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Role of F-18-FDG-PET/CT in restaging of patients affected by gastrointestinal stromal tumours (GIST)

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Abstract

BACKGROUND: Gastrointestinal stromal tumours (GISTs) are a subset of mesenchymal tumours that represent the most common mesenchymal neoplasms of the gastrointestinal (GI) tract and account for less than 1% of all gastrointestinal tumours.
MATERIAL AND METHODS: We retrospectively evaluated 19 patients (6 females and 13 males; median age: 61 years ± 15 standard deviation) affected by GIST histologically documented after surgical intervention or biopsy.
RESULTS: F18-FDG-PET/CT had identified pathologic uptakes and was considered positive for neoplastic tissue in 10 patients (53%) and negative in 9 (47%), in concordance with radiological findings.
CONCLUSIONS: F18-FDG-PET/CT is a feasible, reliable, and accurate method to restage patients affected by previously histologically confirmed GIST, also in the absence of a staging study.
Key words: positron emission tomography, PET, gastrointestinal stromal tumours, GIST, imatinib mesylate

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Introduction

Gastrointestinal stromal tumours (GISTs) are a subset of mesenchymal tumours that represent the most common mesenchymal neoplasms of the gastrointestinal (GI) tract and account for less than 1% of all gastrointestinal tumours. GISTs are tyrosine kinase receptor (c-KIT)-expressing and many have an activating mutation in either KIT or platelet-derived growth factor receptor alpha (PDGFRα) [1, 2]. Their origin was initially attributed to Cajal's cells but it has recently been supposed that they originate from multipotential mesenchymal stem cells [3], which could explicate their resistance to chemotherapy, and which has lead to the introduction of imatinib mesylate therapy (a tyrosine kinase inhibitor for c-KIT). Their incidence is very low (approximately 10–20 per million people, per year) with no demonstrated significant association with ethnicity, race, geographic location, or occupation. The most common locations of GIST are stomach (50–60%), small intestine (30–40%), colon-rectum (5–10%), oesophagus (5%), and other less common locations outside the GI tract (mesentery, retroperitoneum, and omentum) but there have been reported cases in the pancreas, liver, gallbladder, and urinary bladder, and when GISTs occur outside the GI tract they are known as extra-gastrointestinal stromal tumours (EGISTs) [1, 4]. Approximately 70% of the patients are symptomatic complaining of nausea, vomiting, abdominal discomfort, weight loss or early satiety, and, in presence of large lesions (GIST vary greatly in size from a few millimetres to more than 30 centimetres), signs and symptoms related to the presence of a mass or bleeding due to the erosion of the GI tract lumen. Distant metastases most commonly occur in GIST tumours of the peritoneum, omentum, mesenteric areas, and liver, and rectal GISTs frequently metastasize to the lungs [1]. GISTs show a variety of differentiation possibilities ranging from fully differentiated tumours to incomplete or mixed differentiation, and differential diagnosis could be considered for neuroendocrine tumours, fibromatosis or desmoid tumours, leiomyoma, schwannoma, and angiosarcoma [1, 5]. The diagnostic studies include several examinations, such as barium examination of the GI tract, computer tomography (CT), and angiography. Preoperative percutaneous biopsy should

not be used as it is associated with a significant risk of tumour rupture or dissemination [6], but the effective role of endoscopic ultra-sound guided fine needle aspiration has been pointed out in several studies with high reported accuracy [7]. GISTs generally have an unpredictable outcome due to their uncertain clinical behaviour, ranging from benign to frankly malignant, and the most significant prognostic factors seem to be size and mitotic count [1]. Surgical resection of the local disease, when possible, is the gold standard therapy in the absence of regional lymph node resection as it has no value since GIST rarely gives rise to lymph node metastases [1, 8–10]. Complete surgical resection is connected with 65% five-year survival [8], and when complete resection is not feasible, imatinib mesylate therapy is very effective for tumour treatment in advanced or metastatic disease (GISTs have a high risk of metastatic relapse) even if resistance to imatinib mesylate has been reported [3, 11]. The prognosis of low-risk GIST after complete surgical resection is generally good; instead, the prognosis of high-risk GIST is low with a high rate of recurrence even if, after the introduction of molecular targeted therapy with imatinib mesylate, a major improvement in the survival has been shown [12].

Aim

The aim of this study was to evaluate the feasibility, utility, and efficacy of ^{18}FDG-PET/CT in restaging patients affected by GIST who were treated by surgery or imatinib mesylate, in the absence of a staging PET and comparing the results with radiological imaging for a validation.

Material and methods

We retrospectively evaluated 19 Patients (6 females and 13 males; median age: 61 years $\pm$ 15 standard deviation) affected by GIST histologically documented after surgical intervention or biopsy and localized in the stomach in 8 patients (42%), in small intestine in 8 patients (42%), and in colon-rectum in 3 (16%). The first-line treatment after diagnosis was surgery in 13 patients (68%), surgery and imatinib mesylate in 4 patients (21%), and imatinib mesylate only in 2 patients (11%). All Patients underwent F18-FDG-PET/CT for restaging purposes in order to identify possible relapse of disease (average time to restaging: 20 months). PET/CT was performed in the fasting state for at least 6 hours and glucose level lower than 150 mg/dl. An FDG dose of 5.5 MBq/Kg was administered intravenously, and a 2D mode ordered-subset-expectation-maximization (OS-EM) imaging (with septa) was acquired 60 minutes after injection on a Discovery ST PET/CT tomograph (General Electric Company — GE® — Milwaukee, WI, USA) with standard CT parameters (80 mA, 120 Kv without contrast; 4 minutes per bed-PET-step of 15 cm). The reconstruction was performed on a 128 $\times$ 128 matrix and 60 cm field of view. The PET images were analysed visually and semi-quantitatively by measuring the maximum standardized uptake value (SUVmax). SUV was expressed as SUV body weight (SUVbw — g/ml) and automatically calculated by the software (Volumetrix for PET/CT; Xeleris™ Functional imaging workstation; GE®) on the basis of following parameters: weight of the patient expressed in kilograms; height expressed in centimetres; tracer volume expressed in millilitres (ml); radioactivity at injection time expressed in mega-Becquerel (MBq); post injection activity in the vial expressed in MBq; injection time; starting time acquisition; and decay half-time of the radioisotope (standard 109.8 minutes for F18). A written consensus was obtained by all patients before every study. Moreover, 5 patients underwent a second F18-FDG-PET/CT to evaluate subsequent imatinib mesylate therapy response after two months.

Results

F18-FDG-PET/CT has identified pathologic uptakes and has been considered positive for neoplastic tissue in 10 patients (53%) and negative in 9 (47%), considering an SUV value higher than 3 to be significant; pathologic uptakes were localised respectively in the liver in 3 patients, on the peritoneal surface in 1, in the liver, on the peritoneal surface, and on the thoracic wall mass in 1 (Figure 1), in the liver and colon in 1, in the liver and on the peritoneal surface in 1, on the peritoneal surface and in the colon in 1, and in the stomach in 2 (Figure 2; Figure 3). All F18-FDG-PET/CT results were compared with anatomic imaging; in particular, all patients also underwent computed tomography (CT), and 10 underwent echography (ECHO) or magnetic resonance (MR). All patients negative at F18-FDG-PET/CT were also negative at radiologic imaging (considering negative the absence of lesions or the presence of unmodified, previously documented lesions with respect to the post-therapy radiologic studies). All patients positive at F18-FDG-PET/CT were also positive at radiologic imaging. Among the group of positive patients who underwent a second F18-FDG-PET/CT, no pathologic neoplastic uptake was revealed in 2 and persistent but reduced by more than 25% in 3.

Discussion

The role of F18-FDG-PET/CT in staging patients affected by GISTs is well established as these tumours have shown high glucose metabolism [13–17], and a correlation between FDG uptake and malignant potential or prognosis has been shown [18, 19]. Many studies have been published on high metabolism and the malignant potential of GISTs; in particular Yamada et al. compared tumour size, mitotic index, Ki-67 labelling index (LI), and cellularity of the tumour tissue with the SUV of FDG in 21 patients with gastric GISTs after endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) or endoscopic biopsy. They demonstrated a strong correlation between the SUV of FDG and EUS size and mitotic index, concluding that PET may be used to assess the malignancy of GISTs, to determine the management strategy for patients, and to complement the information on the biological behaviour and cellular proliferation of the tumours [20].

Many papers are currently available describing the role of F18-FDG-PET/CT in staging, follow-up, and therapy response monitoring, also as early as one week after starting therapy [14, 15, 21–25]. In particular, Trent et al. used microarray technology, real-time polymerase chain reaction (PCR) validation, and F18-FDG-PET imaging to study the early molecular effects of imatinib antitumour activity in GIST. F18-FDG-PET was performed to correlate radiographic findings with the effects of imatinib on gene expression in GIST. It was shown that imatinib appears to regulate

Nuclear Medicine Review 2010, Vol. 13, No. 2

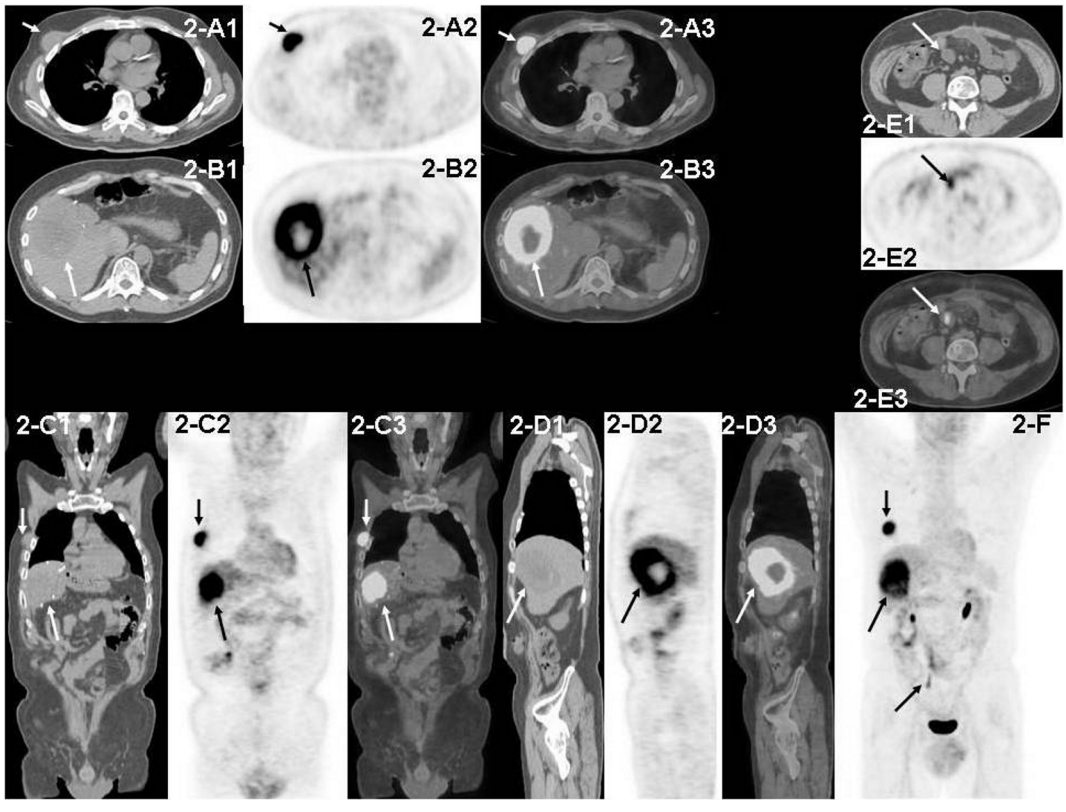

Figure 1. F18-FDG-PET/CT images of a patient with hepatic, peritoneal, and thoracic relapse. Sites of pathologic uptake are highlighted (arrows). In particular, axial CT, (2-A1, 2-B1, 2-E1), PET (2-A2, 2-B2, 2-E2), and fused (2-A3, 2-B3, 2-E3) images, coronal CT (2-C1), PET (2-C2), and fused (2-C3) images, sagittal CT, (2-D1), PET (2-D2), and fused (2-D3) images, and anterior view (2-F) of maximum intensity projection (MIP) images.

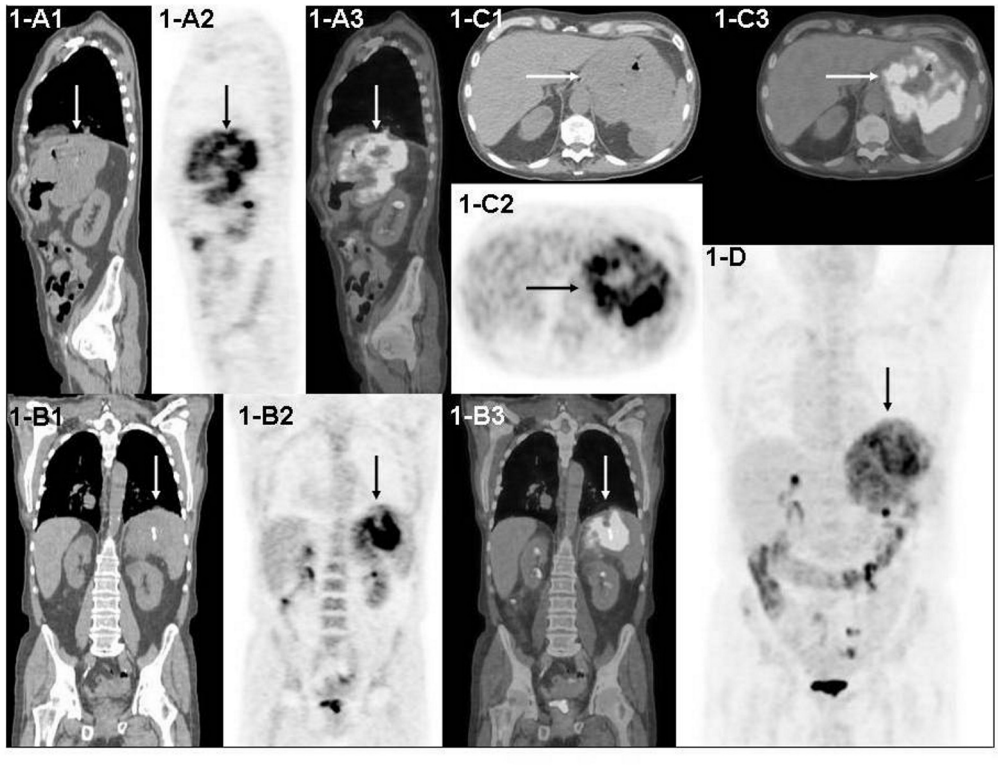

Figure 2. F18-FDG-PET/CT images of a patient with gastric relapse. Sites of pathologic uptake are highlighted (arrows). In particular, sagittal CT, (1-A1), PET (1-A2), and fused (1-A3) images, coronal CT, (1-B1), PET (1-B2), and fused (1-B3) images, axial CT, (1-C1), PET (1-C2), and fused (1-C3) images, and anterior view (1-D) of maximum intensity projection (MIP) images.

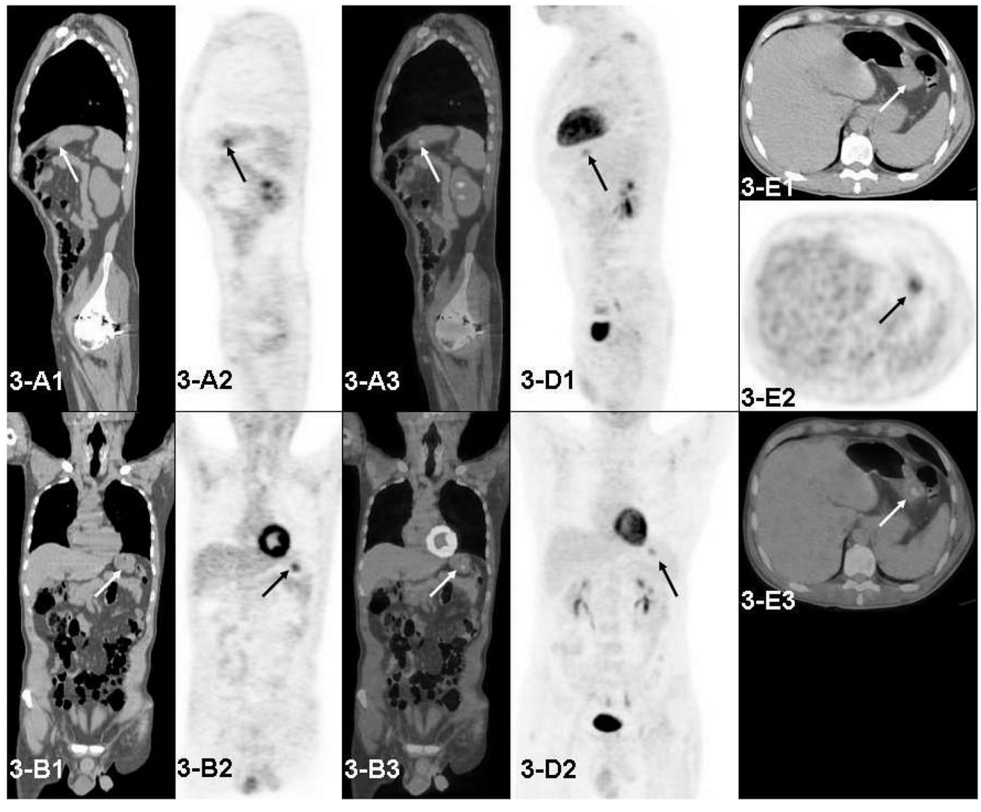

Figure 3. F18-FDG-PET/CT images of a patient with gastric relapse. Sites of pathologic uptake are highlighted (arrows). In particular, sagittal CT, (3-A1), PET (3-A2), and fused (3-A3) images, coronal CT (3-B1), PET (3-B2), and fused (3-B3) images, axial CT, (3-E1), PET (3-E2), and fused (3-E3) images, lateral (3-D1) and anterior view (3-D2) of maximum intensity projection (MIP) images.

numerous genes in GIST cells and tumour samples, inversely correlated with residual FDG uptake early in imatinib therapy [21]. Holdsworth et al. recently studied sixty-three patients enrolled in a multicentre trial evaluating imatinib mesylate therapy for advanced GIST, who underwent F18-FDG PET at baseline and 1 month after initiation of treatment to determine response to prolonged imatinib mesylate treatment. F18-FDG-PET has been useful in determining early response assessment and European Organisation for Research and Treatment of Cancer (EORTC) criteria were predictive of outcome. Choi et al. have evaluated by CT and PET a total of 172 lesions selected by Response Evaluation Criteria in Solid Tumours (RECIST) in 40 patients with metastatic GISTs treated with imatinib before and after therapy, showing the usefulness and accuracy in predicting tumour progression and therapy response assessment [22]. Gayed et al. have studied 54 patients who underwent F18-FDG PET and CT scans within 3 weeks before initiation of imatinib mesylate therapy. The performances of F18-FDG PET and CT have been shown to be comparable in staging GISTs before initiation of therapy; however, F18-FDG PET is superior to CT in predicting early response. Thus, F18-FDG PET has been judged a better guide for imatinib mesylate therapy [15]. Jager et al. evaluated 16 consecutive patients who underwent FDG PET before and after treatment with imatinib mesylate, concluding that FDG PET is a valuable tool in patients with GISTs as it improves staging, accurately separates responders from non-responders in the early phase, and is helpful during follow-up [23]. Antoch et al. compared the value of PET, CT, and PET/CT imaging for assessing response to imatinib mesylate therapy in 20 patients with histologically proven GIST. PET, CT, and PET/CT images were evaluated according to World Health Organization (WHO) Response Evaluation Criteria in Solid Tumours (RECIST), and European Organisation for Research and Treatment of Cancer (EORTC) criteria for therapy response, concluding that image fusion with combined PET/CT can provide additional information in individual cases when compared with side-by-side PET and CT [26]. This hypothesis has been confirmed in a review paper by Van den Abbeele et al. [27]. All possible applications of F18-FDG-PET/CT in GISTs evaluation include initial disease evaluation and early monitoring of imatinib mesylate therapy, evaluating malignant potential at diagnosis, residual viable disease assessment in post-surgery and post-imatinib therapy scenario, detection of acquired resistance to imatinib and disease recurrence, detection of synchronous and metachronous malignancies, and future directions regarding PET/CT-guided personalized management [25].

Despite the small number of cases, in our study we confirmed the role of F18-FDG-PET/CT in GIST evaluation and in assessing therapy response, but mostly that is also a safe, useful, and accurate method to restage patients in the absence of a staging study. Not infrequently, in clinical practise, the impossibility to have a staging study of patients, because of waiting lists, department workloads and clinical necessities, could draw the referring physician to start therapy in the absence of initial evaluation. Undoubtedly this situation precludes the possibility of therapy monitoring of first line treatment, but, according to our results, the

restaging process could be safely based on PET imaging. The concordance between F18-FDG-PET/CT results and radiologic imaging seems to confirm PET accuracy and reliability, suggesting the opportunity to use one total body study only to reduce doses to patients and costs.

Conclusions

F18-FDG-PET/CT is a feasible and reliable method to restage patients affected by previously histologically confirmed GIST, also in the absence of a staging study, in concordance with radiologic findings. The possibility to use a single study to restage patients could reduce absorbed doses, optimize clinical management (reducing time from relapse diagnosis to treatment), and reduce costs. Moreover, these studies could be safely considered the new baseline with which to assess subsequent imatinib mesylate therapy efficacy.

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