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Characteristics of computed tomography imaging of gastrointestinal stromal tumor (GIST) and related diagnostic problems

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Summary

In this article, authors presented several characteristic features of Gastrointestinal Stromal Tumors (GISTs), which may lead to diagnostic errors and unexpected difficulties during interpretation of CT images. In case of GIST, one may encounter problems at every level of diagnostics and treatment response monitoring, especially after introduction of modern molecular targeting therapies. RECIST scale criteria, used until now for evaluation of response to treatment in solid tumors are based merely on the size of the tumor and turned out to be inadequate after introduction of treatment with new molecular target drugs such as Imatinib.

Key words: GIST • CT • imaging

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GIST (gastrointestinal stromal tumor) is currently the most commonly diagnosed sarcoma of the gastrointestinal tract and its incidence is still increasing. Relatively recently, i.e. in 1998, this neoplasm was distinguished from a group of other gastrointestinal tract sarcomas after prof. Hirota had discovered a mutation in cKIT [1] protooncogene, which is crucial for the development of this tumor. Since then, the expression of KIT protein (CD 117 antigen) with tyrosine kinase activity on the surface of the tumor cells has become the main diagnostic criterion.

GIST is resistant to a standard chemo- and radiotherapy. The only curative treatment is radical surgical excision. The effects of treatment of inoperative or metastatic GISTs were, until recently, very poor (median survival after recurrence was 9–20 months). However, in recent years there have appeared radical changes in the therapy of advanced tumors due to the discovery and implementation of treatment with tyrosine-kinase inhibitors. GIST has been the first solid tumor treated with an advanced molecular targeting therapy since 2001, when Imatinib [2,3] was introduced.

Detection of the primary tumor and neoplastic metastases, as well as monitoring of treatment response with radiological imaging sometimes present a challenge for the radiologist because of the diversity of pictures of the disease at every clinical stage. Especially the evaluation of response to molecular targeting therapy in computed tomography (CT) may present problems because radiological images usually differ from those in conventional chemotherapy. Incorrect interpretation of these images due to a strict application of the criteria of response to therapy based merely on changes in tumor size may result in early discontinuation of an effective drug and premature death of a patient.

Difficulties may appear already during diagnostics of the primary tumor. Primary GIST tumors are most often discovered in endoscopic studies as intramural tumors with a frequent characteristic ulceration at the top. However, lesions may be found both inside as well as on the outside of every part of the gastrointestinal tract and also within the omentum and mesentery, without any connection with the gastrointestinal tube, which poses problems or precludes endoscopic detection of the tumor [4]. Figures 1–3 illustrate GIST lesions of various growth patterns.

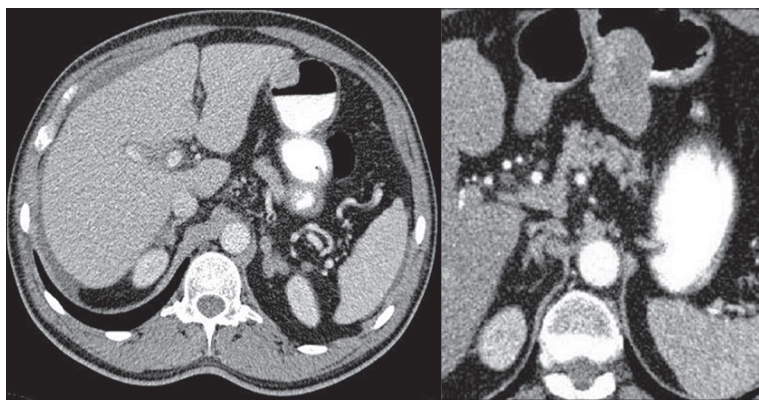


Figure 1. Axial CT scans of the abdomen. Two cases of typical, intramural GISTs in their most frequent location in the stomach.

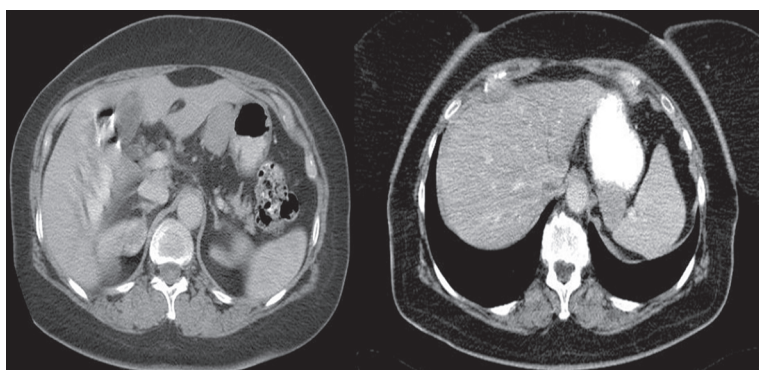


Figure 2. Axial CT scans of the abdomen. Two cases of exophytic GISTs in the stomach.

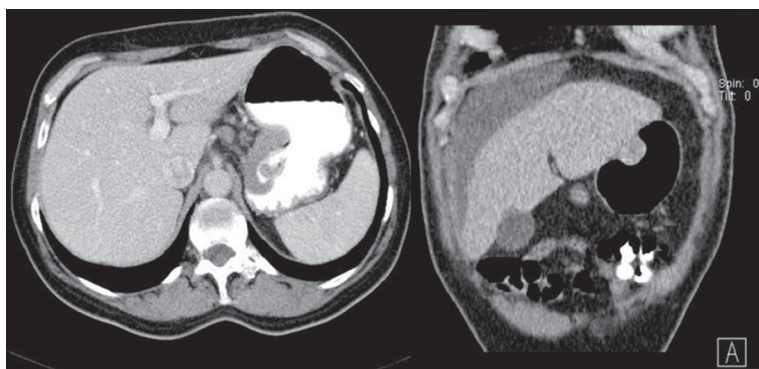


Figure 3. Axial CT scans of the abdomen and reconstruction of the study in the frontal plain. Two cases of endophytic GISTs in the stomach. On the left, there is a large ulceration in the tumor.

Due to a relatively common exophytic growth of the tumor, the lesion may be impossible to detect endoscopically or may cause only slight modeling of the wall from the outside in the involved part of the GI tract. Standard endoscopic examinations are not helpful in the diagnostics of the small intestine either.

Another method frequently used for diagnosing GIST tumors is the ultrasound examination due to its high availability and commonness. Location of lesions inside the wall of the gastrointestinal tract significantly reduces the possibility of their detection in ultrasound scans. In case of lesions that are visible in ultrasound, one may come across great difficulties in regard to identifying the point of origin of the primary lesion and defining its type. Reports of ultrasound examinations, in which primary GISTs were found, are rarely correct in terms of the diagnosis of the tumor originating from the gastrointestinal wall. More often, diagnoses of pancreatic tumors and cysts, tumors of the liver, ovaries, or mesentery, and lymphomas are

encountered, as well as abscesses between intestinal loops, intestinal inflammation or even an enlarged spleen. In the rare cases of retroperitoneal primary lesions, the diagnoses of renal and adrenal tumors predominate.

The role of CT usually comes down to staging and determining whether the lesions found through other diagnostic modalities are suitable for excision, as well as postoperative control and monitoring of chemotherapy. In CT, asymptomatic primary tumors are often incidentally found during studies performed for other reasons.

In CT diagnostics of GISTs one may encounter, although less often, similar difficulties in defining the character and point of origin of lesions as in ultrasound examinations. The following tumor characteristics influence these problems:

- connection with the gastrointestinal wall, often difficult to visualize due to poor filling of the stomach and intestines with fluid or contrast medium,

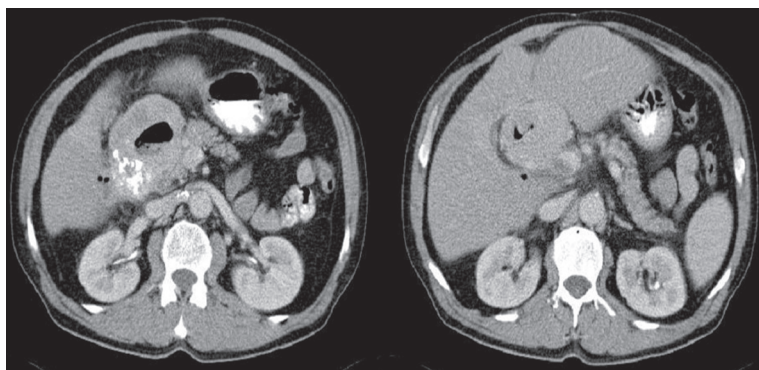


Figure 4. Axial CT scans of the abdomen. Duodenal GIST described as a pathology of the gallbladder: perforated cholecystitis or carcinoma of the gallbladder with cholelithiasis.

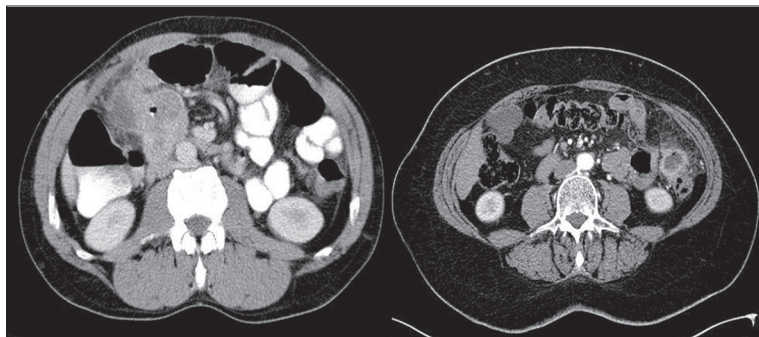


Figure 5. Axial CT scans of the abdomen. Two examples of GISTs described as intraabdominal abscesses or inflammation of the small intestine wall.

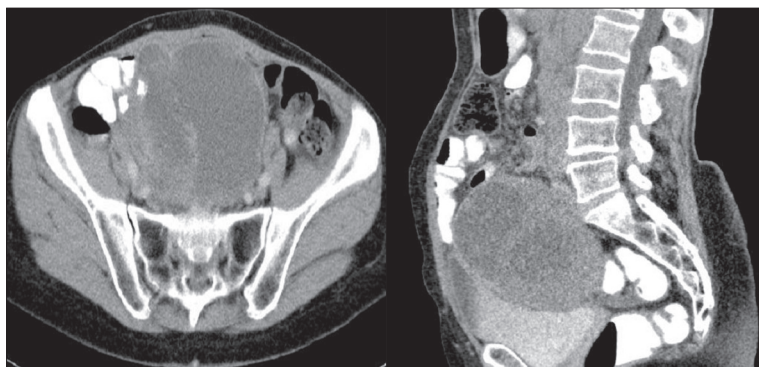


Figure 6. Axial CT scan and reconstruction of the study in the frontal plain. A case of small intestine GIST diagnosed as an ovarian tumor and resected in the gynecology ward.

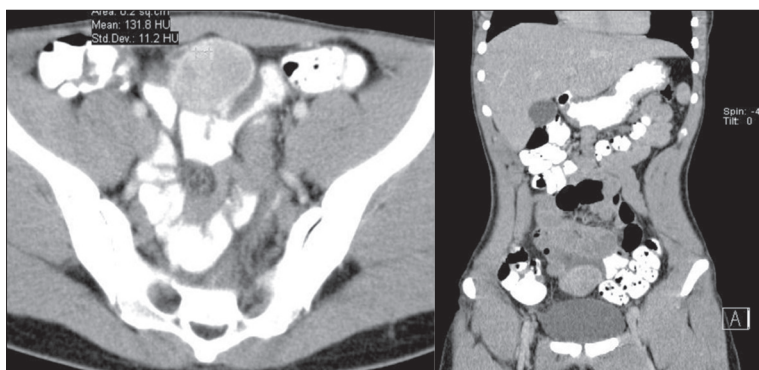


Figure 7. Axial CT scan and reconstruction in the frontal plain. A small intestine GIST reported as endometriosis

- lack of characteristic features of GISTs that would differentiate them from other possible lesions of the gastrointestinal wall, such as sarcomas, neuromas, carcinoid tumors, lymphomas, ectopic pancreas, etc,
- areas of necrosis and cystic degeneration, often very large, result in misdiagnosis of intraabdominal abscesses, inflamed intestinal loops, conglomerates of intestinal loops, cysts and tumors of the pancreas or mesentery etc,
- difficulties in defining the point of origin of large lesions, which invade and push aside surrounding structures and organs, as well as intestinal tumors infiltrating the mesentery,
- heterogenous, low and high initial contrasting of the lesions with possible presence of calcifications; various types and enhancement intensity; and sometimes no strong enhancement typical for sarcomas,

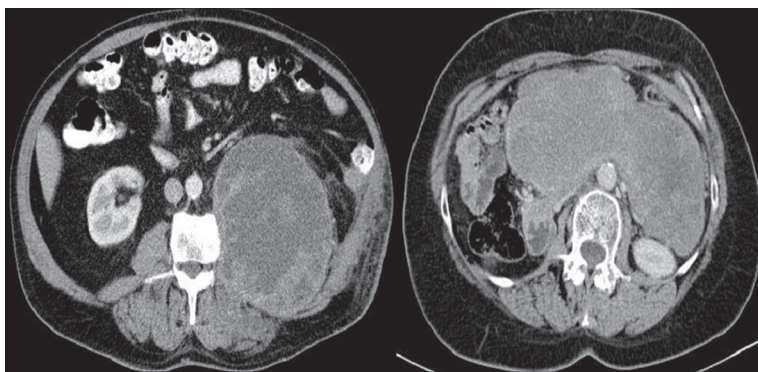


Figure 8. Axial CT scans of the abdomen. Two examples of GIST tumors with uncertain point of origin due to their large sizes. Picture on the left presents a rare primary retroperitoneal tumor.

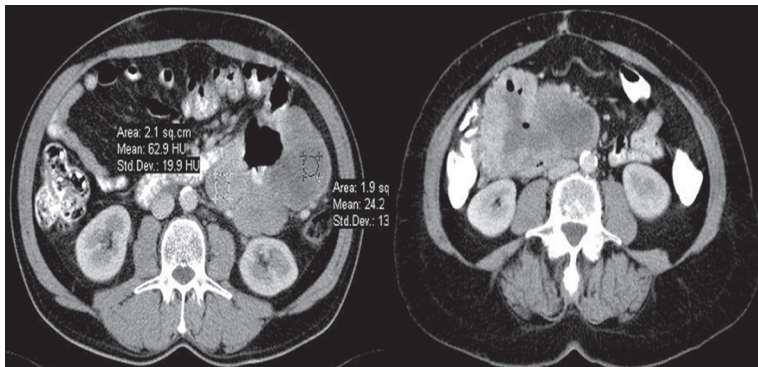


Figure 9. Axial CT scans of the abdomen. Two typical small bowel and duodenal GIST tumors. In these cases, radiological reports suggested primary lymphomas. Lack of enlarged lymph nodes in GISTs makes the differential diagnosis easier.

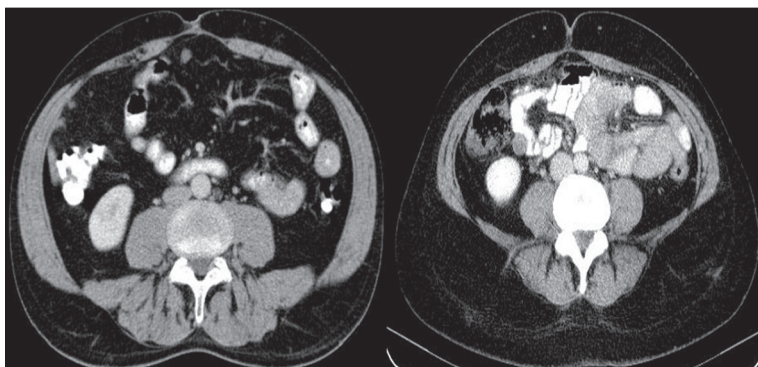


Figure 10. Axial CT scans of the abdomen. Two cases of small peritoneal metastases, which could be easily missed by the radiologist

- rare incidence of this tumor, which inclines the reporting radiologist to diagnose lesions other than GIST.

Figures 4–9 presenting examples of lesions that posed diagnostics difficulties.

Dissemination of the primary process is often found at the moment of diagnosis. It is most commonly seen in the liver or peritoneum [6]. Sporadically, one may encounter primary metastatic tumors in other organs, including lymph nodes – in very advanced stages. While looking for metastatic tumors, one may also encounter problems, especially in case of small nodules and a mild spread to the peritoneum, as shown in Figure 10. In these cases, it is particularly important to fill the lumen of the GI tract with non-contrasting fluid or contrast agent [7,8].

The figures above also prove that ultrasound scan may not be appropriate for periodic follow-up examinations in patients after resection of the primary tumor because the chances for visualizing such lesions are slim. Regrettably,

this is a common practice of some clinicians despite firm guidelines on periodic follow-up using computed tomography [9].

A radiologist searching for sarcoma spread to the liver expects metastatic nodules that become well enhanced after injection of a contrast medium, best visible in the arterial or venous phase of a dynamic study.

However, very diverse pictures may be encountered, which was illustrated in Figures 11–15.

Occurrence of isodense GIST metastases has been described in the literature [10–12]. The degree of their enhancement after application of the contrast agent is similar to that of the surrounding hepatic parenchyma, which may result in overlooking all or some of the lesions, especially in a single-phase study. In case of tumors that are poorly distinguishable from the surrounding tissue there may be problems with taking measurements. Monitoring of response to treatment poses a separate, fundamental diagnostic

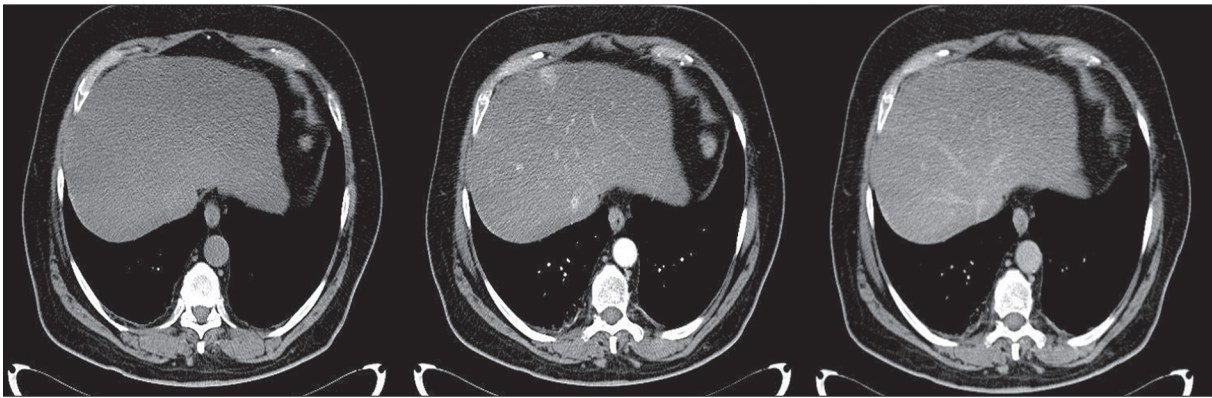


Figure 11. Axial CT scans of the abdomen – consecutive phases of dynamic CT examination. Strongly enhanced metastatic nodules are best visible in the arterial phase.

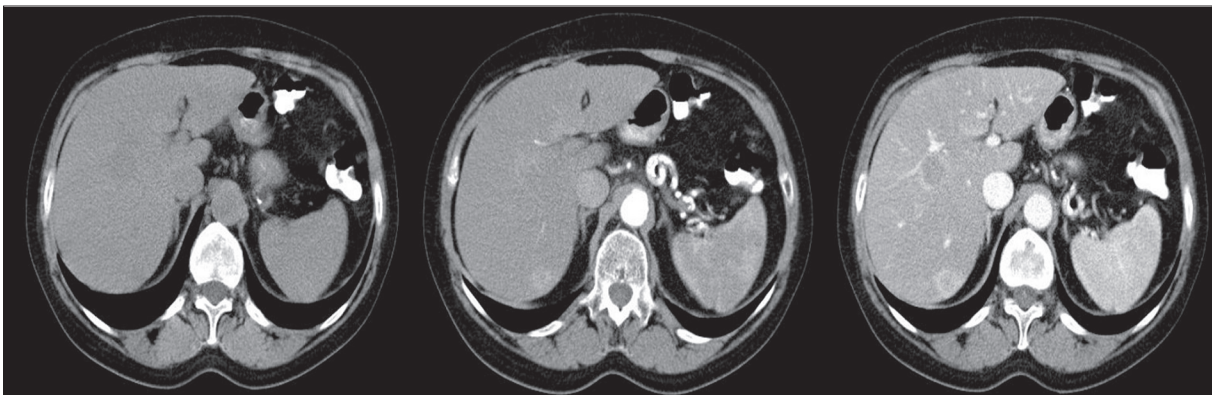


Figure 12. Axial CT scans of the abdomen – consecutive phases of dynamic CT examination. Well-enhancing metastatic nodules with areas of necrosis, located in the liver are best seen in the venous phase of the study.

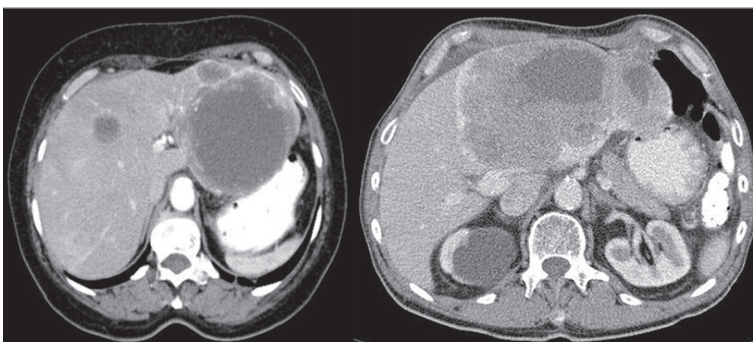


Figure 13. Axial CT scans of the abdomen. Typical presentation of larger GIST metastases of heterogenous density due to the presence of hypodense areas of necrosis.

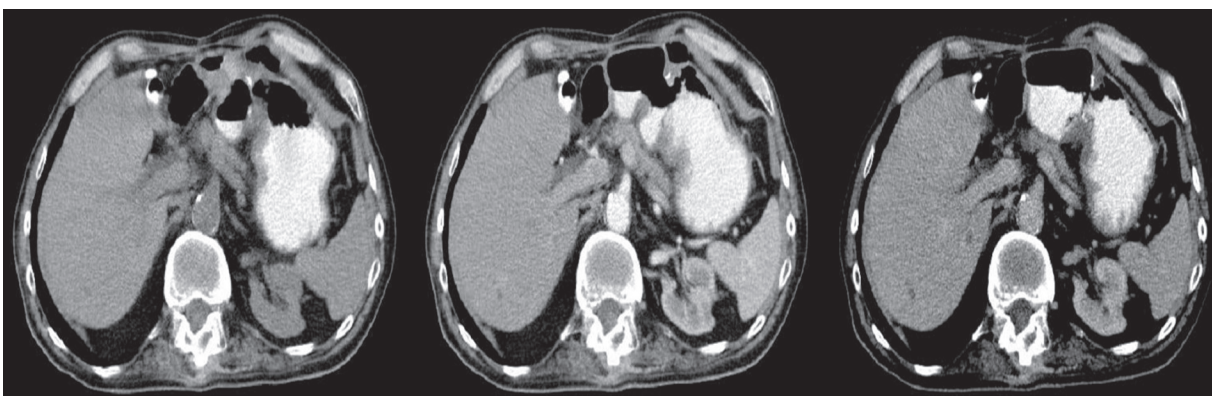


Figure 14. Axial CT scans of the abdomen – consecutive phases of dynamic CT examination. Unusual, because poorly enhancing metastatic nodules are best seen in the venous phase.

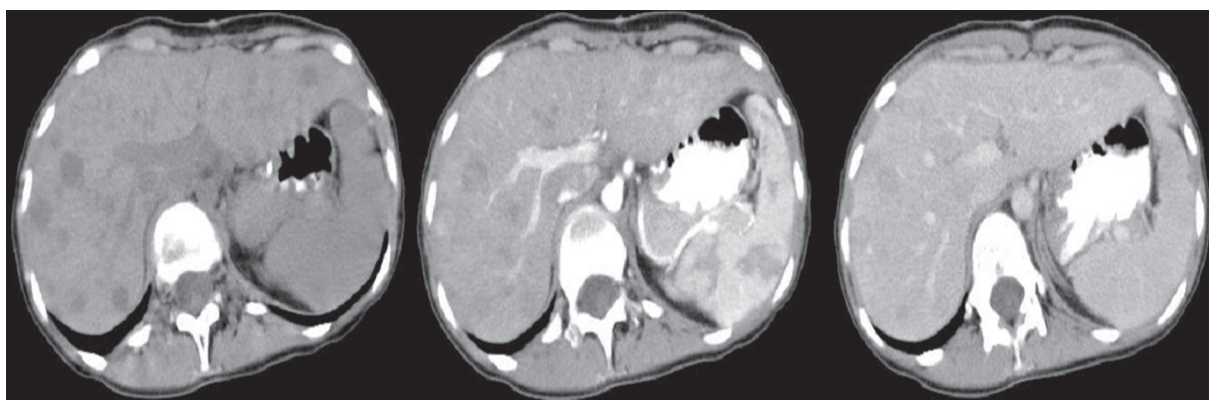


Figure 15. Axial CT scans of the abdomen – consecutive phases of dynamic CT examination. Untypically, metastases are best seen before intravenous injection of contrast medium; the degree of their enhancement is similar to that of liver parenchyma.

Table 1. RECIST classification.

Response to treatment according to RECIST scale		
Complete regression	CR	Regression of all known foci of the disease and lack of new lesions
Partial regression	PR	At least 30% reduction in the sums of dimensions that could be measured, i.e. larger than 1 cm
Stable disease	SD	Dimensions of the lesions do not fulfill criteria of progression or regression
Progressive disease	PD	Enlargement of lesions by at least 20%, appearance of new lesions

Table 2. Classification according to Choi.

Response to treatment according to Choi		
Complete regression	CR	Disappearance of all known foci of the disease and lack of new lesions
Partial regression	PR	Reduction in the sizes of lesions by at least 10% or reduction in post-contrast enhancement by 15% or more
Stable disease	SD	Dimensions and contrasting of the lesions do not fulfill the criteria for progression or regression
Progression	PD	Increase in the size of the lesion by at least 10% without reduction in contrasting, appearance of a new lesion or enhancing nodule within the old lesion

problem because of an untypical picture of a tumor during therapy and danger of discontinuation of the treatment following erroneous interpretation of radiographic images.

According to the RECIST 1.1 scale, commonly used in clinical studies for assessment of response to therapy, the only criterion of response is the reduction in tumor size, as shown in Table 1.

Already in 2004, three years after introduction of Imatinib to treatment of GIST, prof. Choi proposed extending the "response to treatment" scale by adding criteria of evaluation of tumor density changes following treatment, as assessed after injection of a contrast medium [13]. Classification according to Choi was presented in Table 2.

A decrease in density of lesions in CT images in response to effective treatment (confirmed with PET study) is currently a well-documented phenomenon in GIST chemotherapy [12,14,15]. At first, sizes of the lesions may remain unchanged despite good therapeutic response, and the only sign of treatment efficacy is a reduction of density in CT

images. In such cases, the RECIST classification defines the disease as stable, while in fact it is regressing. It has also been found that lowering of density of the lesions has a greater prognostic value in terms of therapeutic efficacy than reduction in their sizes. Figure 16 pictures typical cases of good response to Imatinib treatment.

The most important phenomenon that may occur during GIST chemotherapy is, so called, pseudoprogression of the lesions. It signifies an increase in tumor size despite a very good response to therapy (confirmed by PET study). In such cases, enlargement is always accompanied by a decrease in density in CT [11,16,17]. This phenomenon is relatively rare, but it may have fatal consequences for the patient if therapy response monitoring is performed using only RECIST scale, which takes into consideration only the sizes of lesions. Application of Choi's classification, which includes evaluation of changes in tumor density following treatment, eliminates the threat of discontinuation of an effective drug. Awareness of the pseudoprogression phenomenon in GIST therapy, as well as in targeted molecular therapies of other

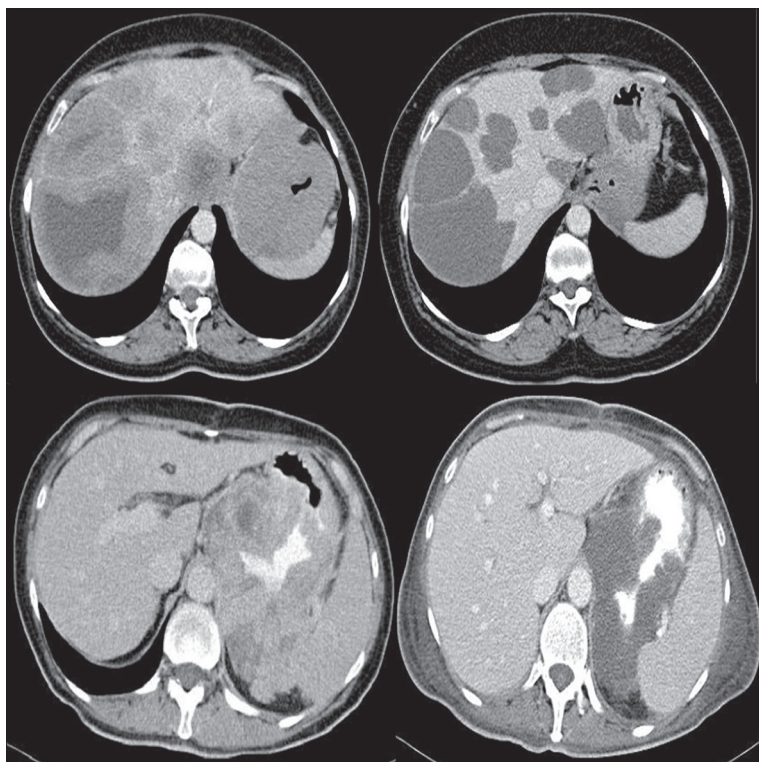


Figure 16. Axial CT scans of the abdomen. Two examples of response to therapy in advanced GISTs. Both tumor sizes and densities have strongly decreased (to the level of fluid density). Liver metastases have a pseudocystic appearance.

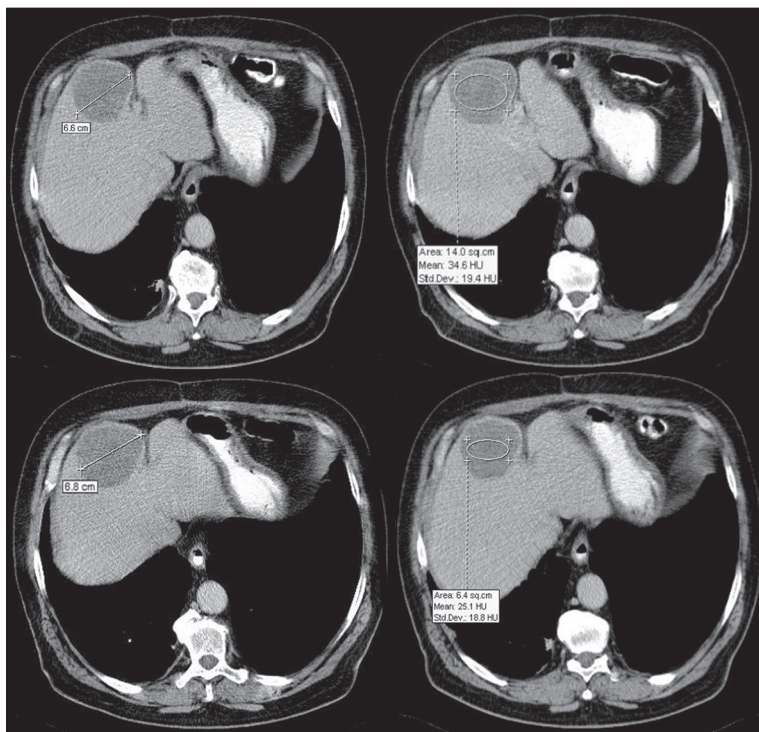


Figure 17. Axial CT scans of the abdomen. Metastatic tumor in the liver before (images in the upper row) and after two months of treatment with Imatinib (the lower row). Tumor size has slightly increased, but its density is significantly lower. Such increase in size during treatment is due to tumor tissue edema and intra-neoplastic hemorrhages.

neoplasms is still not widespread while this problem occurs more and more often as new drugs appear on the market.

Figures 17 and 18 presents case of a slight increase in lesion size after treatment accompanied by lowering of its contrasting, which classifies it as SD according to RECIST scale and as PR according to Choi classification.

Apart from an increase in tumor size during effective chemotherapy, other issues may arise, making a proper radiological interpretation difficult:

- transformation of metastatic foci into lesions imitating simple cysts,
- appearance of images with new metastatic foci during effective chemotherapy,

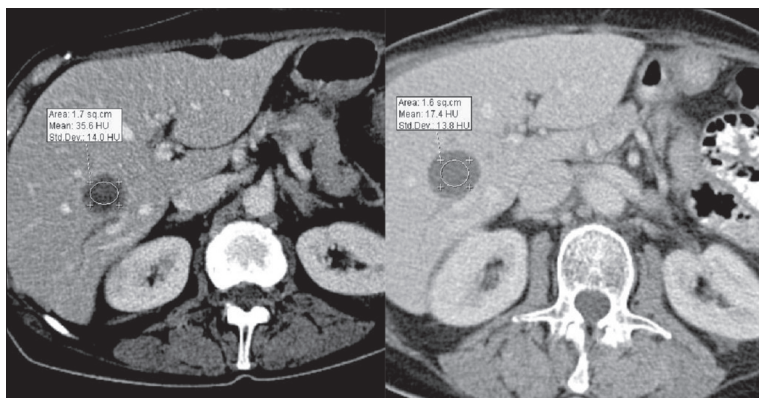


Figure 18. Axial CT scans of the abdomen. Another case of lowering of density of liver metastasis during chemotherapy (picture on the right) with concomitant increase in size.

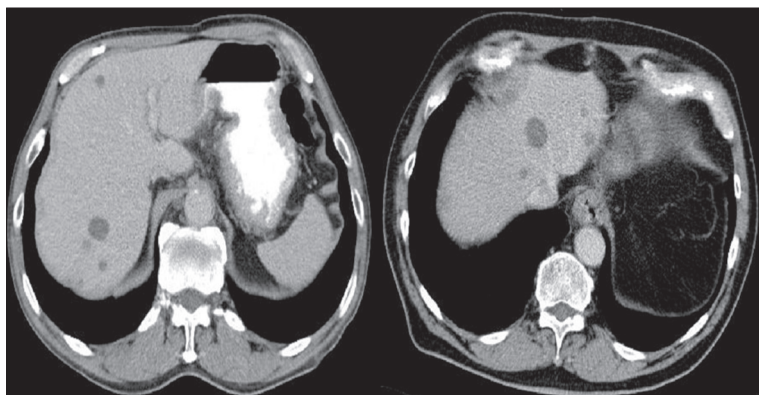


Figure 19. Axial CT scans of the abdomen. Two examples of GIST metastases with pseudocystic appearance due to the fibromyxoid transformation induced by Imatinib treatment. The density of these lesions is usually slightly higher than of simple cysts.

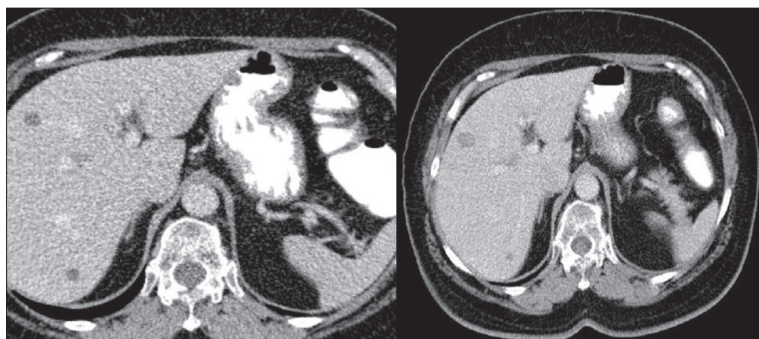


Figure 20. Axial CT scans of the abdomen. A case of pseudocystic liver metastases increasing in size and density – failure of Imatinib treatment and tumor progression.

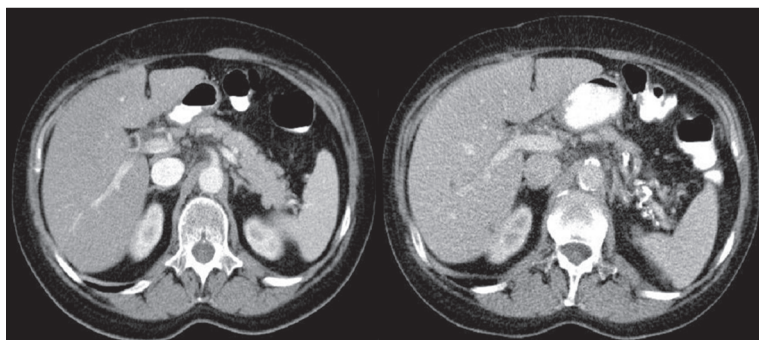


Figure 21. Axial CT scans of the abdomen. A case of small liver metastases that initially were not visible. After several months of treatment, they appeared in CT images due to the lowering of their density. Such lesions may be incorrectly reported as new lesions.

- unexpected changes in size and contrasting of tumors, such as: concomitant reductions and increases in sizes of different lesions, decrease in tumor size despite disease progression, seeming increase in lesion density,
- picture of a very slow progression, which sometimes lasts for years,

- a unique pattern of disease progression in the form of so-called 'nodules within tumors'.

Figures 19 and 20 show hepatic 'cysts' that were formed as a result of treatment but always contain a live neoplastic tissue despite the lack of contrast enhancement. In some situations, when initial CT images and medical

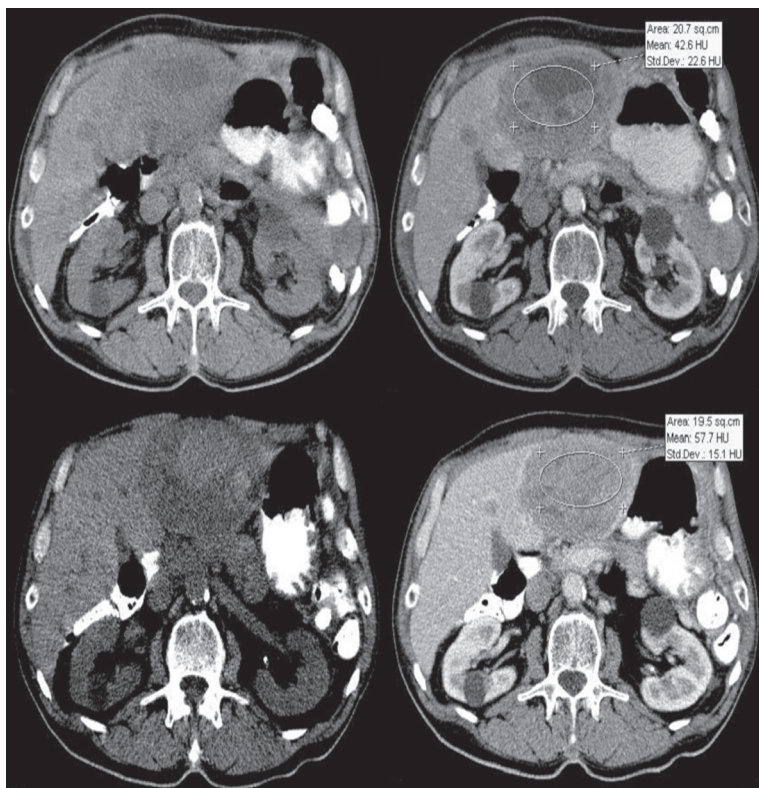


Figure 22. Axial CT scans of the abdomen before and after contrast injection. In the scans taken after treatment with Imatinib (the lower row), there is an increase in tumor density due to hemorrhaging. It is easier to differentiate between a true progression and hemorrhagic changes causing an increase in density of the tumor on images acquired before contrast injection. In such cases, there is no increase in contrast enhancement either.

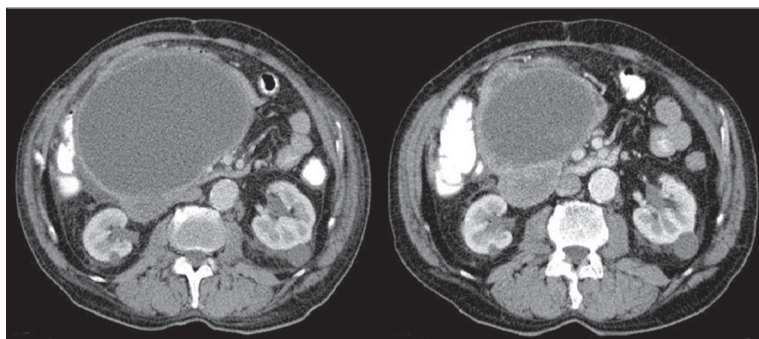


Figure 23. Axial CT scans of the abdomen. Diminishing of the size of peritoneal metastatic tumor during treatment with Imatinib despite an actual progression of the disease as evidenced by the thickening of the walls of a 'neoplastic cyst' and appearance of enhanced paramural nodules.

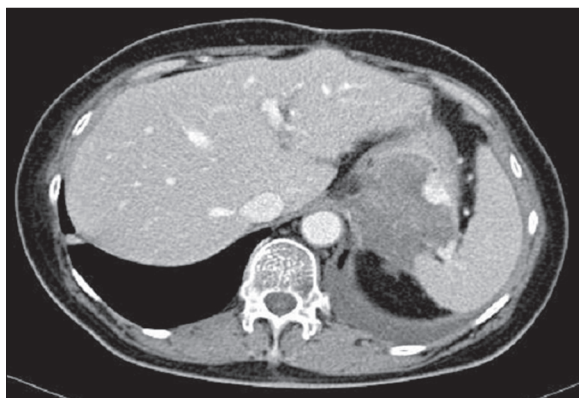


Figure 24. Axial CT scan of the abdomen. The same tumor as in Figure 16 (the bottom row) after approximately three years of treatment with Imatinib. The size of the tumor has further decreased despite actual progression of the neoplastic process as evidenced by the appearance of contrast enhancement within the tumor.

documentation are unavailable for comparison, these 'cysts' may be reported by a radiologist as simple cysts.

During therapy of GIST, a phenomenon of pseudoprogression of a different kind may occur, which can also lead to discontinuation of an effective drug. Some of smaller metastatic lesions in the liver may be at first isodense to the surrounding liver parenchyma and exhibit similar degree of enhancement after application of the contrast medium, which makes them invisible in the initial CT examination. Following treatment, 'new' lesions may appear, which is a result of density lowering in previously present but unrecognized foci. Such situation was illustrated in Figure 21.

During chemotherapy, one may also encounter a 'worrisome' increase in the density of a lesion following treatment, which in fact is caused by hemorrhages within the tumors. Such situation was presented in Figure 22.

There are also surprises regarding changes in tumor size during therapy. One may encounter metastases that

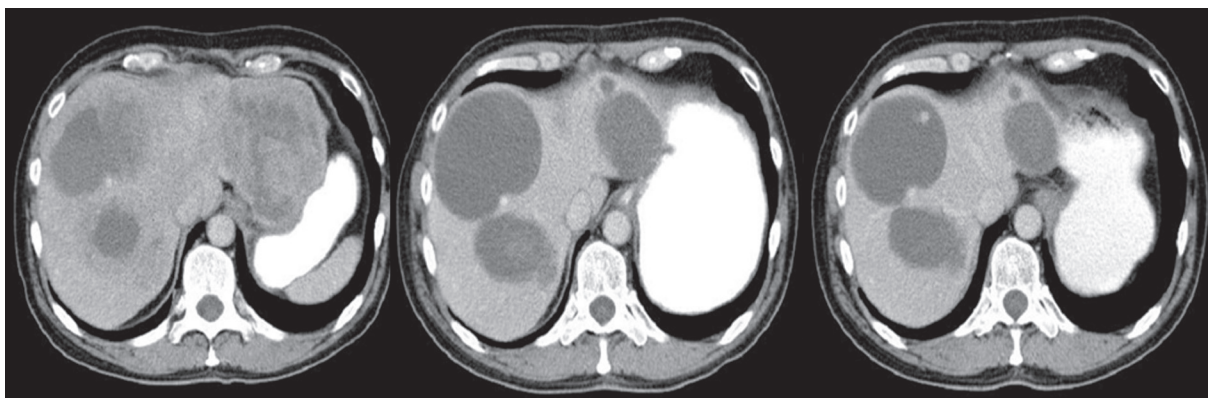


Figure 25. Axial CT scans of the abdomen – consecutive images during treatment with Imatinib within approximately one year. There is an apparent evolution of lesions in the following months of therapy evidenced by decrease in the sizes of tumors and lowering of their densities. The picture on the left shows progression despite continuous diminishing of the lesions. Note the new enhancing nodule within the biggest tumor (a “nodule within a nodule”) after injection of the contrast agent.

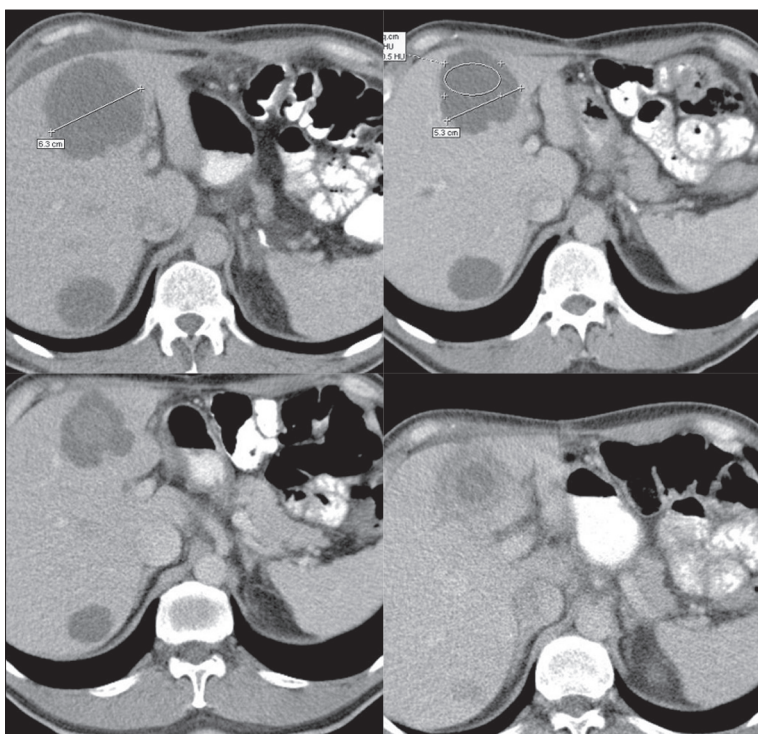


Figure 26. Axial CT scans of the abdomen – consecutive images during treatment with Imatinib. Changing sizes and degrees of contrast enhancement of metastatic lesions in the following months of therapy. Sizes of the tumors were constantly decreasing despite progression of the disease evidenced by appearance of new solid tissue within the neoplastic ‘cyst’.

decrease in size while other lesions remain unchanged or become enlarged, especially the ‘cystic’ lesions. Metastases may also diminish as the disease progresses and the only sign of progression may be an increase in tumor density or thickening of the wall in cases of ‘neoplastic cysts’, which was illustrated in Figures 23–26.

One should also remember about the possibility of so-called slow disease progression. In some patients, enlargement of metastatic changes occurs very slowly and the patient evidently benefits from continuation of chemotherapy. The longest-treated person in Cracow facility has remained in good condition for the last six years despite a massive neoplastic dissemination to the liver and constant enlargement of most foci since the very beginning of the therapy. In such cases, treatment should be carried on despite seeming indications for its discontinuation.

There are also unique images of metastatic nodules within metastatic tumors, first observed in GIST chemotherapy. They are caused by new local mutations within the ‘old’ neoplastic tissue, which gives rise to new lines of cells resistant to the applied drug. In CT, such changes are visualized as new, tiny areas of solid tissue, usually undergoing strong enhancement following contrast injection, usually located near the wall on the inside (rarely on the outside) of the old ‘neoplastic cyst’ that was formed during chemotherapy. As the dimensions of the old tumor usually do not change and may even diminish, they are classified as SD or PR according to RECIST scale, while in reality the disease progresses. Knowledge about this new progression pattern allows for early recognition of resistance to therapy with CT examinations. It should be noted that nodules may appear in every location within the old metastatic lesion. Live neoplastic cells always remain inside, as

a consequence of chemostatic, not chemotoxic mechanism of action of targeted molecular therapies. Resistance to treatment exhibited by some cell lines poses a fundamental problem and indicates the lack of possibility of full recovery from GIST on Imatinib [17–19] treatment.

Conclusions

The variety of problems that arise in diagnostics and treatment monitoring of GIST tumors requires a thorough knowledge of this disease on the part of the reporting radiologist; optimally, provided by training in centers specializing in the treatment of GIST.

Also, the importance of the flow of information between clinicians and radiologists evaluating effectiveness of chemotherapy increases. Radiologists have to possess information on the type of drug the patient receives, its mechanism of action and duration of treatment. They also must know whether there were interruptions in treatment and if so, when it was discontinued. Lack of this information may result in incorrect interpretation of changes seen in radiological studies and have fatal consequences for the patient.

Due to the appearance of new patterns of therapeutic response in targeted molecular therapy and unique patterns of neoplastic progression, the criteria for radiological evaluation using CT that are based on measurements of tumor dimensions should be changed.

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