Gastrointestinal Stromal Tumors: The Role of The Radiologist

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Learning objectives

To review the spectrum of multimodality imaging appearances of gastrointestinal stromal tumors (GISTs).

To understand the role of radiologists and comprehend the imaging signs that allow: 1) detection, diagnosis and characterization of primary tumors; 2) prognostic assessment; 3) assessment of response to systemic treatment; 4) detection of disease recurrence.

To show imaging patterns of treatment response and treatment failure in patients on systemic therapy for metastatic GIST.
Gastrointestinal stromal tumours (GISTs) are rare neoplasms, with an annual incidence around 6.5-14.5 cases per 1,000,000 individuals and accounting for only 0.2% of all gastrointestinal (GI) neoplasms.

Although rare, they are the most common soft-tissue sarcoma and the most common mesenchymal tumour to involve the GI tract.

GISTs are now known to be derived from interstitial cells of Cajal (the pacemaker cells of the GI tract) or their precursors. The characteristic feature in the pathogenesis of GISTs is the presence of activating mutations of the genes encoding the receptor protein tyrosine kinase (KIT or CD117) or the platelet-derived growth factor receptor alpha (PDGFRA), promoting tumor survival and growth. Primary KIT mutations are encountered in 80-85% of GISTs, whereas mutations in PDGFRA are seen in 5-10% of cases. Other rarer forms of GIST are termed wild-type (WT) GIST, for lack of KIT or PDGFRA mutation. Several types of mutations in KIT and PDGFRA genes are known to occur and the type of mutation has important therapeutic implications.

The median age is around 60-65 years, with an equal male-to-female ratio. Paediatric GIST is very rare and represents a distinct subset, marked by female predominance, absence of KIT/ PDGFRA mutations, gastric multicentric location, and possible lymph node metastases. Familial GISTs (with germ-line autosomal dominant mutations of KIT) are a rare finding, presenting with multiple GISTs at an early age. Some syndromes are linked to GISTs, specifically: Carney triad syndrome in succinate dehydrogenase subunit B (SDHB)-deficient GIST, marked by gastric GISTs, paraganglioma, and pulmonary chondromas; Carney-Stratakis syndrome, marked by germ-line mutations of SDH, leading to a dyad of GIST and paraganglioma; neurofibromatosis type 1, marked by wild-type, often multicentric GIST, predominantly located to the small bowel, along with gliomas and neurofibromas.

Although GISTs can occur anywhere along the GI tract, the most common site of GISTs is the stomach (70%), followed by the small bowel (30%), and anorectum (7%). Less often, GISTs are seen in the colon and oesophagus and rarely in the mesentery and omentum. Most GISTs (80-85%) are localised when detected, but they frequently give rise to metastases, usually arising in the liver and within the abdominal cavity, whereas pulmonary, bone, lymph node and brain metastases are uncommon.

The most common presenting symptom are related to mass effect, as abdominal pain or a palpable mass, or to tumor ulcer and acute or chronic bleeding, such as unexplained anemia and/or faecal occult blood. Occasionally, duodenal tumors can
present with obstructive jaundice. Complications such as gastrointestinal bleeding, intestinal obstruction, and tumoural rupture with haemoperitoneum or peritonitis can occur as a result of a GIST and usually represent emergency situations that require accurate preoperative diagnosis and urgent surgery.

The final diagnosis of GIST relies on morphology and immunohistochemistry, the latter being positive for CD117 and/or DOG1. Mutational analysis for known mutations involving KIT and PDGFRA genes can confirm the diagnosis of GIST, if doubtful (particularly in CD117/DOG1-negative suspected GIST). Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy, and prognostic value, so that its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (according to the latest ESMO guidelines). In wild type GIST, immunohistochemistry for SDHB is done.

Prognostic factors are the mitotic rate, tumour size and tumour site (gastric GISTs have a better prognosis than small bowel or rectal GISTs). Tumour rupture is an additional adverse prognostic factor and should be recorded, whether it took place before or during surgery. Mutational status has not been incorporated in any risk classification at the moment, although some genotypes have a distinct natural history, and, above all, KIT/PDGFRA WT GISTs have peculiar clinical presentations and course. A widely used risk classification was proposed by the Armed Forces Institute of Pathology (AFIP), which incorporates the primary tumour site, mitotic count, and tumour size, i.e. the three main prognostic factors in localised GISTs. The TNM classification has several limitations and its use is therefore not recommended.

The standard treatment of localised GIST is its macroscopically complete removal whenever feasible. Preoperative imatinib may be given to shrink a large GIST to improve its operability and to spare normal tissues, in particular when GIST is located at a site where extensive resections of normal tissues would otherwise be required. Patients with a high risk for recurrence are treated after surgery with adjuvant imatinib for 3 years. Imatinib reduces the risk of recurrence and may improve survival, provided that GIST harbours an imatinib-sensitive mutation in KIT or PDGFRA. Adjuvant therapy should not be considered when the risk is low. There is room for shared decision-making when the risk is intermediate.

In locally advanced inoperable and metastatic patients, imatinib is standard treatment and should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumour progression, even when lesions have been previously surgically excised. Close monitoring of the tumour response should be carried out in the early phases of treatment. Follow-up should be continued throughout the treatment, since the risk of secondary progression persists over time.

The increasing recognition of GISTs and prolonged survival of these patients (approximately 60% of patients with operable GIST survive 10 or more years after...
surgery) have made imaging increasingly important not only for diagnosing and staging, but also for monitoring the effects of treatment and detecting tumour progression.
Findings and procedure details

From a GISTs pathological and oncological database at our institution, a retrospective review was made and the best cases selected for multi-modality illustration.

**Computed tomography (CT)** is frequently the initial imaging modality allowing the diagnosis of incidental GISTs. In patients with biopsy proven GISTs, contrast-enhanced abdominal and pelvic CT scan is the imaging modality of choice for staging and follow-up (surveillance of metastatic or recurrent disease after surgery and for monitoring TKI treatment responses). It has also an important role in the assessment of complications regarding surgical procedures and in guiding biopsy for definite diagnosis of lesions not suitable for endoscopic-ultrasound sampling. **Magnetic Resonance imaging (MRI)** is superior to contrast-enhanced CT in evaluating the hepatic metastasis and rectal GIST given the high soft-tissue contrast and direct multiplanar acquisition capability. MRI is also an alternative to CT for follow-up in young patients to minimise radiation exposure and in patients with contra-indications for intravenous iodinated contrast. However, MRI is not the primary imaging modality of choice in evaluating GIST patients because of its general limited sensitivity in detecting peritoneal tumors. The evaluation of fluorodeoxyglucose (FDG) uptake using an FDG-positron emission tomography (PET) scan, or **FDG-PET-CT/MRI**, is useful mainly when early detection of the tumour response to molecular-targeted therapy is of special interest. Therefore, FDG-PET is particularly recommended for those requiring a timely decision for against surgery, such as those with marginally resectable GISTs or resectable GISTs with a risk of significant morbidity. Furthermore, rapid monitoring of therapeutic response by FDG-PET may be needed after adjusting the dose of imatinib. Moreover, whenever there are inconsistencies between clinical features and CT or MRI findings during the course of the disease, FDG-PET is indicated. **Ultrasound** may also be useful to evaluate the liver metastasis. **Endoscopic ultrasonography** provides good morphological details and offers a tool for biopsy of the submucosal GISTs, being most useful in the esophagus, stomach, duodenum, and anorectum.

To optimize the detection and characterization of hypervascular masses like GISTs, the **optimal CT protocol** includes administration of an oral contrast (and rectal contrast whenever possible) and acquisition of a triphasic CT of the abdomen and pelvis prior to and following bolus administration of an iodinated intravenous contrast agent, with acquisition of arterial- and portal-venous phase images. The arterial phase is also mandatory for optimal detection of possible hepatic metastasis. For follow-up, a biphasic CT acquisition with an arterial and a portal venous phase are usually enough.

The **CT features** of GISTs can vary depending on the size, location and aggressiveness of tumor. GISTs are highly vascular subepithelial masses and typically grow outward,
away from the originating bowel lumen, but they may also show endoluminal and intramural growth.

Small tumours are usually found incidentally and typically appear as well circumscribed sub-mucosal masses with homogeneous enhancement (see figure 1).

Large tumours may be mural or exophytic masses with heterogeneous enhancement due to necrosis, cystic degeneration and haemorrhage. Calcification is rare but can occur. Despite their large size, the masses usually only displace adjacent organs and anatomic structures and direct invasion is rare, although it may be present in more advanced lesions.

Atypical appearance on imaging and large or ulceroinfiltrative masses may cause diagnostic confusion and identifying the origin of a large GIST on CT images can often be challenging. To identify the organ of origin, the "embedded organ sign", "beak sign", "prominent feeding artery or draining vein sign", and "renal displacement with axis rotation" are useful for differentiating GISTs from other organ tumours (see figure 2). Central hypodense areas on CT for large GISTs correspond pathologically to haemorrhage, necrosis, and cystic degeneration. Occasionally, when the cystic component of the tumour is dominant, a GIST appears as a cystic mass, thereby mimicking cystic masses from other organs, especially on ecography (see figure 3).

Up to 30% cases of GISTs present with metastases disseminating from haematogenous and peritoneal seeding, with the liver and peritoneum most likely being involved. Unlike gastrointestinal adenocarcinomas, GISTs rarely metastasize to regional lymph nodes; however, metastases to the lymph nodes can occur in advanced diseases and are more commonly observed in epithelioid types than in other types. These metastatic lesions have CT features similar to those of the primary tumors: depending on the tumor size, they may be homogeneously to heterogeneously enhancing soft-tissue masses.

Complications associated with GISTs, including gastrointestinal bleeding, intestinal obstruction, rupture with haemoperitoneum, or peritonitis, occur and cause acute abdominal symptoms. In these situations, accurate diagnosis of the underlying cause on imaging is essential for treatment.

Gastrointestinal bleeding occurs as a result of tumour ulceration at the mucosal level or intraluminal tumour rupture. Clinical presentation varies from anaemia to melaena or haematemesis/haematochezia according to the amount of active bleeding and tumour location in the GI tract. Demonstration of intraluminal extravasation of contrast material by CT allows correct diagnosis of a bleeding GIST (see figure 2). Occasionally, it is important to identify small bleeding GISTs admixed with extravasated contrast material which may not always be easy because a bleeding tumour with reduced perfusion may mimic an intraluminal haematoma.
Most intestinal obstructions caused by GISTs occur in the small bowel with three patterns: 1) intussusception induced by GISTs as a leading mass, with a bowel-within-bowel configuration on CT; 2) direct occlusion of the bowels caused by GISTs with exophytic and endophytic growth; 3) volvulus-like torsion of the small bowel on the mesenteric root, especially exophytic tumour (see figure 3).

About 1 % of GISTs undergo spontaneous rupture. Although the majority of GIST ruptures occur spontaneously within the gastrointestinal lumen (see figure 4), intraperitoneal rupture of GISTs can result in massive haemoperitoneum or peritonitis. The intraperitoneal rupture of GIST is a known negative prognostic factor and radiologists should be aware of the features that are often seen in ruptured GISTs, which include: high-risk pathology, large size, exophytic growth, internal necrosis or cystic degeneration, and interval rapid growth. The regarded mechanisms for GIST rupture or bowel perforation are intratumoural necrosis, intratumoural bleeding, or bowel ischaemia induced by tumour embolisation. Imatinib and Sunitinib, the first and second line agents for advanced GISTs, have an anti-angiogenic effect, which enable prevention and delay of disease progression. However, this effect can result in adverse events such as gastrointestinal perforation and bleeding, although the chances are very rare and the mechanism is unknown. At CT, a ruptured GIST should be considered when necrotic or haemorrhagic portions are seen within the tumour with the presence of ascites or haemoperitoneum, which is rare even in peritoneal metastasis. Panperitonitis and pneumoperitonum can be detected as a consequence of an extensive necrotising GIST with communication to the bowel lumen ruptures.

On MRI, GISTs are usually well-defined hypo to isoattenuating lesions in T1-wheighted images (T1-w) (compared with muscle density) and iso to hyperattenuating ones in T2-wheighted images (T2-w) (see figure 5). MRI can be used to differentiate the hyperattenuating intratumoral density shown on CT images from hemorrhage. Internal hemorrhage is seen as foci of high attenuation in T1-w, while foci of high hyperattenuating with no contrast enhancement on T2-w relay for the cystic degeneration. Intravenous contrast helps to delineate viable solid components and non-enhanced necrotic areas so dynamic contrast-enhanced MRI may be used to evaluate tumor viability and vascularization: as in CT, the tumors enhance after administration of an intravenous contrast agent, homogenously in small lesions and heterogeneously in larger ones.

Recently, diffusion-weighted magnetic resonance imaging (DW MRI) has been applied for monitoring tumour response following therapeutic interventions. Malignant tumours usually show high signal intensity on DW MRI because of high cellular density and limiting the freedom of water molecules to move (see figure 5). The diffusion in tissue can be quantified by calculation of the apparent diffusion coefficient (ADC), inversely related to the DW MRI signal intensity. On DW MRI, lower ADC values are detected in the solid components of larger lesions.
In patients who have undergone surgical resection of GISTs, CT is performed for surveillance of metastatic or recurrent disease after surgery. In patients with unresectable advanced disease or metastasis, CT is an excellent imaging modality for assessing response to tyrosine kinase inhibitors (TKI), such as imatinib and sunitinib.

Treatment response in GIST is better evaluated by Choi criteria (or Modified CT Response Evaluation Criteria), which incorporate size as well as CT density changes (see table 1).

The key findings that require attention on the restaging imaging are changes in the tumour density and volume, appearance of intra-tumoural nodules or enlargement of existing tumour nodules, and appearance of new sites of disease.

**Responding GISTs** are characterized by a dramatic change in the pattern of enhancement on contrast-enhanced CT images, from heterogeneous hyperattenuation to homogeneous hypoattenuation (see figure 6). This change may or may not be associated with concomitant changes in tumour size. Resolution of enhancing tumor nodules and a decrease in tumor vessels are also seen in favourable responses. It should be noted that responding GISTs sometimes increase in size because of intratumoral hemorrhage, necrosis, or myxoid degeneration. In these cases, observation of changes in tumor density and in the enhancement pattern aid to reaching the correct conclusion.

After treatment, tumors become hypodense and their size may gradually decrease and eventually stabilize (see figure 6). A typical favourable response takes 1-2 months to become evident on contrast-enhanced CT. The treatment changes tend to be more dramatic on PET-CT and the decrease in the tumour metabolic activity can be noted as early as within 24h of treatment initiation. MRI provides similar information with responding lesions, becoming more T2 hyperintense, with diminished enhancement. During TKI treatment the cellular density is anticipated to decrease, which is reflected by an increasing tumour ADC. The magnitude of ADC increase will depend on tumour cell death, remodelling of tissues, vascular normalisation, development of fibrosis, and phagocytosis of dead cells.

A subset of patients does not respond to imatinib and demonstrate disease progression during the initial 6 months of treatment, referred to as **primary resistance**. On imaging, primary resistance to imatinib manifests as progressive disease on the first post-treatment imaging study defined as >10% increase in tumour size or appearance of new metastatic lesions, by Choi criteria. However, as mentioned previously, increased tumor size alone without a change in tumor enhancement or tumor vessels may not accurately represent disease progression. As metabolic response precedes anatomical response, PET-CT is particularly useful for early detection of primary resistance.

Unfortunately GISTs that respond to imatinib eventually develop resistance. Disease progression occurring in patients who show initial good response for at least 6 months
qualifies as secondary resistance. The modified tumour response criteria by Choi et al. define disease progression as appearance of new intra-tumoural nodules or increase in size of existing tumours nodules in addition to >10% increase in size of the tumour. Thorough analysis of each treated lesion is required to identify these new intratumoral nodules. Diffuse increase in the density of stable lesions is encountered in some cases due to replacement of the entire cystic mass by enhancing tumour, also referred to as "mass-within-cyst". The tumour nodules have low- to intermediate signal on T2-weighted images in contrast to the near-fluid signal background lesion, show restricted diffusion on diffusion-weighted imaging (DWI) images and show avid enhancement on post-gadolinium MRI images. Following response to imatinib, lesions in GIST are seen as photopenic areas on PET-CT. The re-emergence of metabolic activity in these photopenic lesions is indicative of disease recurrence.

Findings of disease progression allow change of therapeutics by increasing the dose, changing to another TKI (sunitinib, regorafenib) or including these patients onto clinical trials testing other new approaches.
Fig. 1: A 75-year-old man with a primary GITS of the small intestine. Contrast-enhanced CT coronal (A) and axial (B) images at arterial phase show a well-circumscribed, slightly heterogeneous, hyperattenuating ovoid tumour (white arrows) growing out of the small intestine. Pathological analysis revealed a low-risk GIST of the small intestine.

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**Fig. 2:** A 69-year-old woman presenting with anaemia of unknown cause. Contrast-enhanced CT reveals a large exophytic mass (white arrows), with lobulated contours and heterogenous enhancement containing internal hyperdense haemorrhage and fluid portions. Notice the beak-like deformation of the proximal jejunum (yellow arrows). The feeding artery (blue arrow) is supplied from the superior mesenteric artery (green arrow). Pathology confirmed an intermediate risk GIST of the proximal jejunum.

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Fig. 3: A 67-year-old woman presenting with intestinal occlusion. A) Abdominal X-ray shows air-fluid levels on the small intestine; B) and C) Ultrasound showed a well-delimitated heterogeneous mass composed by solid and cystic areas; D) and E) Contrast-enhanced CT axial and coronal images show a large, heterogenous and exophytic solid mass originating from the small bowel (yellow triangle). Notice the whirling of the bowel loops involved (yellow arrow). Bowel loops proximal to the obstructions site are distended (blue x), while the ones distal o the lesion are collapsed (*)

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Fig. 4: A 64-year-old man presenting with intestinal occlusion. Contrast-enhanced CT shows a large mass (white arrow) located in the pelvic cavity, with ulceration and communication with the bowel loop (air inside the lesion) and heterogeneous enhancement in the arterial phase, probably due to intratumoural bleeding/necrosis (*). Additional findings include peritoneal stranding (yellow arrow) and ascites (blue x). Pathology revealed a high risk GIST of the small bowel with an area of cystic degeneration filled by hematic content and with ulceration of the intestinal mucosa.

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<table>
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<th>Response</th>
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| CR       | Disappearance of all lesions  
No new lesions |
| PR       | A decrease in size\(^a\) of ≥10% or a decrease in tumor density (HU) ≥15% on CT  
No new lesions  
No obvious progression of non-measurable disease |
| SD       | Does not meet the criteria of CR, PR, or PD  
No symptomatic deterioration attributed to tumor progression |
| PD       | An increase in tumor size of ≥10% and does not meet criteria of PR by tumor density (HU) on CT  
New lesions  
New intratumoral nodules or increase in the size of the existing intratumoral nodules |

CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease.

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\(^a\)The sum of longest diameters of target lesions as defined in RECIST.

**Table 1:** Modified CT Response Evaluation Criteria.

Fig. 6: A 65-year-old woman with known advanced gastric GIST and hepatic metastasis. A) and B) images represent baseline contrast-enhanced CT. Image C) was obtained 3 months after initiation of therapy with imatinib, showing homogenous decrease in attenuation of the hepatic lesions. Images obtained 9 months after treatment (D) show favorable response with reduction of the size of the lesions.

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Fig. 5: A 68-year-old-female with a ileal GIST. MR images show a solid lesion originating from the small intestine, iso to hypoattenuating in T1-weighted images (A) and hyperattenuating in T2-weighted images (B). In DW-RM (C) the lesion shows high signal intensity, as expected in a malignant tumour.

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Conclusion

In order to take active participation in patient management and treatment planning, radiologists should become familiar with the diverse radiological manifestations of GISTs to ensure accurate diagnosis, staging, assessment of response to systemic treatment and detection of disease recurrence.
References


