The Potential Value of F-18 FDG PET in Comparison to CT in Early Prediction of Response to Imatinib (STI571) Therapy in Patients with Gastrointestinal Stromal Tumors

Mohsen Beheshti [1,2], Shuren Li [2], Reza Vali [1], Wolfgang Schima [3], Robert Dudczak [2], Werner Langsteger [1]

[1]Department of Nuclear Medicine & Endocrinology, PET - CT Center Linz, St Vincent's Hospital, Linz, [2]Department of Nuclear Medicine, [3]Department of Radiology, General Hospital of Vienna, Medical University of Vienna, Vienna, Austria

ABSTRACT

Introduction: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. GIST has been shown to over-express c-KIT (CD117), the receptor tyrosine kinase. Imatinib (STI571 or Glivec) is a new type of tyrosine kinase inhibitor that selectively inhibits various tyrosine kinases and has been successfully used to treat GIST. In this study we have compared the results of F-18 FDG PET with those of CT in patients with GIST before and early after the treatment with Imatinib.

Methods: The performance of CT and FDG PET imaging in the staging and follow-up of GIST lesion was retrospectively evaluated and compared in 15 patients with 67 suspicious lesions. All patients were examined before and after treatment with Imatinib. Findings of CT and FDG PET were compared on both patient- and lesion-based basis for the whole group and for anatomic locations.

Results: Overall 67 lesions were detected in both pre-therapeutic FDG PET and CT imaging. In the pre-treatment studies there was no significant difference between detected lesions on FDG PET and CT (p = 0.19). However, after treatment with Imatinib (follow-up interval of 30 ± 16 days), FDG PET predicted response to therapy earlier than CT in 18% of lesions and 14% of patients, respectively. There was no significant difference in the density of malignant lesions by means of Hounsfield unit (HU) in the baseline PET in comparison to the early post-therapeutic investigations (93 ± 16 vs. 90 ± 22).

Conclusion: For treatment monitoring of Imatinib in GIST patients, FDG PET gives more precise information of active state of disease compared with CT.

Key words: Gastroointestinal stromal tumors, F-18 FDG PET, CT, Imatinib mesylate.

Corresponding Author: Mohsen Beheshti, MD, Department of Nuclear Medicine & Endocrinology, PET - CT Center Linz, St Vincent' s Hospital, Seilerstaette 4, A – 4020 Linz, Austria
E-mail: mohsen.beheshti @bhs.at

Introduction

Usually (commonly), the response to cancer treatment in solid tumors is evaluated by subsequent clinical or radiological assessments of target lesions and is defined as a significant decrease in measurable tumor dimensions (*1, 2*). There are, however, significant limitations for evaluation of tumor response by volume changes, especially in gastrointestinal stromal tumor (GIST). Accurate measurement of tumor dimensions can be extremely difficult in non-well defined lesions in case of bone, bowel or peritoneal metastases (*3*). Reduction in viable tumor cell fraction does not always result in a volume reduction since tumor tissue can be replaced by necrotic or fibrotic tissue and morphological images are unable to differentiate between these different tissue types. Furthermore, volume changes are rather late events (*3*). Usually, the first evaluation of objective responses measured by computerized tomography (CT) are performed not earlier than 2-3 months after the start of treatment because earlier changes are seldom significant (*3*). Therefore, conventional imaging modalities (e.g. CT) can identify an unusual mass and define its anatomical location and extension; they cannot alone exactly differentiate malignant from benign tissue, or recurrent tumor from necrotic tissue.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. They may be best defined as KIT (CD117) immunostaining-positive mesenchymal spindle cell or epitheloid neoplasms originating from the gastrointestinal tract, omentum, or mesentery, and constitute about 5% of all malignant sarcomas (*4, 5*). Pathophysiologically, GISTs are characterized by a gain-of-mutation in KIT receptor tyrosine kinase. The mutations are most commonly located in exon 11 (coding for intracellular juxtamembrane region of the receptor), and in exon 9 (coding for a region located in the extracellular domain). These mutations lead to ligand –independent receptor activation with consecutive malignant proliferation and protection of afflicted cells against apoptosis (*6, 7*). Imatinib mesylate (Glivec[R], formerly STI571, Novartis pharma AG, Basel, Switzerland) - an inhibitor of certain receptor tyrosin kinases involved in cell signaling (*8*) - has shown very promising clinical results in the treatment of patients with progressive GISTs, which are highly refractory to chemotherapy (*9, 10*). The distinction is further compromised in GIST treated with Imatinib mesylate, where significant metabolic tumor response seems to occur before morphologic change is apparent and tumor can persist despite histological evidence of degeneration and fibrosis (*11, 12*). Therefore, it is really important to select a method that provides early and accurate estimation of therapeutic response in patients with GIST.

Initially, F-18 FDG PET was used in the diagnosis and staging of malignancies (*13*), but, in the last years, promising results have also been obtained in the evaluation of the response to treatment, especially in GIST's patients who underwent Imatinib therapy (*5, 14, 15*) . Because glucose provides the primary source of carbons for the *de novo* synthesis of nucleic acids, lipids and amino acids, FDG uptake, a marker of glucose metabolism is closely related to the number and the proliferation capacity of these viable cells (*16*). Treatment – induced changes resulting in tumor cell death or growth arrest should therefore leads in a subsequent reduction in FDG uptake, making this technique a sensitive and early marker of response. Therefore, the aim of this study was if metabolic imaging using FDG PET can be used for the earlier and more accurate evaluation for treatment response of GIST tumors with Imantinib mesylate in comparison with CT.

Methods

Patients

Twenty patients (mean age 73 ± 16; 12 men, 8 women) underwent PET - CT studies before and after treatment with Imatinib mesylate. The average interval between evaluation studies was 4 weeks. All patients entering the study had to have either histological confirmation or positive c-kit expression on the basis of CD117 immunohistochemical staining. Additionally, they had to have a measurable lesion, with evidence of progression. All patients had to fast at least 12 hours to the PET study. Exclusion criteria were chemotherapy, radiation therapy or a second type of cancer. Five patients were excluded from the study because of parallel therapy (i.e. chemotherapy and/or radiotherapy). Four patients, with evidence of recurrence based on clinical nomograms, had an organ restricted operation (i.e. stomach).

Treatment

Patients included in this study received Imatinib mesylate in doses ranging from 400 – 600 mg once daily. Treatment was continuously administered

36

Beheshti et al.   FDG PET vs CT in GIST

except in the case of unacceptable toxicity or refusal from the patient. In case of disease stabilisation and absence of side – effects, treatment had been continued for a mean time of one and half years.

PET - CT Imaging

Dual - modality PET - CT imaging was performed on an integrated PET - CT system (Discovery LS®, GE Medical Systems, Milwaukee, USA). All PET scans were acquired in 2D mode (4 min emission per bed position).

The CT component provided a minimum gantry rotation time of 500 ms and a maximum scan time of 100 s. CT images were acquired with 165 mAs, 120 kV, a slice width of 5 mm, and a table feed of 22.5 mm/rotation. For vascular and parenchymal delineation, 100 ml of an iodinated contrast agent (Visipaque 270mg I/ml or Imagopaque 300mg I/ml) were administered intravenously at 2.5 ml/s (start delay, 50 s) with an automated injector (Medrad Envision CT injector). Sufficient small - bowel delineation was accomplished by administration of 1,000 ml water. A respiration protocol providing a limited breath-hold was used to avoid motion-induced artifacts in the area of the diaphragm (*17*). All patients were instructed to breath shallowly during CT acquisition of the head and neck and upper thorax. To avoid motion - induced misregistration around the diaphragm, all patients were instructed to breathe out at the level of the lower thorax and hold their breath in expiration during image acquisition in the lower thorax and the liver. Patients were then allowed to continue breathing shallowly.

PET imaging was started 60 min after the administration of a mean of 300 MBq F-18 FDG. To document normal blood glucose levels, blood samples were obtained before the tracer injection. The PET component of the combined imaging system represented a full-ring tomograph with an inplane spatial resolution of 4.6 mm and an axial field of view of 15.5 cm for 1 bed position. Images were reconstructed using an iterative reconstruction algorithm "the ordered subsets-expectation maximization method" (OSEM).

Assessment of Therapy Response

PET

PET images were read by 2 nuclear medicine physicians. A semiquantitative analysis was performed by means of maximum standardised uptake value (SUV_{max}), in addition to the visual interpretation for the assessment of each lesion. PET

response was interpreted (*18*) according to the recommendations of the EORTC-PET group (Table 1). The reliability of findings was surveyed by clinical and / or diagnostic imaging during subsequent follow-up evaluations up to 1 year post initial diagnosis.

CT

CT datasets were evaluated by a general radiologist in consensus with PET reports. Responses to therapy (*1, 2*) on CT images were classified according to the World Health Organization (WHO) guidelines and the Response Evaluation Criteria in Solid Tumors (RECIST); fur further details see Table 2. Furthermore, we measured the tumor density by means of Hounsfield Unit (HU).

Statistical Analysis

To compare the effectiveness of the different imaging combinations, data were divided into categories of responders (partial response and complete response) and nonresponders (no change and progressive disease). Determination of agreement of the different imaging procedures were calculated with SPSS software (SPSS, Inc.). McNemar's test was used to compare differences between the imaging procedures in determination of therapy response. A p - value of < 0.05 was considered to be significant.

Results

Lesion - Based Analysis

A total of 67 lesions were detected in pre-therapy evaluation by FDG PET – CT. In the pre - treatment studies there was no significant difference between detected lesions on FDG PET and CT (p = 0.19). However, we have just evaluated the therapy response in malignant lesions detected in both imaging modalities. The anatomical localizations of malignant lesions are summarized in Table 3. There was an agreement in the prediction of therapy response in 60% of the lesions. Fifty-three percent of lesions showed positive response and 7% presented no response to therapy in both imaging modalities. Incongruent results between FDG PET and CT were recorded in 40% of lesions. FDG PET predicted response to therapy earlier than did CT in 18% of lesions (93% PET vs. 75% CT) in a follow-up interval of 30 ± 16 days.

Beheshti et al.   FDG PET vs CT in GIST

37

Table 1- PET response defined according to EORTC PET recommendations

CR	FDG uptake in all lesions comparable to background activity
PR	> 25% decrease of SUV in all target lesions
SD	Changes in SUV of less than 25%
PD	> 25% increase of SUV in at least one target lesion or the appearance of new lesions (regardless of the SUV changes in the target lesions

EORTC, European Organization for Research and Treatment of Cancer

PET, Positron emission tomography

CR, complete response

PR, partial response

SD, stable disease

PD, progressive disease

Table 2- Tumor response in CT based WHO and RECIST criteria

Response	Criteria	
	WHO	RECIST
Complete response	No lesions detectable on follow - up	No lesions detectable on follow - up
Partial response	Target sum reduction of $\geq$ 50%	Target sum reduction of $\geq$ 30%
No change		
Minor response	Target sum reduction of > 25% but < 50%	Target sum reduction of <30%, unchanged, or increase of <20%
Stable disease	Target sum reduction of < 25%, unchanged, or increase of $\leq$ 25%	Target sum reduction of <30%, unchanged, or increase of <20%
Progressive disease	Target sum increase of > 25%	Target sum increase of $\geq$ 20%

WHO: World Health Organization
RECIST: Response Evaluation Criteria in Solid Tumors

Beheshti et al.   FDG PET vs CT in GIST

38

FDG PET showed complete response (CR) in 63% of the lesions with a decrease in maximum SUV to background activity, 30% partial response (PR) with a decrease in mean SUVmax from 7.6 ± 3.0 in pre-therapy studies to 3.8 ± 2 in post-therapy examinations, and lack of response in 7% of the lesions (2 false - positive due to physiologic bowel activity). However, CT showed 23% CR, 52% PR and 25% no response to therapy in early evaluation studies (30 ± 16) was seen.

Table 3- Localization of malignant lesions in FDG PET - CT

Site	Number of lesions
GI-Tract	36
Liver	17
Peritoneum	4
Lymph nodes	8
Lung	1
Bone	1
Total	67

There was no significant difference in the density of malignant lesions by means of Hounsfield unit s(HU) in pretherapy in comparison to early post - therapeutic investigations (93 ± 16 vs. 90 ± 22). However, in 4 patients with subsequent FDG PET - CT studies, HU in responder lesions decreased to a mean of 35 ± 8.0 in follow - up studies 4 - 6 months after beginning of therapy, respectively. When comparing WHO and RECIST criteria for determination of tumor response on CT images, incongruent results were seen in 6 (9%) lesions that WHO correctly determined response to therapy as partial response, but graded as no changes with RECIST after 4 weeks. On further comparison, WHO and RECIST led to equal assessment of tumor response.

Patients - Based Analysis

In early posttherapy evaluation both FDG PET and CT showed therapy response in 13 patients. FDG PET predicted response to therapy earlier than CT in 14% of patients (87% PET vs. 73% CT). However, FDG PET showed CR in 10 (66%) patients, PR in 4 (27%) patients and no response in 1(7%) patient. With CT only 4 (27%) patients showed CR, 9 (60%) patients PR and 2 (13%) had no therapy response.

In patients-based analysis, WHO and RECIST criteria demonstrated similar results concerning tumor response on CT.

Discussion

Metabolic imaging with FDG PET seems to be an excellent technique for evaluating the efficacy of treatment in patients with GIST tumors undergoing Imantinib mesylate therapy.

The better understanding of pathophysiology of different cancer types has led (19) to the development of a whole new class of anti - cancer drugs, the protein tyrosine kinase inhibitors (PTKI). Imatinib mesylate is the first small molecule of PTKI that has been successfully introduced into human clinical practice. Early clinical therapy trials in GISTs conducted in Europe and the United States showed a significant improvement in progressive - free survival (PFS) and overall survival in comparison to previous studies (10, 11). Therefore, it has now been approved for the treatment of chronic myeloid leukemia (CML) and unresectable and/or metastatic GISTs.

Although a subjective tumor response was seen within a few days in responders, objective tumor shrinkage - detectable in morphological imaging modalities e.g. CT - was sometimes minimal and tended to occur only after several weeks (9-11). Tumor biopsies taken within one month after the beginning of therapy showed in some patients a myxoid degeneration of the tumor with only a few foci of viable GIST cells remaining, thus proving the underestimation of true response as measured by CT (9-11).

The superiority of the metabolic response assessment with FDG PET was first reported by Joensuu and colleagues (9) in the first GIST patient ever treated with Imatinib mesylate. Although the liver metastasis became ' cyst - like ' on CT already 4 weeks after the first therapy - suggesting structural and functional changes in the tumor mass - major tumor shrinkage was first seen after eight months therapy. On FDG PET, however, all hypermetabolic lesions became totally inactive after 1 month of treatment. The value of FDG PET was later confirmed in the reports of the early clinical investigations (10, 11); metabolic responses occurred early after (14) the start of treatment (e.g. 24 hours) and predicted the subsequence CT response. In most of these literatures (14,15); they had briefly paid attention to the PET results comparing to the radiological techniques such as CT.

Beheshti et al.   FDG PET vs CT in GIST

39

In this study, we attempted to establish the role of FDG PET in patients with recurrent and metastatic malignant GISTs in early evaluation of therapy response in comparison with CT. FDG PET was able to predict response to therapy earlier than did CT in 18% of lesions and in 14% of patients 4 weeks after the beginning of therapy (Fig. 1 and 2).
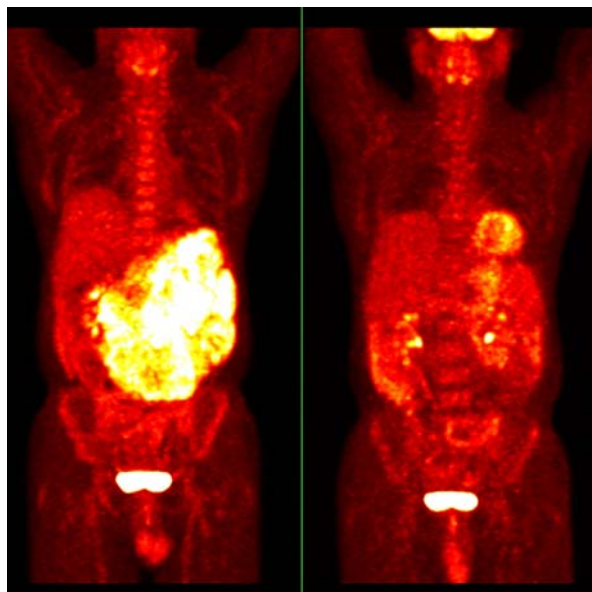

Fig 1. FDG PET, Left: Pre-theray staging diffuse abdominal involvement. Right: Two weeks after therapy with Imatinib, a significant reduction of FDG uptake.

Thus, work-up of suspected malignant GIST recurrence would necessitate initial CT and FDG PET scans for diagnosis and staging. Patients without metastasis and surgically resectable lesions probably will not benefit from a subsequent FDG PET scan; except clinical evidence of recurrence. However, patients with unresectable disease or multiple metastases who are candidates for therapy with Imatinib mesylate probably will need follow-up FDG PET only. Our results do not support significant additional value for CT in the follow-up evaluation of patients who received Imatinib mesylate, especially in the initial period after the initiation of therapy. Therefore, metabolic evaluation with FDG PET gives significant information implying treatment's evaluation with Imatinib mesylate in GIST.

On the other hand, in cytotoxic treatment regimens, reduction in glucose metabolism can already be seen after one cycle of chemotherapy (20-22) and this gradually declines further effective treatment (23, 24). In contrast to this continuous reduction in FDG uptake during cytotoxic treatment, a rapid and almost complete shutdown of glucose metabolism is observed immediately after the start of Imatinib mesylate treatment (3). The molecular mechanism responsible for this rapid decrease in glycolytic activity remains unknown; for that issue a direct inhibition of hexokinase activity by Imatinib mesylate ihas to be discussed (25). Boren and colleagues suggested that, the response assessment with FDG PET is only measuring the downstream effects of the blockade of the c-kit receptor than being a direct marker of cell viability or proliferation (25). This hypothesis should be further evaluated by using not only FDG, but also thymidine analogues like Fluoro-L-Thymidine (FLT) for measuring in vivo DNA synthesis in these patients during Imatinib mesylate treatment (3).

F-18 FDG PET has been shown to improve the assessment of tumor behavior by highlighting early functional changes in tumor glucose metabolism that appear to correlate closely with metabolic tumor response to Imatinib mesylate.

Recently, Choi et al. (14) evaluated the tumor response by quantitative CT response criteria using both tumor size and density by means of HU. They found a decrease in tumor size of more than 10% or a decrease in tumor density of more than 15% on CT had a sensitivity of 97% and a specificity of 100% in identifying PET responders versus 52% and 100% by RECIST, in 2-month follow-up. However, in our study we found no significant decrease in density in responders even in a short time follow – up period (mean ~ 4 weeks).

A limitation of our study was its retrospective nature and the fact that the FDG PET and CT scans were in one imaging procedure and interpreted by nuclear medicine physicians and radiologists, who probably had access to fusion images which may influence the interpretation; and it could be the reason for low number of false positive lesions in these imaging modalities.

In conclusion, FDG PET imaging shows a more accurate and much earlier evaluation of active state of disease compared with CT for follow - up of GIST patients under Imatinib mesylate therapy.

Beheshti et al.   FDG PET vs CT in GIST
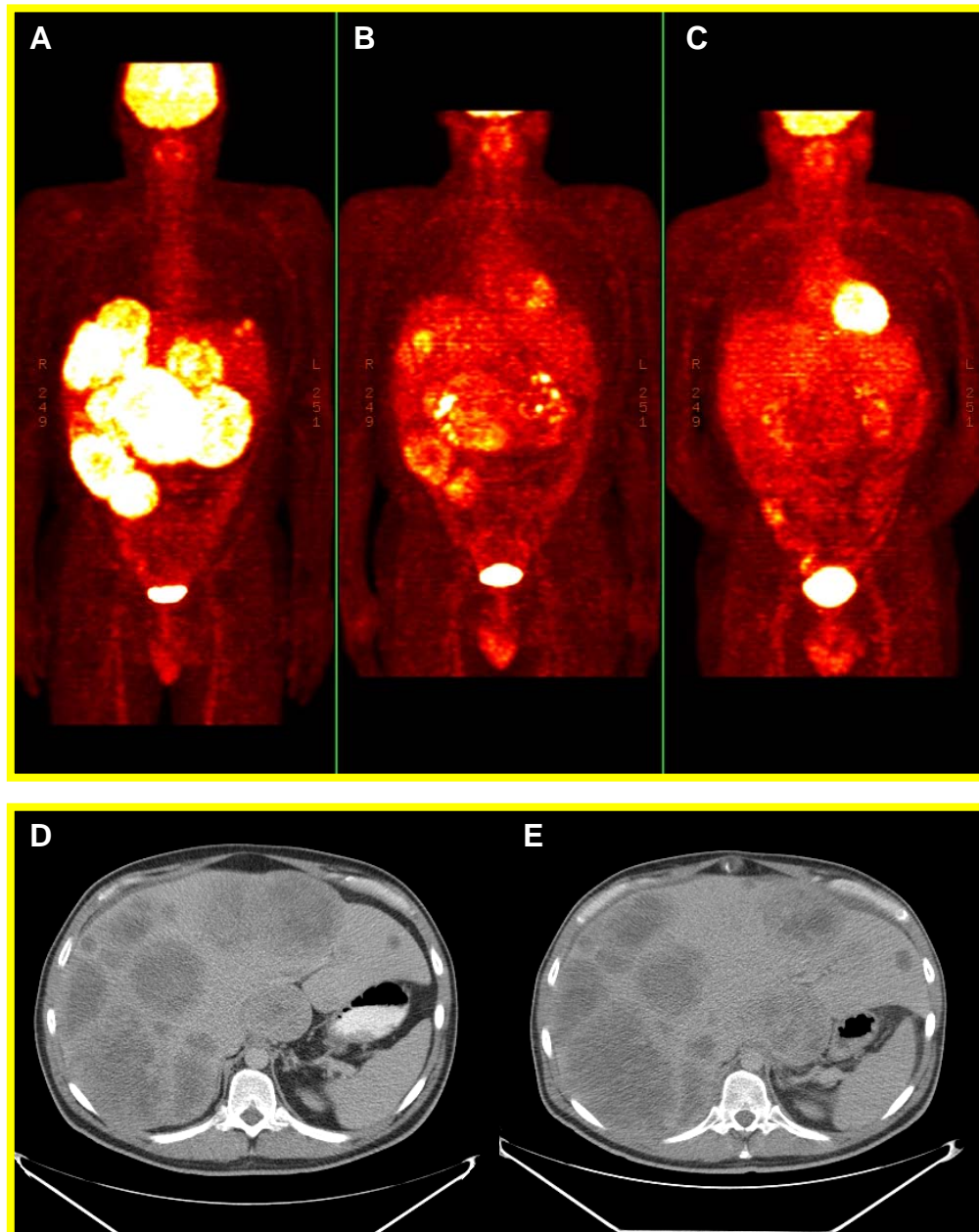
40

Fig 2. FDG PET – CT in the follow – up of a GIST patient

A: Pre - therapy staging of a patient with GIST with multiple abdominal malignant lesions.

B: Therapy evaluation two weeks after therapy with Imatinib with a significant reduced uptake.

C: Follow - up seven months after therapy.

D: CT, two weeks after beginning of the therapy correlated with image " B ".

E: CT, seven month after therapy correlated with image " C " showed no response to therapy.

Beheshti et al.   FDG PET vs CT in GIST

41

References

1. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92(3):205-216.

2. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment 1979;Geneva, Switzerland: World Health Organization(Offset Publication No. 48).

3. Stroobants S, Goeminne J, Seegers M, Dimitrijevic S, Dupont P, Nuyts J, et al. 18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with Imatinib mesylate (Glivec). Eur J Cancer. 2003;39(14):2012-2020.

4. Cheuk W, Lee KC, Chan JK. c-kit immunocytochemical staining in the cytologic diagnosis of metastatic gastrointestinal stromal tumor. A report of two cases. Acta cytologica. 2000;44(4):679-685.

5. Plaat BE, Hollema H, Molenaar WM, Torn Broers GH, Pijpe J, Mastik MF, et al. Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. J Clin Oncol. 2000;18(18):3211-3220.

6. Lasota J, Jasinski M, Sarlomo-Rikala M, Miettinen M. Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. Am J pathol. 1999;154(1):53-60.

7. Moskaluk CA, Tian Q, Marshall CR, Rumpel CA, Franquemont DW, Frierson HF, Jr. Mutations of c-kit JM domain are found in a minority of human gastrointestinal stromal tumors. Oncogene. 1999;18(10):1897-1902.

8. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J pharmacol exp thert 2000;295(1):139-145.

9. Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med. 2001;344(14):1052-1056.

10. van Oosterom AT, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, et al. Safety and efficacy of Imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet. 2001;358(9291):1421-1423.

11. Demetri GD. Identification and treatment of chemoresistant inoperable or metastatic GIST: experience with the selective tyrosine kinase inhibitor Imatinib mesylate (STI571). Eur J Cancer. 2002;38 Suppl 5:S52-59.

12. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of Imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472-480.

13. Hustinx R, Benard F, Alavi A. Whole-body FDG PET imaging in the management of patients with cancer. Semin Nucl Med. 2002;32(1):35-46.

14. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with Imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007;25(13):1753-1759.

15. Gayed I, Vu T, Iyer R, Johnson M, Macapinlac H, Swanston N, et al. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. J Nucl Med. 2004;45(1):17-21.

16. Minn H, Joensuu H, Ahonen A, Klemi P. Fluorodeoxyglucose imaging: a method to assess the proliferative activity of human cancer in vivo. Comparison with DNA flow cytometry in head and neck tumors. Cancer. 1988;61(9):1776-1781.

17. Beyer T, Antoch G, Blodgett T, Freudenberg LF, Akhurst T, Mueller S. Dual-modality PET/CT imaging: the effect of respiratory motion on combined image quality in clinical oncology. Eur J Nucl Med Mol Imaging. 2003;30(4):588-596.

18. Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer. 1999;35(13):1773-1782.

19. Levitzki A. Protein tyrosine kinase inhibitors as novel therapeutic agents. Pharmacology & therapeutics. May-Jun 1999;82(2-3):231-239.

20. Smith IC, Welch AE, Hutcheon AW, Miller ID, Payne S, Chilcott F, et al. Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. J Clin Oncol. 2000;18(8):1676-1688.

21. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. J Clin Oncol. Nov 1993;11(11):2101-2111.

22. Rommer W, Habauske A, Ziegler S, Thödtmann R, Weber W, Fuchs C, et al. Positron emission tomography in non-Hodgkin's lymphoma : assessment of chemotherapy with Flourodeoxyglucose. Blood. 1998;91.4464-447.

23. Bruchler B, Weber W, Bauer M, Fink U, Avril N, Stein HJ, et al. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001;233.300-309.

24. Vansleenkiste J, Stroobants S, De Leyn P, Dupont PJ, Verbeken EK.. Potential use of FDG PET scan after induction chemotherapy in surgically staged IIIa.N2 non-small-cell lung cancer: a prospective pilot study. The Leuven Lung Cancer Group. Ann Oncol 1998;9.1193-1198.

25. Boren J, Cascante M, Marin S, Comín-Anduix B, Centelles JJ, Lim S, et al. Gleevec (STI571) influences metabolic enzyme activities and glucose carbon flow toward nucleic acid and fatty acid synthesis in myeloid tumor cells. J Biol Chem. 2001;276(41):37747-37753.