Response Evaluation of Gastrointestinal Stromal Tumors

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Abstract

Clinical management of patients with gastrointestinal stromal tumors (GISTs) has dramatically changed with the introduction of novel therapeutics, such as imatinib mesylate. This has created a need to re-evaluate the existing criteria used to assess treatment response. The current Response Evaluation Criteria in Solid Tumors are based on unidimensional tumor size, and do not take into account changes in responding GISTs such as a decrease in tumor density and decrease in the number of intratumoral vessels with computed tomography (CT). Positron emission tomography (PET) has been found to be highly sensitive in detecting early response, and to be useful in predicting long-term response to imatinib in patients with metastatic GIST; however, widespread use of PET is limited because of a lack of scanner availability and cost constraints. Modified CT criteria using a combination of tumor density and tumor size are promising in early response evaluation, and have excellent prognostic value. Identifying appropriate treatment response criteria is essential to optimize treatment for patients with GIST. The Oncologist 2008;13(suppl 2):4–7

Introduction

Gastrointestinal stromal tumors (GISTs) are a subset of soft tissue sarcomas that develop primarily along the gastrointestinal tract and often spread within the abdomen. While GISTs account for only 0.2% of all gastrointestinal tumors, 80% of all gastrointestinal sarcomas are GISTs [1]. The prognosis for GIST has traditionally been notoriously poor [2, 3], with a dearth of effective therapies. However, clinical management of GIST patients has changed dramatically. With the identification of Kit receptor within the interstitial cells of Cajal of tumor cells and the introduction of a Kit receptor blocker, imatinib mesylate (Gleevec®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), there has been a dramatic response in advanced disease. This dramatic response to imatinib has redefined not only the clinical management of GIST patients but also the response evaluation in imaging.

The current international Response Evaluation Criteria in Solid Tumors (RECIST) identify computed tomography (CT) and magnetic resonance imaging (MRI) as the best available and most reproducible methods for measuring target lesions [4]. In GIST, positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (18FDG) has been shown to be highly sensitive in detecting early response and to be useful to predict the long-term response to imatinib in patients with metastatic GISTs expressing c-Kit receptor tyrosine kinase [5]. Unfortunately, access to PET technology is still limited for GIST patients because of scanner availability and cost constraints. In some instances, glucose uptake before treatment is not sufficient for detection by 18FDG-PET. Our recent study showed that 36 of 173 (21%) lesions, ranging in size from 1.0 to 4.7 cm, did not demonstrate appreciable glucose uptake on pretreatment 18FDG-PET [6]. Among these 36 lesions, 17 (47%) were >2 cm in size (unpublished data). CT is widely accessible and is currently the imaging modality of choice in monitoring GIST patients treated with imatinib during the course of treatment and surveillance.
**Response Evaluation**

GISTs can occur anywhere along the gastrointestinal tract and rarely within the peritoneum. Contrast-enhanced CT is a powerful technique for GIST diagnosis, allowing for characterization of tumors [7] (Fig. 1). Once GIST is treated, the tumor size usually decreases upon response. In some responding tumors, the tumor size increases [6] as a result of intratumoral hemorrhage, necrosis, or myxoid degeneration. More dramatic changes in responding GISTs, however, occur within the tumor mass; the density of the tumor decreases significantly, as does the number of intratumoral vessels. The tumor becomes homogeneous and hypodense (Figs. 1 and 2). The enhancing components within the tumor disappear. In contrast, tumor density change can be seen within a month and as early as 1 week of imatinib treatment. In many tumors, the decrease in tumor size is only minimal at an early post-treatment stage (Fig. 1), failing to satisfy the traditional response criteria, RECIST.

Based on these clinical observations, 173 lesions of advanced GIST were analyzed on CT images for their subjective and objective responses to imatinib treatment. The subjective evaluation was performed based on the changes in overall tumor status (OTS), a combination of tumor size, density, and vascularization. The objective evaluation was performed based on the measurements of tumor density (HU) and size (cm). These CT responses were compared with PET responses (maximum standardized uptake value \([SUV_{max}]\) on \(^{18}\)FDG-PET) evaluated based on the European Organization for Research and Treatment of Cancer 1999 criteria [6]. That study showed that tumor size and mean HU on CT and \(SUV_{max}\) on PET all decreased significantly at 8 weeks \((p = .0025)\) (Fig. 3) [6]. There was a high correlation between the responses based on OTS on CT and \(SUV_{max}\) on \(^{18}\)FDG-PET (Table 1) and a trend toward a good correlation between HU density and \(SUV_{max}\) [6]. The tumor size change by the RECIST, however, showed no correlation with PET response (Table 2) [6]. In an attempt to identify better response evaluation criteria than “tumor size” on CT, “good response” on \(^{18}\)FDG-PET was redefined as a decrease in \(SUV<70\%\) from baseline or a drop in the absolute value of \(SUV_{max}<2.5\), based on the work of Van den Abbeele et al. [5]. From these data, \(97\%\) of good responders on \(^{18}\)FDG-PET had a \(\geq10\%\) decrease in tumor size or a \(\geq15\%\) decrease in tumor density on CT at 8 weeks of imatinib treatment.

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**Figure 1.** Typical appearance of a responding gastrointestinal stromal tumor (GIST) in a man aged 70 years with a metastatic gastric GIST. (A): An enhanced computed tomography image obtained prior to imatinib treatment shows large hepatic and peritoneal metastases. Note the tumor vessels within the enhancing solid component along the periphery. (B): The tumor has become homogeneous and hypodense at 2 months of treatment. Notice that the tumor vessels and peripheral tumor nodules are no longer evident, with little, if any, decrease in tumor size.

**Figure 2.** Typical appearance of a responding gastrointestinal stromal tumor (GIST) in a man aged 56 years with a metastatic gastric GIST to the liver. (A): A contrast-enhanced computed tomography (CT) image obtained prior to imatinib treatment shows an enhancing hepatic metastasis in segment 3 of the left lobe of the liver. Follow-up CT scans obtained at 2 months (B) and 4 months (C) show a continuous decrease in tumor size from 3.3 cm prior to treatment to 2.3 cm and 1.9 cm, respectively. Notice the dramatic changes in tumor density from 63 HU prior to treatment to 38 HU at 2 months and 32 HU at 4 months. The tumor becomes hypodense and homogeneous quickly.

**Figure 3.** Objective tumor response evaluation on computed tomography (CT) and fluorine-18-fluorodeoxyglucose positron emission tomography (\(^{18}\)FDG-PET). (A): Change in mean tumor size (cm) on CT. The decrease in mean tumor size at 2 months after treatment was significant \((p = .0025, t\text{-test}; p = .0013, \text{signed-rank test})\). (B): Change in tumor density (HU) on CT. The decrease in mean HU at 2 months after treatment was significant \((p < .0025, t\text{-test}; p < .0011, \text{signed-rank test})\). (C): Change in mean glucose metabolism, maximum standardized uptake value \((SUV_{max})\), on \(^{18}\)FDG-PET images. The decrease in mean \(SUV_{max}\) at 2 months after treatment was significant \((p < .0001, t\text{-test}; p < .0001, \text{signed-rank test})\).
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These modified CT criteria have been shown to be highly capable of separating responders and nonresponders and provide an excellent prognostic indicator in terms of progression-free survival (Fig. 4) [9], although further validation is needed in larger populations.

Surveillance

Once GIST patients are treated, the main role of imaging is surveillance and early detection of recurrence or disease progression. Traditionally, diagnosis of recurrence or progression on imaging is based on an increase in tumor size and identification of new lesions at either local or distant sites. In GISTs, an “increase in tumor size” is still important as long as the overall appearance of the tumor is thoroughly scrutinized for changes in tumor density and degree and pattern of enhancement on contrast-enhanced CT images. In addition, it should be noted that recurrence in GIST can occur within the treated hypodense tumor without changing the tumor size (Fig. 5) [7]. Development of an intratumoral nodule is often the first sign of progression and should be added to conventional progression criteria in monitoring GIST patients.

With recognition of the new features of GISTs, CT remains an excellent imaging modality of choice to monitor disease during the course of treatment and surveillance. It

### Table 1. Association between OTS on CT and SUVmax by grade of change after treatment

<table>
<thead>
<tr>
<th>Grade of change in SUVmax on 18FDG-PETb</th>
<th>n of patients by grade of change in OTSb</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total n of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (≥25% increase)</td>
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<td>Grade 4 (61%–100% decrease)</td>
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<tr>
<td>Total</td>
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<td>5</td>
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</tbody>
</table>

bBased on the modified European Organization for Research and Treatment of Cancer 1999 criteria.

### Table 2. Association between tumor size and SUVmax by grade of change after treatment

<table>
<thead>
<tr>
<th>Grade of change in SUVmax on 18FDG-PET</th>
<th>n of patients by change in size (RECIST)b</th>
<th>Progressive disease</th>
<th>Stable disease</th>
<th>Partial response</th>
<th>Complete response</th>
<th>Total n of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (≥25% increase)</td>
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<td>2</td>
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<tr>
<td>Grade 2 (&lt;15% decrease or &lt;25% increase)</td>
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<td>Grade 3 (15%–60% decrease)</td>
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<tr>
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<tr>
<td>Total</td>
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<td>0</td>
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</table>

bBased on the modified European Organization for Research and Treatment of Cancer 1999 criteria.

### Table 3. Relationship between change in tumor size and tumor density on CT and tumor response by 18FDG-PET (n = 40)

<table>
<thead>
<tr>
<th>Tumor response by 18FDG-PET</th>
<th>n of patients with ≥10% decrease in tumor size (%)</th>
<th>n of patients with ≥15% decrease in tumor density (%)</th>
<th>n of patients with ≥10% decrease in tumor size or ≥15% decrease in tumor density (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good (n = 33)</td>
<td>31 (94)</td>
<td>27 (82)</td>
<td>32 (97)</td>
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<tr>
<td>Poor (n = 7)</td>
<td>0 (0)</td>
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</table>

Abbreviations: CT, computed tomography; 18FDG-PET, fluorine-18-fluorodeoxyglucose positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors; SUVmax, maximum standardized uptake value.


should be noted, however, that 18FDG-PET should be used whenever the CT findings are inconclusive or inconsistent with the clinical findings.

**Conclusions**

Size-based response criteria such as the RECIST significantly underestimate the response to imatinib in GIST. Subjective evaluation using changes in tumor nodules, density, and tumor vascularization, in addition to changes in tumor size, is the best way to evaluate response by CT. Objective criteria using a combination of tumor density (>15% change) and modified tumor size (>10%) are promising in early response evaluation and have excellent prognostic value. Identifying an intratumoral nodule within the treated GIST is a unique and important imaging finding in recurrent GIST.

**References**