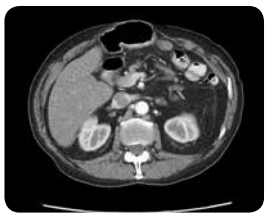

GASTROINTESTINAL STROMAL TUMORS; IS IT APPROPRIATE TO USE RECIST CRITERIA IN ALL CASES? CASE PRESENTATION AND REVIEW

Tumores estromales gastrointestinales, ¿es adecuado el uso de los criterios RECIST en todos los casos?

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Tomography, X-ray computed

Palabras clave (DeCS)
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Summary
The Gastrointestinal Stromal Tumor [GIST] is the most common non-epithelial tumor of the gastrointestinal tract (90%) and 2-3% of all gastric malignancies, with an annual incidence of 4500-6000 cases in the United States. On the other hand, they are tumors whose incidence is estimated at 6 to 20 per million. The response of these tumors to conventional cytotoxic treatment does not have the same impact as other tumors, which is why new substances have arisen to combat them; Amongst them Imatinib, which is a selective and potent competitive inhibitory molecule of the tyrosine kinase enzymes and the transcription of some mutated proto-oncogenes. Additionally, the conventional scale for staging and follow-up RECIST does not accurately reflect the evolution of these tumors and their response to treatment, as does the Choi scale. On the other hand, the emergence of FDG-PET has allowed a much more accurate evaluation of the evolution and response to treatment of these tumors.

Resumen
El tumor gastrointestinal estromal (GIST, por siglas en inglés), es el tumor no epitelial más común del tracto gastrointestinal (90 %) y el 2-3 % de todas las malignidades gástricas, con incidencia anual de 4.500-6.000 casos en Estados Unidos. Por otro lado, son tumores cuya incidencia se calcula entre 6 y 20 por millón. La respuesta de estos tumores al tratamiento citotóxico convencional no tiene el mismo impacto que otros tumores, razón por la cual surgieron nuevas sustancias para combatirlos; entre ellas, el imatinib, el cual es una molécula inhibidora competitiva, selectiva y potente de las enzimas tirosinacinasa y de la transcripción de algunos protooncogenes mutados. Adicionalmente, la escala convencional para estadificación y seguimiento RECIST tampoco refleja de forma acertada la evolución de estos tumores y su respuesta al tratamiento, como sí lo hace la escala de Choi. El surgimiento del FDG-PET ha permitido una valoración mucho más fehaciente de la evolución y respuesta al tratamiento de estos tumores.

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1. Case presentation

Patient of 78 years of age, with diagnosis of gastrointestinal stromal tumor of 6 years of evolution, of high malignant potential in the stomach, managed with vertical gastrectomy and imatinib of palliative form, given that he had relapse with appearance of masses in the gastric wall of the major curvature, of exophytic growth and with heterogeneous enhancement after the administration of intravenous contrast medium. The patient manifests abdominal pain, diarrhea and vomiting attributed to adverse event of interaction with other drugs, so imatinib is suspended for three months; however, it is restarted by peritoneal progression. Additionally, there is evidence of peritoneal nodules in the major omentum similar to the gastric lesion described.

This patient underwent scans on three different dates separated by eight and four months, respectively.

In the initial images (figures 1a and b) a solid mass of low density is observed in the wall of the gastric antrum in the major curvature, of exophytic growth, without enhancement with the contrast medium. It is also possible to identify other intramural lesions, of similar characteristics, but of smaller size in the greater curvature of the stomach. In addition, some intraperitoneal nodules located in the major omentum of heterogeneous density and without enhancement inside with the contrast medium are identified (Figures 1 c and d). Figures 1e and f show the densities obtained for gastric mass (16.7 UH) and mesenteric mass (29 UH).

In the follow-up, eight months later, the significant increase in the dimensions of the gastric mass was observed, and heterogeneous enhancement (figures 2 a and b). The additional lesions of the gastric wall were not modified, but the intraperitoneal nodules did increase their dimensions significantly (figures 2 c and d), and small irregular areas of enhancement could be observed inside the nodules with the contrast medium (figure 2 d). A gastric mass density of 43.9 UH (Figure 2 e) and a mesenteric mass of 29 UH (Figure 2 f) were identified.

Within four months after the images mentioned above were taken, the gastric mass of the greater curvature described had increased in size much more and was evidenced by greater enhancement with the contrast medium (Figures 3 a and b). The other gastric wall nodules remained unchanged. It is interesting to note that the nodules of the major omentum had decreased in size, though they presented new irregular areas of heterogeneous enhancement with the contrast medium (Figures 3 c and d). A density of 67 UH in the gastric mass and 70 UH in the mesenteric mass (figures 3 e and f) could be observed in this last examination.

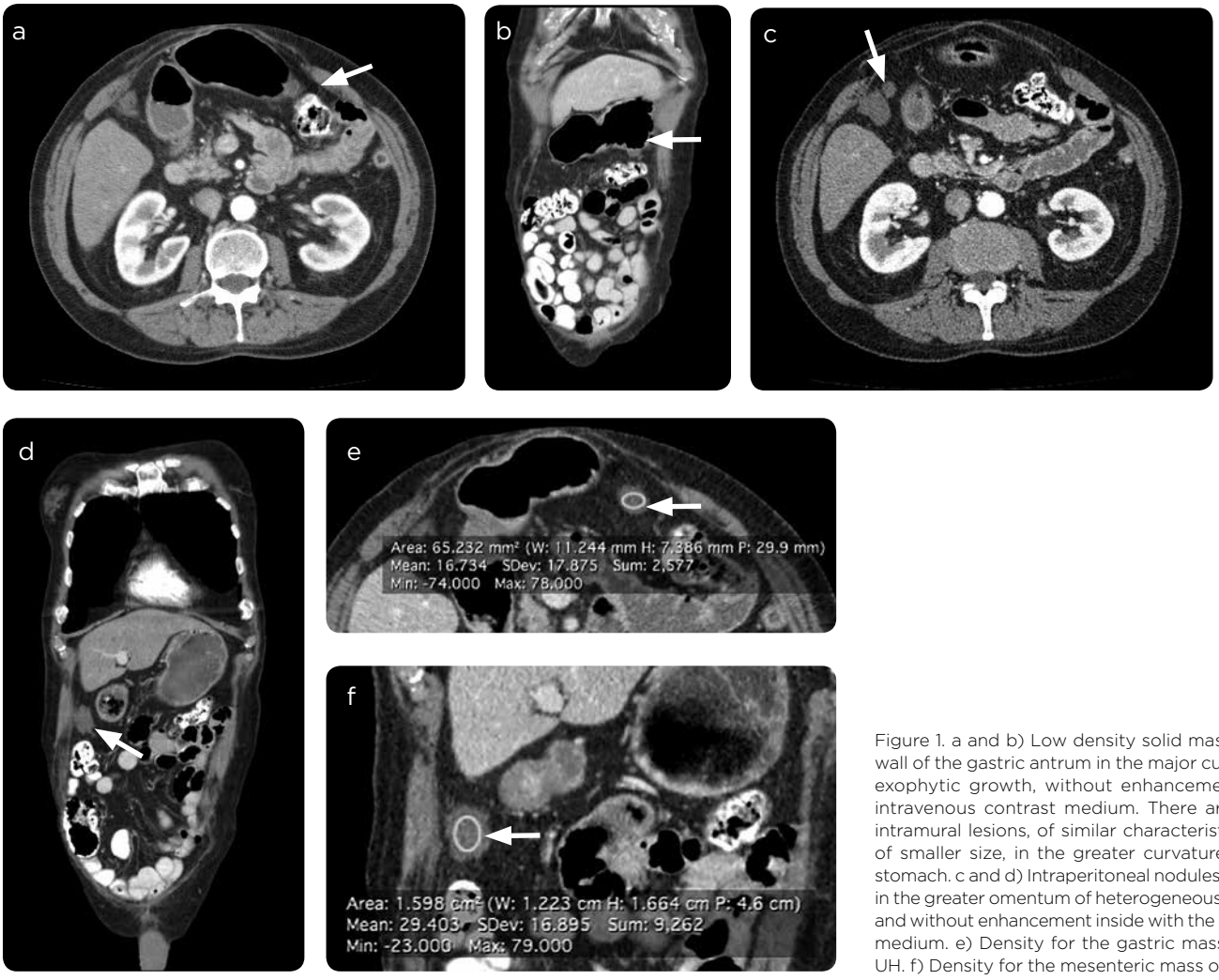

Figure 1. a and b) Low density solid mass in the wall of the gastric antrum in the major curvature, exophytic growth, without enhancement with intravenous contrast medium. There are other intramural lesions, of similar characteristics, but of smaller size, in the greater curvature of the stomach. c and d) Intraperitoneal nodules located in the greater omentum of heterogeneous density and without enhancement inside with the contrast medium. e) Density for the gastric mass of 16.7 UH. f) Density for the mesenteric mass of 29 UH.

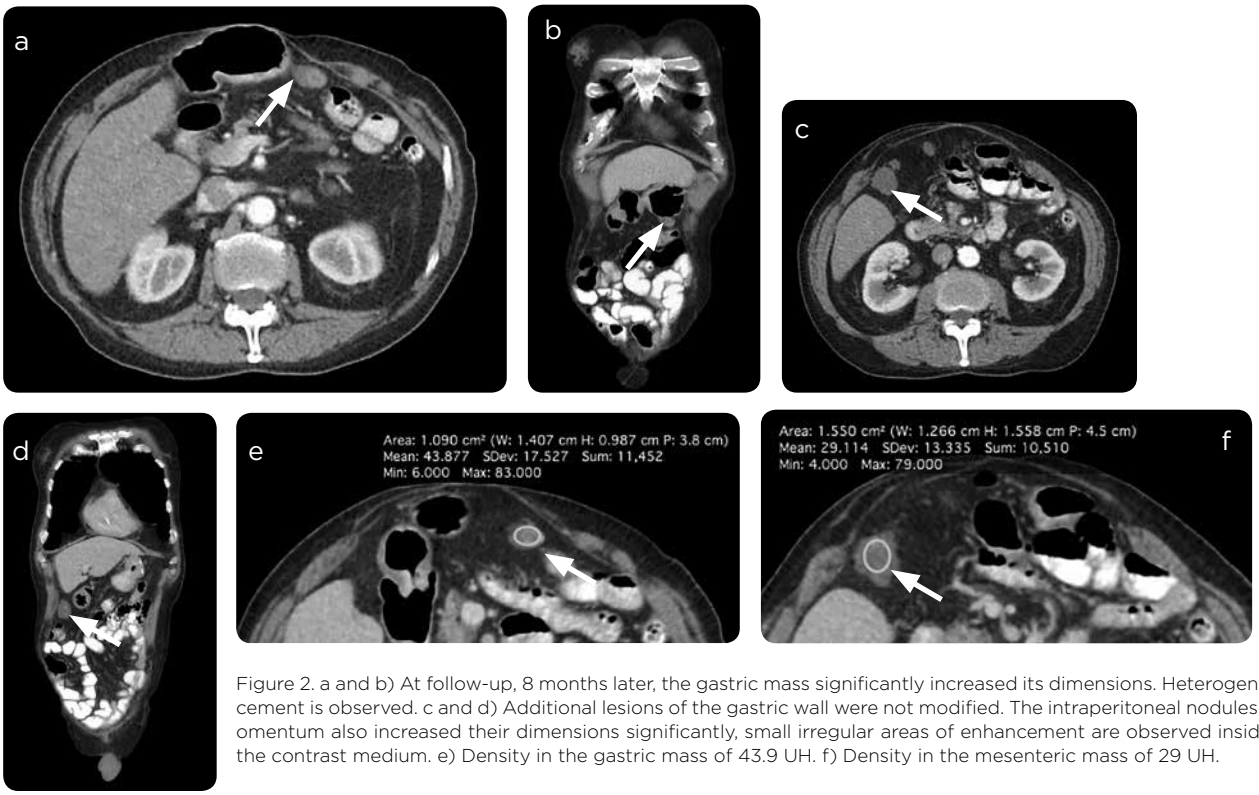

Figure 2. a and b) At follow-up, 8 months later, the gastric mass significantly increased its dimensions. Heterogeneous enhancement is observed. c and d) Additional lesions of the gastric wall were not modified. The intraperitoneal nodules in the major omentum also increased their dimensions significantly, small irregular areas of enhancement are observed inside them with the contrast medium. e) Density in the gastric mass of 43.9 UH. f) Density in the mesenteric mass of 29 UH.

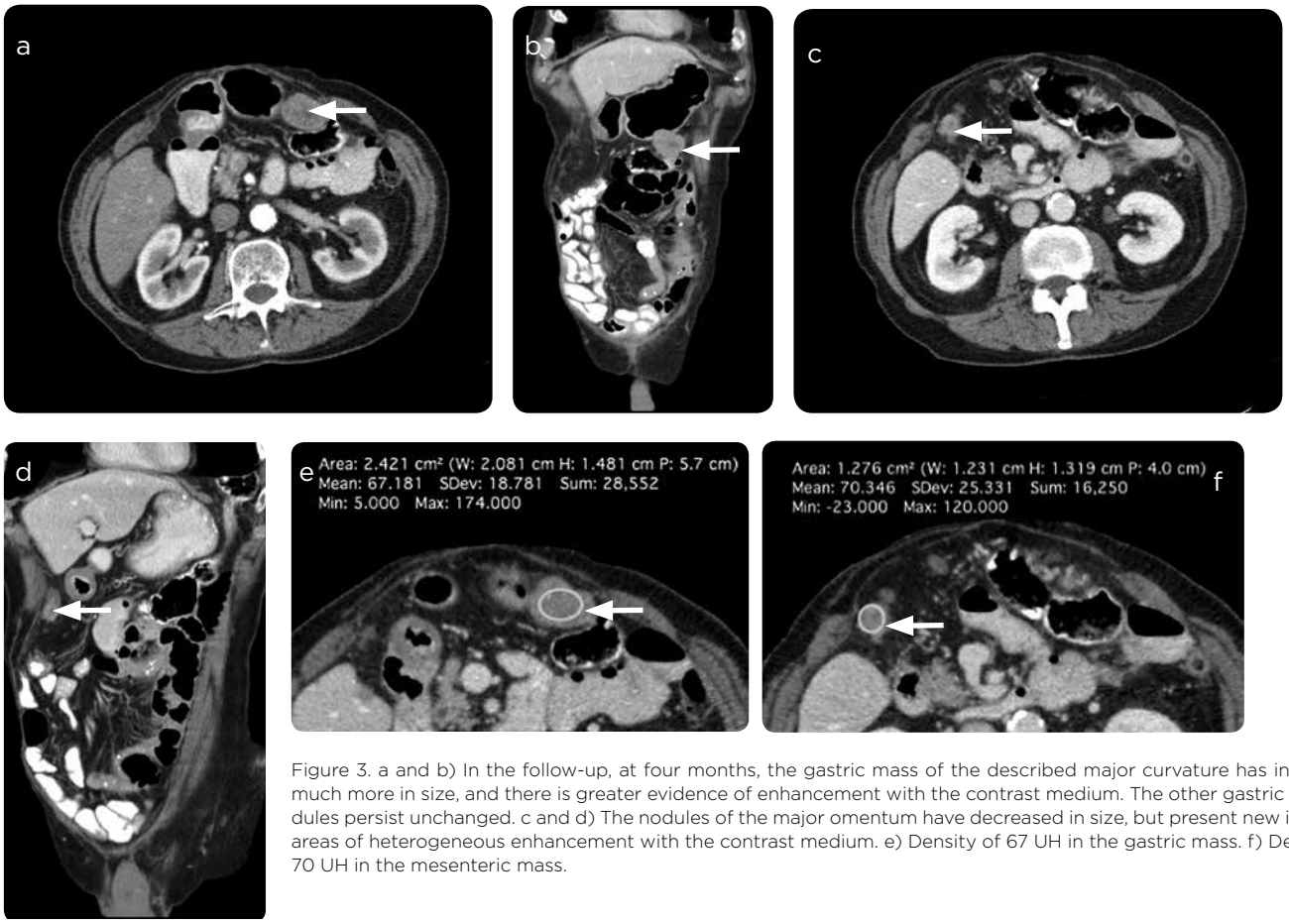

Figure 3. a and b) In the follow-up, at four months, the gastric mass of the described major curvature has increased much more in size, and there is greater evidence of enhancement with the contrast medium. The other gastric wall nodules persist unchanged. c and d) The nodules of the major omentum have decreased in size, but present new irregular areas of heterogeneous enhancement with the contrast medium. e) Density of 67 UH in the gastric mass. f) Density of 70 UH in the mesenteric mass.

2. Discussion

Gastrointestinal stromal tumours (GIST) correspond to 0,1-0,3 % of all gastrointestinal tumours, 80 % of gastrointestinal sarcomas and 5,7 % of sarcomas in general (1-5). The age of onset is between 60 and 69 years; in a series only 2,7 % of gastric and 0,6 % of small intestine sarcomas were detected in children under 20 years of age, no clear predilection of gender, ethnicity, occupation or geographical distribution has been identified (1,6-17). They have an incidence of approximately 7 to 20 cases per million (1,6-8,9,12,18).

These neoplasms arise from the interstitial cells of Cajal, which are specialized leiomyocytes, with conductive capacity, located in the myenteric plexus and intermingled among the rest of the smooth muscle layers, whose function is to serve as a pacemaker in intestinal peristalsis, to produce cyclic depolarizations of slow waves (3,12,19,20). These cells have transmembrane tyrosine kinase receptors encoded by the KIT gene. These receptors, when stimulated by a ligand, autophosphorylate and initiate an intracellular cascade of second intracellular messengers with phosphorylation or enzyme dephosphorylation. This generates a stimulus of transcription factors and enzymes, with variable effects, predominantly metabolic (20-22). About 80-95 % of GISTs have oncogenic mutation in the KIT gene (CD117), in particular exon 11 (although also exons 9, 13 and 17), and about 70 % additionally express CD34. Other markers may be present, such as PDGFRA TK1 (exons 12, 14 and 18), smooth muscle actin (30-40 %), H-caldesmon and protein S100 (5 %) (1,2,5-7,10-13,15,16,19,21,23-31). However, there are "KIT-negative" GIST tumours, which correspond to approximately 5% (1,15,26,27,32).

They can be located anywhere in the gastrointestinal tract (1,2,7,11,21,33,34):

- Stomach: 50-70 %.
- Small intestine: 20-30 %.
- Colon: 10 %.
- Omentum and mesentery: 7 %
- Esophagus: 5 %.
- Appendix: <1 %.

These are usually solitary and benign lesions, particularly when they are less than 2 cm, but their size can vary from a few millimetres to 30 cm or more; however, in general, 20-30 % of gastric GIST and 40-50 % of the intestines are malignant in their initial presentation (1,2,3,7,11, 28,33). Clinically, the existence of these tumors may be suspected because they present with intra-abdominal or gastrointestinal hemorrhage (30-40 %), perforation, intestinal obstruction, intra-abdominal mass or as an incidental finding in surgery or diagnostic images. Most of their symptoms (60-70 %) are non-specific (early satiety, indigestion and poorly defined abdominal pain), which, added to their exophytic growth, means that they are usually detected late (1,3,4,7,14,17,19,35). In up to 70% of the cases the patients are symptomatic, in 20% they are asymptomatic and their finding is incidental and in 10% they are detected in autopsy (21).

Patients with neurofibromatosis type I have a higher prevalence of GIST. Additionally, gastrointestinal stromal tumors are a common finding in the Carney triad, which is a rare condition associated with epithelioid leiomyosarcoma, paraganglioma, and pulmonary chondroma (2,7,11,12,16,27,36).

The worst prognostic factors are: advanced age, large tumors (>5 cm), irresectability, metastasis at initial presentation, tumor necrosis, high mitotic index and distal intestinal localization. The disease-free survival rate in non-metastatic GIST malignant is about 5 years and only 10-20 months if metastases are present (2,3,6,7,11,12,27,31,35,37).

Metastases appear in 50-60% of cases, first in the liver followed by peritoneum, retroperitoneum, lung, subcutaneous, pleura and bone (1-3,19,21,37). They usually develop 1 to 2 years after an apparent complete excision, while some GIST develop late metastases in 5 to 15 years after primary surgery (7,13). Lymph node metastases, contrary to adenocarcinomas, are very rare and these lesions tend to have imaging characteristics similar to those of the primary tumor (3,19).

Differential diagnosis is given by other mesenchymal neoplasms, such as schwannomas, neurofibromas, leiomyomas, leiomyosarcomas and neuroendocrine tumors (solitary carcinoid tumors). Occasionally, an adenocarcinoma or gastric lymphoma may have an intramural tumor growth that is similar to GIST; however, in its advanced stages it is usually associated with perigastric or celiac adenopathies, which is rare in GIST (1-3,12,33).

Surgical resection continues to be the main therapeutic measure in the treatment of localized primary GIST that has no evidence of metastasis and should be the initial therapy if the tumor is resectable with an acceptable risk of morbidity; however, in most patients there is recurrence (even in complete resection with tumor-free margins), in an average time of two years (1,7,11,12,18,35,37).

The response of these tumors to conventional cytotoxic treatment is not effective (1,2,18,24,26,38,39). On the other hand, surgery is particularly useful after tyrosine kinase inhibitor (TKI) therapy (1,3,14,15,26,28,37,39,40). Lymphadenectomy is usually unnecessary, since lymph node metastasis is rare in GIST and sarcomas in general (2,3,27,41).

It is therefore essential to discuss the new molecular therapies, among which imatinib mesylate stands out as the main treatment for these tumors in patients who do not meet the surgical requirements. This drug competitively and selectively inhibits tyrosine kinase enzymes, including KIT receptors (CD117), PDGFR and leukemic cell-specific BCR-ABL chimera (1, 10, 21, 23). Mutations and activation in the first two receptors are associated with oncogenic signaling in GIST tumors, as well as with unrestricted growth and resistance to apoptosis. Immunohistochemical identification of these receptors is key in the diagnosis of up to 95% of cases (2,6,7,10-13,18,23,27,42).

Imatinib is associated with partial objective response in about 70-80 % of patients, even with follow-up at one and a half years, and a therapeutic effect can be observed in an average of three months since its inception (1,23,27,28,39). Most patients with metastasis respond to imatinib therapy, with remission after two years of treatment. It should be noted that the maximum response to imatinib, in terms of tumor size at any location, may not occur until after 6 to 12 months of drug use, as discussed below (1,14,21,23,28,39).

3. Diagnostic images

Scanning with endovenous contrast medium is the technique of choice for characterising these tumours, for monitoring the effects of treatment and for detecting their progression (1,19,34,43).

The characteristics of GIST scans vary considerably depending on the size and aggressiveness throughout the course of the disease; However, these are typically large solid masses (average 13 cm +/- 6, range 4-31 cm), hypervascular, with a predominantly peripheral enhancement pattern (up to 92 %), commonly less homogeneous (25 %), usually exophytic (extraluminal) growth (75 %), well-delimited margins with heterogeneous density by necrosis, haemorrhage or cystic degeneration, even in their initial presentation, and with heterogeneous enhancement with endovenous contrast medium. Most occur in the stomach, but only 14% of cases are observed as an intraluminal polypoid mass and calcifications are a very unusual finding (< 5%) (1,2,3,19,33,34,44).

In the case series published by Warakaulle, central fluid attenuation was found in up to 67% of tumors, indicative of internal necrosis and is usually more common in tumors larger than 3 cm (45). In addition, fistulization towards the light of the gastrointestinal tract and pressure ulceration is also possible, occurring in 50% of lesions larger than 2 cm, a finding known as the "target sign" (2,3,19,34,43,44).

The use of intravenous contrast is essential for the evaluation of the degree and pattern of enhancement and for observing the tumour vessels, which will define their response to treatment and their evolution. However, a conventional portal phase may mask the hypervascular liver metastatic lesions of the GIST, since the tumor enhancement becomes similar to that of the healthy liver parenchyma, so a multiphase scan is required, including simple slices to assess for intratumoral hemorrhage (1,3,19).

Similar to lymphomas, GIST may present with abnormal dilation of the loops of the gastrointestinal tract. This is due to cavitation of these fast-growing tumors that result in an apparent increase in intestinal lumen and myenteric plexus injury. The location of the air in the non-dependent portion of the cavitation is called the "sign of growing Torricelli-Bernoulli necrosis" (33). However, if there are associated lymphadenopathies, these favor the diagnosis of lymphoma (2,33,34).

4. Response evaluation

Scanning is recommended for follow-up of patients who underwent surgical resection, to establish whether there is metastasis or recurrence, every three to six months, and to monitor systemic therapy with TKI from three months of onset (1).

Generally, lesions after one to two months (and sometimes up to a week) are observed with low density or low attenuation, with disappearance of the tumor vessels and nodules that enhance with contrast medium, even when there is no decrease in tumor size and calcifications exist. Additionally, the decrease in tumour size may not go hand in hand with changes in density and patients may have significant symptomatic improvement, even though the tumour has not decreased or even increased in size. For this reason, the increase in size alone does not indicate progression, as it may occur due to hemorrhage or myxoid degeneration. Progression, even after successful treatment of metastatic disease, can be observed with high-density intratumoral nodules, without changes in lesion size or as growth of such nodules. Likewise, after imatinib treatment, a lesion that has grown and is homogeneously hypodense, without nodules that enhance with contrast dye, should not be misinterpreted as disease progression (1,5,19,46,47).

The RECIST criteria are not sensitive to assess response to TKI (1, 5, 19, 46-48). In fact, the Choi criteria are better predictors of tumor progression time and survival than the evaluation of response using the RECIST criteria; the response rate according to the Choi criteria is almost double that compared to the response according to the RECIST criteria (46,47).

Choi's criteria use both density and tumor size to evaluate response to treatment; RECIST criteria value the sum of the largest dimensions of white lesions. They are therefore much more effective at predicting response to imatinib than the RECIST criteria, as a post-treatment GIST tumour may be similar in size or even grow (1,5,19,46-49). These criteria are described in Table 1.

Table 1. Choi Criteria of Tumor Response

Tipo de respuesta	Definition
Complete Response	1. Disappearance of all lesions. 2. No new injuries.
Partial response	1. Decrease in tumor size of 10% or more, or decrease in tumor density (UH) of 15% or more on scan. 2. No new lesions. 3. No obvious progression of non-measurable disease as defined by the RECIST criteria.
Stable disease	1. Does not meet the criteria for full, partial or progressive response. 2. No symptomatic deterioration attributed to tumor progression.
Progressive disease	1. Increase in tumor size of 10% or more and does not meet criteria for partial response by tumor density (UH) on scan. 2. With new lesions. 3. New intratumoral nodules or increased size of existing intratumoral nodules.

Source: Choi et al (49).

In addition, it has also been shown that the RECIST criteria are not as accurate in evaluating response to treatment as PET-FDG is, a tool with which it is possible to stage, restate and monitor the therapeutic response to TKIs, or if the scan is inconclusive or the findings inconsistent with the clinical (1, 4, 19, 48, 50). This examination is more sensitive than the contrast scan (although it does not replace it), since it allows differentiating an active tumor from an inactive necrotic or scar tissue, benign malignant tissue and recurrent tumor from benign changes (1, 5, 28, 50).

Since tumour cells have an increased demand for glucose and fluorodeoxyglucose uptake is proportional to their glycolytic metabolic rate, PET-FDG is of great value, as metabolic changes often precede anatomical changes. Its results can be obtained pseudo-quantitatively with the standardized uptake value (SUV), which is expressed as changes in the SUV or SUVmax, as an absolute value or as a percentage change relative to the baseline measurement, obtained before the start of treatment with TKI. Some of its main utilities are the staging and detection of metastases that are not evident with other examinations, the detection of an unknown primary tumor, the monitoring of response to therapy, the detection of resistance to TKI and the resolution of ambiguities in the scan with contrast medium (1, 19, 28, 48, 50).

If tumors are evaluated with the RECIST criteria, given the minimal reduction or even increase in the size of GIST after treatment, the response may be underestimated and qualified as stable disease. On the other hand, with PET-FDG, reductions of up to 99 % in the maximum standardized uptake value (SUVmax) can be observed compared to the initial value in the majority of patients evaluated (48, 51). Although at the moment there are no clear guidelines available that specify the radiological evaluation of tumour response with this method, a decrease in the max SUV values to < 2.5 or a decrease in the SUV to < 70 % of the baseline study can be considered as a true significant change in glucose metabolism not attributable to imprecision of the technique. A change of more than 25 % of uptake with respect to the baseline study is considered a real change (5, 47, 51). In those who respond more than 10% decrease in tumor size or more than 15% decrease in density can be identified on scan eight weeks after imatinib treatment began (5, 51).

It is striking that this occurs even in a short time; in the first 24 hours a response can be seen and in only one week after treatment a significant response is observed (48, 51). All this implies a greater sensitivity (70-100%) and specificity of this method for the evaluation of the tumour response, based on the tumour metabolism (45, 48, 51).

The lack of glucose uptake in PET-FDG images may be related to the degree of tumor necrosis, myxoid degeneration, pre-chemotherapy and post-treatment scarring. Since the decrease in glucose uptake in some cases cannot be attributed to any of these causes, this method cannot be used to assess tumor response if the base PET-FDG shows negative results for FDG uptake (48, 51). However, in cases in which an increase in the size or density of a lesion is observed by means of scans, to resolve the doubt as to whether it is progression or simple response to treatment with intratumoral haemorrhage, PET-FDG (1) is extremely useful.

In the exposed case, it could be observed that the soft tissue mass located in the major curvature of the stomach (figures 1 a and b, 2 a and b, 3 a and b) gradually grew and presented progressively greater enhancement with the contrast medium, despite management with imatinib, taking into account that there was suspension of the medication at a certain time. In addition, the mass of the right side of the major omentum (figures 1 c and d, 2 c and d, 3 c and d) initially grew, but later decreased in size. If the RECIST criteria are used, and based exclusively on the sum of the larger dimensions, there could be ambiguity in the results since, if the gastric mass and that of the omentum were target lesions and were measured, stability of the disease could be observed since the mass of the omentum decreased significantly in size. However, if Choi's criteria are used, it is observed that, in addition to the fact that the gastric mass had increased in size, its enhancement had also increased and, likewise, the enhancement of the mass of the omentum had increased with respect to the previous study, which would lead to interpreting the study as a disease in progression.

5. Conclusion

Gastrointestinal stromal tumors may have significant anatomical, pathophysiological, and imaging variations from tumors of other cell lines. Additionally, and as could be seen, they present a very particular behavior after therapy. For this reason, it is important to recognize these facts when approaching their diagnosis and response, by means of scan images and FDG-PET, and for this purpose the Choi criteria must be used, which do take these differences into account.

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