Review

Imaging of Gastrointestinal Stromal Tumors: From Diagnosis to Evaluation of Therapeutic Response

FEDERICA VERNUCCIO, ADELE TAIBBI, DARIO PICONE, LUDOVICO LA GRUTTA, MASSIMO MIDIRI, ROBERTO LAGALLA, GIUSEPPE LO RE and TOMMASO VINCENZO BARTOLOTTA

Department of Radiology, DIBIMED, University of Palermo, Palermo, Italy

Abstract. *Once considered an obscure tumor entity with poor prognosis, gastrointestinal stromal tumors (GISTs) are nowadays recognized as the most common mesenchymal tumors of the alimentary tract. GISTs differ from other mesenchymal neoplasms at pathology since 90% of them exhibit strong immunohistochemical staining for KIT, a tyrosinase kinase growth factor receptor. In the early 2000s, the ability of imatinib mesylate, a tyrosine kinase inhibitor, to inhibit KIT established a new paradigm for cancer treatment. A reduction in lesion size may not be observed or may appear many months after therapy; thus, tumor response criteria alternative to the Response Evaluation Criteria in Solid Tumors were developed. This review highlights the role of imaging in the detection, characterization, preoperative staging, postoperative assessment, therapy-response evaluation and treatment-related toxicities. All this information is crucial in optimizing patient management. Contrast-enhanced computed tomography is the most commonly used modality for staging the disease and assessing treatment response, whereas positron-emission tomography adds valuable functional information. Magnetic resonance imaging (MRI) may also be useful, especially in ano-rectal GISTs. Diffusion-weighted MRI may provide promising indicators of tumor response to targeted molecular therapy. Radiologists and oncologists should be aware of all these issues related to GISTs, since multidisciplinary teams gathering different expertise are usually needed to properly treat patients with GISTs.*

Correspondence to: Federica Vernuccio, Via Santa Maria di Gesù 25, 90124 Palermo (PA), Italy. Mobile: +39 3208863468, e-mail: federicavernuccio@gmail.com

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumorS of the gastrointestinal tract, with an incidence of up to 14-20 cases per million and a prevalence of about 130 cases per million population (1, 2). GISTs are considered originating from the interstitial cells of Cajal, which are located in the myenteric plexus of the gastrointestinal tract being responsible for its peristaltic contractions (3-5). GISTs differ from other mesenchymal neoplasms at histology since 90% of them display strong immunohistochemical staining for KIT (CD 117), a tyrosinase kinase growth factor receptor (6). The morphological types of GIST are spindle cell (70%), epithelioid (20%), and mixed (10%) (7). Spindle-cell morphology has a worse prognosis than the epithelioid type. Some GISTs are associated with inherited syndromes, notably neurofibromatosis type 1, Carney triad (gastric GIST, pulmonary chondroma and paraganglioma), Carney-Stratakis syndrome (gastric GIST and paraganglioma), and familial GIST syndrome (2, 7). These inherited GISTs differ from sporadic GISTs since they occur at a younger age (first two decades of life) and have a female preponderance, whereas sporadic GISTs can arise at any age, even though more than 80% are reported in individuals older than 50 years (median age=63 years), without any significant difference between men and women (2).

GISTs may occur anywhere along the gastrointestinal tract; they are most commonly located in the stomach (50-60%) and the small intestine (30-35%) and less frequently in the colon and rectum (5%) and the esophagus (<1%) (8). More rarely, GISTs may arise from other intra-abdominal soft tissues within the abdominal cavity, usually in the omentum, mesentery, or the retroperitoneum (<5% of all GISTs); in this latter case it is considered extra-gastrointestinal tract tumor (8). The malignant potential of GISTs ranges from small harmless tumors to aggressive, metastasizing and life-threatening sarcomas (1).

Although most patients have symptoms or a palpable tumor at presentation, 25% of GISTs are incidentally discovered at imaging or surgery, and a few of them (about 5%) are found at autopsy (2). The most frequent symptoms
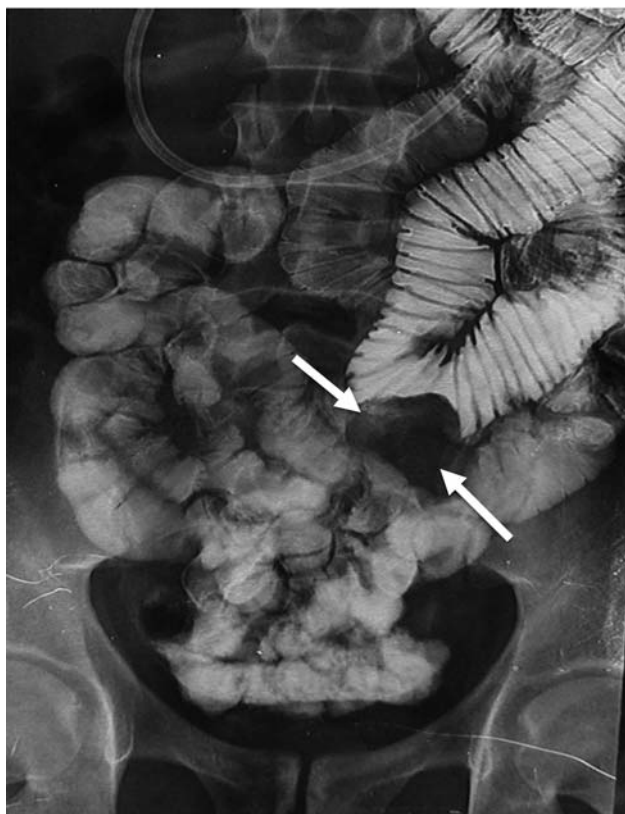
Figure 1. *Barium imaging in a 48-year-old male with jejunal gastrointestinal stromal tumor. A large exophytic submucosal mass with a sharply defined, smooth filling defect is visible in the jejunum (arrows).*

Figure 2. *Abdominal ultrasound of a 46-year-old male with gastric gastrointestinal stromal tumor and liver metastasis. Subcostal ascendent ultrasound image shows a 4.7 cm hypoechoic metastasis in the sixth hepatic segment in the subcapsular region (calipers).*

are bleeding into the bowel or abdominal cavity, anemia, and abdominal pain, but others can include dyspepsia, nausea or vomiting, constipation or diarrhea, frequent urination, and fatigue (9). Hemorrhage, tumor rupture, and bowel perforation or obstruction might need emergency surgery; however, symptoms are not predictive of patient survival (9).

This review presents imaging features of GISTs with emphasis on detection and characterization by different imaging techniques, differential diagnosis, staging and follow-up, including issues related to new molecular targeted therapies.

Imaging Evaluation

GISTs show a wide spectrum of radiological appearances depending on imaging technique and tumor size, site of origin and growth pattern.

GISTs on different imaging techniques. Conventional radiographs may incidentally show a non-specific soft-tissue mass, rarely with calcifications, displacing the gastric air shadow in the gastric location or associated with small intestinal dilatation in the small intestine location (10).
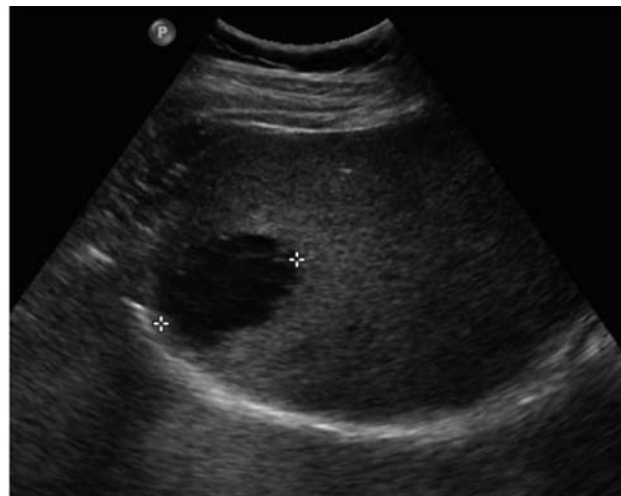
Barium imaging has a limited role in staging GI tract tumors by showing the features of intraluminal or submucosal masses, smoothly circumscribed and with the margins forming obtuse or right angles with the gastric wall, usually with sharply defined margins but with some possible luminal irregularity or focal ulceration (Figure 1) (10, 11). These tumors may also show mass effect and cavity and fistula formation may occur (10).

Abdominal ultrasound (US) frequently depicts a large mass filling the abdomen, of heterogeneous reflectivity and with frequent necrosis. The site of origin is often undetectable at US (12). Liver metastases from GIST are usually hypoechoic relative to background hepatic parenchyma (Figure 2). Contrast-enhanced US (CEUS) is a useful tool for detecting the presence of viable tumoral tissue in the primary tumor, and in the detection of liver metastases (Figure 3) (13). Endoscopic US is a valuable imaging technique for diagnosing small (<2 cm), incidentally detected submucosal GISTs, by clearly delineating the gut wall layers and also allowing biopsy confirmation (14).

The intraluminal, mural and extra-serosal components of GISTs are better depicted on computed tomographic (CT) images (15). Since GISTs usually involve the outer muscular layer, they usually exhibit exophytic growth. Therefore, the most common appearance is that of a mass arising from the wall of the gastrointestinal tract and projecting into the abdominal cavity (16). Mucosal ulceration is seen on the luminal surface of the tumor in up to 50% of cases (17). The majority of GISTs appear to be well-defined, extraluminal or intramural masses, with varying attenuation on CT based on size.

Figure 3. *Contrast-enhanced ultrasound in a 70-year-old female with jejunal gastrointestinal stromal tumor and liver metastasis. Intercostal ultrasound image acquired 15 s after i.v. injection of a microbubble-based contrast agent shows a 2.8 cm hypervascular lesion (left side) in the fifth hepatic segment in the subcapsular region (arrows).*

Small GISTs (<5 cm), which are usually benign, usually appear on CT as sharply margined, smooth-walled, homogeneous, soft-tissue masses, involving the wall of the stomach or small intestine and often presenting an intraluminal component (18). Moreover, they tend to be homogeneous on contrast-enhanced CT images (Figure 4) although focal areas of low attenuation on CT, due to hypocellular tumor, hemorrhage, necrosis, cystic degeneration and fluid in an ulcer, may be present but without any proven relationship with malignant potential (19, 20).

Larger lesions normally have well- or ill-defined margins, inhomogeneous density both on unenhanced and contrast-enhanced CT scans, with combined intraluminal/extraluminal growth and a tendency to spread to surrounding structures. Large tumors (>6 cm) frequently exhibit central areas of necrosis or hemorrhage, while mural calcifications are rarely seen (Figure 5) (16). Contrast-enhanced CT usually depicts heterogeneously enhancing masses with peripheral enhancing areas due to viable tumoral tissue and central low attenuating areas due to previous hemorrhage, necrosis, or cystic degeneration (10). Large GISTs may also present with a 'dumbbell-like' appearance, with masses protruding both

into the lumen and growing exophytically from the serosa of the bowel wall (14). Large GISTs may also appear as well-demarcated extraluminal masses, and this appearance can make it difficult to appreciate the real origin of the tumor. Multiplanar reconstructions on multidedector row CT may help in the identification of the organ of origin (15, 21). Calcification, either mottled or extensive, is an unusual feature of GISTs (10, 15). Larger lesions with extensive hemorrhage or necrosis may form large cystic spaces or cavities that may communicate with the lumen and contain air, air-fluid levels, or oral contrast medium (10, 22).

Thanks to its high soft-tissue contrast, magnetic resonance imaging (MRI) allows visualization of the extent of the tumor and central necrosis, including hemorrhage (23). MRI findings confirm that small GISTs tend to be round and with strong homogeneous arterial enhancement, whereas large GISTs tend to be lobulated and usually show mild, heterogeneous, gradual enhancement with intratumoral cystic change (24). The degree of necrosis and hemorrhage greatly affects the signal-intensity pattern. The solid portions of tumor typically exhibit low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and

Figure 4. *Contrast-enhanced computed tomography in a 60-year-old male with gastric gastrointestinal stromal tumor. Contrast-enhanced computed tomographic in the portal phase depicts a small intraluminal submucosal mass with sharply defined margins and homogeneous contrast enhancement in the stomach (arrow).*

Figure 5. *Contrast-enhanced computed tomography in a 72-year-old female with gastric gastrointestinal stromal tumor. Contrast-enhanced computed tomography in the portal venous phase depicts an intraluminal submucosal mass with a sharply defined margin, but inhomogeneous contrast enhancement in the stomach (arrow).*

enhancement after administration of contrast medium (10). Areas of hemorrhage within the tumor will exhibit from high to low signal intensity on both T1- and T2-weighted images, depending on the age of the hemorrhage (25). MRI is a useful adjunct to CT, particularly in the evaluation of large tumors (22, 26).

Differential diagnosis of GISTs depending on location. Gastric GISTs must be differentiated from other mesenchymal neoplasms that may arise in the gastric wall such as leiomyomas, leiomyosarcomas, schwannomas, neurofibromas, and neuroendocrine neoplasms (*e.g.* solitary gastric carcinoids). In a series of 120 patients, non-cardial location, heterogeneous enhancement, presence of necrosis, larger lesion size, and absence of lymphadenopathy are highly suggestive CT findings for large gastric GISTs in differentiation from schwannomas or leiomyomas (27). Gastric schwannomas more frequently exhibit an exophytic or mixed growth pattern, homogeneous enhancement pattern and peritumoral lymph nodes and grow more slowly than GISTs (28). Gastric adenocarcinoma and lymphoma rarely demonstrate marked exophytic growth, but they may occasionally mimic GISTs, with a predominantly mural location or an intraluminal component. Advanced gastric carcinomas and lymphomas commonly have associated perigastric, hepatoduodenal ligament, and celiac lymphadenopathy, which are not usually seen in malignant GISTs (29).

Duodenal GISTs are well-circumscribed, round or oval masses, and more commonly occur in the second portion of the duodenum, without lymphadenopathy or duodenal obstruction. Duodenal GISTS frequently metastasize to the liver and peritoneum (30). The differential diagnosis for small intestinal GISTs includes primary and metastatic small intestinal neoplasms. Adenocarcinoma is the most common primary malignancy of the small bowel, usually appearing as an annular lesion in the proximal small intestine; thus, its appearance usually does not overlap with that of GISTs. Lymphoma, however, produces large masses within the small intestine that may ulcerate, cavitate, and extend into the adjacent mesentery. In these cases, lymphoma may be indistinguishable from a GIST on radiological images, although the presence of associated lymphadenopathy would favor a diagnosis of lymphoma (10).

Neoplasms that originate from the mesentery and secondarily involve the small intestine, such as mesenteric fibromatosis (desmoid tumor), inflammatory pseudotumor, lymphoma, sclerosing mesenteritis, and metastatic disease, should also be included in the differential diagnosis (10).

Anorectal GISTs are well-circumscribed, non-circumferential, predominantly infralevator, intramural or exophytic, fluorodeoxyglucose (FDG)-avid, hypoattenuating masses, and present without lymphadenopathy or intestinal obstruction (31). Cross-sectional imaging allows a good visualization of the origin of the mass, its internal components, and other organ involvement, and is indicated for surgical planning (26). The differential diagnosis for anorectal GISTs includes both epithelial and nonepithelial neoplasms of the anorectal region. Rectal adenocarcinoma, anal squamous cell carcinoma, lymphoma, malignant
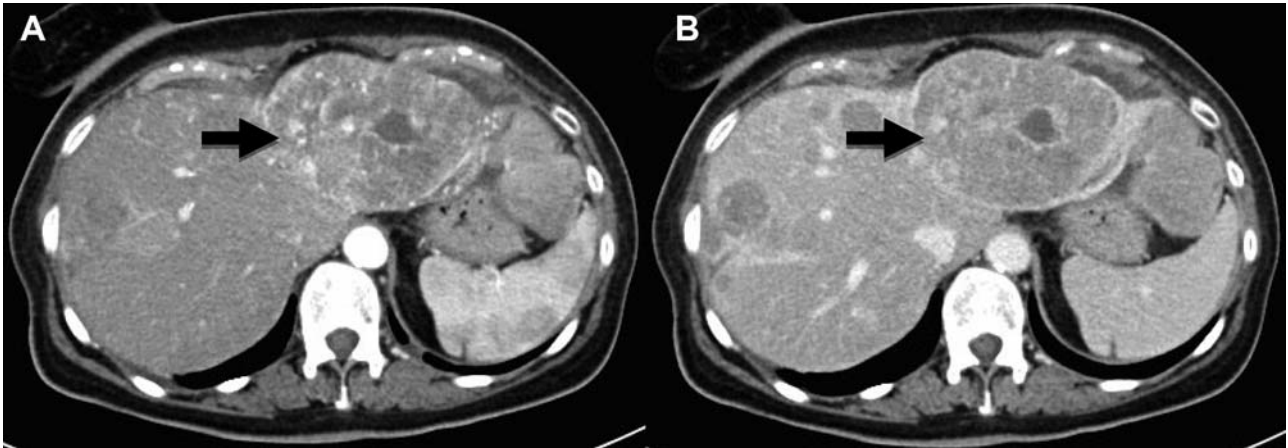
Figure 6. *Contrast-enhanced computed tomography in a 70-year-old female with jejunal gastrointestinal stromal tumor liver metastasis. Contrast-enhanced computed tomography in the arterial phase (A) depicts a large, inhomogenoeus, hypervascular metastasis in the left lobe of the liver (arrow). In the portal phase the lesion shows 'wash-out' (arrow) (B).*

melanoma, carcinoid, leiomyoma, and leiomyosarcoma may have imaging appearances similar to that of GISTs, although leiomyosarcoma may have a dominant polypoid intraluminal component (10). Carcinomas tend to have irregular margins and may be associated with perirectal lymphadenopathy, whereas GISTs tend to have well-defined margins without any perirectal adenopathy. GISTs with perirectal extension may be mistaken as tumor arising from adjacent structures, such as prostatic adenocarcinoma or sarcomas of the prostate and perineum. Anorectal lymphoma may be seen in patients with AIDS; radiographically it presents as an eccentric or annular mural mass that may be associated with mucosal ulceration or perianal fistulation.

Primary esophageal and colonic GISTs, as well as mesenteric or omental GISTs, are much less common than gastric, small bowel, and anorectal GISTs (10).

Pre-operative staging. Since 30% of GISTs are frankly malignant, an accurate assessment is crucial in order to identify resectable disease and to evaluate the need for adjuvant or neo-adjuvant therapy. The clinical diagnosis is mainly based on imaging, as biopsy runs the risk of tumor rupture or seeding of the biopsy tract, in otherwise resectable disease (32). When recommended, a biopsy sample obtained by endoscopy is preferable to transcutaneous biopsy because of the lower risk of tumor spillage into the abdominal cavity. If accessible liver metastases are present, a biopsy specimen from a metastasis can establish the diagnosis (2). Contrast-enhanced CT is the investigation of choice in the imaging algorithm of GIST. Usually GISTs displace adjacent organs and vessels, whereas direct invasion of the adjacent structures is rarely

seen, usually in advanced disease (15). CT and MRI may also demonstrate omental and peritoneal spread of tumor, or liver metastasis, whereas ascites and metastatic lymphadenopathy are uncommon features (10). Extension of gastric GISTs may occur into the gastrohepatic ligament, into the gastrosplenic ligament, or posteriorly into the lesser sac (10). The main sites of metastases are the liver and the peritoneal cavity, including the omentum and the mesentery (33). Hepatic metastases are usually hypervascular on arterial-phase images with wash-out in the venous phase and can remain occult on portal venous-phase images or in single-phase scans (Figure 6) (34). Rarely GISTs metastasize to the lymph nodes, bones, lungs, or to subcutaneous tissues (35). The presence of an ulcer, mesenteric fat infiltration, direct organ invasion, and metastasis were more frequently observed in gastric GISTs with a high mitotic rate, but no CT feature other than size was found to have any predictive value (36). Furthermore, although the risk of metastases is highest in patients with large tumors with a high mitotic index, small tumors with low mitotic activity may still metastasize, making it difficult to reliably predict malignant potential (37). The correlation between the degree of contrast-enhancement and the malignant potential of GISTs is still unclear. In a study focused on MRI, markedly enhancing GISTs had a high mitosis index (23). On the other hand, on MRI, the presence of intratumoral cystic change and a low mean apparent diffusion coefficient (ADC) value were found to be helpful for predicting the high malignant potential of GISTs, but no correlation was found between the degree of enhancement and risk of malignancy (38). For large exophytic tumors and GIST of the anorectum, the multiplanar capability of MRI

may be of particular importance in determining the organ of origin of large tumors and the relationship of the tumor to other organs and major blood vessels (22, 26).

Positron-emission tomography (PET) provides functional information that may help in staging, especially when combined with morphological information provided by CT (22). PET/CT may be useful for differentiating viable tumour from necrotic tissue, malignant from benign tissue, and recurrent tumor from scar tissue, especially acting as a baseline, pre-treatment scan (22).

Post-operative surveillance. The optimal treatment for GISTs is surgical resection, although even after complete (R0) resection, a substantial proportion of patients will suffer disease recurrence, with an overall 5-year survival ranging between 40 and 65% (39). In a pooled analysis of data from 2,459 patients, estimated 5- and 15-year recurrence-free survival rates for GISTs treated with surgery alone were 70.5% and 59.9%, respectively (8). Only a few tumors recurred after the first 10 years of follow-up, suggesting that most patients (about 60%) with operable GIST are probably cured by surgery (2). The most important independent prognostic factor for GIST recurrence after surgery is a high tumor mitotic rate but also large tumor size, tumor site (gastric GISTs being less aggressive than other GISTs), and tumor rupture before surgery or at surgery have been identified as independent prognostic factors for recurrence (2, 6, 40-43). Hence, these prognostic factors have been used to create the modified US National Institutes of Health classification (43).

Since extra-abdominal metastases are infrequent, contrast-enhanced CT or MRI of the abdomen and pelvis is usually adequate for post-operative surveillance, but the optimum follow-up scheme is still subject to debate (2). The high incidence of GIST recurrence in the high-risk group in the first 3 years after surgery supports the use of intensive imaging surveillance (*i.e.* intervals of 3-4 months) during this period. Relapse is often asymptomatic and commonly occurs in the liver, omentum and mesentery. Stratification by tumor factors and replacing CT with MRI for young people may enable improved tailoring of surveillance protocols within the high-risk group in the future (44).

Response assessment of treated GISTs. In the early 2000s, the knowledge of the pathogenic role of activating mutations in the receptor tyrosine kinase KIT and the ability of imatinib mesylate, a small-molecule tyrosine kinase inhibitor (TKI), to inhibit KIT established a new standard of care for treating KIT-positive, inoperable, and metastatic GISTs (34, 45). Before the imatinib era, the median survival of patients with recurrent or metastatic GIST was 10-20 months, whereas after the introduction of TKI, survival rose to 51-57 months (46-48). Nowadays, first-line systemic treatment of advanced GIST is with imatinib, unless the tumor has a gene mutation that encodes an imatinib-resistant kinase. Thanks to imatinib, 83-89% of patients will have either a response or a durable stable disease, whereas only 11-17% of cases will progress (47, 49). Response evaluation during early stages of targeted therapy is crucial in order to optimize treatment and prevent unnecessary delays, toxicity and costs (50, 51).

Contrast-enhanced CT is the most commonly used modality for evaluating response to treatment of GISTs. Multiphasic CT with unenhanced, arterial-, and venous-phase images helps better define both the primary tumor and metastatic disease. Unenhanced CT images help detect hemorrhage and calcifications (although these are uncommon) and act as a baseline for assessing enhancement (15, 34, 52, 53). According to the Response Evaluation Criteria in Solid Tumors (RECIST), tumoral response to conventional cytotoxic drugs is categorized as partial response, stable disease, and progressive disease on the basis on the size reduction of a tumor using one-dimensional measurement (54, 55). However, targeted therapies will also determine changes in the tumoral composition, such as cystic areas or calcifications. These changes, as well as reduced lesion vascularity, cavitations and intratumoral hemorrage, are evidence of disease response in patients after imatinib therapy, even without any size reduction (56, 57) (Figure 7). Thus, RECIST criteria might not be a reliable indicator for monitoring metastatic GISTs, especially in the early stage of imatinib treatment (58). Considering that imatinib acts more as a cytostatic than cytotoxic drug, treated metastatic lesions often exhibit minimal vascularity and cellular density, with extensive cystic or myxoid degeneration and no necrosis or inflammation (59). Paradoxically, instead of a decrease in size, a transient increase in size may be seen early in some cases owing to cystic change and intratumoral hemorrhage (60). Hence, alternative tumor response criteria were developed by Choi *et al.* in order to incorporate density changes along with size reduction (61). According to the Choi criteria, a decrease in tumor CT attenuation by 15%, or 10% decrease in unidimensional size is indicative of treatment response, as opposed to a 30% decrease in the longest dimension by RECIST (61). Furthermore, the early detection of a nodule within a mass is an important sign of recurrent GIST, as well as the appearance of new solid lesions after maximal dose of imatinib suggesting disease progression, and might be helpful in early intervention such as surgery or use of new tyrosine kinase inhibitors (62, 63). Choi response criteria are reproducible, more sensitive, and more precise than RECIST in assessing the response of GISTs to imatinib and correlate with time to tumor progression and disease-specific survival (64).

PET has been found to be highly sensitive in detecting early response, and to be useful in predicting long-term
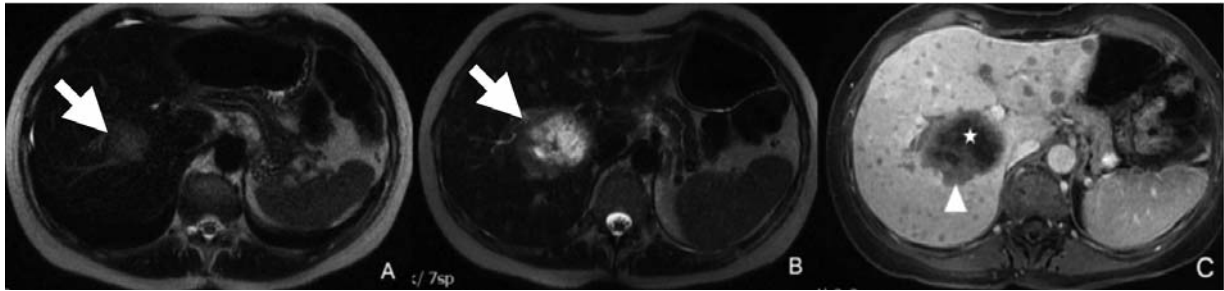
Figure 7. *T2-Weighted fast spin-echo magnetic resonance imaging (T2-w FSE MRI) in a 57-year-old female with jejunal gastrointestinal stromal tumor and liver metastasis. A: T2-w FSE MRI shows a moderately hyperintense metastasis in the fifth segment (arrow). After 5 months of imatinib therapy, T2-w FSE MRI shows lesion enlargement (arrow) with markedly hyperintense areas of cystic change (B) and T1-w gradient echo image in the portal phase after intravenous injection of gadolinium well depicts peripheral areas of contrast enhancement due to viable tumoral tissue (arrowhead) and central area of cystic change (asterisk) (C).*

response to imatinib in patients with metastatic GIST (65). The European Organization for Research and Treatment of Cancer (EORTC) has provided both qualitative and semi-quantitative criteria of FDG uptake, such as the standardized uptake value (SUV), to assess metabolic response (66, 67). A decrease of more than 25% in the maximum SUV from the baseline value was documented within the first month of imatinib therapy and as early as 24 h after a single dose of imatinib (68). The integration of FDG-PET and CT, as in the combined hybrid PET/CT scanners now available, offers a way to optimize the evaluation of patients with GIST treated with molecularly targeted drugs, as well as providing a problem-solving technique when CT or MRI are inconclusive (69). However, in more than 20% of lesions, glucose uptake before treatment is not sufficient as to be detected with PET, thus reducing its clinical applications (70).

Diffusion-weighted MRI (DWI), a particular techique sensitive to the microscopic motion of water molecules, may provide a functional quantitative indicator, the ADC, as a surrogate marker of tissue cellularity (71-73). On DWI, response to treatment is indicated by increase in ADC values compared to the pretreatment values, and may be seen as early as 1 week after imatinib therapy (74, 75). Recent developments in DWI may also provide new prognostic biomarkers and indicators of tumor response to targeted molecular therapy (76).

Contrast material–enhanced US was also suggested as a possibly biomarker of vascularization and in a study was found that decreased contrast material uptake at 7 and 14 days after treatment was correlated with good response of GISTs to imatinib (77).

Although effective in most patients with GIST, the development of resistance or intolerance to imatinib has been encountered. Such patients may experience clinical benefit from other molecular targeted therapy, as sunitinib and regorafenib (78). The clinical benefit rates of sunitinib and regorafenib using the different response to treatment criteria (RECIST or Choi) have been evaluated only in small cohorts of patients and should be validated using larger study cohorts (79, 80).

Treatment-related complications. Imaging may help in the early diagnosis of imatinib-related complications, such as bleeding into the gastrointestinal tract or intratumoral sites and fluid retention: pleural effusion, pulmonary edema, and ascites (81, 82). Other common abdominal toxicities related to molecular targeted therapies include hepatitis, cholecystitis, pancreatitis and infection (81). Radiologists should also be aware of intestinal complications associated with molecular targeted therapy, including pneumatosis, bowel perforation, and fistula formation (83).

Conclusion

Once considered an obscure tumor with poor prognosis, GISTs are nowadays recognized as the most common mesenchymal tumors of the alimentary tract and set as a new paradigm for cancer treatment. Imaging provides valuable information on detection, characterization, staging and prediction of treatment response of GISTs, contributing to optimization of patient management in all phases of treatment. Radiologists should be aware of all imaging issues related to GISTs, since a multidisciplinary team gathering different expertise is usually needed to properly treat patients with GISTs.

Conflicts of Interest

None.

References

1　Miettinen M and Lasota J: Gastrointestinal stromal tumors. Gastroenterol Clin North Am *42*: 399-415, 2013,

2　Joensuu H, Hohenberger P and Corless CL: Gastrointestinal stromal tumour. Lancet *382*: 973-983, 2013.

3　Miettinen M and Lasota J: Histopathology of gastrointestinal stromal tumor. J Surg Oncol 104: 865-873, 2011.

4　Corless CL, Barnett CM and Heinrich MC: Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer *11*: 865-878, 2011.

5　Min KW: Gastrointestinal stromal tumor: an ultrastructural investigation on regional differences with considerations on their histogenesis. Ultrastruct Pathol *34*: 174-188, 2010.

6　Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH and Weiss SW: Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol *33*: 459-465, 2002.

7　Marrari A, Wagner AJ and Hornick JL: Predictors of response to targeted therapies for gastrointestinal stromal tumors. Arch Pathol Lab Med *136*: 483-489, 2012.

8　Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Sufliarsky J, Federico M, Jonasson JG, Dei Tos AP and Rutkowski P: Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol *13*: 265-274, 2012.

9　Caterino S, Lorenzon L, Petrucciani N, Iannicelli E, Pilozzi E, Romiti A, Cavallini M and Ziparo V: Gastrointestinal stromal tumors: correlation between symptoms at presentation, tumor location and prognostic factors in 47 consecutive patients. World J Surg Oncol *9*: 13, 2011.

10　Levy AD, Remotti HE, Thompson WM, Sobin LH and Miettinen M: Gastrointestinal stromal tumors: radiologic features with pathologic correlation. RadioGraphics *23*: 283-304. 456, 2003.

11　Li YZ and Wu PH: Conventional radiological strategy of common gastrointestinal neoplasms. World J Radiol *7*: 7-16, 2015.

12　King DM: The radiology of gastrointestinal stromal tumours (GIST). Cancer Imaging *5*: 150-156, 2005.

13　Bartolotta TV, Taibbi A, Midiri M and Lagalla R: Focal liver lesions: contrast-enhanced ultrasound. Abdom Imaging *34*: 193-209, 2009.

14　Kochhar R, Manoharan P, Leahy M and Taylor MB: Imaging in gastrointestinal stromal tumours: current status and future directions. Clin Radiol *65*: 584-592, 2010.

15　Bartolotta TV, Taibbi A, Galia M, Cannella I, Lo Re G, Sparacia G, Midiri M and Lagalla R: Gastrointestinal stromal tumour: 40-row multislice computed tomography findings. Radiol Med *111*: 651-660, 2006.

16　Chourmouzi D, Sinakos E, Papalavrentios L, Akriviadis E and Drevelegas A: Gastrointestinal stromal tumors: a pictorial review. J Gastrointestin Liver Dis *18*: 379-383, 2009.

17　Suster S: Gastrointestinal stromal tumors. Semin Diagn Pathol *13*: 297-313,1996.

18　Ghanem N, Altehoefer C, Furtwängler A, Winterer J, Schäfer O, Springer O, Kotter E and Langer M: Computed tomography in gastrointestinal stromal tumors. Eur Radiol *13*: 1669-1678, 2003.

19　Sandrasegaran K, Rajesh A, Rushing DA, Rydberg J, Akisik FM and Henley JD: Gastrointestinal stromal tumors: CT and MRI findings. Eur Radiol *15*: 1407-1414, 2005.

20　Kim HC, Lee JM, Kim SH, Park SH, Lee JW, Lee M, Han JK and Choi BI: Small gastrointestinal stromal tumours with focal areas of low attenuation on CT: pathological correlation. Clin Radiol *60*: 384-388, 2005.

21　Catalano O, De Lutio di Castelguidone E, Nunziata A, De Rosa V and Siani A: Gastrointestinal stromal tumours: Pictorial review. Radiol Med *110*: 484-491, 2005.

22　Lau S, Tam KF, Kam CK, Lui CY, Siu CW, Lam HS and Mak KL: Imaging of gastrointestinal stromal tumour (GIST). Clin Radiol *59*: 487-498, 2004.

23　Amano M, Okuda T, Amano Y, Tajiri T and Kumazaki T: Magnetic resonance imaging of gastrointestinal stromal tumor in the abdomen and pelvis.Clin Imaging *30*: 127-131, 2006.

24　Yu MH, Lee JM, Baek JH, Han JK and Choi BI: MRI features of gastrointestinal stromal tumors. AJR *203*: 980-991, 2014.

25　Hasegawa S, Semelka RC, Noone TC, Woosley JT, Marcos HB, Kenney PJ and Siegelman ES: Gastric stromal sarcomas: correlation of MR imaging and histopathologic findings in nine patients. Radiology *208*: 591-595, 1998.

26　Jiang ZX, Zhang SJ, Peng WJ and Yu BH: Rectal gastrointestinal stromal tumors: imaging features with clinical and pathological correlation. World J Gastroenterol *19*: 3108-3116, 2013.

27　Choi YR, Kim SH, Kim SA, Shin CI, Kim HJ, Kim SH, Han JK and Choi BI: Differentiation of large (≥5 cm) gastrointestinal stromal tumors from benign subepithelial tumors in the stomach: radiologists' performance using CT. Eur J Radiol *83*: 250-260, 2014.

28　Choi JW, Choi D, Kim KM, Sohn TS, Lee JH, Kim HJ and Lee SJ: Small submucosal tumors of the stomach: differentiation of gastric schwannoma from gastrointestinal stromal tumor with CT. Korean J Radiol *2012;13*: 425-433, 2012.

29　Hargunani R, Maclachlan J, Kaniyur S, Power N, Pereira SP and Malhotra A: Cross-sectional imaging of gastric neoplasia. Clin Radiol *64*: 420-429, 2009.

30　Cheng JM, Tirumani SH, Shinagare AB, Jagannathan JP, Hornick JL, Raut CP and Ramaiya NH: MDCT of primary, locally recurrent, and metastatic duodenal gastrointestinal stromal tumours (GISTs): a single-institution study of 25 patients with review of literature. Clin Radiol *69*: 137-144, 2014.

31　Koch MR, Jagannathan JP, Shinagare AB, Krajewski KM, Raut CP, Hornick JL and Ramaiya NH: Imaging features of primary anorectal gastrointestinal stromal tumors with clinical and pathologic correlation. Cancer Imaging *12*: 557-565, 2012.

32　Connolly EM, Gaffney E and Reynolds JV: Gastrointestinal stromal tumours. Br J Surg *90*: 1178-1186, 2003.

33　Burkill GJ, Badran M, Al-Muderis O, Meirion Thomas J, Judson IR, Fisher C and Moskovic EC: Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. Radiology *226*: 527-532, 2003.

34　Tirumani SH, Jagannathan JP, Krajewski KM, Shinagare AB, Jacene H and Ramaiya NH: Imatinib and beyond in gastrointestinal stromal tumors: A radiologist's perspective. AJR *201*: 801-810, 2013.

35　Dematteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM and Brennan MF: Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg *231*: 51-58, 2000.

36 Kim HC, Lee JM, Kim KW, Park SH, Kim SH, Lee JY, Han JK and Choi BI: Gastrointestinal stromal tumors of the stomach: CT findings and prediction of malignancy. AJR *183*: 893-898, 2004.

37 Dematteo RP, Heinrich MC, El-Rifai WM and Demetri G: Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol *33*: 466-477, 2002.

38 Yu MH, Lee JM, Baek JH, Han JK and Choi BI: MRI features of gastrointestinal stromal tumors. AJR *203*: 980-991, 2014.

39 Casali PG and Blay J-Y: Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *21(Suppl. 5)*: v98-102, 2010.

40 Miettinen M, El-Rifai W, H L Sobin L and Lasota J: Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. Hum Pathol *33*: 478-483, 2002

41 Miettinen M and Lasota J: Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med *130*: 1466-1478, 2006.

42 Miettinen M, Sobin LH and Lasota J: Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohisto-chemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol *29*: 52-68, 2005.

43 Miettinen M, Makhlouf H, Sobin LH and Lasota J: Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol *30*: 477-489, 2006.

44 Plumb AA, Kochhar R, Leahy M and Taylor MB: Patterns of recurrence of gastrointestinal stromal tumour (GIST) following complete resection: implications for follow-up. Clin Radiol *68*: 770-775, 2013.

45 Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B and Demetri GD: Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastro-intestinal stromal tumor. N Engl J Med *344*: 1052-1056, 2001.

46 Joensuu H, Fletcher C, Dimitrijevic S, Silberman S, Roberts P and Demetri G: Management of malignant gastrointestinal stromal tumours. Lancet Oncol *3*: 655-664, 2002.

47 Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, Corless CL, Fletcher CD, Roberts PJ, Heinz D, Wehre E, Nikolova Z and Joensuu H: Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol *26*: 620-625, 2008.

48 Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, Raymond AK, Bramwell VH, Baker LH, Maki RG, Tanaka M, Hecht JR, Heinrich MC, Fletcher CD, Crowley JJ and Borden EC: Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the KIT receptor tyrosine kinase: S0033. J Clin Oncol *26*: 626-632, 2008.

49 Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, Issels R, van Oosterom A, Hogendoorn PC, Van Glabbeke M, Bertulli R and Judson I: Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet *364*: 1127-1134, 2004.

50 Stroszczynski C, Jost D, Reichardt P, Chmelik P, Gaffke G, Kretzschmar A, Schneider U, Felix R and Hohenberger P: Follow-up of gastro-intestinal stromal tumours (GIST) during treatment with imatinib mesylate by abdominal MRI. Eur Radiol *15*: 2448-2456, 2005.

51 Keun Park C, Lee EJ, Kim M, Lim HY, Choi DI, Noh JH, Sohn TS, Kim S, Kim MJ, Lee HK and Kim KM: Prognostic stratification of high-risk gastrointestinal stromal tumors in the era of targeted therapy. Ann Surg *247*: 1011-1018, 2008.

52 De Leo C, Memeo M, Spinelli F and Angelelli G: Gastrointestinal stromal tumours: experience with multislice CT. Radiol Med *111*: 1103-1114, 2006.

53 Da Ronch T, Modesto A and Bazzocchi M: Gastrointestinal stromal tumour: spiral computed tomography features and pathologic correlation. Radiol Med *111*: 661-673, 2006.

54 Nishino M, Jagannathan JP, Ramaiya NH and Van den Abbeele AD: Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. AJR *195*: 281-289, 2010.

55 van Persijn van Meerten EL, Gelderblom H and Bloem JL: RECIST revised: implications for the radiologist. A review article on the modified RECIST guideline. Eur Radiol *20*: 1456-1467, 2010.

56 Warakaulle DR and Gleeson F: MDCT appearance of gastrointestinal stromal tumors after therapy with imatinib mesylate. AJR *186*: 510-515, 2006.

57 Tirkes T, Hollar MA, Tann M, Kohli MD, Akisik F and Sandrasegaran K: Response criteria in oncologic imaging: review of traditional and new criteria. Radiographics *33*: 1323-1341, 2013.

58 Choi H, Charnsangavej C, de Castro Faria S, Tamm EP, Benjamin RS, Johnson MM, Macapinlac HA and Podoloff DA: CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR *183*: 1619-1628, 2004.

59 Abdulkader I, Cameselle-Teijeiro J and Forteza J: Pathological changes related to imatinib treatment in a patient with a metastatic gastrointestinal stromal tumour. Histopathology *46*: 470-472, 2005.

60 Hong X, Choi H, Loyer EM, Benjamin RS, Trent JC and Charnsangavej C: Gastrointestinal stromal tumor: role of CT in diagnosis and in response evaluation and surveillance after treatment with imatinib. Radiographics *26*: 481-495, 2006.

61 Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA and Benjamin RS: Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol *25*: 1753-1759, 2007.

62 Shankar S, vanSonnenberg E, Desai J, DiPiro PJ, Van den Abbeele A and Demetri GD: Gastrointestinal stromal tumor: new nodule-within-a-mass pattern of recurrence after partial response to imatinib mesylate. Radiology *235*: 892-898, 2005.

63 Phongkitkarun S, Phaisanphrukkun C, Jatchavala J and Sirachainan E: Assessment of gastrointestinal stromal tumors with computed tomography following treatment with imatinib mesylate. World J Gastroenterol *14*: 892-898, 2008.

64 Benjamin RS, Choi H, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA and Charnsangavej C: We should desist using RECIST, at least in GIST. J Clin Oncol *25*: 1760-1764, 2007.

65 Heinicke T, Wardelmann E, Sauerbruch T, Tschampa HJ, Glasmacher A and Palmedo H: Very early detection of response to imatinib mesylate therapy of gastrointestinal stromal tumours using 18fluoro-deoxyglucose positron-emission tomography. Anticancer Res 25: 4591-4594, 2005.

66 Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, Pruim J and Price P: Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 35: 1773-1782, 1999.

67 D'Amico A: Review of clinical practice utility of positron emission tomography with 18F-fluorodeoxyglucose in assessing tumour response to therapy. Radiol Med 120: 345-351, 2015.

68 Van den Abbeele AD, Badawi RD, Cliche JP, Spangler T, Janicek MJ, Israel DA, Heinrich MC, Silberman SS, Dimitrijevic S and Demetri GD: FDG-PET as a surrogate marker for the response to Gleevec (imatinib mesylate) in patients with advanced gastrointestinal stromal tumors (GIST). J Nucl Med 44(suppl): 24-25, 2003.

69 Van den Abbeele AD: The lessons of GIST–PET and PET/CT: a new paradigm for imaging. Oncologist 13: 8-13, 2008.

70 Choi H: Response evaluation of gastrointestinal stromal tumors. Oncologist 13(Suppl 2): 4-7, 2008.

71 Bammer R: Basic principles of diffusion-weighted imaging. Eur J Radiol 45: 169-184, 2003.

72 Giganti F, Salerno A, Ambrosi A, Chiari D, Orsenigo E, Esposito A, Albarello L, Mazza E, Staudacher C, Del Maschio A and De Cobelli F: Prognostic utility of diffusion-weighted MRI in oesophageal cancer: is apparent diffusion coefficient a potential marker of tumour aggressiveness? Radiol Med 121: 173-180, 2016.

73 Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, Hammoud DA, Rustin GJ, Taouli B and Choyke PL: Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 11: 102-125, 2009.

74 Tang L, Zhang XP, Sun YS, Shen L, Li J, Qi LP and Cui Y: Gastrointestinal stromal tumors treated with imatinib mesylate: apparent diffusion coefficient in the evaluation of therapy response in patients. Radiology 258: 729-738, 2011.

75 Gong NJ, Wong CS, Chu YC and Gu J: Treatment response monitoring in patients with gastrointestinal stromal tumor using diffusion-weighted imaging: preliminary results in comparison with positron emission tomography/computed tomography. NMR Biomed 26: 185-192, 2013.

76 Zhou HY, Zhang XM, Zeng NL, Jian SH and Tang W: Use of conventional MR imaging and diffusion-weighted imaging for evaluating the risk grade of gastrointestinal stromal tumors. J Magn Reson Imaging 36: 1395-1401, 2012.

77 Lassau N, Lamuraglia M, Chami L, Leclère J, Bonvalot S, Terrier P, Roche A and Le Cesne A: Gastrointestinal stromal tumors treated with imatinib: monitoring response with contrast-enhanced sonography. AJR 187: 1267-1273, 2006.

78 Garlipp B and Bruns CJ: State of the art in the treatment of gastrointestinal stromal tumors. Gastrointest Tumors 1: 221-236, 2014.

79 Shinagare AB, Jagannathan JP, Kurra V, Urban T, Manola J, Choy E, Demetri GD, George S and Ramaiya NH: Comparison of performance of various tumour response criteria in assessment of regorafenib activity in advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib. Eur J Cancer 50: 981-986, 2014.

80 Schramm N, Englhart E, Schlemmer M, Hittinger M, Übleis C, Becker CR, Reiser MF and Berger F: Tumor response and clinical outcome in metastatic gastrointestinal stromal tumors under sunitinib therapy: comparison of RECIST, Choi and volumetric criteria. Eur J Radiol 82: 951-958, 2013.

81 Dagher R, Cohen M, Williams G, Rothmann M, Gobburu J, Robbie G, Rahman A, Chen G, Staten A, Griebel D and Pazdur R: Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 8: 3034-3038, 2002.

82 Kim KW, Shinagare AB, Krajewski KM, Pyo J, Tirumani SH, Jagannathan JP and Ramaiya NH: Fluid retention associated with imatinib treatment in patients with gastrointestinal stromal tumor: quantitative radiologic assessment and implications for management. Korean J Radiol 16: 304-313, 2015.

83 Howard SA, Krajewski KM, Thornton E, Jagannathan JP, O'Regan K, Cleary J and Ramaiya N: Decade of molecular targeted therapy: abdominal manifestations of drug toxicities–What radiologists should know. AJR 199: 58-64, 2012.

84 Shinagare AB, Howard SA, Krajewski KM, Zukotynski KA, Jagannathan JP and Ramaiya NH: Pneumatosis intestinalis and bowel perforation associated with molecular targeted therapy: an emerging problem and the role of radiologists in its management. AJR 2012; 199: 1259-1265, 2012.