
The Role of ^{18}F -FDG PET in Staging and Early Prediction of Response to Therapy of Recurrent Gastrointestinal Stromal Tumors

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Gastrointestinal stromal tumors (GISTs) are gaining the interest of researchers because of impressive metabolic response to the targeted molecular therapeutic drug imatinib mesylate. Initial reports suggest an impressive role for ^{18}F -FDG PET in follow-up of therapy for these tumors. However, the role of ^{18}F -FDG PET versus that of CT has not been established. Therefore, we compared the roles of ^{18}F -FDG PET and CT in staging and evaluation of early response to imatinib mesylate therapy in recurrent or metastatic GIST. **Methods:** The study included 54 patients who underwent ^{18}F -FDG PET and CT scans within 3 wk before initiation of imatinib mesylate therapy. Forty-nine of these patients underwent repeat scans 2 mo after therapy. The numbers of sites or organs containing lesions on ^{18}F -FDG PET and CT scans were compared. Corresponding lesions on ^{18}F -FDG PET and CT scans or those confirmed to be malignant in appearance by other imaging modalities or on follow-up were considered true positives. Lesions seen on ^{18}F -FDG PET or CT scans but not seen or confirmed to be of benign appearance with other imaging modalities or on follow-up were considered false positives. Measurements of the maximum standard uptake value (SUV) on ^{18}F -FDG PET scans and tumor size on CT scans were used for quantitative evaluation of early tumor response to therapy. **Results:** A total of 122 and 114 sites and/or organs were involved on pretherapy ^{18}F -FDG PET and CT scans, respectively. The sensitivity and positive predictive values (PPVs) for CT were 93% and 100%; whereas these values for ^{18}F -FDG PET were 86% and 98%. However, the differences between these values for CT and ^{18}F -FDG PET were not statistically significant ($P = 0.27$ for sensitivity and 0.25 for PPV). This suggests comparable performance of ^{18}F -FDG PET and CT in staging GISTs. Repeat scans at 2 mo after therapy showed agreement between ^{18}F -FDG PET and CT scans in 71.4% of patients (57.1% having a good response to therapy and 14.3% lacking a response). Discrepant results between ^{18}F -FDG PET and CT were recorded for 28.6% of the patients. ^{18}F -FDG PET predicted response to therapy earlier than did CT in 22.5% of patients during a longer follow-up interval

(4–16 mo), whereas CT predicted lack of response to therapy earlier than ^{18}F -FDG PET in 4.1%. One patient did not undergo long-term follow-up. These findings suggest that ^{18}F -FDG PET is superior to CT in predicting early response to therapy in recurrent or metastatic GIST patients. **Conclusion:** The performances of ^{18}F -FDG PET and CT are comparable in staging GISTs before initiation of imatinib mesylate therapy. However, ^{18}F -FDG PET is superior to CT in predicting early response to therapy. Thus, ^{18}F -FDG PET is a better guide for imatinib mesylate therapy.

Key Words: gastrointestinal stromal tumors; PET; imatinib mesylate

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Gastrointestinal stromal tumors (GISTs) constitute approximately 0.1%–3.0% of all gastrointestinal tract neoplasms and 6% of all sarcomas (1). These tumors also account for 1%–3% of gastric neoplasms, 20% of all small-intestine neoplasms, and up to 1% of all colorectal neoplasms. GISTs tend to occur in patients who are middle-aged and older. GISTs are usually asymptomatic when <5 cm in their longest dimension and become symptomatic when they grow to >5 cm (2). The usual presenting symptoms are gastrointestinal bleeding, anemia, abdominal pain, dyspepsia, or an abdominal mass. The tumors most often arise in the stomach (70%), followed by the small intestine (20%), large intestine (5%), and esophagus (<5%) (3). Seventy percent of GISTs are benign, and 30% are malignant. Malignant GISTs tend to recur and metastasize, most often to the liver and peritoneum. Other metastatic sites include the lungs, pleura, retroperitoneum, bone, and subcutaneous tissues (1). The median time of survival from diagnosis in patients with metastatic or recurrent disease has been reported to be in the range of 12–19 mo (4,5). Prediction of benign or malignant behavior of a GIST after initial resection is difficult. However, prognostic factors that have been suggested as important include tumor size > 5 cm, ability

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to perform a complete initial resection of the tumor, and tumor grade and site (6). For example, intestinal tumors are more malignant than gastric tumors. Finally, a recurrent or metastatic GIST responds very poorly to chemotherapy and irradiation (7,8). Surgical resection is the mainstay of treatment in resectable tumors.

GISTs have been misclassified as leiomyomas, leiomyosarcomas, and leiomyoblastomas. With the advent of immunohistochemistry and electron microscopy, it was discovered that GIST cells of origin are probably related not to smooth muscle cells but to the cells of Cajal (9,10). Both GIST cells and cells of Cajal have been shown to express the cell surface receptor C-kit, which is identified by CD117 (11). C-kit functions as a tyrosine kinase, which is activated as a ligand in the presence of a stem cell factor. In 1998, Hirota et al. (12) reported a mutation of the C-kit protooncogene that activates tyrosine kinase in the absence of a stem cell factor, leading to uncontrolled cell proliferation. Thus, the etiology of GIST has been identified.

Imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp.) acts as a tyrosine kinase inhibitor and resulted in an impressive response with the first single-patient trial reported in 2001 (13–15). This patient's condition improved clinically, on MRI, and on ^{18}F -FDG PET. Drug efficacy trials and studies of the role of different imaging modalities in the evaluation of GIST response to imatinib mesylate are in progress (16,17). We retrospectively compared the performance of ^{18}F -FDG PET and CT in staging and evaluating response to therapy with imatinib mesylate in patients with recurrent or metastatic GIST after resection.

MATERIALS AND METHODS

Fifty-four patients (23 women, 31 men) with a mean age of 56.4 y (range, 30–82 y) were included in this study. Pretherapy scans were acquired between January and August of 2001. ^{18}F -FDG PET scans were obtained after demonstration of surgically unresectable disease on CT scans, thus qualifying the patients for imatinib mesylate therapy. We reviewed the reported findings on CT and ^{18}F -FDG PET scans performed within 3 wk before therapy (median, 1 d; mean, 3.6 d). Scans also were repeated 2 mo after initiation of therapy. Because most patients had many lesions, the sites or organs involved with metastases were recorded instead of the actual number of lesions. Patients with >3-wk intervals between CT and ^{18}F -FDG PET imaging were excluded from the analysis. Patients who had previously undergone chemotherapy or radiation therapy or had a second type of cancer also were excluded. Five lesions seen on ^{18}F -FDG PET (2 humeri, 2 femurs, 1 thyroid) were outside the field of view of the CT scans and were excluded from the analysis. Patients were considered to have a true-positive site or organ of recurrence or metastasis when ^{18}F -FDG PET and CT agreed or confirmation was made using another imaging modality, biopsy analysis, or evidence of progression on follow-up scans. True negatives were difficult to characterize. False-positive findings were defined as those read as a recurrence or metastasis on ^{18}F -FDG PET or CT scans but proven to be benign using other imaging modalities, biopsy analysis, or follow-up studies. False-negative sites were sites of recurrence or metastasis not shown on CT or ^{18}F -FDG PET scans but confirmed

using other imaging modalities, biopsy analysis, or follow-up studies. The findings on follow-up scans performed at 2 mo also were correlated with patients' symptoms. Symptoms followed included pain, changes in bowel habits or appetite, nausea, vomiting, fatigue or weakness, shortness of breath, and dysphagia. These symptoms were monitored on a scale of 0–10 during subsequent follow-up visits. Patients also were monitored for weight loss, gastrointestinal bleeding, and palpable masses. Data were accumulated for analysis after obtaining the approval of the institutional review board.

^{18}F -FDG PET Scans

Patients were instructed to eat a high-protein, low-carbohydrate diet on the day before undergoing ^{18}F -FDG PET to reduce cardiac uptake of ^{18}F -FDG, and to fast for 6 h before initiation of imaging. On the day of scanning, each patient was injected with 555 MBq ^{18}F -FDG after ensuring that blood sugar did not exceed 200 mg/dL. The patient was placed in a quiet room, and imaging began 1 h later. Scans were acquired from the base of the skull to the mid thighs using an ECAT-HR Plus ring PET system (Siemens Medical Solutions USA, Inc.). Transmission and emission images were acquired over 3 and 5 min per position, respectively, using the 2-dimensional mode (with septa). Transmission images were acquired using a ^{68}Ge source. Images were reconstructed using iterative reconstruction with segmented attenuation correction. Attenuation-corrected slices were used for interpretation of the study.

CT Scans

Chest CT images were obtained as axial slices from the thoracic inlet through the lung base with collimation of 7.5 mm using a helical scanner after intravenous administration of iodinated contrast medium. Reconstructions were made at 3.8 mm.

Abdominal and pelvic CT images were obtained as axial slices from the dome of the diaphragm through the ischial tuberosity after oral and rectal administration of barium and before and after intravenous administration of iodinated contrast, with slice collimation of 7.5 mm using a helical scanner.

Quantitative Analysis

The longest dimension of the largest lesion at different sites on the CT scans was used for quantitative measurement of the extent of disease. A decrease of $\geq 5\%$ was considered a response to therapy. An increase of $> 5\%$ in the longest dimension of these lesions was considered a progression of disease. A combination of $\geq 5\%$ decrease in some lesions and $\geq 5\%$ increase in others was considered a mixed response. Similarly, the maximum standard uptake value (SUV) of the largest lesion at every site on the ^{18}F -FDG PET scans was used to evaluate the initial metabolic activity of the recurrent tumors or their metastases. On follow-up scans, a $> 25\%$ decrease and $> 25\%$ increase in SUV were considered response to therapy and progression of disease, respectively (18). Less than 25% change in SUV was considered stable disease. Finally, a combination of an increased SUV in some lesions and decreased SUV in others was considered a mixed response. Lesions measured in baseline studies were used for comparison in subsequent studies when they could still be visualized.

Statistical Analysis

The number of detected sites of recurrence and metastasis and their characterization as true positives, false positives, or false negatives according to the criteria described previously were sum-

TABLE 1
Frequency of Sites or Organs Involved with Lesions on ¹⁸F-FDG PET and CT Scans

| Site or organ | CT | FDG PET |
|-----------------|-----|---------|
| Liver | 35 | 42 |
| Pericollic area | 8 | 8 |
| Mesentery | 10 | 9 |
| Peritoneum | 7 | 10 |
| Bone | 16 | 1 |
| Pelvis | 12 | 12 |
| Lungs/pleurae | 8 | 14 |
| Lymph nodes | 6 | 1 |
| Stomach | 3 | 3 |
| Other sites | 17 | 14 |
| Total | 122 | 114 |

marized in frequency tables. Sensitivity and positive predictive value were computed for each patient using site/organ data collected from both CT and ¹⁸F-FDG PET scans. In addition, to account for inherent correlation between pairs of probabilities for each imaging modality, separate analyses were performed for paired observations and compared with those performed for unpaired or independent observations. The 2 modalities were compared according to each probability measure using the Wilcoxon signed rank test for paired observations and Wilcoxon 2-sample rank sum test for independent observations. The overall mean sensitivity and positive predictive value were computed using weighted averages from both the paired and the independent observations. The resulting *P* values in both comparisons were combined using a method proposed by Tippett (19). All reported *P* values were 2-sided, and a *P* value of ≤ 0.05 was considered significant.

RESULTS

Pretherapy Staging Scans

A total of 54 ¹⁸F-FDG PET scan and 54 correlating CT scan reports of 54 patients who had undergone previous resection of their primary tumors was reviewed. Twenty-two patients underwent CT of the chest, abdomen, and pelvis, and 32 underwent CT of the abdomen and pelvis only. The total number of sites and organs involved was 122 on ¹⁸F-FDG PET and 114 on CT scans. Forty patients had

TABLE 2
Frequency Table Comparing Performances of CT and ¹⁸F-FDG PET in Staging Recurrent GISTs

| Site or organ finding | CT | ¹⁸ F-FDG PET* |
|-----------------------|-----|--------------------------|
| True positive | 114 | 110 |
| True negative | 2 | 1 |
| False positive | 0 | 5 |
| False negative | 21 | 25 |

*Seven lesions were seen on ¹⁸F-FDG PET scans but had no other confirming findings. They were considered as unknown and were not included in table.

TABLE 3
Causes of False-Positive ¹⁸F-FDG PET Findings

| Cause | Number of sites |
|---|-----------------|
| Postsurgical changes in mid abdomen | 1 |
| Degenerative arthritis in spinal facet joints | 2 |
| Altered weight bearing in sacroiliac joint | 1 |
| Physiologic bowel activity | 1 |
| Total | 5 |

multiple sites of involvement, 4 patients had 2, and 10 patients had a single site. The distribution of the sites and organs involved on ¹⁸F-FDG PET and CT scans is summarized in Table 1. True-positive, true-negative, and false-negative findings on the pretherapy scans were used to compare the performance of ¹⁸F-FDG PET and CT in staging GISTs (Table 2). The sensitivity and positive predictive values were 93% and 100%, respectively, for CT and 86% and 98%, respectively, for ¹⁸F-FDG PET. No statistical difference was found in CT and ¹⁸F-FDG PET sensitivity or positive predictive values (*P* = 0.27 and 0.25, respectively). The causes of false-positive findings on ¹⁸F-FDG PET scans and false-negative findings on ¹⁸F-FDG PET and CT scans are outlined in Tables 3–5. False negatives on ¹⁸F-FDG PET scans were most often related to small lesions in the liver, lung, and peritoneum that were probably below the resolution of the PET scanner. The sites of false-negative findings on CT scans were most often in flat bones, which are more difficult to detect on CT scans. The maximum SUV of all 122 sites and organs was measured using the pretherapy ¹⁸F-FDG PET scans (mean maximum SUV, 5.1 ± 3.2 ; range, 1.0–14.5). In addition, the mean longest dimension of 114 lesions measured on CT was 6.5 ± 5.5 cm (range, 0.4–22.0 cm).

Posttherapy Scans

¹⁸F-FDG PET and CT scans were repeated at 2 (49 patients), 4–6 (17 patients), and 12–14 mo (18 patients) after initiation of imatinib mesylate therapy. At 2 mo after therapy, both ¹⁸F-FDG PET and CT scans showed a response to therapy in 28 patients (57.1%) (Table 6). Of these patients, 17 experienced clinical improvement and 11 remained asymptomatic. The maximum SUV decreased to that of the background activity in all sites in 25 patients (51%) and by at least 30% in the remaining 3 patients (6%). The mean decrease in tumor size on CT scans for these

TABLE 4
Sites of False-Negative ¹⁸F-FDG PET Findings

| Site | Number of sites |
|----------------------------|-----------------|
| Liver | 7 |
| Lungs | 6 |
| Peritoneum | 3 |
| Other sites in the abdomen | 8 |
| Total | 24 |

TABLE 5
Sites of False-Negative CT Findings

| Site | Number of sites |
|-------------------|-----------------|
| Bone | 13 |
| Hilum/mediastinum | 3 |
| Axilla | 2 |
| Paravertebral | 2 |
| Abdomen | 1 |
| Total | 21 |

patients was 3.6 ± 2.9 cm. Seven patients (14.3%) showed no response on either ^{18}F -FDG PET or CT scans: 6 had no clinical change in symptoms and 1 experienced deterioration. ^{18}F -FDG PET and CT scans produced discrepant results in 14 patients (28.6%). Of these, 10 patients were asymptomatic before initiation of treatment and remained asymptomatic at 2 mo. The remaining 4 patients showed improvement in symptoms. Longer follow-up (average, 8.2 mo) of these 14 patients showed that ^{18}F -FDG PET correctly predicted response to therapy earlier than CT (average, 6.0 mo) in 10 patients (20.4%) and lack of response in 1 patient (2%) who was initially asymptomatic and became symptomatic after 8 mo. CT correctly predicted lack of response earlier than ^{18}F -FDG PET in 2 patients (4.1%). In 1 of these, CT demonstrated lack of response followed by progression at 2 and 6 mo in a patient who became symptomatic in the interval, whereas ^{18}F -FDG PET showed response followed by progression. In the second patient, CT showed consistent lack of response at 2 and 6 mo in a patient who became symptomatic, whereas ^{18}F -FDG PET showed mixed response followed by no response. Finally, 1 patient with discrepant results underwent no follow-up scans after 2 mo.

TABLE 6
Correlation of ^{18}F -FDG PET and CT Agreement with Clinical Status of Patients 2 Months After Imatinib Mesylate Therapy

| ^{18}F -FDG PET/CT findings | Number of patients | | | |
|--------------------------------------|--------------------|-----------------------|----------------------|-------------------|
| | Symptoms improved | Remained asymptomatic | Remained symptomatic | Symptoms worsened |
| +/+ | 17 | 11 | 0 | 0 |
| +/- | 3 | 8 | 0 | 0 |
| -/+ | 0 | 1 | 0 | 0 |
| -/- | 0 | 0 | 6 | 1 |
| M/- | 2 | 0 | 0 | 0 |
| Total | 22 | 20 | 6 | 1 |

+/+ = improvement on ^{18}F -FDG PET and CT; +/- = improvement on ^{18}F -FDG PET only; -/+ = improvement on CT only; -/- = no response on ^{18}F -FDG PET and CT; M/- = mixed response on ^{18}F -FDG PET only.

DISCUSSION

The impact of electron microscopy, immunohistochemistry, and gene analysis on understanding the cause and pathology of GISTs, and the consequent discovery of imatinib mesylate as a specific targeted molecular therapeutic agent for these tumors in such a short time, are considered breakthroughs that may open the door to therapy of many other untreatable cancers. The roles of different imaging modalities in evaluating responses to this effective new therapy have not been established. However, some researchers believed that CT underestimated the therapeutic effect of imatinib mesylate during clinical trials of the drug (20). This resulted mainly from the strict Response Evaluation Criteria in Solid Tumors (RECIST) requirement that tumor size must be reduced by at least 30% on CT scans if the treat-

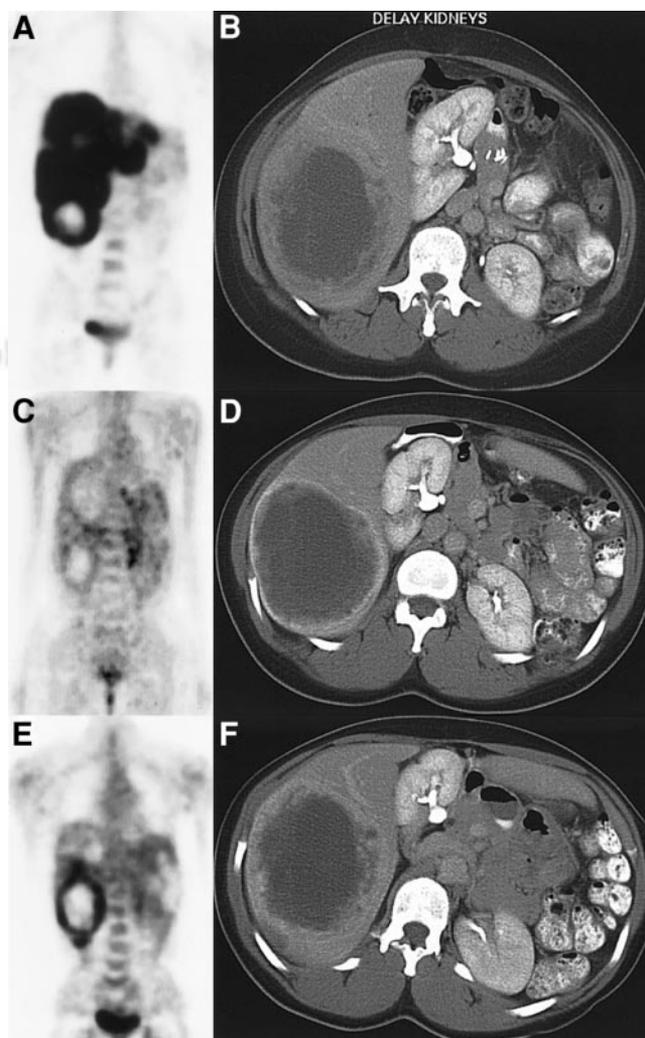


FIGURE 1. ^{18}F -FDG PET and CT scans of patient with metastatic GIST in abdomen and liver before therapy (A and B); at 12 mo of imatinib mesylate therapy (C and D); and at 13 mo after withdrawal of imatinib mesylate for 1 mo (E and F). Maximum SUV of abdominal mass changed from 10.1 (A) to 1.3 (C) to 4.5 (E), and tumor size in longest dimension changed from 10.9 cm (B) to 11.3 cm (D) to 11.5 cm (F).

ment is to be considered a partial response. (21). It was subsequently found that many of these tumors may not change significantly in size or may even grow larger in response to imatinib mesylate administration (22). Before GISTs start shrinking, they undergo cystic changes and changes in density (Fig. 1). Choi et al. (23) demonstrated that the overall disease status evaluated objectively according to changes in size, density, and number of tumor nodules and vessels within the lesion correlated best with the reduction of maximum SUV on ^{18}F -FDG PET scans.

We attempted to establish the role of ^{18}F -FDG PET in staging and early evaluation of response to therapy in comparison with CT in patients with recurrent and metastatic malignant GISTs. Our results indicated that CT and ^{18}F -FDG PET have comparable sensitivity and positive predictive value in initial staging of malignant GISTs. Although CT scans had better anatomic resolution of the sites of lesions, the difference in performance between CT and ^{18}F -FDG PET was not statistically significant. ^{18}F -FDG PET scans were able to predict response to imatinib mesylate therapy 2 mo earlier than CT in 22.5% of the patients. Thus, work-up of suspected malignant GIST recurrence would necessitate initial CT and ^{18}F -FDG PET scans for diagnosis and staging. Patients with surgically resectable lesions and no metastasis probably will not benefit from a subsequent ^{18}F -FDG PET scan. However, patients with unresectable disease or multiple metastases who are candidates for therapy with imatinib mesylate probably will need follow-up ^{18}F -FDG PET scans 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.

A limitation of our study was its retrospective nature and the fact that the ^{18}F -FDG PET and CT scans were interpreted by many nuclear medicine physicians and radiologists, who may have introduced some variability in the reports. Also, the criteria of 5% change in tumor size on CT scans was established in retrospect after analysis of what radiologists previously reported as a response or lack of response to imatinib mesylate therapy. At the present time there seems to be no clearly defined radiologic CT criteria for evaluation of GIST response to therapy. The 5% reduction in tumor size or the cystic and necrotic changes in these tumors may be more sensitive parameters than the presently used RECIST criteria (23). An investigation of new and better criteria for CT in evaluating treatment response of GISTs is in progress at our institution.

CONCLUSION

CT and ^{18}F -FDG PET have comparable sensitivity and positive predictive values in staging malignant recurrent GISTs. However, ^{18}F -FDG PET is superior in predicting early response to therapy. Therefore, CT or ^{18}F -FDG PET can be performed for initial diagnosis and staging of malignant recurrent GISTs but ^{18}F -FDG PET is preferred for evaluation of early response to imatinib mesylate therapy.

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