Gastrointestinal Stromal Tumors

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3.1 Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. According to tumor size, GIST incidence varies from a highly prevalent tumor the "micro-GIST," which is < 2 cm wide [1] and is estimated to occur in up to 22% of the general population, to a rare disease characterized by a tumor > 2 cm and with an annual incidence of about 15/1,000,000 [2]. While the clinical relevance of microGIST is still under evaluation, at this point it is considered to be minimal. GISTs may develop from the esophagus to the rectum and are most common in the stomach (60–70% of the cases) followed by the small intestine (30%), and lastly by the rectum (< 10%) [3]. Although no GIST > 2 cm can be considered benign, the risk of local relapse and metastasis varies according to tumor size and site of origin, and the number of mitoses evaluated on 50 microscopic high-power fields. This risk stratification proposed by Miettinen and Lasota [3] is widely used as a prognosticator after complete surgery, which is still the mainstay of therapy. However, despite complete surgical removal of the tumor, the 50% relapse rate is surprisingly consistent throughout different large series [4]. Relapse may occur locally but mostly involves the peritoneum and liver. Patients with relapse not amenable to surgery previously died within 12 months [5] due to the chemoresistance of GIST, in which the response rate to chemotherapy is < 5% [6].

However, after Hirota et al. [7] showed that GIST proliferation was caused by constitutive activation of the type III tyrosine kinase (TRK) receptor KIT in nearly all tumors and less often by the platelet-derived growth factor recep-

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tor-α(PDGFR-α) [8], new approaches to the treatment of this rare disease were attempted. An extraordinarily successful treatment of a woman with widespread GIST with the KIT inhibitor imatinib was reported on the New England Journal of Medicine in 2001 [9]. Since the publication of this case report, imatinib has become the unquestionable model of targeted therapy with small-molecule inhibitors. Two extensive phase III studies showed that imatinib was active and effective in advanced GIST, sharply increasing both progression-free survival and overall survival [10, 11]. An earlier phase II study had shown that the heterogeneity of GISTs could be explained by the presence and the type of mutation of their oncogenes [12]. Thus, a spectrum of genetically different diseases is currently recognized, in which mutations in different oncogenes and different types of mutations nonetheless give rise to the same pathological entity [13]. In the imatinib era, this new classification of GISTs represents an extraordinary clinical tool in disease management. Indeed, the molecular information on which it is based confirms the importance of a multidisciplinary, patient-tailored therapeutic approach in order to achieve the best possible results according to the different presentations of this tumor. International guidelines [14, 15] classify GISTs as localized, locally advanced or metastatic. Based on disease extension and site of origin, the proposed clinical management may vary considerably.

3.2 Therapeutic Strategy

In localized GIST, surgery is still the first and most critical approach, as it must guarantee adequate margins and minimize the risk of tumor rupture (which may also occur spontaneously) given that tumor spilling implies a 95% risk of relapse [16]. The surgical feasibility of adequate margins and tumor rupture also guides clinical decision-making for patients with locally advanced GISTs. Moreover, since imatinib may shrink the tumor, patients initially treated with the drug may require less aggressive surgery, with the possibility of functional sparing (i.e., avoiding total gastrectomy or perineal-abdominal amputation). The safety and results of this neo-adjuvant approach have been published by different groups [17]. In metastatic disease, there is no role for surgery, or, at most, as an exploratory measure on an individualized basis. Nevertheless, in patients with metastatic GIST imatinib may sometimes shrink the tumor as well as the metastases to an extent that allows complete excision of all detectable disease. This possibilty has been explored by different groups and, once again, the results have been very similar [18-20].

It is therefore clear that imatinib mesylate is the cornerstone of the clinical strategy in patients with GIST. The success of this drug is due to the higher incidence in GIST of mutations in exons 9 and 11 of KIT, which predicts the achievement of stable disease in nearly 85% of the patients. Indeed, the underlying genotype is of the greatest relevance in predicting outcome. Thus, a wild-type or resistant genotype (e.g., PDGFR-α exon-18 D842V) sharply

reduces or abrogates any role for the currently available targeted therapies [21]. In general, four different therapeutic scenarios can be described: the adjuvant setting, the neo-adjuvant setting, advanced disease, and beyond multikinase inhibitor failure.

3.2.1 Adjuvant Therapy

Patients receiving 400 mg of imatinib for 1 year have prolonged recurrence-free survival after complete surgery of a tumor of almost any size [22]. Unplanned analyses have shown that there is no advantage for tumors bearing exon-9 mutation and for wild-type GIST, whereas almost all other subtypes achieve an advantage by medical therapy after surgery. At the 2011 ASCO meeting, Joensuu [23] presented the results obtained in GIST patients administered imatinib at the same dose for 3 years, concluding that relapse-free and overall survival were prolonged in patients with high-risk and very high-risk GISTs.

3.2.2 Neo-adjuvant Therapy

Soon after the publication of the B2222 data [14], it became clear that patients with either large or critically located (e.g., rectum) GIST could benefit from tumor shrinkage and thus from imatinib therapy. In an attempt to improve the quality of surgery and to reduce related morbidity, candidates for surgery were pre-operatively treated with imatinib. However, 10 years later, a formal proof for the success of this strategy is still lacking. Nonetheless, based on small mono-institutional series, it remains a commonly accepted integrated approach to minimize surgical damage or inadequate results [14].

3.2.3 Advanced Disease

In these patients, tumor genotype guides medical therapy. Thus, tumors with an exon 11 mutation are best treated with a daily dose of 400 mg of imatinib whereas those with an exon 9 mutation require 800 mg daily [24]. In GISTs arising from a mutated PDGFR-α, the standard dose is 400 mg daily, but there is a well-known mutation affecting exon-18 (D842V) that is refractory to imatinib therapy. Wild-type GISTs have a lower sensitivity to imatinib therapy, but there is no indication supporting an increase in the imatinib dose. However, the problem remains that secondary imatinib resistance develops in less than 24 months in 50% of the patients. Consequently, there is a large consensus to double the dose of imatinib, if initiated at 400 mg [25], and, in case of failure, to start therapy with the TRK inhibitor sunitinib malate 50 mg daily for 4 weeks on and 2 weeks off or at a dose of 37.5 mg on a continuous daily base [26, 27].

3.2.4 Beyond Multikinase Inhibitor Failure

Patients whose disease does not respond to sunitinib are offered as-yet experimental third-line therapies based on the multikinase inhibitors sorafenib, regorafenib, and dasatinib [28, 29]. None of these drugs is approved for clinical use. Recently, a phase III trial demonstrated a statistically significant advantage of masatinib over sunitinib as a third-line therapy. Since these data are preliminary and not yet available in the literature, they should be interpreted with caution. Currently, the preferred approach in patients with progression after sunitinib and/or other inhibitors is to re-challenge the GISTs with the highest tolerated dose of imatinib. Although not evidence-based, this treatment option may delay progression, by the action of the drug on still sensitive neoplastic clones.

3.3 The Issue of Targeted Therapy Response Evaluation

In this complex and multidisciplinary approach, it is clear that the imaging evaluation of GIST is of utmost importance. Imaging along with the pathology report guides clinical decision-making and after staging it defines the first-line therapy. Thereafter, it allows monitoring of the response guiding the integration of medical and surgical therapies. This is a crucial point in all GISTs, in light of the report [9] that despite the unprecedented activity of imatinib it did not necessarily cause tumor shrinkage, as often observed after traditional forms of chemotherapy. Consequently, dimensional criteria such as RECIST, while certainly useful and reproducible, may be only belatedly applicable since changes in tumor dimension may first occur later in the course of treatment. Therefore, dimension per se might not help in the early identification of responders. This limitation is also relevant when therapy is not effective. TRK inhibitors are expensive and toxic and they should be discontinued in patients with resistant disease, which might be better treated with other drugs. Clearly, the ability to identify responsive patients is a clinical issue and not only an academic one. Any effort to improve our understanding of TRK activity is a step forward in the better clinical use of these innovative therapies.

Thus, rather than tumor shrinkage, pathological and functional/molecular response are probably better tools to objectively identify and measure imatinib activity earlier and more accurately. In fact, as reported by Mankoff et al. in 2007 [30], tumor shrinkage is only the final step in a complex cascade of cellular and subcellular changes after imatinib treatment. Molecular imaging could play an important role in the evaluation of the cellular changes occurring in the early stages of treatment. For example, it could detect decreases in cell proliferation, increases in cell death, and a decline in the number of viable tumor cells. This approach considers that while targeted therapies reduce GIST diameters, this might occur as late as months after the initiation of therapy. Accordingly, the evaluation of response based solely on dimensional criteria is

not as accurate as in other oncological settings. In light of these conclusions, a need was recognized for imaging strategies that improve the readout of imatinib activity and thus for criteria to identify patients benefiting from treatment [31-35]. This effort has proven to be of great value not only in patients receiving imatinib therapy, but also in those treated with other kinase inhibitors [36]. Moreover, the success of these efforts extends beyond GIST to other types of tumors [37].

3.4 A CT Assessment of the Response to Treatment: The RECIST Criteria

Several imaging modalities are available to assess the response to therapy in patients with metastatic GIST. As discussed in Chap. 2, imaging can yield anatomical/topographical or functional/molecular information. In GIST, the most commonly used modality to follow these patients is CT, which allows assessment of both the side effects of targeted therapies and the response to treatment [38]. Both in the initial staging and during follow-up, CT should be performed following a bolus injection of iodine contrast material using a triphasic protocol. The arterial phase begins 35–40 s from the start of the injection, and the portal phase 70–75 s post-injection. Since the most common site of metastasization is the liver, where lesions are usually hypervascular, these tumors are best appreciated in arterial phase while often go undetected in portal phase (Fig. 3.1a).

In the last ten years, the response to treatment of GISTs has been evaluated, as for other tumors, using the RECIST criteria [39]. However, as noted above, there are several pitfalls in the assessment of GIST by means of unidimensional criteria, since imatinib often induces cystic changes due to myxoid degeneration. At CT, changes in lesion density and size, with tumor liquefaction, may be observed. Here, the potential pitfalls reflect the fact that at this stage there may be an increase in lesion size and an apparent increase in lesion number. Occasionally, hepatic metastases that were difficult to visualize on pre-treatment CT can be seen on follow-up CT scans as hypodense lesions, potentially misinterpreted as disease progression (Fig. 3.1). As previously reported for other cancers, it is important to underline that the inter-observer variability in the measurement of tumor size in patients receiving imatinib therapy is very high [40].

Compared to the other imaging techniques, CT plays a key role in evaluating treatment response as well as therapy-related adverse effects. CT can show the adverse effects of TRK inhibitors, which, in general are limited to minor ascites and pleural and pericardial effusion (Figs. 3.2, 3.3).

However, in < 5% of patients with bulky tumors, there may be severe intratumoral bleeding requiring surgical treatment (Fig. 3.4). Other important complications are massive necrosis with perforation or abscess formation [38].

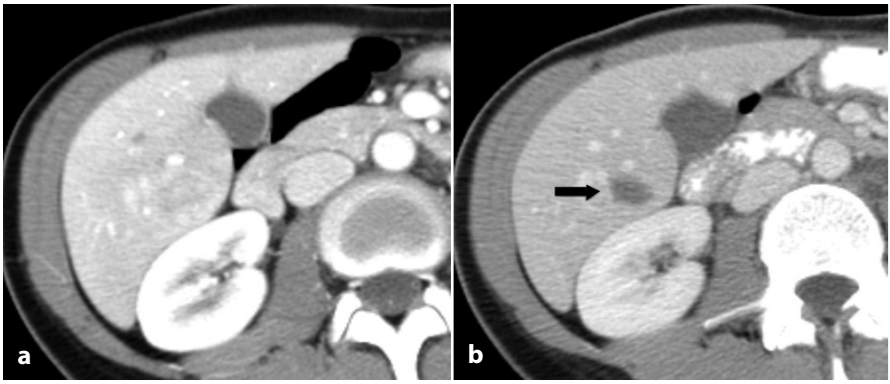

Fig. 3.1 **a** Pre-treatment portal phase CT scan does not show liver lesions. **b** Follow-up CT, performed after therapy with imatinib, shows a 2 cm hypodense lesion in the medial aspect of segment 6 (*arrow*). In GIST, the appearance of new liver lesions is not always a sign of disease progression

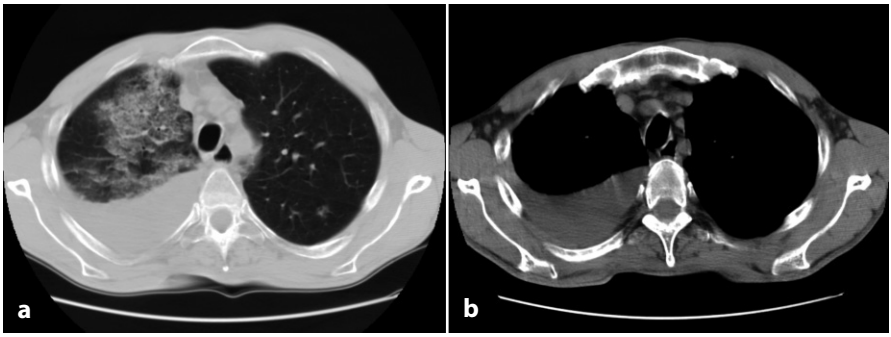

Fig. 3.2 A 49-year-old man with a gastric GIST. The CT scan performed following imatinib therapy shows (**a**) consolidation in the upper right lobe and (**b**) right-sided pleural effusion

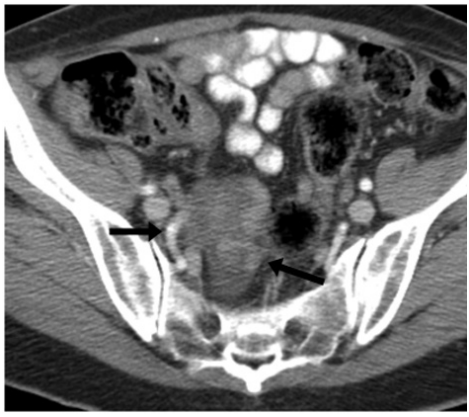

Fig. 3.3 A 67-year-old male with gastric GIST: CT after imatinib therapy shows the appearance of ascites, a collateral effect of therapy

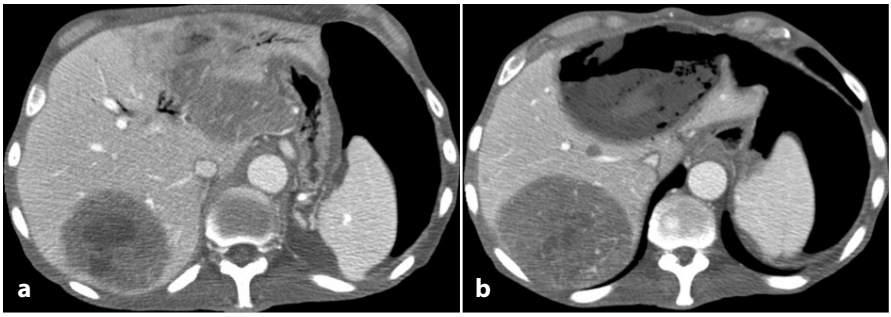

Fig. 3.4 A 71-year-old man with gastric GIST and several large hepatic metastases. **a** Following imatinib therapy, CT shows a pneumoperitoneum due to intestinal perforation. **b** A second, more caudal CT scan shows a large necrotic liver metastasis connecting to the peritoneal cavity

3.5 New Approaches in CT Monitoring of the Response to Targeted Therapies

Several reports have shown that RECIST criteria may underestimate the extent of response to new targeted therapies [33, 38, 41-44]. GIST lesions have been shown to initially increase in size following imatinib therapy, even in cases of a favorable outcome, due to intratumoral necrosis or bleeding (Fig. 3.5) [38]. In a landmark contribution, Choi et al. [33] compared unidimensional RECIST criteria, tumor CT attenuation coefficient, and ^{18}F-FDG PET to clinical endpoints. No significant difference was observed in the long-term prognosis of good vs. poor responders, when the RECIST criteria were used. Conversely, when tumor response was evaluated on the basis of a combination of tumor

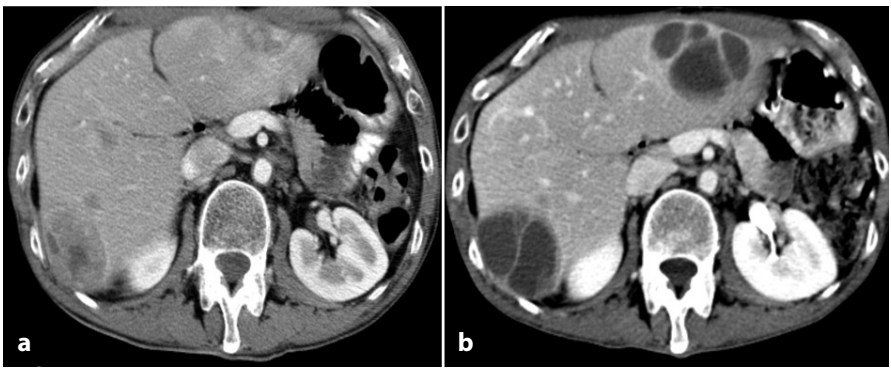

Fig. 3.5 A 56-year-old male with a gastric GIST. **a** After the identification of hepatic metastases, the patient was started on imatinib at a daily dose of 400 mg. **b** After 2 months of therapy, the CT image showed a significant increase in the size of two metastases but a concomitant density reduction, indicating that treatment may have been effective

Table 3.1 Choi CT criteria to assess response to imatinib treatment (modified from [33])

Type of response	CHOI Criteria (after 2 months of therapy)
Complete response	Disappearance of all lesions, no new lesion
PR	A decrease in size of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT, no new lesions, no obvious progression of non-measurable disease
SD	Does not meet the criteria for complete response, partial response or progressive disease, no symptomatic deterioration attributed to tumor progression
Progressive disease	An increase in tumor size of ≥ 10% and does not meet criteria of partial response by tumor density (HU) on CT, new lesions, new intratumoral nodules or an increase in the size of the existing intratumoral nodules

PR, partial response; *SD,* stable disease.

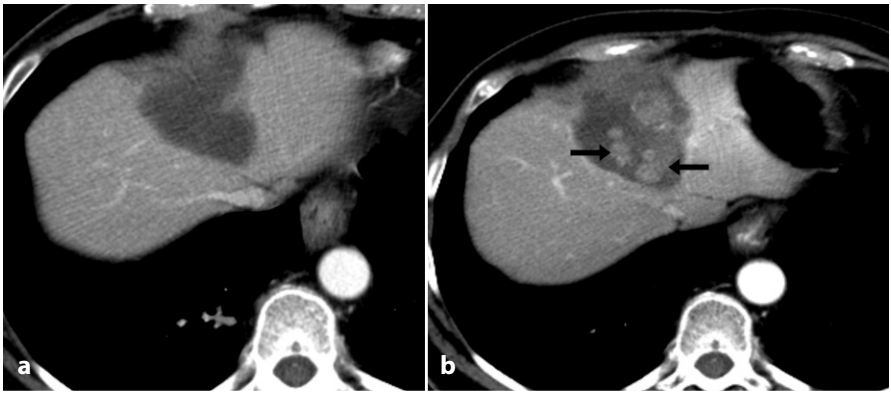

Fig. 3.6 A 64-year-old female with a gastric GIST. After the identification of hepatic metastases, the patient was started on 400 mg of imatinib, administered daily. The CT scan after 2 months of therapy (**a**) and after 12 months of therapy (**b**). The appearance of enhanced nodules (*arrows*) within a responsive tumoral lesion over time is a sign of disease progression

size and tumor density, a significant difference in the long-term prognosis of good vs. poor responders was observed. In particular a reduction in tumor size > 10% and a decrease in the attenuation coefficient of > 15% in the 2 months after treatment had a sensitivity of 97% (vs. 52% for the RECIST criteria) and a specificity of 100% in detecting responders. On the basis of these data, Choi et al. [33] suggested new, modified CT response evaluation criteria based not only on 1D measurements but also on changes in CT density (Table 3.1).

According to the Choi criteria, the appearance of new enhanced nodules within the tumor, an increase in the solid part of the tumor, and an increase in tumor vascularization are all signs of disease progression (Fig. 3.6) [33].

In summary, parameters such as tumor density, size, vascularization, and intratumoral nodules allow the radiologist to correctly assess treatment response [45]. However, the prognostic value of the Choi criteria have yet to be determined. In a recent study, Dudeck et al. [46] demonstrated that patients

classified as having a stable disease according to RECIST criteria had a similar progression-free survival and overall survival as patients classified as partial responders or with stable disease according to the Choi criteria. Other limitations of these criteria are their inappropriateness in the evaluation of secondary relapses [47] and the potential effects on density values due to the presence of intratumoral hemorrhage.

3.6 Therapy Response Evaluation with ^{18}F-FDG PET/CT

In the last few years several studies have compared the value of PET and CT in detecting tumor response to therapy in patients with GIST. In 2004, Antoch et al. [48] used the WHO, RECIST and EORTC criteria to evaluate response in 20 patients with GIST who underwent ^{18}F-FDG PET/CT before and 1, 3, and 6 months after the start of imatinib therapy. The combination of PET and CT images showed the highest accuracy. Indeed, the number of lesions detected by CT and PET alone and by fused PET/CT at baseline was 135, 249, and 282, respectively. PET/CT correctly characterized tumor response in 95% of patients at 1 month and in 100% after 3 and 6 months; PET correctly evaluated therapy response in 85% of patients at 1 month and in 100% at 3 and 6 months; finally, CT accurately diagnosed tumor response only in 44% of the patients at 1 month, in 60% at 3 months, and in 57% at 6 months. In the same year, Choi et al. [49] correlated changes in tumor density on CT with changes in glucose metabolism on ^{18}F-FDG PET. In responders, they showed the occurrence of a significant decrease in both tumor density and SUV_{max}. Although no statistically significant association was found between these two parameters, 70% of the patients with tumors that showed response to ^{18}F-FDG PET demonstrated at least a partial response using the tumor density criteria, while 75% of the patients were classified as having stable disease according to the RECIST criteria. Gayed et al. [50] compared PET with CT in 49 patients 2 months after completion of imatinib therapy. PET was shown to predict the response to therapy earlier than CT in 22.5% of patients. Lastly, Holdsworth et al. [51] studied 63 patients with GIST who underwent PET and CT imaging studies after 1 month of treatment. In this patient group, the time to treatment failure was best predicted by a SUV_{max} threshold of 3.4 at 1 month (p = 0.0001) and a reduction in the SUV_{max} of 40% (p = 0.0002) [51]. Their results suggested that conventional objective response criteria are not generally applicable to prognosis in therapies involving the new molecularly targeted agents.

3.6.1 Early Response Assessment and Prediction of Response

Experimental data have shown that the exposure of GIST cells to imatinib results in a rapid decline of GLUT-2 receptor recruitment to the cell membrane; GLUT-2 has been identified as the principal glucose transporter in GIST cells

[52]. Using a small-animal model, Cullinane et al. [53] were able to demonstrate that FDG uptake into tumors expressing the c-KIT V560G mutation was significantly reduced as early as 4 h after the beginning of imatinib treatment. Clinically, some studies showed that a GIST response to imatinib is associated with a rapid reduction in FDG uptake, preceding changes in conventional response criteria by several weeks [50]. In the clinical scenario, ^{18}F-FDG PET response could be appreciated as early as day 8 after the initiation of imatinib (Fig. 3.7); PET responders had a significantly longer progression-free survival at one year than non-responders (92% *vs*. 12% respectively) [54].

In 2004, Goerres et al. [55] observed that patients responding to treatment, as measured by normalization of FDG-avid areas, had a better clinical outcome than patients in whom FDG uptake persisted. Indeed, in their study the median survival of patients with an ^{18}F-FDG PET response was 100% at 2 years compared to 49% in the group with residual tumor uptake. The authors also compared the prognostic significance of PET and contrast-enhanced CT in 28 patients, concluding that a single post-treatment PET scan, but not a single post-treatment contrast-enhanced CT scan, can provide prognostic information on overall survival and on time to progression. Indeed, the first follow-up CT was considered normal in only two of 28 patients. The measurement of changes between pre-treatment PET and the first follow-up PET scan and between pre-treatment CT and the first follow-up CT scan showed a significant

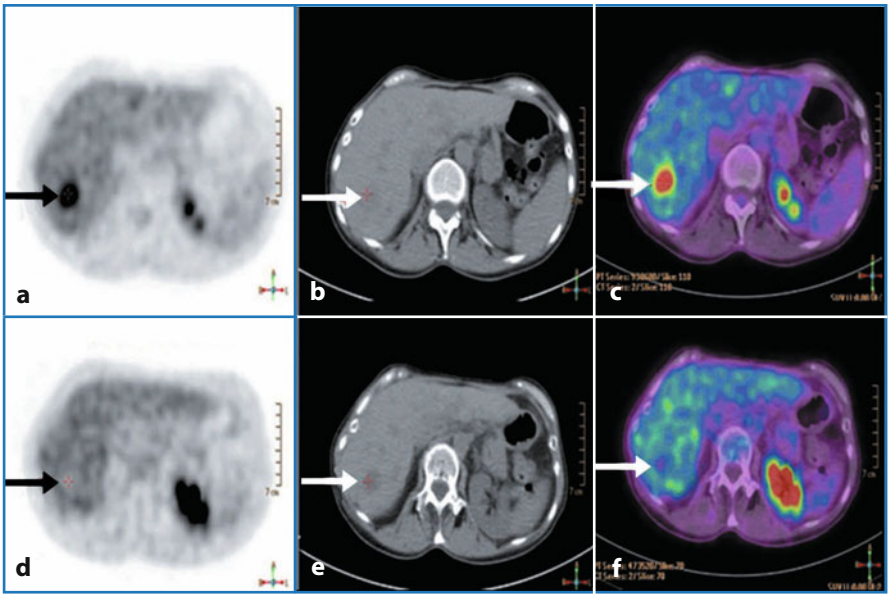

Fig. 3.7 Sixty-year-old woman with liver metastases from GIST. **a** At baseline ^{18}F-FDG PET/CT shows focal uptake in segment 6. **b** Non-contrast CT shows a hypodense lesion in the same liver segment. **c** Correlation between PET and CT images is confirmed by the fusion image. **d-f** After one week of 400 imatinib PET shows complete metabolic response

role only for PET imaging in predicting the overall survival of responders (PET changes: log-rank test $p = 0.009$; CT changes: log-rank test $p = 0.706$). More recently, Prior et al. [36] found that a PET scan performed 4 weeks after initiating treatment with sunitinib after imatinib failure is useful for the early assessment of treatment response and for the prediction of clinical outcome in GIST patients. In their study, progression-free survival correlated with early ^{18}F-FDG PET metabolic response; when a single ^{18}F-FDG PET was considered after 4 weeks of sunitinib, median progression-free survival was 29 weeks for SUVs < 8 g/mL vs. 4 weeks for SUVs ≥ 8 g/mL ($p < 0.0001$) [36].

3.6.2 Caveats in ^{18}F-FDG PET/CT Response Assessment

On PET/CT, response is characterized by a decrease in FDG uptake, with the measurement of SUV used to quantify the decrease. However it is important to underline that a positive baseline PET/CT examination is a prerequisite in therapy evaluation, as not all GIST lesions display appreciable glucose uptake. Furthermore, small lesions can occasionally be difficult to detect within bowel folds, in the pelvis, or in the omentum. SUV measurements are subject to variability related to the determination of a region of interest (ROI) by the test interpreter. A strong standardization of acquisitions and interpretation procedures along with the assessment of variability across readers should be conducted before intitiating ^{18}F-FDG PET response assessments.

3.7 Emerging Imaging Techniques in the Assessment of Response to Treatment in Patients with GIST

The role of MRI in assessing early treatment response has been recently evaluated. Tang et al. [56] investigated the apparent diffusion coefficient (ADC, see Chapter 2) as a predictor of early response in patients with GIST. The authors observed a significant increase in ADC values in responding lesions vs. a very modest increase in the poor-response group (44.8% vs. 1.5% at week 1), thus concluding that a marked increase in the ADC values 1 week after the beginning of imatinib therapy is associated with a good response. Technical advances now allow whole-body DW-MRI to be performed on a routine basis (Fig. 3.8). In the future, this new technique will likely play a key role in diseases staging and in the evaluation of treatment response [57].

A pilot study recently evaluated CT perfusion patterns in GIST lesions in patients undergoing therapy with sunitinib and imatinib [58]. With respect to extrahepatic and hepatic lesions, perfusion was significantly lower in good responders than in poor responders. The authors concluded that CT perfusion could in the future be adopted as a biomarker for treatment response.

Dual-energy CT allows the evaluation of iodine-related attenuation (IRA), which can be considered as a surrogate of perfusion and vascularization; in

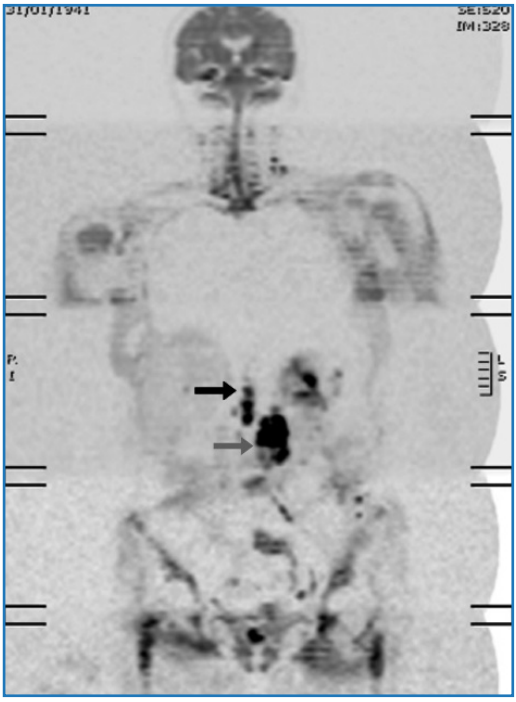

Fig. 3.8 A 58-year-old man with a GIST in the small intestine. Whole-body DW-MRI shows the primary tumor as well as the peritoneal metastases (*gray* and *black arrows*, respectively)

fact, the amount of iodinated contrast medium in a tissue depends on the degree of vascularization. In a recent study, Apfaltrer et al. [59] demonstrated a good correlation between IRA and the Choi criteria: IRA appeared to be a more robust parameter of response than density because it is not influenced by intratumoral hemorrhage.

3.8 Imaging Assessment Proposal

Based on the specific contribution that each imaging technique gives to the assessment of GIST in the era of targeted therapy we propose the following guidelines.

Base line evaluation. In patients with advanced disease, the integration of CT and PET/CT certainly yields the highest amount of information regarding both the true extension of the disease and the interpretation of odd features of response, e.g. cystic transformation in pre-existing necrotic tissue. Moreover, ^{18}F-FDG PET/CT could allow early prediction of response to treatment.

Patients that are borderline for surgery, because of tumor in critical sites, (e.g. the rectum) or due to tumor size, may benefit the most from baseline assessment.

Ongoing therapy evaluation. In general, CT is a suitable instrument to confirm and monitor the benefit of ongoing therapy. Radiologists should look for any density changes and carefully evaluate the peritoneum, where the detection of new metastases is often more difficult. ^{18}F-FDG PET is more sensitive in detecting early progression after response. However, it is not yet demonstrated that this affects prognosis. We suggest that, whenever residual surgery is considered, ^{18}F-FDG PET be added to patient evaluation in order to increase the likelihood of detecting formerly unrecognized sites of disease.

Second/further line therapy evaluation. CT is the first level test to monitor patients with GIST. Given the lower therapeutic index of second-line therapies, it is clinically important to ascertain the degree of tumor control achieved by the administered drug. ^{18}F-FDG PET detects sunitinib activity earlier than CT, but early identification of response has not been proven to affect patient outcome.

3.9 Conclusions

The advent of targeted therapies has greatly altered the horizon of tumor therapy, from cellular destruction to cellular silencing. This innovation requires further improvement in our ability to detect intratumoral events so as to identify the patients who will genuinely benefit from these innovative but expensive therapies. The integration of CT, MRI, and PET/CT seems the most promising approach to more correctly stage and evaluate the response to imatinib and other multikinase inhibitors in patients with GIST.

Clinical Case

A 78-year-old female presented with abdominal discomfort. On ultrasound, a 20-cm-wide mass was visible in the mid-left abdominal quadrant in proximity to the pancreas and stomach, which were considered the two most likely site of origin. The neoplasm surrounded the upper mesenteric artery. An ultrasound-guided core biopsy was performed and histopathology confirmed a CD117-positive GIST with 15 mitoses per 50 high-power fields. A *KIT* exon 11 mutation was also detected. Staging was then completed with an abdominal CT scan and ^{18}F-FDG PET (Fig. 3.9).

Imatinib at a dose of 400 mg/day was started. After 1 week of treatment, the patient complained of abdominal pain and fluid retention, with a sharp body weight increase (+ 3 kg). An abdominal ultrasound did not show significant changes compared to the baseline study except for the presence of ascites, mostly in the pelvis. Imatinib was continued and nimesulide (200 mg daily) and furosemide (25 mg daily) were added, achieving pain and fluid-retention control. Therapy was then uneventfully continued. After 2 months, a CT scan showed a dimensional reduction (wider axis reduced from 20 to 15 cm), a sharp density reduction, and the appearance of hypodense hepatic metastases (Fig. 3.10). The radiologic features of these apparently new lesions raised the suspicion of a progressing disease despite the partial response of the primary tumor. However, this is a typical picture of response to targeted therapy in GIST, in which any tumoral lesion needs to be interpreted bearing in mind that isodense lesions may become readily detectable after therapy because of intense vascular collapse due to imatinib. Therefore, any apparently new lesion has to be, retrospectively, thoroughly searched and interpreted in

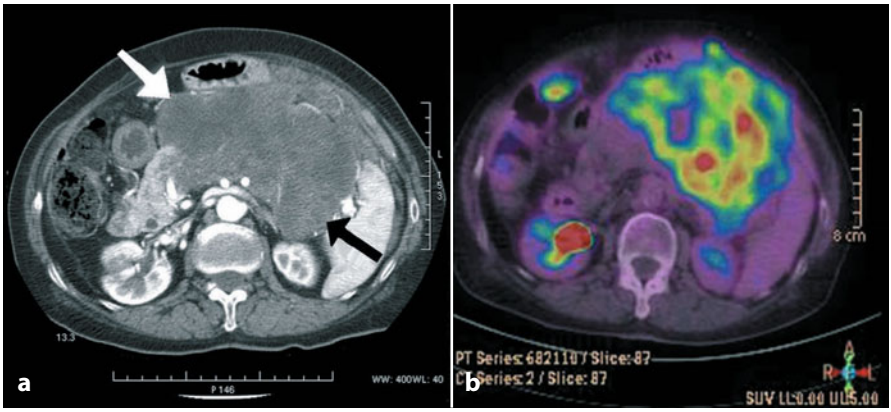

Fig. 3.9 a The axial CT scan shows an enormous primitive tumor of the peritoneum. **b** ^{18}F-FDG PET highlights the high metabolic activity of the lesion

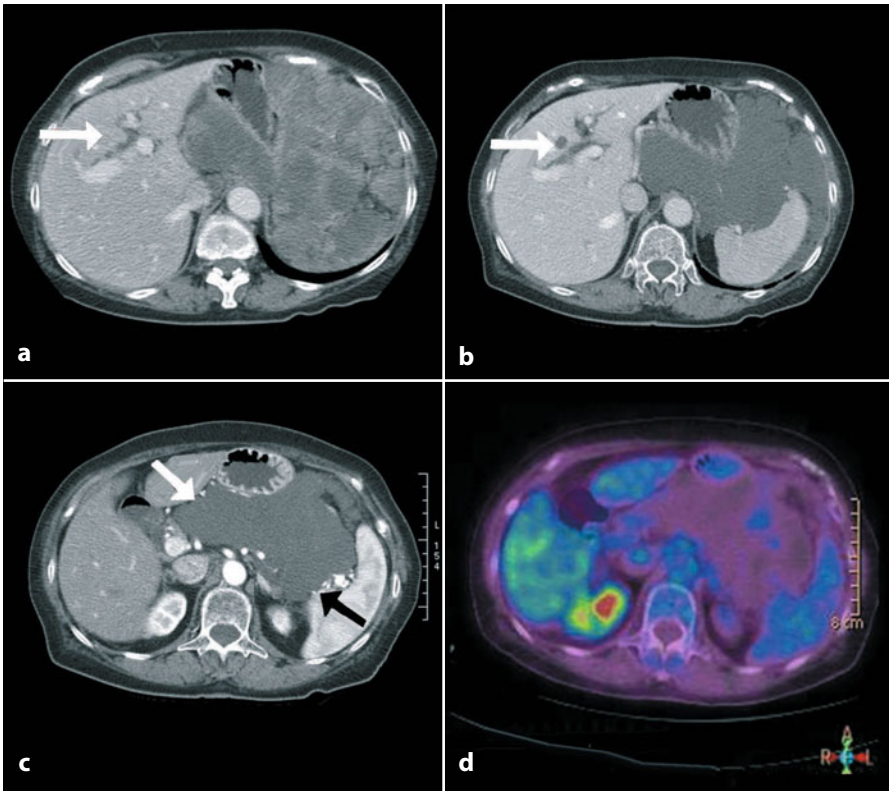

Fig. 3.10 An isodense lesion at the pre-treatment scan (**a**) became readily detectable at CT (**b**) after therapy, because of the intense vascular collapse mediated by imatinib. **c** A sharp decrease in the tumor density is observed also within the primitive lesion. **d** In the latter, there is no residual metabolic activity at ^{18}F-FDG PET

light of its radiological features, especially the density change. The patient remained on the same dose of imatinib for another 21 months, when a CT scan control showed a further shrinkage of the hypodense tumor (wider axis 12.5 cm) and the appearance of a new hyperdense nodule (Fig. 3.11a). The suspicion of localized disease progression was confirmed by a ^{18}F-FDG PET. Figure 3.11b shows a clear hot-spot within the large mass confirming the suspicion of disease progression. The radiological picture of a "nodule within a nodule" is a well-recognized sign of progression. Therefore, per se further ^{18}F-FDG PET confirmation is not required. In this context, PET may be used with a dual purpose: (1) to precociously identify progressive disease after a change in therapy; (2) in the case of local therapy aimed at controlling focal progression, to verify limited progression. In this patient, who at the time was 78 years old, ^{18}F-FDG PET was performed in order to quickly determine the potential ben-

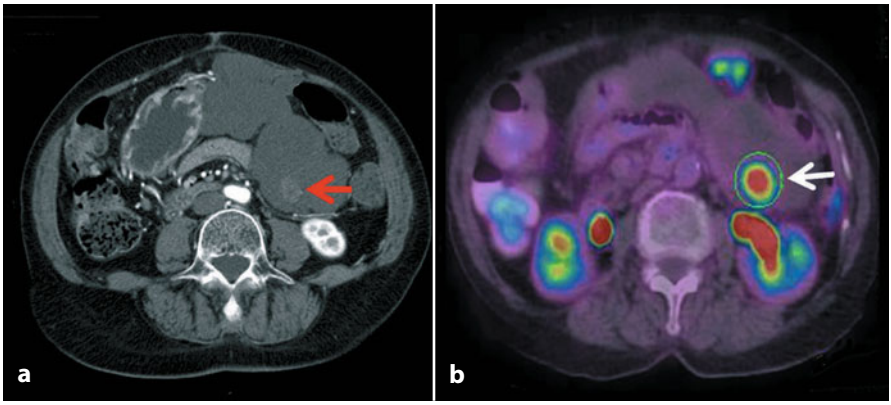

Fig. 3.11 An example of non-dimensional progression. The "nodule within a nodule" is readily appreciated both at CT (*red arrow*) (**a**) and ^{18}F-FDG PET (*white arrow*) (**b**)

efit/failure of an increased dose of imatinib, as a daily dose of 800 mg can be difficult to maintain in the elderly due to anemia, fluid retention, and fatigue. The certainty of benefit can increase patient compliance as can tailoring the dose to the patient.

The imatinib dose was increased to 800 mg/day but had to be discontinued after 4 weeks due to fluid retention (increased body weight of 3.5 kg). Diuretics were started and after 5 days the patient was again administered imatinib, at a dose of 300 mg twice daily, which thereafter was maintained. After 6 weeks, the patient was re-evaluated by CT and ^{18}F-FDG PET, which showed a complete response to the increased dose (Fig. 3.12). Unfortunately, a new metastasis had rapidly grown next to the abdominal wall. At the last follow-up, the patient, now on sunitinib 37.5 mg daily, had no evidences of further disease progression.

This case report demonstrates the different aspects of TRK inhibitor therapy. First, accurate initial imaging is a key aspect of disease management in later stages. Second, dimensional criteria are only one step in the radiological evaluation of the response to TKIs. Third, ^{18}F-FDG PET may help in the interpretation of a mixed response or in case of focal progression, contributing to the clinical decision-making required by these challenging situations. Fourth, proactive adverse event management may substantially increase patient adherence to prescribed doses, which is crucial to achieving lasting disease control; an adjusted dose might allow frail patients, e.g. the elderly, to continue treatment for years. Finally, second-line treatment should be offered to elderly patients regardless of their co-morbidities tailoring the dosage to each single patient and to the side effects observed.

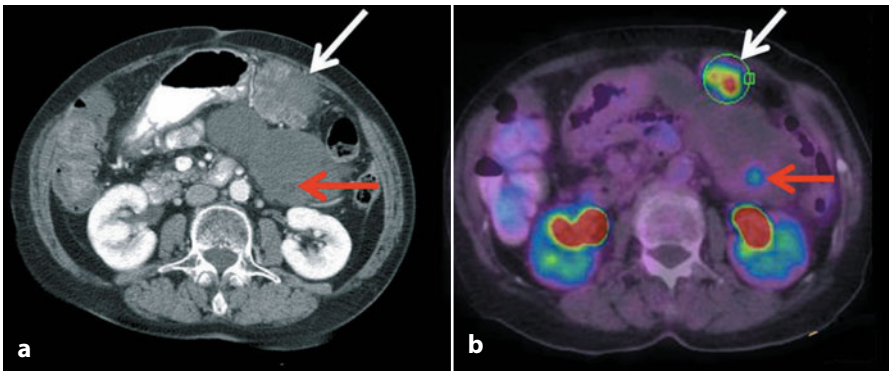

Fig. 3.12 After 6 weeks, both arterial phase CT (**a**) and ^{18}F-FDG PET (**b**) show a response at the previous site of disease (*red arrows*). However, a new lesion appeared in the anterior aspect of the peritoneal cavity (*white arrows*)

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