Early response evaluation using F-18-FDG-PET/CT does not influence management of patients with metastatic gastrointestinal stromal tumors (GIST) treated with palliative intent

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Evaluierung des frühen Ansprechens mit ^{18}F-FDG-PET/CT hat keinen Einfluss auf das Management von Patienten mit metastasierten gastrointestinalen Stromatumoren (GIST) und palliativer Behandlung

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ABSTRACT

Aim The aim of this study was to investigate the impact of ^{18}F-FDG-PET/CT on treatment decision making in metastatic gastrointestinal stromal tumor (GIST) patients.

Methods This study retrospectively evaluated ^{18}F-FDG-PET/CT scans to monitor response of metastatic GIST patients treated with palliative intent. Data from the Dutch GIST Registry was used. Early scans (< 10 weeks after start of treatment) and late scans (> 10 weeks after start of treatment) were scored on the impact in change of treatment.

Results Sixty-one PET/CT scans were performed for treatment evaluation in 39 patients with metastatic GIST of which 36 were early scans and 25 were late scans. Early PET/CT scans led to a change in management in 5.6 % of patients and late PET/CT scans led to a change in management in 56 % of patients. Change in management was more often seen after scans with lack of metabolic response (48 % vs. 11 % in scans with metabolic response, p = 0.002). Neither metabolic response nor change in treatment were more often seen in patients with *KIT* mutations compared to patients with non-*KIT* mutations (metabolic response 65 % *KIT* vs. 46 % non-*KIT*, p = 0.33, and change in management 28 % *KIT* vs. 21 % non-*KIT*, p = 0.74).

Conclusion ^{18}F-FDG-PET/CT is not recommended for early response evaluation in an unselected patient population with metastatic GIST, since it does not influence treatment decisions. ^{18}F-FDG-PET/CT, however, can be useful for late response assessment, especially in case of indeterminate CT results.

ZUSAMMENFASSUNG

Ziel Das Ziel dieser Studie war es, den Einfluss der ^{18}F-FDG-PET/CT auf die Behandlungsentscheidung bei Patienten mit metastasierten gastrointestinalen Stromatumoren (GIST) zu untersuchen.

Methoden Diese Studie wertete retrospektiv ^{18}F-FDG-PET/CT-Aufnahmen aus, um das Ansprechen von Patienten mit metastasiertem GIST und palliativer Behandlung zu überwachen. Es wurden Daten aus dem niederländischen GIST-Register verwendet. Frühe Aufnahmen (< 10 Wochen nach Beginn der Behandlung) und späte Aufnahmen (> 10 Wochen nach Beginn der Behandlung) wurden hinsichtlich der Auswirkung auf eine Änderung der Behandlung bewertet.

Ergebnisse 61 PET/CT-Aufnahmen wurden zur Evaluation der Behandlung bei 39 Patienten mit metastasiertem GIST durchgeführt, von denen 36 frühe Aufnahmen und 25 späte Aufnahmen waren. Frühe PET/CT-Aufnahmen führten bei 5,6 % der Patienten und späte PET/CT-Aufnahmen bei 56 % der Patienten zu einer Änderung der Behandlung. Eine Änderung der Behandlung wurde häufiger nach Aufnahmen mit fehlendem metabolischem Ansprechen gefunden (48 % vs. 11 % bei Aufnahmen mit metabolischem Ansprechen; p = 0,002). Weder metabolisches Ansprechen noch eine Änderung der Behandlung wurden bei Patienten mit *KIT*-Mutationen häufiger beobachtet als bei Patienten mit Nicht-*KIT*-Mutationen (metabolisches Ansprechen: 65 % *KIT* vs. 46 % Nicht-*KIT*, p = 0,33; Änderung der Behandlung: 28 % *KIT* vs. 21 % Nicht-*KIT*, p = 0,74).

Schlussfolgerung ^{18}F-FDG-PET/CT wird nicht für die Evaluation des frühen Ansprechens in einer nichtselektierten Patientenpopulation mit metastasiertem GIST empfohlen, da es keinen Einfluss auf Behandlungsentscheidungen hat. ^{18}F-FDG-PET/CT kann jedoch zur Beurteilung des späten Ansprechens nützlich sein, insbesondere bei unklaren CT-Ergebnissen.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. GIST mainly occurs in elderly patients of both sexes and has an estimated incidence of 1–2 per 100.000 per year [1]. Metastatic or unresectable disease is described in 10 to 30 % of patients with GIST [2, 3]. In metastatic GIST, systemic treatment with imatinib is the primary choice of treatment. Imatinib is a tyrosine kinase inhibitor that targets Bcr-ABL, c-KIT and PDGFRA. Since the introduction of imatinib, the survival of patients with GIST has improved significantly, with an increase in median overall survival from 18 months to 5–6 years in patients with advanced disease [4, 5, 6, 7]. Treatment with imatinib leads to disease control in 70–85 % of patients with advanced GIST with activating mutations in *KIT* exon 11, which is the most frequent site of mutation [4].

Treatment response monitoring is often performed using size and density measurements on CT scan [8, 9]. The vast majority of GIST demonstrates high FDG uptake (82–96 %) at baseline [10, 11]. Previous studies have shown that metabolic response measured by ^{18}F-FDG-PET/CT could predict imatinib responses within 1–8 days [12, 13, 14]. In patients treated with neo-adjuvant intent, ^{18}F-FDG-PET/CT has shown to change treatment in 27 % of patients [10]. As a result, the current ESMO guidelines incorporated the advice that an FDG-PET may be useful during early assessment of tumor response if the response is uncertain or when early prediction of the response is particularly helpful (e. g. in the neoadjuvant setting) [8].

Up until now, no studies have been conducted assessing the influence of early response evaluation using ^{18}F-FDG-PET/CT in metastatic GIST patients. The aim of this study was to investigate the impact of ^{18}F-FDG-PET/CT on treatment decision making in GIST patients treated with palliative intent.

Methods

All GIST patients treated with palliative intent who were entered in the Dutch GIST Registry (DGR) and underwent ^{18}F-FDG-PET/CT were included in this study. The DGR includes data of all GIST patients diagnosed since January 2009 in the five GIST centers in the Netherlands. These centers include the Netherlands Cancer Institute, Erasmus MC Cancer Institute, Leiden University Medical Center, University Medical Center Groningen and Radboud University Medical Center Nijmegen. Data acquisition was approved by the local independent ethics committees and was conducted in accordance with the Declaration of Helsinki.

Patient and tumor characteristics were derived from the DGR. Mutational analyses were routinely conducted as per institutional guidelines. Baseline and response ^{18}F-FDG-PET/CT scans of metastatic GIST patients were evaluated and change in treatment was determined by assessing patients' medical records. Metabolic response was derived from the imaging report with metabolic response being defined as decrease or complete absence of FDG-uptake compared to baseline imaging, whilst no response was defined as no change or increase in FDG-uptake. Only in patients with a baseline ^{18}F-FDG-PET/CT, response evaluation was assessed and included in the analyses.

Change in treatment was defined as a switch in treatment strategy directly influenced by ^{18}F-FDG-PET/CT results and was divided in two categories: 1) change in surgical treatment (e. g. surgery cancelled or change in surgical approach); 2) change in systemic treatment (change in dose, switch or stop systemic treatment). The treatment evaluation scans were divided in two

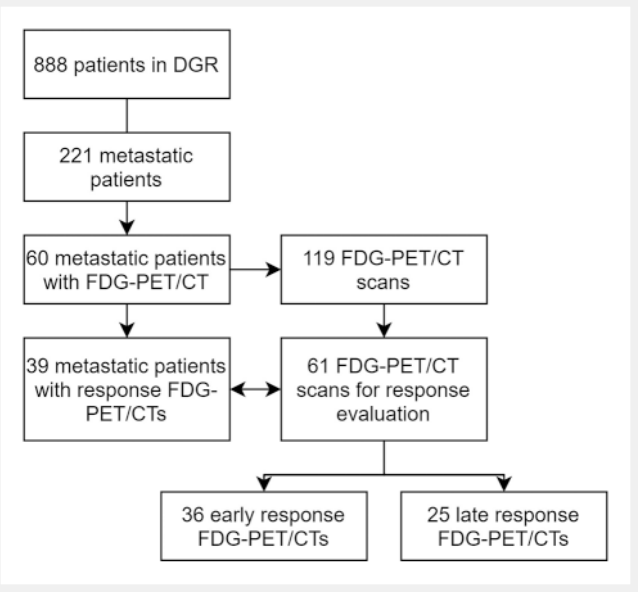
▶ **Table 1** Patient Characteristics.

Characteristic	Patients ($n = 39$)
Gender	
Male	24 (61.5 %)
Female	15 (38.5 %)
Age in years (median; range)	71 (33–85)
Location primary tumor	
Gastric	21 (53.8 %)
Small bowel	12 (30.8 %)
Duodenal	2 (5.1 %)
Colon	2 (5.1 %)
Other	2 (5.1 %)
Mutation status	
KIT mutation *	33 (84.6 %)
▪ *KIT* exon 11	30
▪ *KIT* exon 9	2
▪ *KIT* exon 13	2
▪ *KIT* exon 17	2
PDGRFA exon 18	1 (2.6 %)
PDGRFA exon 12	1 (2.6 %)
Unknown	4 (10.3 %)
Secondary mutations	
Not reported/undetected	36 (92.3 %)
Present	3 (7.7 %)
Baseline Comorbidity – Charlson index score	
< 4	34 (87.2 %)
≥ 4	5 (12.8 %)
Baseline PET available?	
Yes, FDG-avid	37 (94.9 %)
Yes, but not FDG-avid	0 (0.0 %)
No baseline available	2 (5.1 %)

* Three patients had multiple *KIT* mutations: one patients had a *KIT* exon 11 and *KIT* exon 13 and two patients had a *KIT* exon 11 and *KIT* exon 17 mutation.

categories: early response scans and late response scans, with a cut-off of 10 weeks after start of treatment. This cut-off was based on the fact that response monitoring by CT in the majority of cases is performed approximately 10 weeks after start of treatment. In previous studies CT scans were performed every 8 to 12 weeks, therefore a cut-off at 10 weeks seemed to be consistent with what is presumed to be early response evaluation in literature [15]. Two investigators (SF, MH) independently determined whether the reports of the ^{18}F-FDG-PET performed for response monitoring directly led to a change in management. Discrepancies were solved by consensus.

Statistical analyses were performed using IBM SPSS Statistics. Associations between change in management, the timing and results of ^{18}F-FDG-PET/CT and demographic and biological characteristics were assessed using Fisher's Exact tests for categorical variables and Mann-Whitney-U test for continuous variables. Kaplan Meier estimates for progression free survival (PFS) were generated for patients treated with first line imatinib therapy. PFS was calculated from the date of start of systemic treatment until the



▶ **Fig. 1** Study flowchart.

date of progression, defined as the date on which treatment stopped due to disease progression. PFS was compared between metabolic responders versus non-responders using log-rank test. A p-value of < 0.05 was considered statistically significant.

Results

888 GIST patients were entered in the DGR-database. Out of these 888 patients, 221 had metastatic disease (25 %). In total, 119 ^{18}F-FDG-PET/CT scans were performed in 60 metastatic GIST patients. From these scans, 61 ^{18}F-FDG-PET/CTs were performed for response evaluation in 39 patients (▶ **Fig. 1**). The patient characteristics of these 39 patients are described in ▶ **Table 1.** The median number of response evaluation ^{18}F-FDG-PET/CT scans per patients was one, with a range from 1 to 7 scans to evaluate response per patient (▶ **Table 2**).

Patients received first line imatinib treatment in 52 out of 61 response evaluation scans (85.2 %), second line sunitinib treatment in six scans (9.8 %) and third line treatment (once with regorafenib and twice with nilotinib) in three scans (4.9 %). In 36 out of 61 response scans (59 %) a metabolic response was detected. In total, 16 out of 61 (26 %) ^{18}F-FDG-PET/CT scans led to change in management. Eleven out of 16 ^{18}F-FDG-PET/CT scans were performed to assess metabolic response following response evaluation performed by CT in order to clarify the indeterminate results of the CT. The other five ^{18}F-FDG-PET/CT scans were performed to assess whether metabolic progression was seen in one or more lesions prior to surgery or switch in systemic treatment. The two investigators determining whether the ^{18}F-FDG-PET/CT led to a change in management, had only one discrepancy which was solved by consensus.

Thirty-six early response PET scans were performed with a median of 24 days after start of or change in systemic treatment (range 3–70, SD 18.7). Twenty-five late response PET scans were

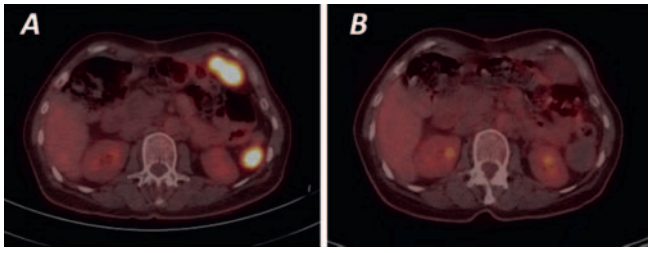
▶ **Table 2** Overview of ^{18}F-FDG-PET/CT scans in clinical practice in current cohort.

No. of ^{18}F-FDG-PET/CT scans	No. of patients
Baseline scans (n = 37 scans)	37
Response evaluation scans (n = 61 scans)	39
No. of response evaluation scans per patient	
1 scan	30
2 scans	5
3 scans	1
4 scans	0
5 scans	1
6 scans	1
7 scans	1

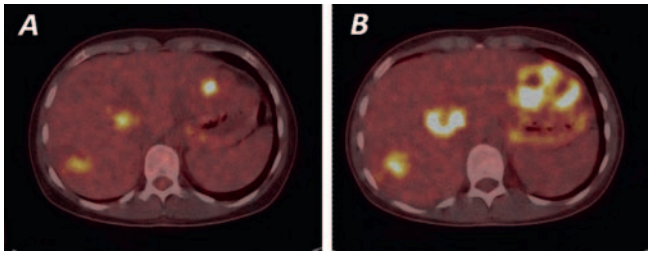
performed with a median of 293 days after start of or change in systemic treatment (range 80–1212, SD 332). Metabolic response was detected in 28 early response scans (78 %) and in eight late response scans (32 %; ▶ **Table 3**). Neither metabolic response nor change in treatment were more often seen in patients with *KIT* exon 11 mutations compared to patients with non-*KIT* exon 11 mutations (metabolic response 65 % *KIT* vs. 46 % non-*KIT*, p = 0.33, and change in management 28 % *KIT* exon 11 vs. 21 % non-*KIT* exon 11, p = 0.74).

Out of 36 early response ^{18}F-FDG-PET/CTs two scans led to a change in management (5.6 %; ▶ **Fig. 2**), while 14 out of 25 (56 %) late response ^{18}F-FDG-PET/CTs led to a change in management. Change in management was more often seen after late response ^{18}F-FDG-PET/CTs (56 % vs. 5.6 % in early response, p < 0.001) and after scans with lack of metabolic response (48 % vs. 11 % in scans with metabolic response, p = 0.002). One early scan led to a change in surgical management, concerning a cancellation of planned surgery due to unexpected progression in multiple lesions. The other ^{18}F-FDG-PET/CT scan led to a change in systemic treatment (switch from first line imatinib to second line sunitinib). Nine late ^{18}F-FDG-PET/CT scans led to a change in surgical management. In these nine scans, a heterogeneous mixed response was observed, showing progression of a solitary metastasis. This led to a metastasectomy of the progressive lesion in combination with continuation of the systemic therapy (TKI) to treat the remaining well responding lesions. The results of five late scans led to a change in systemic management, three of these scans led to an increase in dose and two scans led to a switch to sunitinib (▶ **Fig. 3**).

Survival analyses showed no significant difference in progression free survival between responders and non-responders treated with first line imatinib, with median PFS of 55 months (95 % confidence interval (95 % CI) 22–87 months) and 51 months (95 % CI 16–86 months) respectively (p = 0.54).



▶ **Fig. 2** Example of ^{18}F-FDG-PET/CT images that did not lead to a change in management, but shows great response after early response evaluation by ^{18}F-FDG-PET/CT. (**A**) Baseline ^{18}F-FDG-PET/CT of a GIST patient with a *KIT* exon 11 mutation. (**B**) Complete metabolic response 2 weeks after start of imatinib 400 mg daily.



▶ **Fig. 3** Example of ^{18}F-FDG-PET/CT images that led to a change in management after late response evaluation by ^{18}F-FDG-PET/CT. (**A**) ^{18}F-FDG-PET/CT of a GIST patient with a *KIT* exon 11 mutation, after 3 weeks of treatment with imatinib 800 mg. (**B**) Metabolic progression observed after 7 months of treatment with imatinib 800 mg daily, resulting in change of systemic treatment to sunitinib 37.5 mg daily.

Discussion

In the current study, we investigated the influence of ^{18}F-FDG-PET/CT on treatment strategies in patients with metastatic GIST treated with palliative intent. Prior studies have found that response monitoring using ^{18}F-FDG-PET/CT can be evaluated as early as 48 hours after initiation of treatment. These studies, however, did not evaluate the impact of their findings on patient management changes [14, 15, 16, 17, 18]. The current study is, to our best knowledge, the first study that assessed the actual impact of response monitoring using ^{18}F-FDG-PET/CT on treatment decision making in metastatic GIST. In our current retrospective analysis, almost 95 % of early response scans have not led to a change in management, whereas the late response scans did lead to a change in management in over half of the scans (56 %).

One of our previous studies, performed in patients with localized GIST, who were treated with neoadjuvant intent, found a significant impact of ^{18}F-FDG-PET/CT on patient management decisions in patients harboring a non-*KIT* exon 11 mutation [10]. In the present study, in patients with metastatic GIST, however, no correlation was found between change in management and primary mutation. A recent study, assessing the impact of ^{18}F-FDG-PET/CT during follow-up in previously resected GIST or in case of suspected recurrence, found that 18 out of 100 scans prompted change in management [19]. In our study, change in management was mainly a result of a mixed response, with a non-re-

▶ **Table 3** ^{18}F-FDG-PET/CT outcomes in 39 patients with response evaluation.

^{18}F-FDG-PET/CT outcomes	Total (n = 61)	Early response evaluation (n = 36)	Late response evaluation (n = 25)
Systemic treatment			
First line treatment	52 (85.2 %)	32 (88.9 %)	20 (80.0 %)
Second line treatment	6 (9.8 %)	2 (5.6 %)	4 (16.0 %)
Third line treatment	3 (4.9 %)	2 (5.6 %)	1 (4.0 %)
Metabolic response?			
Yes, complete response	16 (26.2 %)	14 (38.9 %)	2 (8.0 %)
Yes, partial response	20 (32.8 %)	14 (38.9 %)	6 (24.0 %)
No response	23 (37.7 %)	7 (19.4 %)	16 (64.0 %)
No baseline available	2 (3.3 %)	1 (2.8 %)	1 (4.0 %)
Response PET resulting in any change of management?			
Yes	16 (26.2 %)	2 (5.6 %)	14 (56.0 %)
No	45 (73.8 %)	34 (94.4 %)	11 (44.0 %)
Response PET resulting in a change in surgical treatment?			
Yes	10 (16.4 %)	1 (2.8 %)	9 (36.0 %)
No	51 (83.6 %)	35 (97.2 %)	16 (64.0 %)
Response PET resulting in a change in systemic treatment?			
Yes	6 (9.8 %)	1 (2.8 %)	5 (20.0 %)
No	55 (90.2 %)	35 (97.2 %)	20 (80.0 %)
Time between Response PET and start of treatment (days)			
Median (range)	57 (3–1212)	24 (3–70)	293 (80–1212)

sponse or progression in one solitary metastasis. Based on the findings of the ^{18}F-FDG-PET/CT the TKI was continued to treat the well responding lesions and the single site disease progressive lesion was resected. Interestingly, no difference in PFS was found between non-responders and responders. This implies that the ^{18}F-FDG-PET/CT based change in treatment might have been effective.

Despite these clear findings, it is reasonable to assume that the retrospective nature of the current study could have introduced some selection bias. Besides, the limited number of patients in this retrospective study might have hindered to assess the true impact of PET in identifying primary refractory disease, which would be the only situation which results in early management changes. Another possible explanation for the low amount of changes in management decisions after early PET/CT scans could be the high amount of patients with *KIT* exon 11 mutations in the current cohort, who were mostly treated with imatinib. It is known that response rates to imatinib in patients with *KIT* exon 11 mutations are high. Therefore, an FDG-PET/CT that would confirm treatment response, would not lead to a change in treatment. However, despite the low number of scans resulting in a change in treatment in our cohort, this does not mean that early response PET/CT scans could not have an impact. Especially for non-*KIT* exon 11 mutations, early PET/CT scanning could be helpful to identify nonresponders at an early timepoint and adapt their therapy accordingly. Furthermore, the timing of the ^{18}F-FDG PET/CT scans was not standardized causing a wide range of time points, and the 10 week cut-off value to discriminate between early and late scans was not validated due to the lack of prospective standardized studies. However, since this is a reflection of daily clinical practice, we do believe our results are informative. Conversely, a significant proportion of initially responsive GIST eventually become resistant but here the small number of late response assessments (PET was performed in 11 % of all patients with metastatic disease), could have underestimated the impact ^{18}F-FDG PET/CT in late response assessment. On the other hand the percentage of management changes observed in the current study could also reflect selection bias based on equivocal prior CT results. Furthermore, a recent meta-analysis in 88 patients published by Yokoyama et al., showed that ^{18}F-FDG PET/CT has a higher sensitivity than CT scans for detection of early treatment response and therefore presumes an additional value of PET/CT scans after CT scans for response revaluation in GIST patients [20]. During the inclusion period, no (institutional) guidelines were available defining which patients should or should not undergo an ^{18}F-FDG PET/CT or the timing thereof.

Based on the current results, however, we suggest that ^{18}F-FDG-PET/CT is not recommended to be performed for early response evaluation in an unselected patient population with metastatic GIST, since it does not influence treatment decisions. ^{18}F-FDG-PET/CT, however, can be useful for late response assessment, especially in case of indeterminate CT results.

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Conflict of Interest

Hans Gelderblom received research funding to the institute from Novartis, Ipsen, Deciphera and Daiichi Sankyo. Neeltje Steeghs had an advisory role for Boehringer Ingelheim, Ellipses Pharma and AIMM Therapeutics and she received research funding to the institute from Astrazenica/MedImmune, Bayer, Bristol-Myers Squibb, Novartis, GlaxoSmithKline, Pfizer, Roche, Genentech/Roche, Boehringer Ingelheim, Blueprint Medicines, AB Science, Deciphera, Genentech, Merck Sharp & Dohme, Amgen, Merus, Lilly, Incyte, Pierre Fabre, Abbvie, Actuate Therapeutics, Sanofi, Cytovation, InteRNA, Array BioPharma, Cantargia AB, Taiho Pharmaceutical and Takeda.

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