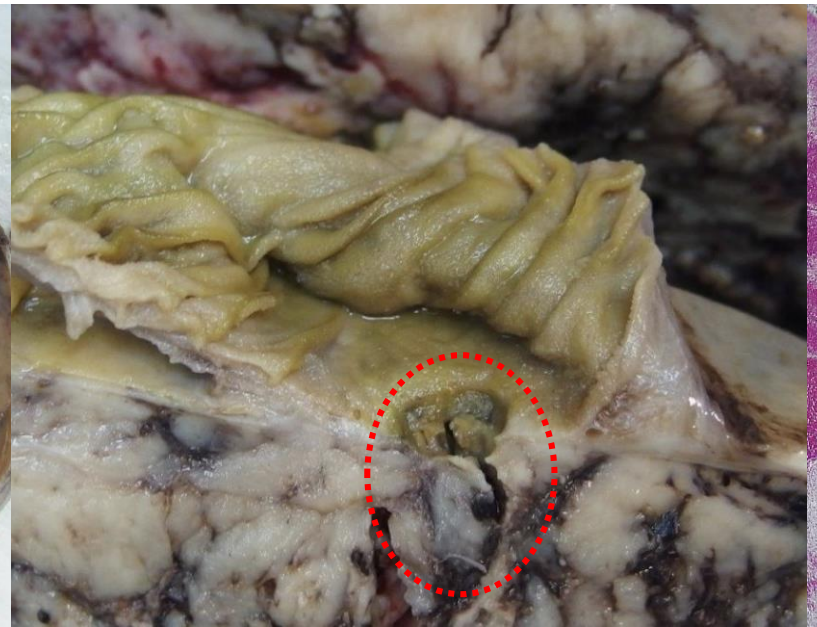


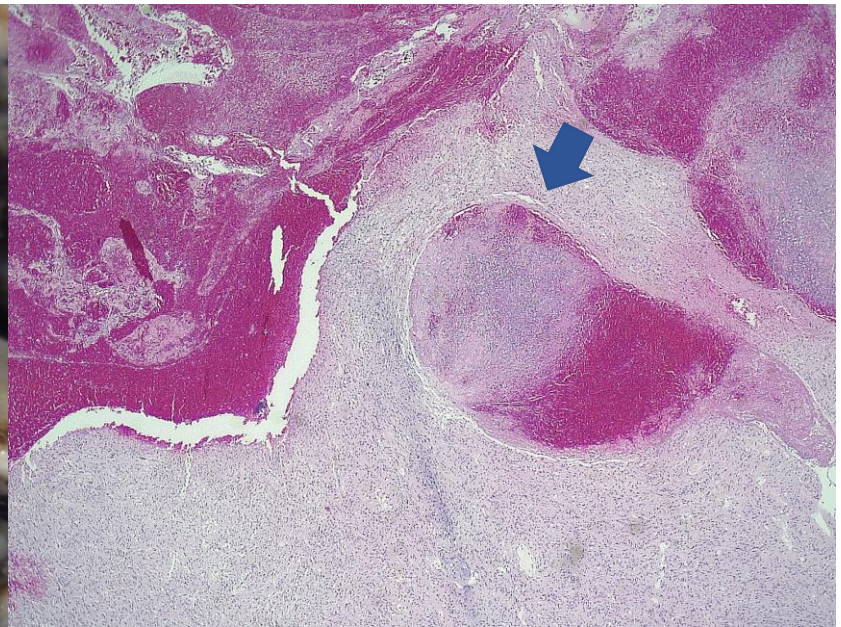
Complicated GIST

- **Gross specimen:** A volumous lesion with central extensive necrosis and areas of hemorrhage. Also note the ulceration between the small bowel and the lesion beneath (red circle)
- **Microscopic (H&E):** Tumor infiltration with area of hemorrhage (blue arrow), affecting several segments of bowel.
- **ICH:** strongly positive for CD117. Negative for: actin, S100 protein and CD34.

- **Final diagnosis: GIST complicated with gastrointestinal bleeding** *(from the small bowel/mesentery. At histology it was not possible to confirm the location of the primary tumor, since both areas had tumor).*



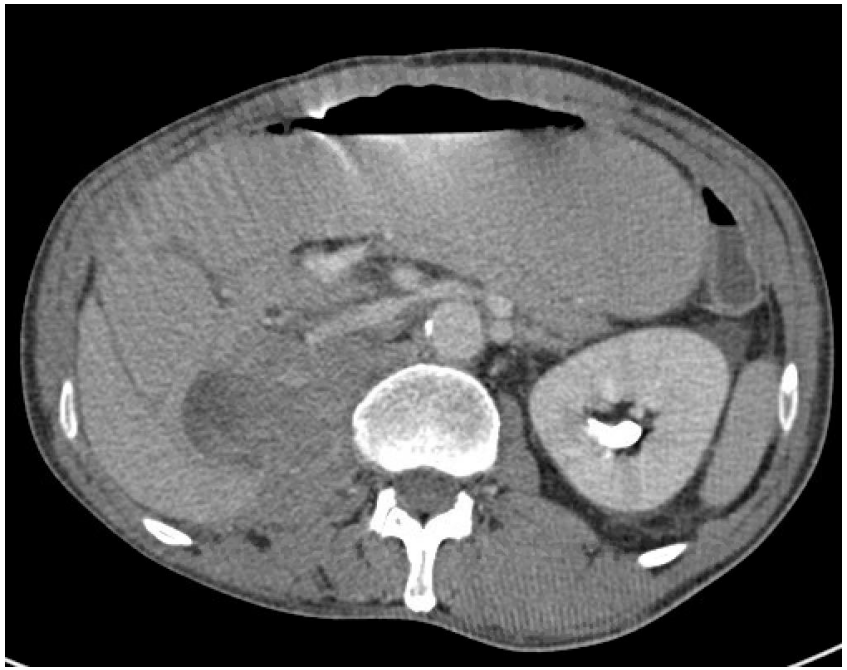


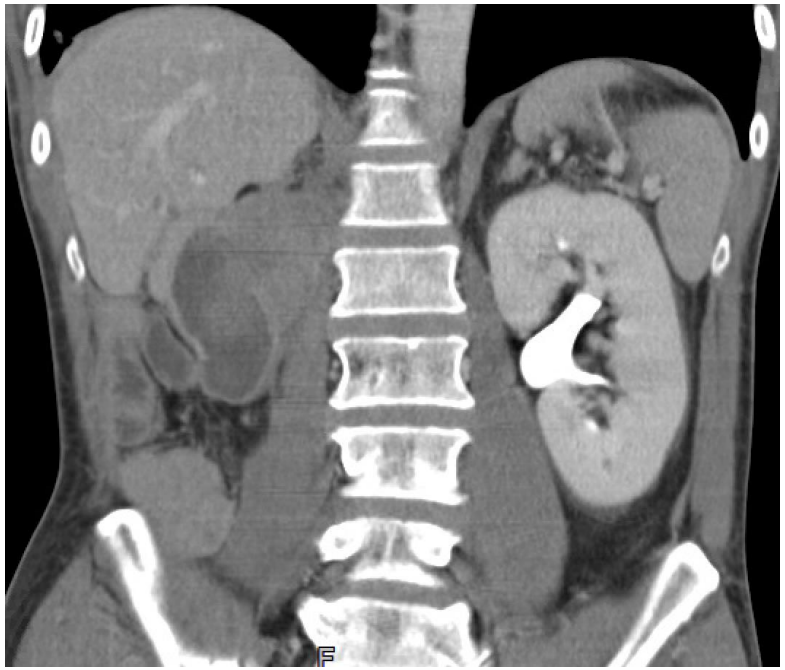


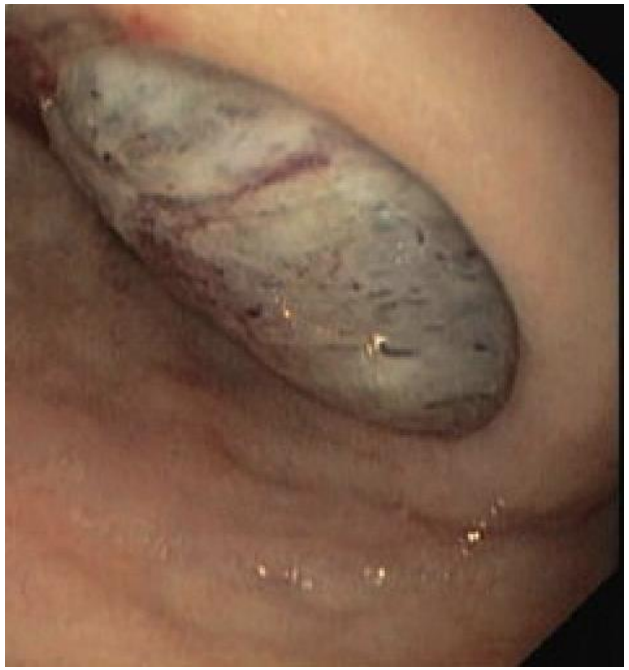
Complicated GIST

A 62 year old man presenting at emergency department with abdominal pain and vomiting.

- **Abdominal CT:** an intraduodenal mass, with heterogeneous enhancement, leading to stomach distention and obstruction.
- **Endoscopy:** demonstrated a vegetating lesion in D2-D3. Biopsy was made .
- **Final diagnosis: duodenal GIST complicated with gastrointestinal obstruction.**



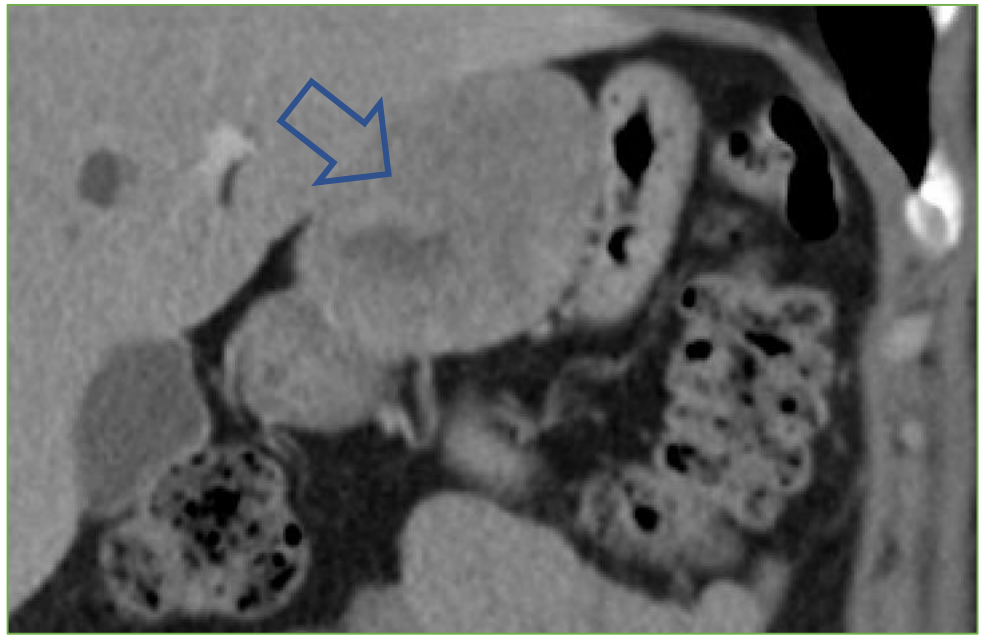




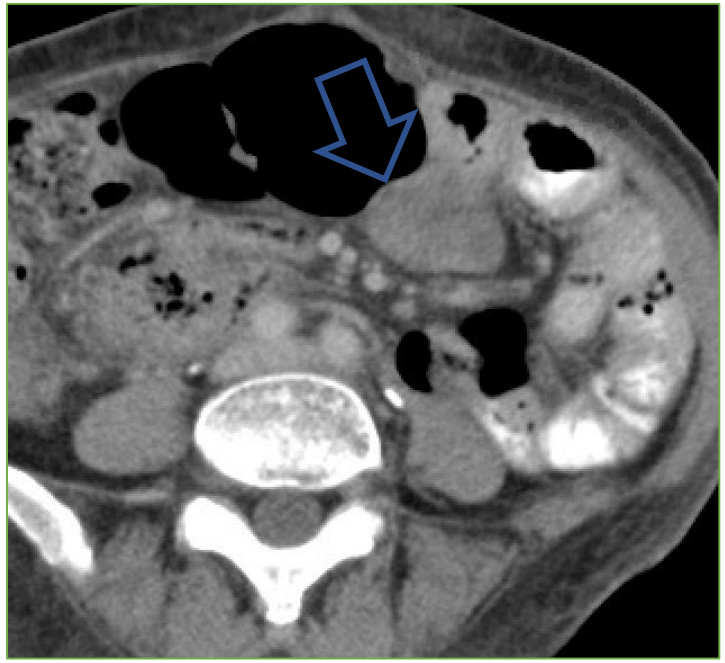
GIST differential diagnosis

- Other gastrointestinal mesenchymal tumors
  - Leiomyoma
  - Leiomyosarcoma
  - Schwannoma
- Gastrointestinal lymphoma
- Gastrointestinal carcinoid

GIST differential diagnosis



Duodenal leyomioma
A heterogeneous solid gastric mass with central hypodensity and well-defined.
At ICH the lesion was desmin and actine positive.
It was negative for DOG1, CD117 and S100, with atypical mitosis.



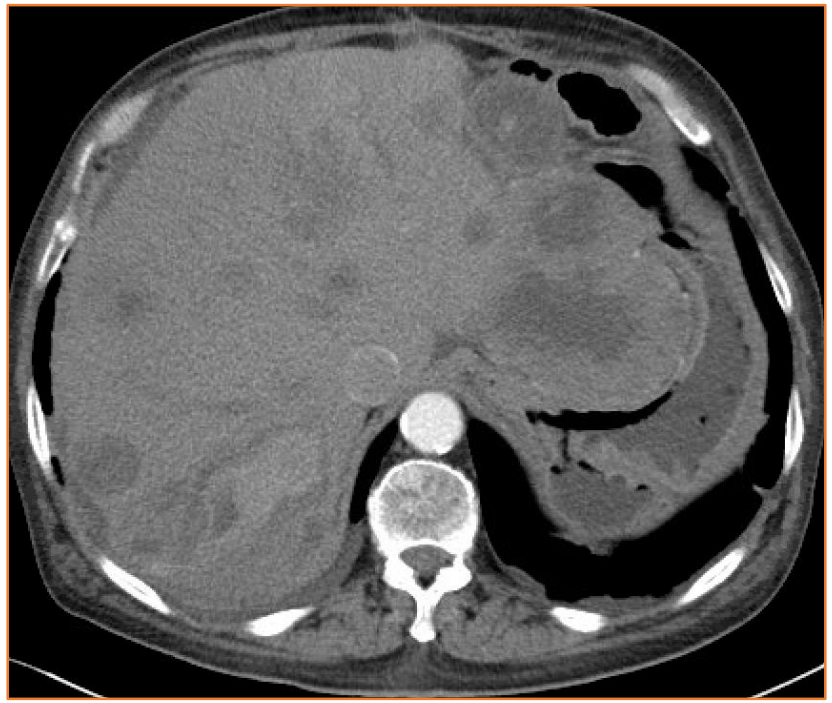
Duodenal leyomiosarcoma
Solid mass in the duodenum.
ICH was also positive for desmin and actine and negative for DOG1, CD117 and S100, with fusiform cells showing nuclear pleomorphism.

Metastasis

- **50%** os patients with GISTs present with metastases and the most common sites are:
  - Liver
  - Peritoneum

- The liver is the most common site of metastasis (65-72%)
  - The imaging characteristics of liver metastases are similar to the primary tumor
  - Most metastases present **hypervascular** with a low density center, but few hepatic metastases show hypovascularity

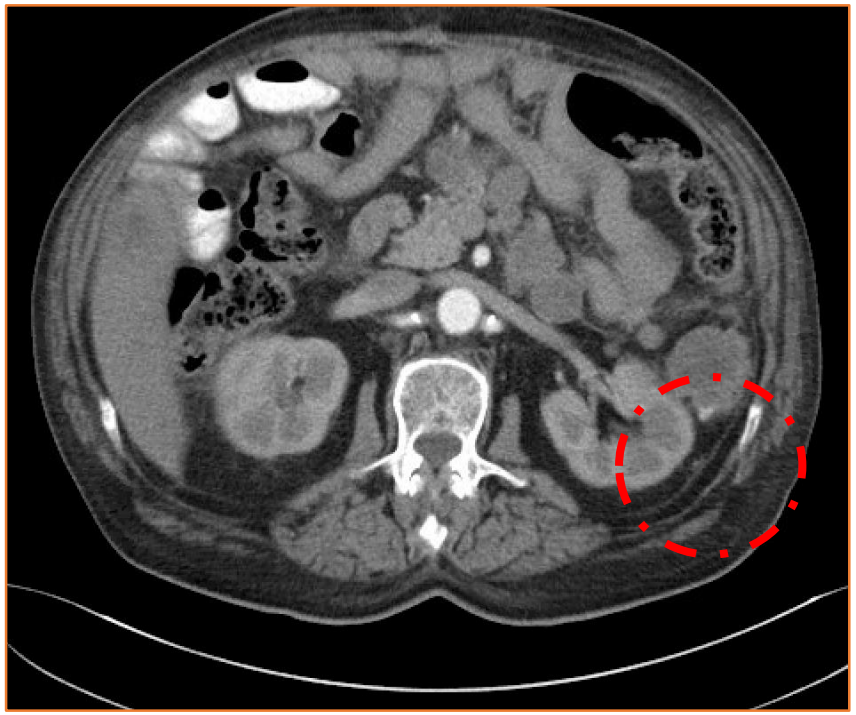
- Very rarely, GISTs metastasize to the lungs — associated with rectal location or very advanced disease



Peritoneal Disease

- The peritoneum is the second most common site of metastasis spread
  - 21-64%
- **Diffuse peritoneal disease** is categorized into
  - Peritoneal carcinomatosis
  - Sarcomatosis
  - Lymphomatosis

- Peritoneal lesions of GISTs are included in **peritoneal sarcomatosis** which presents multiple bulky heterogeneous masses and little ascites **without lymphadenopaty** → *lymphadenectomy is unnecessary except in rare circumstances when an enlarged or otherwise suspicious lymph node is encountered*



Risk stratification

- Given the complex biological behavior of GISTs, the predication of malignant potential at presentation is challenging

- The **histologic grade** is not well suited to GISTs, because most of these tumors have low mitotic rates below thresholds used for grading soft tissue tumors, even GISTs with aggressive features
  - G1 — Low grade, mitotic rate ≤5/5 mm^2
  - G2 — High grade; mitotic rate >5/5 mm^2

FAVORABLE PROGNOSIS
Low mitotic rate
Low size (≤ 2cm)
Origin in the stomach

Risk stratification

TUMOR PARAMETERS		RISK OF PROGRESSION			
Mitotic rate	**Size**	**Gastric**	**Duodenum**	**Jejunum/ileum**	**Rectum**
≤5 per 5 mm²	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	> 2 and ≤ 5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	> 5 and ≤ 10 cm	Low (3.6%)	(insufficent data)	Moderate (24%)	(insufficent data)
	> 10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
> 5 per 5 mm²	≤ 2 cm	None ##	(Insufficent data)	High ##	High (54%)
	> 2 and ≤ 5	Moderate (16%)	High (50%)	High (73%)	High (52%)
	> 5 and ≤ 10 cm	High (55%)	(Insufficent data)	High (85%)	(Insufficient data)
	> 10 cm	High (86%)	High (86%)	High (90%)	High (71%)

[#] *Defined as metastasis or tumor-related death.*

[##] *Denotes small number of cases.*

Adapted from Miettinen and Lasota.

Reference:

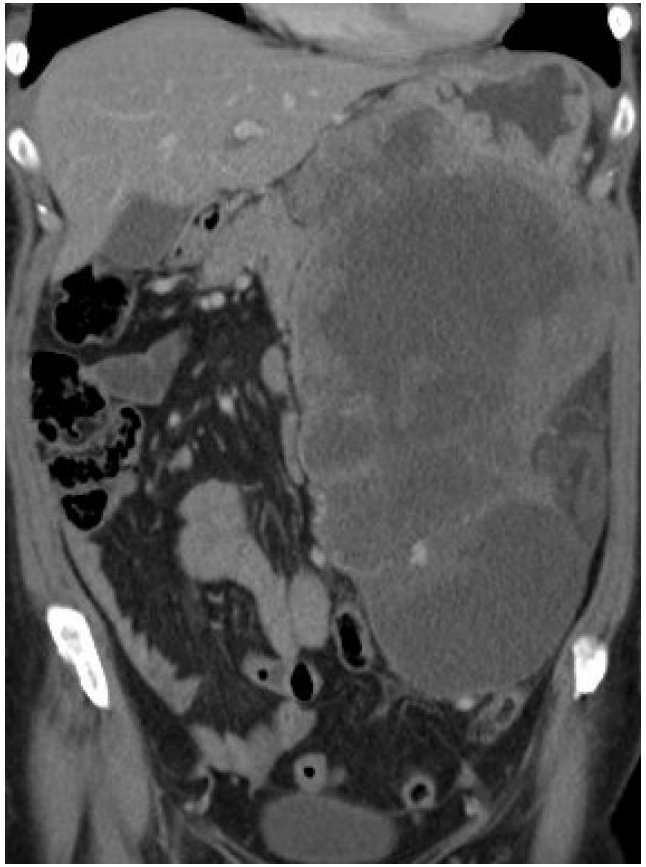
https://www.cap.org/protocols-and-guidelines/cancer-reporting-tools/cancer-protocol-templates

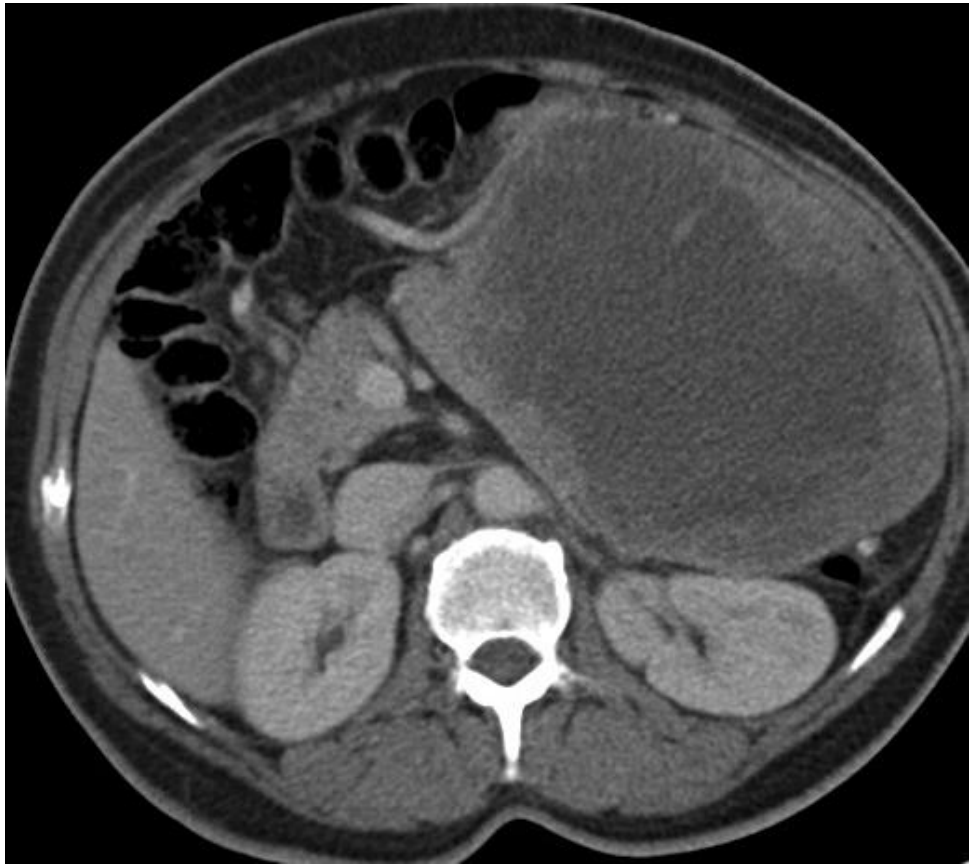
Risk stratification

Gastric GIST

> 10 cm with **low mitotic rate**

(≤5 per 5 mm²)





MODERATE RISK OF PROGRESSION (10%)

Treatment

- A greater understanding of the molecular pathogenesis of GISTs led to the use of tyrosine kinases inhibitors (TKI) for treatment of GISTs
  - *Significantly improves outcomes in patients with advanced GIST compared with conventional therapies*

- **Localized disease**
  - Surgery for all resectable GISTs
  - Some patients may receive neoadjuvant imatinib to decrease tumor size prior to resection
  - Following resection, a 3-5 year course of adjuvant imatinib is administered to prolong disease free survival
- **Metastatic disease**
  - Imatinib is first line

How to evaluate response to treatment?

- **<u>Tumor response</u>**
  - **Necrosis with cystic or myxoid degeneration** → decreased HU density
  - Rarely intratumoral hemorrhage → increased in density

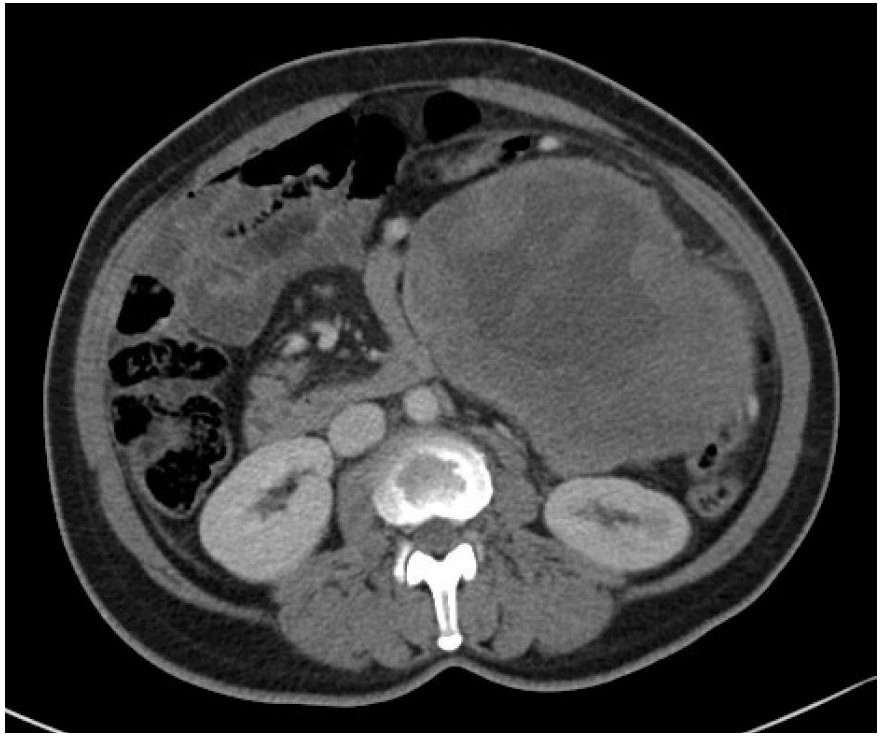
- Response of GIST to targeted therapy may occur without reduction of tumor size
- RECIST 1.1 may underestimate initial tumor response

Choi et al have proposed the measurement of CT attenuation values as a potential indicator of GIST response in patients undergoing targeted therapy.
Tumor density is determined by drawing regions of interest (ROI) circumscribing the margin of the tumor on **PORTAL VENOUS-PHASE CT IMAGES.**

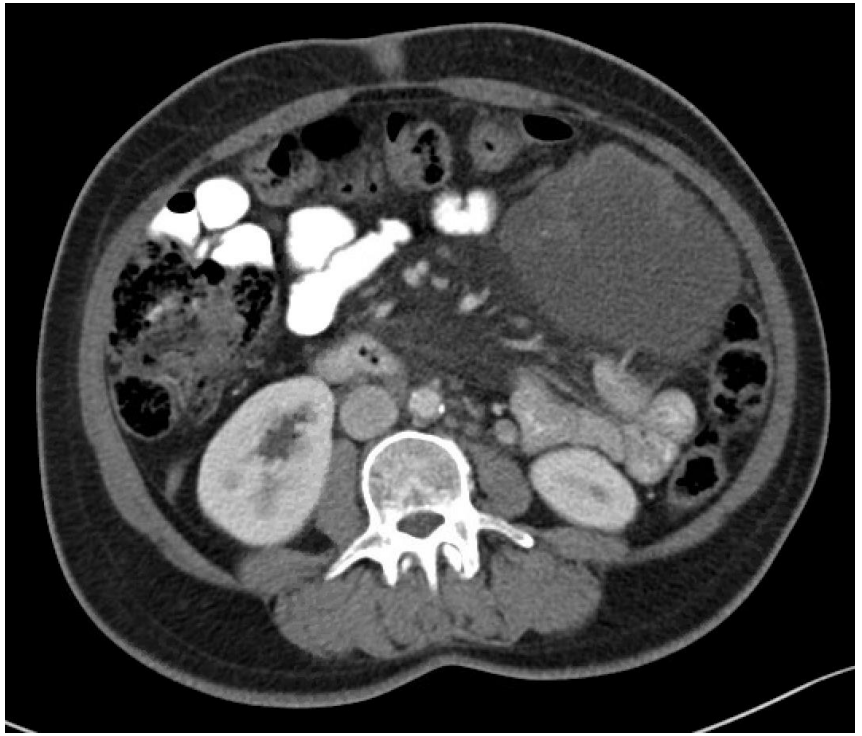
How to evaluate response to treatment?

RESPONSE	CHOI CRITERIA	RECIST 1.1
COMPLETE RESPONSE	• Disappearance of all target lesions • No new lesions	Disappearance of all target lesions
PARTIAL RESPONSE - PR	• Decrease in size **≥ 10% OR** • Decrease in tumor attenuation of **≥ 15%** on CT • No new lesions	**≥ 30%** decrease in the sum of diameters from the baseline
PROGRESSIVE DISEASE - PD	• An increase in tumor size **≥ 10%** in sum of longest diameters (SLD) **AND** • Does not meet PR criteria, by virtue of tumor attenuation on CT/new or na increase of intratumoral nodules	**≥20%** increase in the sum of diameters with absolute increase **≥ 5mm**
STABLE DISEASE	• Does not meet above criteria for PR or PD	Does not meet above criteria for PR or PD

How to evaluate response to treatment?



After imatinib



Partial response according to Choi et al.

Depicting reducing in size of more than 10% and decrease mean attenuation of more than 15%.

Conclusion

- GISTs are the most common mesenchymal tumors of the GI tract.
- Clinical manifestations are variable and reflect the variability of radiographic appearances, location and biological behavior, ranging from an incidental finding to a serious clinical picture.
- Large GISTs are heterogeneous because of cystic degeneration and hemorrhage.
- 50% of patients with GISTs present with metastases and the most common sites are the liver and peritoneum.
- Choi criteria may be used to evaluate response to treatment.
- A correlation of imaging features and pathological findings may also help to determine the risk and further treatment planning.