^{18}F-FDG PET/CT in GIST treatment response evaluation beyond Imatinib

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Abstract
Positron emission tomography/computed tomography (PET/CT) represents a reliable promising tool in treatment response evaluation of new therapies beyond Imatinib in gastrointestinal stromal tumors (GIST). This narrative review aims to discuss the literature about the role of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT in evaluating response in new tyrosine kinase inhibitors (TKI) and radiotherapy (RT) in GIST patients. A comprehensive literature search was performed to retrieve original studies published on PubMed, Scopus and Google Scholar databases. Eighteen studies including 382 patients with GIST were selected. Main findings of included studies are presented. Fluorine-18-FDG PET/CT may enhance performance in GIST management providing significant information in evaluation of treatment response and representing a strong predictor of clinical outcome.

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Introduction

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors of the gastrointestinal system accounting for less than 1% of all gastrointestinal tumors, with an annual incidence of 6.8-14.5 per million individuals [1-3]. Gastrointestinal stromal tumors are tyrosine kinase receptor (c-KIT)-expressing tumors, possibly presenting an activating mutation in either KIT or platelet-derived growth factor receptor alpha (PDGFR-α) [4,5].

Their origin has been attributed to Cajal's cells, but it has recently been proposed that they originate from multipotential mesenchymal stem cells [6], feasibly explaining their resistance to chemotherapy. The malignant behavior and aggressiveness of GIST was conventionally evaluated using class risk category introduced by Fletcher et al. (2002), [7] based on mitotic count and tumor size.

Aggressive GIST can have a high risk of relapse, recurrence, or distant metastasis, so they must be carefully observed and early detected in order to improve survival rates.

Surgical resection is the standard of care for non-metastasized GIST and current guidelines recommend wide resection with negative margins [8].

The introduction of targeted therapies by means of the tyrosine kinase inhibitor (TKI) Imatinib mesylate, and more recently of other similar and effective drugs, has changed the management of advanced GIST. These TKI are used both as adjuvant and/or neoadjuvant therapy improving survival rate and reducing morbidities [9,10]. Figure 1 schematically represents TKI mechanism of action.

Despite the encouraging results obtained by Imatinib in terms of survival, resistance to this TKI may emerge in case of c-KIT mutations, leading to the introduction of new drugs as alternative systemic therapies.

To date, in certain circumstances, radiotherapy (RT) is included in the multidisciplinary treatment strategy of GIST as adjuvant, neoadjuvant to surgery or as a local treatment for GIST developing in duodenal or esophageal locations [11-14].

The range of therapies available for the treatment of GIST requires an in-depth knowledge of the most suitable imaging methods for evaluating the response. Nowadays, ^{18}F-FDG PET/CT is the most widely used imaging modality for the assessment of therapy response in most oncological pathologies, including GIST, considering its association of functional PET data with the morpho-structural data provided by CT allowing multimodality imaging, providing a more accurate performance than the two scans performed separately [15] and being capable of reliability predicting treatment response [16, 17].

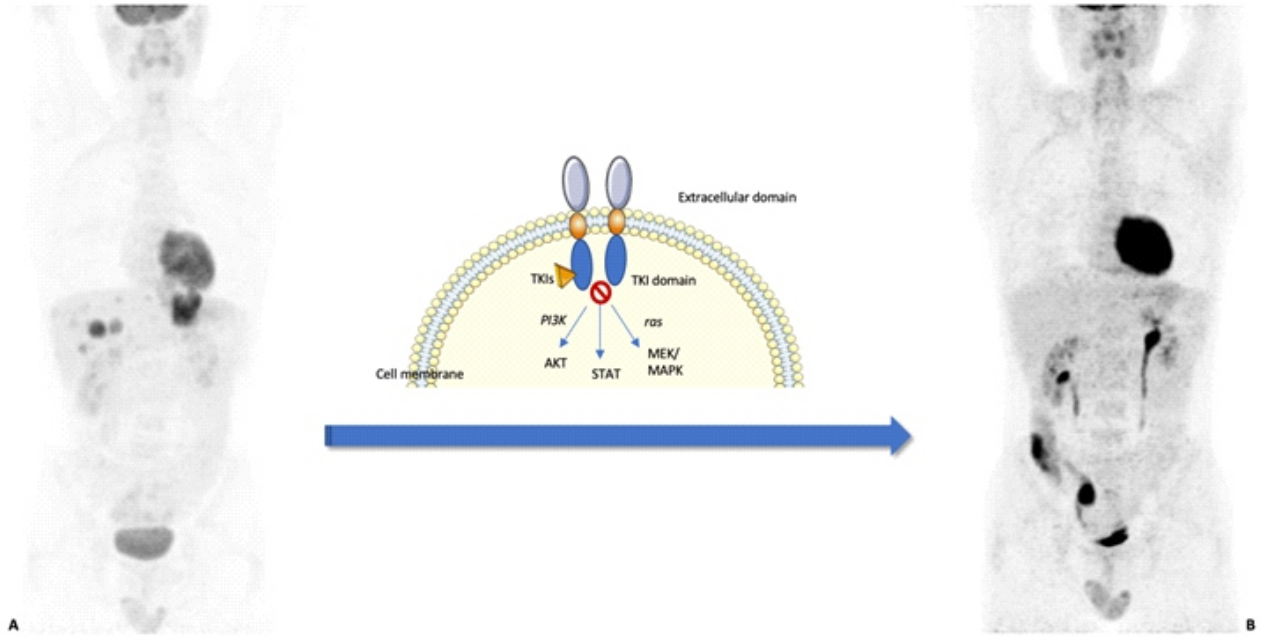

Figure 1. Schematic representation of TKI mechanism of action in a 53 year old man affected by metastatic GIST (A). The post treatment ^{18}F-FDG PET/CT demonstrates the resolution of hepatic metastases and a reduction of ^{18}F-FDG uptake in the primary tumor (B).

This paper aims to provide an update overview of the role of ^{18}F-FDG PET/CT in evaluating treatment response in patients with GIST.

Methods

Search strategy

A comprehensive computerized literature search of the PubMed, Scopus and Google Scholar databases was conducted to find relevant published articles about the role of ^{18}F-FDG PET/CT in evaluating patients with GIST. The search algorithm was based on a combination of the terms (a) "GIST" OR "gastrointestinal stromal tumors"; (b) "positron emission tomography" OR "PET"; (c) "response" AND (d) "Computed Tomography" or "CT". The bibliographies of retrieved papers and reviews were also sought to identify other relevant articles for inclusion.

Study selection

Studies or subsections in studies investigating the role of ^{18}F-FDG PET/CT in evaluating patients with GIST were eligible for inclusion. Review articles, editorials or letters, comments, conference proceedings and preclinical studies were excluded from this review. Considering the low incidence of gastrointestinal stromal tumors and the innovativeness of several therapeutic strategies, case reports were included in the selection.

Only those papers that satisfied all the following criteria were included: (1)^{18}F-FDG PET/CT performed in patients with GIST to evaluate treatment response; (2) articles in the English language; (3) articles published from 2011 onwards. Articles were rejected if they were clearly ineligible.

Data abstraction

For each included study, information was collected concerning basic study (author names, journal, year of publication, country of origin), patient characteristics (number of patients with GIST evaluated, gender, and mean age), drugs evaluated, and technical aspects (timing of PET, device used, PET and CT criteria used in the evaluations). The main findings of the articles included in this review are reported in the Results section.

Results

Literature search

The comprehensive computerized literature search from the PubMed, Scopus and Google Scholar databases revealed 195 articles. Upon review of the titles and abstracts, 117 articles were excluded because the reported data were not within the field of interest of this review; furthermore 25 articles were excluded because they were editorials or reviews and 8 articles because they were preclinical studies (Figure2).

Forty five articles were selected and retrieved in full-text version; two additional studies were found after screening the references of these articles. From these 47 articles potentially eligible for inclusion, after reviewing the full-text article, we excluded 29 articles because they were not in English. Overall, 11 articles and 7 case reports were included in this literature review. The characteristics of the included studies are presented in Table 1.

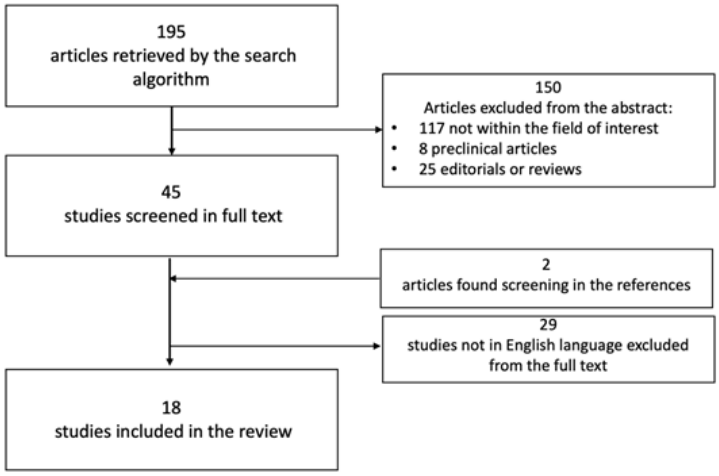

Figure 2. Flowchart of the search for eligible studies on the role of ^{18}F-FDG PET/CT in treatment response evaluation to Imatinib or other drugs in patients with GIST.

Table 1. *Basic study and patient characteristics of the included articles.*

Authors	Journal	Country	Year	N° of GIST patients	Mean Age	Gender (% Male)
Benjamin et al.	Cancer Chemother Pharmacol	USA	2011	138	61	61%
Judson et al.	Clin Canc Res	UK	2014	25	56	68%
Bauer et al.	B J Cancer	Germany	2014	12	56	58%
Van Weehaeghe et al.	BMC Cancer	Belgium	2018	1	37	100%
Lassau et al.	Invest New Drugs	France	2012	20	54	60%
Revheim et al.	Mol Imaging Biol	Norway	2011	-	-	-
Montemurro et al.	Cancer	Switzerland	2018	42	61	57%
Ramaswamy et al.	J Gastrointest Oncol	India	2016	11	45	91%
Fargose et al.	Indian Jour of Nucl Med	India	2018	1	55	100%
Cuaron et al.	Radiat Oncol	USA	2013	15	68	53%
Knowlton et al.	Rare Tumors	USA	2011	1	37	100%
Di Scioscio et al.	Rare Tumors	Italy	2011	3	66	33%
Lolli et al.	Rare Tumors	Italy	2011	1	48	0%
Yilmaz et al.	Reports of Practical Oncology and Radiotherapy	Turkey	2020	1	31	100%
Tezcan et al.	Med Oncol	Turkey	2011	1	83	100%
Yoshikawa et al.	Surg Today	Japan	2013	10	62	70%
Joensuu et al.	Radiotherapy and Oncol	Finland	2015	25	61	68%
Tong et al.	PlosOne	USA	2012	25	18	72%

Literature data Discussion

^{18}F-FDG PET/CT in evaluating treatment response to Imatinib and new chemotherapies in patients with GIST

Concerning CT evaluation, the poor sensitivity of RECIST criteria [18] led Choi et al. (2012) [19] to successfully develop new CT imaging criteria for objectively evaluating tumor response in patients with metastatic GIST, adding the decrease in tumor density by at least 15% criterion as an alternative to the decrease in size of at least 10% for partial responses. Thus, the RECIST criteria proved to be unreliable for monitoring GIST since they underestimated the tumor response to Imatinib mesylate during the early stage of treatment.

Since 2001,several studies compared the efficacy of ^{18}F-FDG PET/CT in evaluating treatment response to CT findings in patients undergoing therapy with Imatinib, enhancing ^{18}F-FDG PET/CT ability to predict subsequent CT findings early after the onset of the TKI [20]. The same evidence was obtained by Demetri et al. (2010) with a subsequent evidence of a markedly decreased ^{18}F-FDG uptake in the tumor from baseline 24h after a single dose of Imatinib, thus^{18}F-FDG PET/CT proved to be a sensitive, rapid and reliable indicator of response or resistance to Imatinib with a well-established correlation between visual findings and standardized uptake values (SUV) compared to the overall response to treatment [21,22] and, in several subsequent studies, to the overall survival (OS) [23,24].

Later in time, many studies have focused on the ability of ^{18}F-FDG PET/CT to provide a more precise and earlier evaluation of response to therapy than CT-based evaluations.

In a Phase 2 multicenter study by Benjamin et al. (2011) [25] 138 patients with advanced GIST were enrolled to assess the tolerability and efficacy of Motesanib, an oral inhibitor of KIT, platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) in patients with Imatinib-resistant GIST, to confirm objective tumor response according to RECIST criteria and evaluate progression free survival (PFS) and time to progression (TTP) by ^{18}F-FDG PET/CT compared to Choi criteria [26].

Patients underwent ^{18}F-FDG PET scans and CT at baseline and after 8 weeks. Fluorine-18-FDG PET/CT evaluated tumor response rate based on EORTC criteria [27], which accounted for 30%, compared with a 3% response rate based on RECIST criteria; considering Choi response criteria, 41% of patients had a tumor response after 8 weeks of treatment. Therefore, objective response rates were observed according to the EORTC and Choi criteria.

In phase II study by Judson et al. (2014) ^{18}F-FDG PET/CT and CT were used to investigate the antitumor activity of Cediranib in patients with metastatic GIST resistant or intolerant to Imatinib mesylate. Patients received Cediranib and changes in SUVmax were monitored. Fluorine-18-FDG PET scans were performed at baseline (up to 14 days before study treatment), on day 8 (week 1) and on day 29 (week 4).

There was some evidence of activity according to ^{18}F-FDG PET/CT with confirmed decreases in SUVmax of ≥10% in 5 patients at day 29 and 2 confirmed partial metabolic responders (PMR) (≥25% decrease). Conversely, there was no RECIST-confirmed objective tumor responses, but stable disease (SD) was achieved in 62.5% of patients, with 14 of 20 evaluable patients achieving disease stabilization for ≥16 weeks [28].

In 2014 Bauer et al. used ^{18}F-FDG PET/CT together with CT in a Phase I study to evaluate combined therapy with Panobinostat, a pan-deacetylase inhibitor that overcomes Imatinib resistance in preclinical models of GIST, and Imatinib in treatment-refractory metastatic patients, enhancing ^{18}F-FDG PET/CT accuracy in the early evaluation of treatment response. Twelve heavily pretreated GIST patients were enrolled in two dose levels, following a 7-day run-in phase of imatinib (400mg per day), escalating doses of Panobinostat were added following a '3 plus 3' design. Full-dose CT scans were performed at least 14 days before randomization and at least every 56 days and evaluated according to RECIST criteria. Metabolic imaging studies were conducted at baseline after the run-in period with Imatinib (day 7) before administration of the first dose of Panobinostat and repeated on day 29 of the first cycle and evaluated according to EORTC Criteria.

No objective responses per RECIST were observed (8 stable disease, 3 progression disease) and a decrease in size or change of density was rarely seen in single lesions, while, according to ^{18}F-FDG PET/CT scans 11 patients showed complete metabolic response (CR), and 1 patient treated at dose level 1 achieved a partial metabolic response (PMR) as defined by EORTC Criteria [27]. Another 7 patients exhibited stable metabolic disease (SMD), and 3 patients had metabolically progressive disease (MPD) [29].

Recently in 2018, ^{18}F-FDG PET/CT and CT assessment of treatment response was further analyzed through a case report by Van Weehaeghe et al., presenting a 37-year-old male with a histological diagnosis of GIST with c-KIT exon 11 deletion and diffused peritoneal implants undergoing therapy with Imatinib and Sunitinib. Serial ^{18}F-FDG PET/CT and CT scans were performed both before treatment and after every therapy switch, to evaluate treatment response. Due to disease progression illustrated on baseline versus follow-up ^{18}F-FDG PET/CT scans, therapy was switched from Imatinib 400 mg/day to imatinib 800mg/day and later to Sunitinib 50 mg/day. Upon further disease progression 10 months later, third line treatment with Regorafenib 160mg/day was initiated.

Pre and post-therapy with Regorafenib ^{18}F-FDG PET/CT images with the differences in maximal standardized uptake value (ΔSUV_{max}) and differences in maximal diameter ($\Delta diam_{max}$) showed that lesion with complete metabolic response had a ΔSUV_{max} of -91% and a $\Delta diam_{max}$ of -1.7%. The lesion with the partial metabolic response had a ΔSUV_{max} of -56% and a $\Delta diam_{max}$ of -21%; while both lesions were evaluated as stable disease on CT scan according to the RECIST1.1 criteria [30].

These results endorse the ongoing discussion about RECIST insensitivity in determinate treatment response to target therapy.

In a preclinical study, Revhiem et al. (2010) demonstrated that novel targeted therapies can be evaluated in the GIST xenograft model using ^{18}F-FDG PET/CT scans. They compared treatment responses induced by the two tyrosine kinase

inhibitors, Imatinib and Sunitinib in a GIST xenograft using ^{18}F-FDG PET/CT scanner. Nude mice bearing human GIST xenografts with mutations in exons 11 and 17 were randomly allocated to treatment with Imatinib, Sunitinib, or placebo daily for 7 consecutive days. Fluorine-18-FDG PET/CT was performed at baseline and 1 and 7 days after onset of treatment observing minor reductions in tumor volume, assessed with CT-coregistrated images, in both treatment groups, while in the two treatment groups, significantly decreased tumor-to-liver uptake ratios were observed both at day 1 (Imatinib, -41%, P=0.002; Sunitinib, -55%, pG.001) and at day 8 (Imatinib, -5%, pG.001; Sunitinib, -50%, P=0.001), when compared to individual baseline values. For the control tumors, neither tumor volumes nor tumor-to-liver uptake ratios were altered during the 8 days the experiment lasted [31].

Lassau et al. (2012) selected ^{18}F-FDG PET/CT as the reference in their study, as this technique has become the gold standard for the assessment of GIST, after the introduction of hybrid PET/CT scanners, which integrate the classical anatomic data obtained with CT with the functional imaging data obtained best imaging technique for the early assessment of response to TKI. They compared dynamic contrast enhanced ultrasonography (DCE-US) performance to results obtained by ^{18}F-FDG PET/CT imaging in the evaluation of 20 metastatic patients treated with Masatinibmesylate, performing ^{18}F-FDG PET/CT at baseline, before treatment and after 1 month. Maximum SUV was calculated on each lesion, comparing SUVmax and AUC in DCE-US for the same target [32].

Montemurro et al. (2018) used ^{18}F-FDG PET/CT to evaluate efficacy of Dasatinib, a potent inhibitor of BCR-ABL, KIT, and SRC family kinases as well as Imatinib-resistant cells. In this 2-stage phase 2 trial, Dasatinib was administrated to patients with histologically proven, TKI-naive, ^{18}F-FDG PET/CT positive GIST. The primary endpoint was ^{18}F-FDG PET/CT response. It was assessed according to EORTC criteria at 4 weeks compared with baseline and classified into 4 categories based on the change in the SUV from baseline to week 4. Adverse events were graded according to the common terminology criteria for Adverse Events (CTCAE), version 3.0. The ^{18}F-FDG PET/CT response rate (complete plus partial responses) at 4 weeks was 74% (95% confidence interval, 56%-85%; 14 patients had a complete response, 17 had a partial response, 6 had stable disease, 3 had progressive disease, and 2 were not evaluable). The median progression-free survival was 13.6 months, and the median overall survival was not reached, enriching high metabolic response rates to Dasatinib in TKI-naive patients with ^{18}F-FDG PET/CT-positive GIST [33].

Fluorine-18-FDG PET/CT proved once again its high sensitivity for the evaluation of therapy response in a study of 2016 by Ramaswamy et al. (2016), which analyzed therapy response in patients treated with Pazobanib, a broad spectrum TKI targeting KIT, PDGFR and VEGF receptors. Eleven patients were assessed for response either by CT and ^{18}F-FDG PET/CT baseline and at 3 months-follow up, and continued pazopanib until progression or unacceptable toxicity.

Median duration of follow-up was seven months and treatment response was evaluated according to RECIST criteria 1.1 and in terms of PFS and OS [34].

Fargose and Basupresented a case report where ^{18}F-FDG PET/CT was used to evaluate response to first, second and third-line therapy with Pazobanib in a case of recurring GIST of the stomach that presented with the involvement of spleen, where ^{18}F-FDG PET/CT images documented the failure of the first two therapy lines with Imatinib and sunitinib, confirming the stability of the disease once Pazobanib was started [35].

^{18}F-FDG PETimaging in the evaluation of radiotherapy treatment response

Considering radiotherapy as a not suitable option for GIST treatment and the standard imaging evaluation provided by CT or MRI according to RECIST criteria, just few authors reported RT treatment response using ^{18}F-FDG PET/CT.

Up to now, RT has not been considered as a proper therapeutic option for GIST because of its low therapeutic ratio resulting from involvement of large abdominal fields and a narrow therapeutic window due to the dose tolerance of small bowel. However, although initial response rates to biologically targeted agents are excellent, many patients develop resistance or metastatic diseases and the latest techniques such as forward-planned intensity modulated radiotherapy (for-IMRT), inverse-planned IMRT (inv-IMRT), helical tomotherapy (HT), and tomotherapy compared each other with three-dimensional conformal radiotherapy (3DCRT), gained in precision in treated fields and producing different dose distributions to the normal tissue [36].

The control of tumor at the locally treated sites, with progression at the sites of metastasis while on TKI, suggests that radiation helped eradicate resistant clones. This further supports the potential role for radiation in locally advanced GIST that is technically unresectable; in fact, as adjuvant, RT could potentially limit the development of resistance and serve as an important adjunct to imatinib.

For tumors at high risk of local recurrence or R1 resection, with or without imatinib, preoperative RT could be considered for cytoreductive effect and neoadjuvant radiotherapy could allow for increased sparing of normal tissue and safer dose escalation.

Radiotherapy can also be used as a local treatment for GIST that develops in duodenal or esophageal locations where resection could cause functional problems. In the setting of locally progressive and/or metastatic GIST, short courses of RT have been shown to be effective for tumor control and symptom management, with low rates of toxicity [13,14,37-41].

Radiotherapy, to date, has been little investigated but several publications provide insight into its efficacy.

The effectiveness of RT in GIST' treatment was investigated in a study of 2013 by Cuaron et al. (2013), reporting local control in 15 of 17 lesions of patients with GIST treated with radiotherapy. A high rate of palliation was achieved for symptomatic tumors in a cohort of advanced stage, heavily pretreated patients. Treatment was well tolerated, and concurrent use of TKI therapy was not associated with additional toxicity. While follow-up was short, durable control is possible for some patients, providing evidence that GIST is not universally radioresistant and that RT can provide an important benefit in patients with progressive or metastatic disease [14].

A 20-year durable local control was also reported by Knowlton et al. (2011) in a 37-year-old man treated with debulking surgery and 36Gy for an unresectable, non-metastatic GIST prior to the widespread use of Imatinib [40] and postoperative radiation was administered following a R1 resection of a 7cm rectal GIST with a two-year-PFS [39].

A few case studies have addressed concurrent radiotherapy and TKI.

Radiotherapy in combination with Sorafenib, in a case report of 2011 by Lolli et al., resulted in a clinical and radiographic response, and the treated tumor remained stable [38]. Analogously, an incompletely resected pelvic mass treated with radiation and Imatinib together, regressed completely and remained locally controlled, despite the growth of a liver metastasis [37].

Major disease control in GIST patients with oligometastases was reached in a study by Tong et al. (2012) with the combination of Sunitinib and image guided radiotherapy (IGRT) [42]; while a multicenter phase II study by Joensuu et al. (2015) observed a durable stabilization of target lesions even with infrequent response to radiotherapy [43].

Although several studies confirmed the important role of ^{18}F-FDG PET/CT in the evaluation of GIST' metabolic response to therapy, literature about its usefulness in radiotherapy response remains poor.

Recently, Yilmaz et al. (2012) presented the case of a 31-year-old male with a GIST presented with solitary bone metastasis at the right iliac bone treated with stereotactic ablative radiotherapy (SABR), achieving an excellent local control. Baseline ^{18}F-FDG PET/CT showed radiotracer uptake in the same area revealed by CT scan, confirming the diagnosis, and showing a complete response at the three months follow-up [44].

This result proves the possibility of ^{18}F-FDG PET/CT scan to be considered a useful tool for the assessment of therapy response not only to TKI but also to radiotherapy alone or combined with first, second- and third-line treatments.

Discussion

In the last years new c-KIT inhibitors or different concomitant treatments are emerging as an alternative chemotherapy to imatinib in GIST patients with intolerance or resistance to therapy.

The overall articles analyzed in this review and the following data confirm ^{18}F-FDG PET/CT usefulness in the evaluation of treatment response in patients with GIST.

Standard morphologic criteria (based on changes in tumor size) are not suitable for an early assessment of treatment response in GIST patients since these criteria do not directly reflect biologic changes in tumor and have no prognostic value for further outcome [22,45].

Treatment with c-KIT inhibitors, in fact, induces functional changes in the tumor, such as a reduced vascularity, hemorrhage or central necrosis, myxoid or cystic degeneration. Moreover, decrease in ^{18}F-FDG PET/CT, which reflects the metabolism of the tumor cell, precedes changes in tumor size. These features are not necessarily associated with a change in tumor volume; actually, the pattern of radiological response based on traditional criteria of changes in size proved to be unreliable, or even misleading, for monitoring GIST, since it underestimated the tumor response during the early stage of treatment.

Figures 3 and 4 show representative clinical cases of ^{18}F-FDG PET/CT evaluation in treatment response to different TKI drugs.

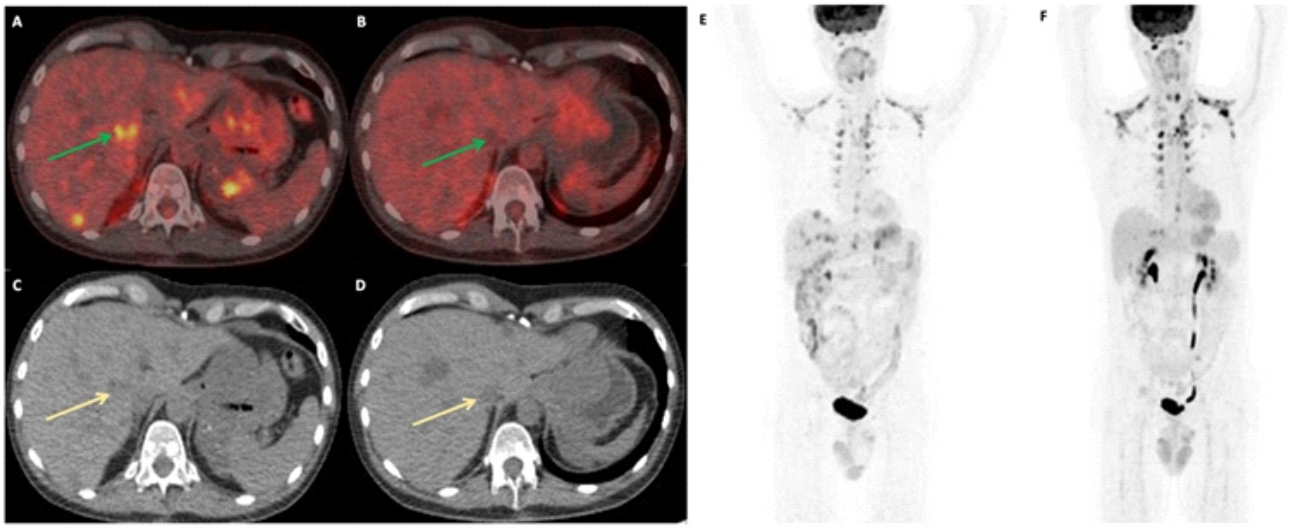

Figure 3. Fluorine-18-FDG PET/CT in a patient with metastatic Imatinib-resistent GIST of the gastric found before and four weeks after onset of therapy with Sunitinib demonstrates metabolic resolution of the hepatic metastases (green arrow) and the decrease of ^{18}F-FGD uptake in the primary tumor (SUVmax 3.5 vs 7.8)(A-B). Axial CT slices before and 4 weeks after Sunitinib initiation show the persistence (yellow arrow) of the hepatic lesions (C-D). Maximum intensity projection images (MIP) of the same patient (E-F).

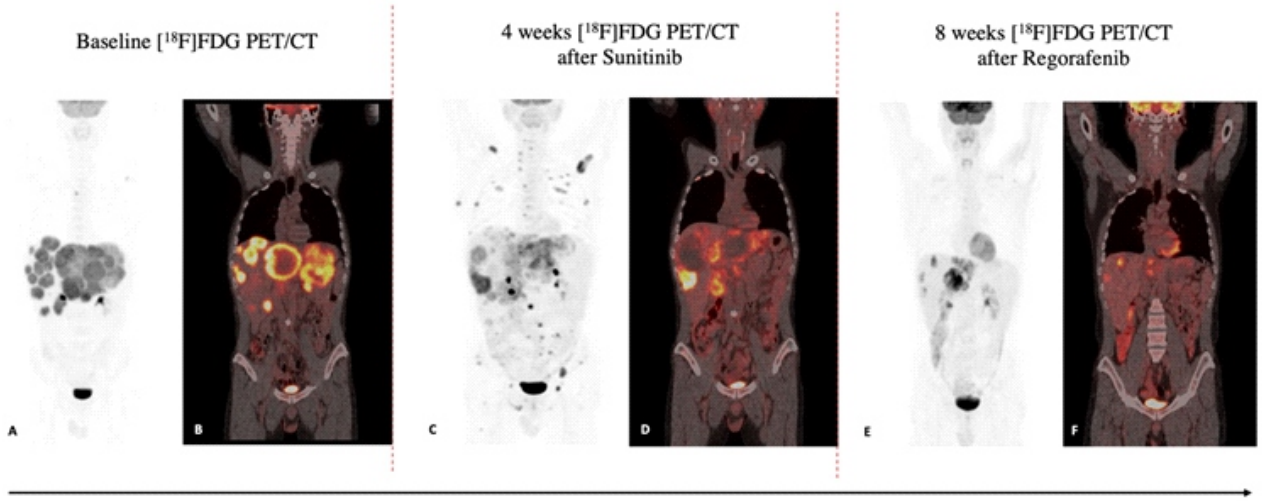

Figure 4. Response assessment on ^{18}F-FDG PET/CT after baseline PET/CT images (A-B) performed in a patient with a Imatinib -resistent metastatic GIST of the small bowel. High-grade ^{18}F-FDG uptake is seen in small bowel (SUVmax 12.6) and also in the hepatic metastases (SUVmax 15.3). Four-week follow up ^{18}F-FDG PET/CT after after II line therapy with sunitinib demonstrates persistent high grade uptake in the primary tumour (SUVmax 13.1) and in the hepatic metastases (SUVmax 9.8) and several new skeletricallesions (SUVmax 6.3) (C-D). Findings are in keeping with progressive disease. Eight-weeks follow-up ^{18}F-FDG PET/CT after after III line therapy with Regorafenib showed major reduction of ^{18}F-FDG uptake in the primary tumor (SUVmax 4.8) and in the hepatic lesions (SUVmax 5.7). Skeletal metastases are no longer detectable (E-F).

In this regard, the earlier predictive benefit of ^{18}F-FDG PET/CT has been enhanced in many studies [19, 22, 46-49], who all identified GIST patient responders to imatinib or other drugs earlier with PET than with CT.

Indeed, in most recent studies, ^{18}F-FDG PET/CT was selected as the reference technique as it's been considered as a reference for the evaluation of other imaging techniques in the assessment of treatment response in patients with GIST and for the evaluation of response to treatment with RT.

Thus, according to the largest majority of the above mentioned studies, it appears that ^{18}F-FDG PET/CT gained a high prognostic relevance in providing information about the therapy response and clinical outcome in comparable for managing treatment planning.

In conclusion, from this review of the literature about the role of ^{18}F-FDG PET/CT in evaluating treatment response in patients with GIST, we conclude that:

(1) ^{18}F-FDG PET/CT has a significant value in assessing treatment response to other drugs beyond imatinib in GIST patients, considering its possibility to evaluate also RT treatment response;

(2) Changes in ^{18}F-FDG uptake in GIST patients during treatment allow an early assessment of treatment response and are strong predictors of clinical outcome.

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