CT Evaluation of the Response of Gastrointestinal Stromal Tumors After Imatinib Mesylate Treatment: A Quantitative Analysis Correlated with FDG PET Findings

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OBJECTIVE. We correlated changes in tumor density on CT with changes in glucose metabolism, or the maximum standardized uptake value (SUV_{max}), on FDG PET and sought to develop CT imaging criteria that can be used to objectively evaluate tumor response in patients with metastatic gastrointestinal stromal tumors (GISTs) who undergo treatment with imatinib mesylate.

MATERIALS AND METHODS. Using the criteria established by the Response Evaluation Criteria in Solid Tumors (RECIST) group, we selected 173 tumors (in 36 patients) for study. Tumor size and density were determined objectively, and overall tumor response (OTR) was evaluated subjectively on CT images. The changes in these parameters before and after treatment were correlated with changes in SUV_{max}.

RESULTS. Significant decreases were seen in both tumor density (mean, 12.3 H [16.5%]; $p < 0.0001$) and SUV_{max} (mean, 3.43 [64.9%]; $p < 0.0001$). OTR evaluated subjectively, correlated well with changes in SUV_{max} ($p < 0.0001$). No statistically significant association was found between changes in tumor density and changes in SUV_{max} ($p = 0.3088$), but 70% (14/20) of the patients with tumors that showed response on FDG PET exhibited at least a partial response by a change in tumor density. Tumor size was found to have decreased significantly 2 months after treatment ($p = 0.0070$). However, in 75% of the patients, the disease was stable according to the traditional tumor response criteria of RECIST.

CONCLUSION. FDG PET is sensitive and specific for evaluating tumor response but cannot be used in patients whose baseline FDG PET results are negative for tumors. Although subjective evaluation was a better indicator of treatment response than was tumor density alone, the tumor density measurement is a good indicator and provides a reliable quantitative means of monitoring the tumor. RECIST, using only tumor size, was unreliable for monitoring GISTs during the early stage of imatinib mesylate treatment.

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The accurate objective assessment of tumor response has become increasingly important with the rapid and continuous development of new drugs. International guidelines for objective evaluation of tumor response were first established in early 1980 on the initiative of the World Health Organization (WHO) [1]. These guidelines were originally based on tumor size determined from the sum of the products of 2D measurements. Since their introduction, the guidelines have been simplified so that 1D tumor measurements may be used [2, 3]. This new approach has been validated by the Response Evaluation Criteria in Solid Tumors (RECIST) group and integrated into current guidelines for evaluating the tumor response to anticancer therapy [2]. However, this morphologic information based on 1D or 2D measurement does not directly reflect biologic changes in tumors and can be misleading in the clinical management of tumors and investigation of new drugs.

In general practice, contrast-enhanced CT is routinely used to monitor tumor response. The degree and pattern of enhancement observed on CT scans are useful for differentiating malignant from benign tumors and identifying posttreatment changes. To a certain extent, the degree of enhancement may reflect the vascular and interstitial volumes of the tumor and may provide information about its biologic behavior [4]. Recently, FDG PET has been suggested as a sensitive method for monitoring changes in the glu-

cose metabolism in tumors for the early assessment of metabolic tumor response to anticancer drugs [5–7]. However, FDG PET is costly and available at only limited number of institutions.

Our institution recently participated in a multicenter phase III trial to assess the activity of the tyrosine kinase inhibitor, imatinib mesylate (Gleevec, Novartis Pharmaceuticals), in patients with metastatic gastrointestinal stromal tumors (GISTs) expressing the c-*kit* receptor tyrosine kinase (CD117) [8–10]. GIST is an uncommon neoplasm, but it accounts for most nonepithelial tumors of the gastrointestinal tract. By definition, almost 100% of patients with GIST express c-*kit* receptor tyrosine kinase because the tumor is derived from interstitial Cajal cells. In most GISTs, an activating mutation of c-*kit* leads to ligand-independent activation of KIT tyrosine kinase and promotes tumor survival and tumor growth [11]. Metastatic GISTs have a poor prognosis [8–10]. Moreover, no effective therapy for advanced GIST was available until the remarkable efficacy of a new drug—the tyrosine kinase inhibitor, imatinib mesylate—was reported recently [12].

Imatinib mesylate, a phenylaminopyrimidine derivative, is a small molecule known to inhibit specific protein kinases such as Abl and the chimeric Bcr–Abl fusion protein found in certain leukemias (e.g., chronic myeloid leukemia); the platelet-derived growth factor receptor (PDGF-R); and KIT, the product of the c-*kit* protooncogene found in GISTs [13–15].

The purposes of our study were twofold: to correlate the changes in tumor density seen on CT with the changes in glucose metabolism seen on FDG PET and to develop CT criteria that could be used to objectively evaluate tumor response and that may reflect the biologic changes in tumors after treatment with imatinib mesylate in patients with metastatic GISTs.

Materials and Methods

Materials

For this retrospective analysis, we selected the first 36 consecutive patients with metastatic GIST who were enrolled in the ongoing phase III clinical trial of imatinib mesylate at our institution from December 2000 to September 2001. The study was conducted under the approval of the institutional review board, and all of the patients who participated in this study signed consent forms. Our patients were 18 men and 18 women, with an age range of 28–86 years. In all, 173 lesions (116 in the liver, 52 in the peritoneal cavity, and five in the pleura) were evaluated on contrast-enhanced helical CT before and 2 months after the treatment with imatinib mesylate. For 12 patients, we had access to CT scans obtained at 2-month intervals for up to 8 months after treatment. Lesions were selected on the basis of RECIST [2] (Appendix 1) from each organ and body compartment involved by the tumors. Lesions smaller than 1.5 cm in the longest diameter were excluded. In 29 of 36 patients, pretreatment FDG PET scans were obtained, with one follow-up scan obtained 2 months after treatment. All FDG PET scans were obtained within 1 week of the CT scans.

Imaging Techniques

CT was performed with a LightSpeed or HiSpeed Advantage helical scanner (GE Healthcare) using a monophasic scanning technique. We scanned the abdomen and pelvis at 7.0- or 7.5-mm collimation from the level of the diaphragm to the pubic symphysis. The scanning delay was 60 sec after the start of administration of 150 mL of 60% nonionic contrast agent (Optiray 320, Mallinckrodt) at a rate of 3 mL/sec. In 11 patients, a triphasic scanning technique was used, with scanning delays of 20, 40, and 60 sec for the early arterial, late arterial, and portal venous phases, respectively, after IV injection of the contrast agent at a rate of 5 mL/sec.

FDG PET was performed using a CTI ECAT HR+ PET scanner (Siemens) after administration of 10–15 mCi (370–555 MBq) of FDG. All patients had nothing by mouth at least 6 hr before scanning. After a 60-min uptake phase, patients were scanned from the neck to the pelvis. A 5-min emission scan and 3-min transmission scan (for attenuation correction) were obtained for each field of view in 2D mode. The images were interpreted using volumetric projection and multiple orthogonal projection analysis.

Image Analysis

CT attenuation coefficients.—On an Advantage workstation (GE Healthcare), we measured the CT attenuation coefficient (density) of the tumor in Hounsfield units by drawing a region of interest circumscribing the margin of the tumor. In patients scanned using triphasic techniques, the portal venous phase images were used for the tumor density measurement. The tumor density measurements of all lesions in a patient were combined, and an average Hounsfield unit was computed for each patient. The percentage of change in tumor density from the pretreatment evaluation to the 2-month evaluation was computed for each lesion, and the average percentage of change was then computed for each patient. The percentage of change in tumor density was graded on a scale of 1–4 that was based on a median 13.2% decrease: grade 4, decrease of more than 30%; grade 3, 11–30% decrease; grade 2, decrease of 10% or less or increase of 10% or less; and grade 1, increase of more than 10%.

Before measuring the CT attenuation coefficients of the tumors, we tested the reliability of different monitors (CT operator's console, Advantage workstation, and workstation [Stentor] in a radiologist's office) using acrylic, water, and air phantoms; no significant differences were found in the CT attenuation coefficients of the phantoms measured on these different monitors. Then, the CT attenuation coefficients of the largest artery (e.g., aorta or iliac artery) and paraspinal muscle at the level of each selected lesion were measured using the same method. The ratios of the lesion to vessel and lesion to muscle were calculated for each lesion.

Tumor size.—Using the Advantage workstation, we measured tumor size at the longest cross-sectional dimension of each lesion at each time point. The sum of the longest diameters of the selected lesions in each patient was generated. The percentage of change in the sum of the longest dimensions from the pretreatment evaluation to the

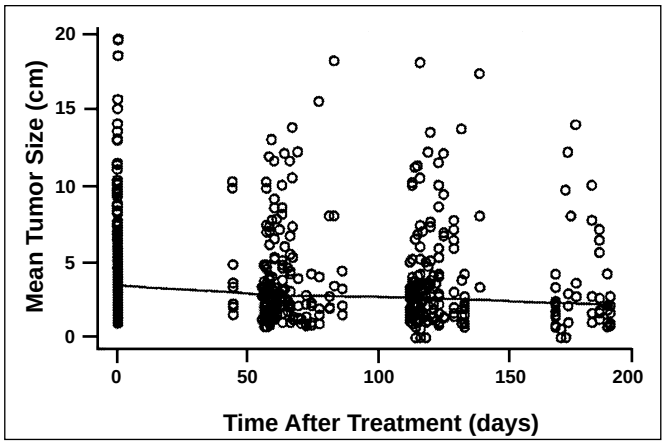

Fig. 1.—Scatterplot shows sizes of 173 lesions in 36 patients during treatment. Change in absolute tumor size was small but statistically significant up to 8 months after treatment (p = 0.0070, linear regression analysis).

2-month evaluation was then computed for each patient. The percentage of change was graded using RECIST: complete remission, disappearance of lesions; partial remission, more than a 30% decrease; stable disease, neither partial remission nor progression of disease; and progression of disease, more than a 20% increase [2].

"*Overall tumor response* (OTR)."—The OTR on CT was determined subjectively by a consensus opinion of two experienced radiologists on the basis of the size and number of tumors, the degree and extent of enhancement, the presence or absence of tumor vessels, and the presence or absence of solid nodules within the tumors in each patient. For each patient, the OTR between the pretreatment evaluation and the 2-month evaluation was graded on a scale of 1–4: 4, best; 3, better; 2, stable; and 1, worse.

Standardized uptake value (SUV) on FDG PET.—Using vendor-specific software for the scanner, we measured the maximum SUV (SUV_{max}) on FDG PET by drawing a region of interest slightly outside each lesion corresponding to the lesion used to measure tumor density on CT. SUV_{max} measurements of all lesions in each patient were combined, and an average SUV_{max} was computed for each patient. The percentage of change in the SUV_{max} of each lesion between the pretreatment evaluation and the 2-month evaluation was computed, and the average percentage of change was computed for each patient. The percentage of change in the SUV_{max} was then graded on a scale of 1–4: 4, 61–100% decrease; 3, 15–60% decrease; 2, decrease of less than 15% or increase of less than 25%; and 1, increase of 25% or more. These grades were modified from the 1999 European Organization for Research and Treatment of Cancer criteria [16] (Appendix 2) to match the grading system used for other measurements in this study.

Data Analysis

Multivariate analysis was performed using the following parameters: the size and attenuation coefficients (in Hounsfield units) of the lesions on CT images; lesion-to-vessel and lesion-to-muscle ratios calculated from the CT attenuation coefficients of the lesions, vessels, and muscles measured at the same level to adjust for technical differences among CT examinations; the OTR determined subjectively on the basis of the changes in the size, number, and density of tumors; the extent and degree of enhancement, and the presence of tumor vessels seen on CT images; and the SUV_{max} on FDG PET images of each lesion corresponding to the lesion used to measure size and attenuation on CT images.

Statistical Analysis

Tumor size, density (in Hounsfield units), and lesion-to-vessel and lesion-to-muscle ratios were plotted against time, and linear regression analyses were performed with time as the regressor vari-

TABLE 1 Spearman's Rank Correlation Coefficients for Pairs of Individual Changes in Density of Lesion, Lesion-to-Vessel Ratio, and Lesion-to-Muscle Ratio

Variable	*r*	*p*[a]
Lesion density and lesion-to-vessel ratio	0.70	< 0.0001
Lesion density and lesion-to-muscle ratio	0.94	< 0.0001
Lesion-to-vessel and lesion-to-muscle ratios	0.72	< 0.0001

[a]All are statistically significant.

TABLE 2 Tumor Size, Density, and Maximum Standardized Uptake Values Before and After Treatment

Values, by Technique	Mean ± SD	Range	Median
CT			
Size (cm)			
Before treatment	4.9 ± 3.5	1.1–19.6	4.3
After treatment	4.2 ± 3.3	1.1–18.1	3.3
% Change	–13.0 ± 21.1	–61.4 to 33.9	–14.9
Density (H)			
Before treatment	67.6 ± 23.8	23.5–156.7	61.8
After treatment	56.1 ± 25.1	27.0–135.0	50.9
% Change	–15.9 ± 25.8	–63.2 to 47.9	–12.8
FDG PET			
Maximum standardized uptake (SUV_{max})			
Before treatment	5.8 ± 2.6	1.3–12.5	5.8
After treatment	2.3 ± 4.2	0.0–14.3	0.0
% Change	–64.9 ± 53.5	–100.0 to 59.3	–100.0

Note.—Data were analyzed for the 29 patients who underwent both CT and FDG PET.

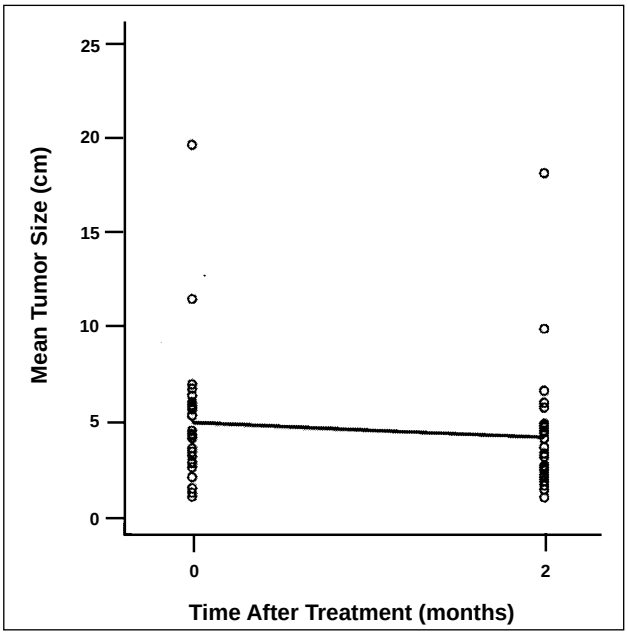

Fig. 2.—Graph shows change in mean tumor size on CT images in 29 patients. Decrease in mean tumor size measured 2 months after treatment was significant ($p = 0.0025$, Student's *t* test; $p = 0.0013$, Wilcoxon's signed rank test).

able. To assess the reliability of tumor density in Hounsfield units and the lesion-to-vessel and lesion-to-muscle ratios, we used Spearman's rank correlation coefficients to compute the rate of change over time.

The mean percentages of change in tumor density on CT images and SUV_{max} on FDG PET images between the pretreatment evaluation and the 2-month posttreatment evaluation were computed for each patient and compared using the paired Student's *t* test and the Wilcoxon's signed rank test.

Two-way classification tables and chi-square tests were used to assess associations between the grading of the average percentage of change in SUV_{max} on FDG PET images and the grading of the average percentage of change in tumor size, density, and overall treatment response on CT images at the 2-month posttreatment evaluation.

Results

The size of the 173 lesions in the 36 patients ranged from 1.0 to 19.5 cm (mean, 4.7 cm) before treatment and from 1.0 to 18.1 cm (mean, 4.0 cm) 2 months after treatment. For up to 8 months after treatment, the changes in tumor size between pretreatment and posttreatment measurements on CT images were statistically significant ($p = 0.0070$, linear regression analysis) (Fig. 1). The mean CT attenuation coefficients of these 173 lesions also were found to have decreased significantly 2 months after treatment (by 12.3 H, 16.5%) ($p < 0.0001$, linear regression analysis). The lesion-to-vessel and lesion-to-muscle ratios decreased significantly after treatment ($p < 0.0001$, linear regression analysis). Changes in the CT attenuation coefficients of tumors and in lesion-to-vessel and lesion-to-muscle ratios over time were highly correlated with each other (Table 1). On the basis of these results, the CT attenuation coefficient was chosen as the sole indicator of tumor density with which to correlate the SUV_{max} on FDG PET scans.

In the 29 patients who underwent both CT and FDG PET, the mean tumor size had decreased by 13% 2 months after treatment ($p = 0.0025$, Student's paired *t* test; $p = 0.0013$, Wilcoxon's signed rank test) (Table 2 and Fig. 2). For the total population of 36 patients, however, RECIST showed that the disease was stable in 27 (75%), had partially regressed in six (17%), and had progressed in three (8%).

The mean SUV_{max} on FDG PET in the 29 patients who underwent both CT and FDG PET decreased significantly (mean, 3.43 [64.9%]) 2 months after treatment ($p < 0.0001$, Student's *t* test; $p < 0.0001$, Wilcoxon's signed rank test) (Table 2 and Fig. 3). In 20 patients who had a grade 4 response, the mean reduction in SUV_{max} was 99%. The mean tumor density on CT in the 29 patients decreased significantly 2 months after treatment ($p = 0.0025$, Student's *t* test; $p = 0.0011$, Wilcoxon's signed rank test) (Fig. 4). The mean change in tumor density on CT in the group with grade 4 response in SUV_{max} was 15 H (22.6%).

Tables 3–5 show the associations among tumor size, density, and overall treatment response on CT and the SUV_{max} on FDG PET. In 80% (16/20) of those who had a grade 4 response on FDG PET, the disease either had progressed or was stable according to RECIST criteria (Table 3). In the 29 patients who underwent both CT and FDG PET, no significant association was found between the percentage of change in tumor density on CT and the SUV_{max} on FDG PET ($p = 0.3088$, chi-square test). However, 70% (14/20) of the patients with a grade 4 response on FDG PET showed either grade 3 or 4 response in tumor density (Table 4), whereas 86% (12/14) of those with a grade 3 or 4 response according to CT density criteria had a grade 4 response on FDG PET. The OTR evaluated subjectively on CT correlated better with the

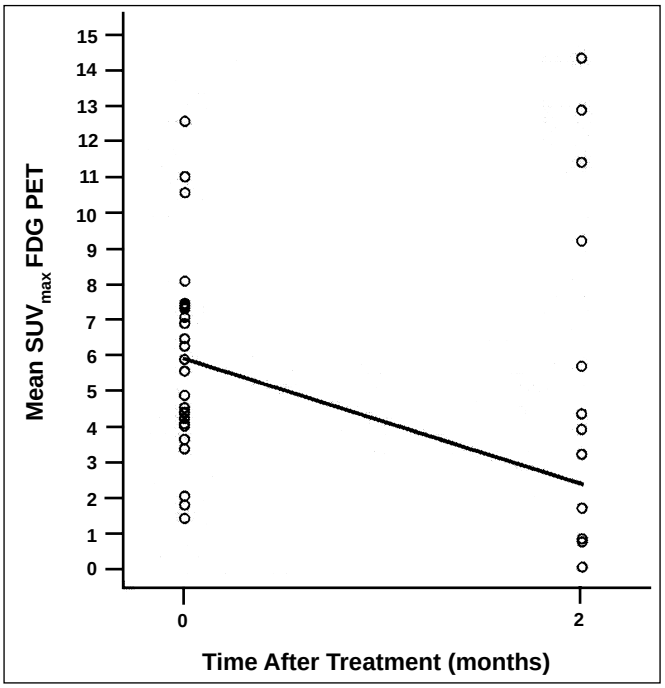

Fig. 3.—Graph shows change in mean glucose metabolism, or maximum standardized uptake value (SUV_{max}) on FDG PET images in 29 patients. Decrease in mean SUV_{max} 2 months after treatment was significant ($p < 0.0001$, Student's *t* test; $p < 0.0001$, Wilcoxon's signed rank test).

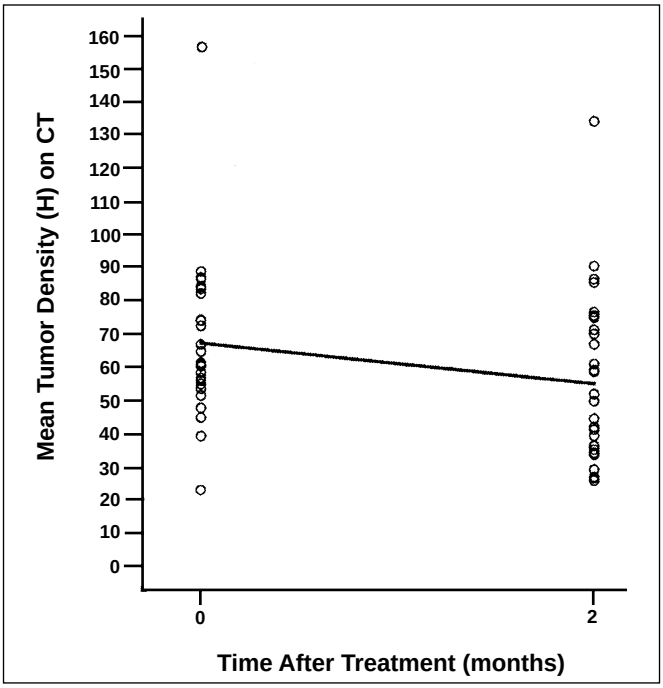

Fig. 4.—Graph shows change in mean tumor density in Hounsfield units in 29 patients. Decrease in mean Hounsfield units 2 months after treatment was significant ($p < 0.0025$, Student's *t* test; $p < 0.0011$, Wilcoxon's signed rank test).

percentage of change in SUV_{max} on FDG PET than with CT density criteria alone ($p < 0.0001$, chi-square test) (Table 5).

Discussion

The tumor response to treatment is traditionally evaluated on the basis of morphologic features. The current gold standard to evaluate the effects of anticancer therapy is monitoring changes in tumor size. WHO criteria defined the partial response as a 50% decrease in tumor size, which was influenced substantially by the limitation of a reliable estimate of tumor size at physical examination [3]. The present guidelines from the RECIST group for evaluating objective tumor response radiographically is the 1D measurement of tumor size [2, 3].

In our study, although the changes in tumor size on CT measured 2 months after treatment with imatinib mesylate therapy were statistically significant, they were small (mean, 13% decrease). If the tumors were evaluated using RECIST, most patients (75%) were categorized as having stable disease, despite the fact that 70% of them had grade 4 responses with a 99% reduction in the mean SUV_{max} on FDG PET. Thus, tumor size determined using the sum of the longest dimensions (RECIST) was not reliable and underestimated the tumor response to imatinib mesylate during the early posttreatment stage in patients with metastatic GIST. In some patients, tumor size actually increased despite significant clinical improvement and a significant decrease in FDG uptake (Fig. 5). On the other hand, the mean tumor density had decreased significantly 2 months after treatment compared with the pretreatment values (Fig. 6). The intratumoral hemorrhage can result in misleading tumor density values because of a spurious increase in tumor attenuation. However, a decrease in tumor density was observed 2 months after treatment in some lesions with intercurrent intratumoral bleeding. The subjective evaluation using a combination of tumor size, tumor density, and absence or presence of tumor nodules and tumor vessels was a better indicator of the tumor response to imatinib mesylate than was tumor density alone. Change in tumor vessels was the most specific indicator of treatment response (Fig. 7), but such changes could be observed in only a limited number of lesions, even on CT images obtained with the triphasic technique.

FDG PET is a sensitive and specific method with which to evaluate tumor response on the basis of changes in tumor metabolism [17]. In our study, a dramatic decrease in FDG uptake was observed at an early stage after imatinib mesylate treatment (Figs. 5 and 6), consistent with a previous observation [12]. However, as with CT, technical limitations were encountered with PET. In one patient, multiple hyperdense lesions in the liver and peritoneum were visualized on pretreatment CT, but on FDG PET, find-

TABLE 3 **Association Between CT Tumor Size and Maximum Standardized Uptake Value (SUV_{max}) by Grade of Change After Treatment**

Grade of Change in SUV_{max} on FDG PET[a]	No. of Patients by Grade of Change in Size[b]				
	Progressive Disease	Stable Disease	Partial Remission	Complete Remission	Total
Grade 1 (≥ 25% increase)	0	2	0	0	2
Grade 2 (< 15% decrease or < 25% increase)	1	5	0	0	6
Grade 3 (15–60% decrease)	0	1	0	0	1
Grade 4 (61–100% decrease)	1	15	4	0	20
Total	2	23	4	0	29

Note.—Data were analyzed for the 29 patients who underwent both CT and FDG PET.

[a]Tumor response based on 1999 criteria developed by the European Organization for Research and Treatment of Cancer [16].

[b]Tumor response based on Response Evaluation Criteria in Solid Tumors [2].

TABLE 4 **Association Between CT Tumor Density and Maximum Standardized Uptake Value (SUV_{max}) by Grade of Change After Treatment**

Grade of Change in SUV_{max} on FDG PET[a]	No. of Patients by Grade of Change in Density[b]				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Grade 1 (≥ 25% increase)	0	1	1	0	2
Grade 2 (< 15% decrease or < 25% increase)	1	4	1	0	6
Grade 3 (15–60% decrease)	0	1	0	0	1
Grade 4 (61–100% decrease)	2	4	4	10	20
Total	3	10	6	10	29

Note.—Data were analyzed for the 29 patients who underwent both CT and FDG PET, $p = 0.388$ using the chi-square test.

[a]Tumor response based on 1999 criteria developed by the European Organization for Research and Treatment of Cancer [16].

[b]Tumor response based on tumor density measured in Hounsfield units on CT.

TABLE 5 **Association Between "Overall Tumor Response (OTR)" on CT and Maximum Standardized Uptake Value (SUV_{max}) by Grade of Change After Treatment**

No. of Patients by Grade of Change in SUV_{max}[a]	No. of Patients by Grade of Change in OTR[b]				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Grade 1 (≥ 25% increase)	0	2	0	0	2
Grade 2 (< 15% decrease or < 25% increase)	6	0	0	0	6
Grade 3 (15–60% decrease)	0	0	1	0	1
Grade 4 (61–100% decrease)	0	1	4	15	20
Total	6	3	5	15	29

Note.—Data were analyzed for the 29 patients who underwent both CT and FDG PET, $p < 0.001$ using the chi-square test, which is statistically significant.

[a]Tumor response based on 1999 criteria developed by the European Organization for Research and Treatment of Cancer [16].

[b]Tumor response based on subjective evaluation on CT.

ings were completely negative (Fig. 8). Also, 36 (21%) of the 173 lesions that were 1.0–4.7 cm in the longest dimension on CT images did not show appreciable glucose uptake on pretreatment FDG PET images. Our results are similar to the reported 70–100% general sensitivity of FDG PET for tumor localization [17]. A lack of glucose uptake on FDG PET images might be related to the degree of tumor necrosis, myxoid degeneration, and scarring that may develop after treatment [12]. In addition, previous chemotherapy could decrease glucose uptake [5]. An inconsistent tumor growth fraction in the tumor growth curve (Gompertzian growth model) might also influence the degree of glucose metabolism [18]. In our patient with a negative FDG uptake on pretreatment FDG PET images, the lack of glucose uptake could not be attributed to a definite cause. The patient had no history of treatment, and many of the hepatic lesions were solid with significant enhancement on CT images. Tumor grade may also be responsible for a lack of glucose uptake [19]. Regardless of the cause for the lack of glucose uptake, FDG PET cannot be used to evaluate treatment response if pretreatment FDG PET shows negative results for tumor detection.

The lack of concordance between the percentage of changes in tumor density on CT and the SUV_{max} might have resulted from the differences in measurement methods. In this study, we determined the status of glucose metabolism on FDG PET images by measuring only the areas with maximum glucose metabolism (SUV_{max}) within each tumor as opposed to measuring the entire lesion, including the central low-attenuation

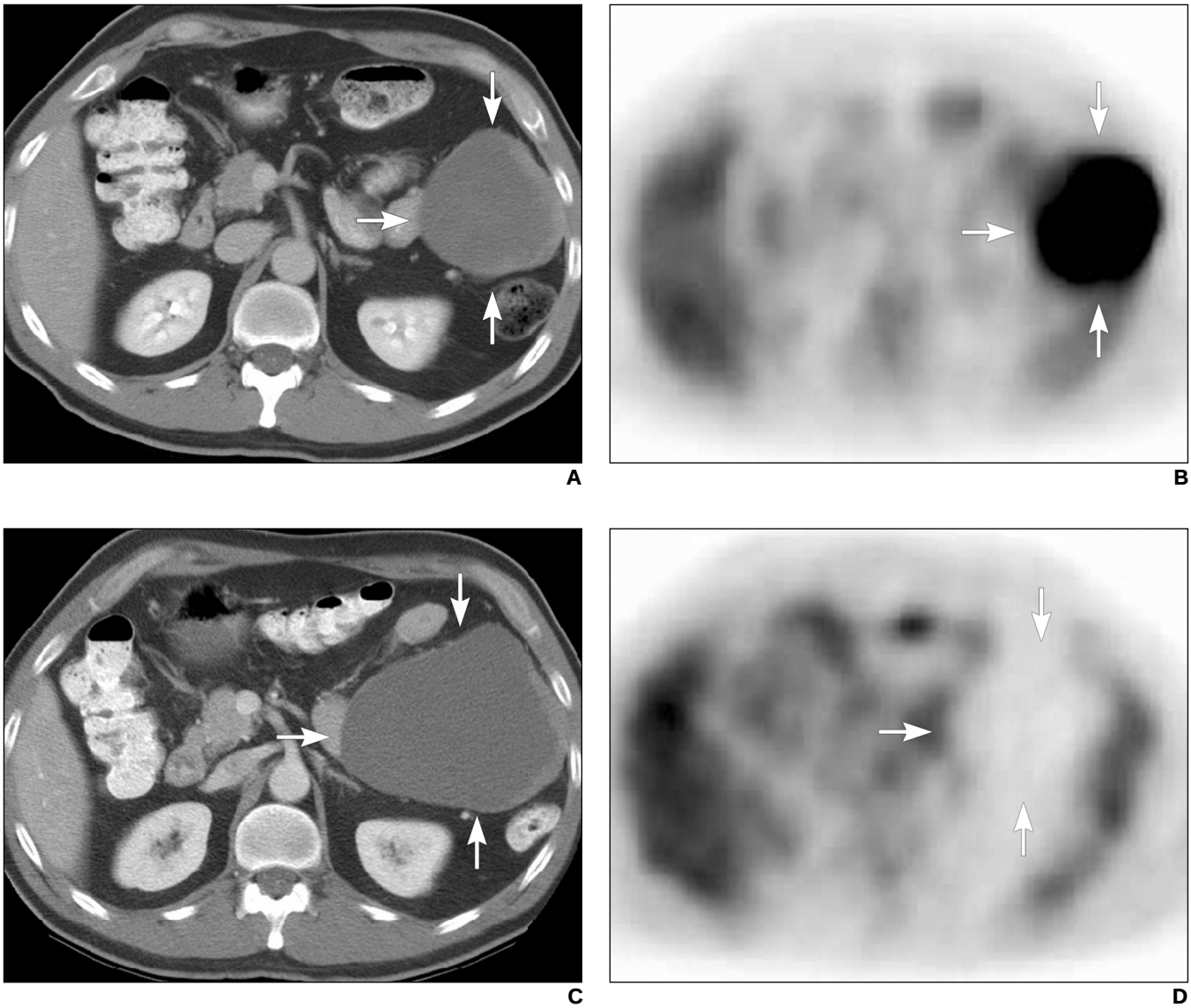

Fig. 5.—51-year-old man with primary gastrointestinal stromal tumor in colon and recurrent disease with peritoneal metastases.
A and **B,** Pretreatment CT scan (**A**) shows peritoneal mass (*arrows*, **A**) with relatively low density (42 H) corresponding to lesion with markedly increased glucose uptake (*arrows*, **B**) on FDG PET scan (**B**).
C and **D,** CT scan (**C**) obtained 2 months after treatment shows that mass has become larger (*arrows*, **C**). CT density (30 H), however, had decreased with no appreciable glucose uptake (*arrows*, **D**) seen on FDG PET scan (**D**), corresponding to clinical improvement.

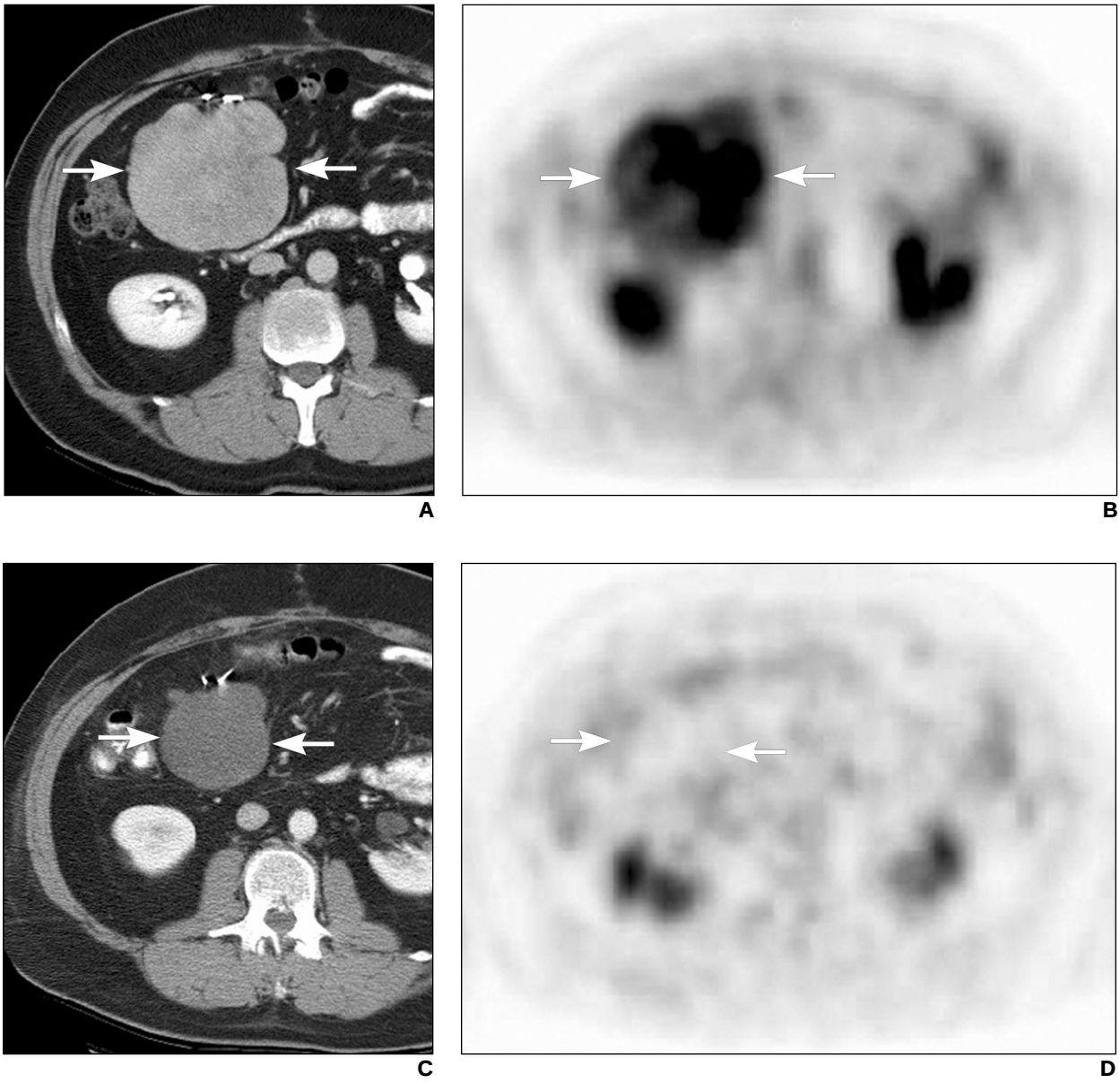

Fig. 6.—45-year-old man with recurrent gastrointestinal stromal tumor of small-bowel mesentery and hepatic metastasis.
A and **B,** Pretreatment CT scan (**A**) shows hyperdense (87 H) mesenteric mass (*arrows*, **A**) in region of previous surgery corresponding to lesion with markedly increased glucose uptake (*arrows*, **B**) on FDG PET scan (**B**).
C, CT scan obtained 2 months after treatment shows that mass (*arrows*) has significantly decreased in both density (29 H) and size.
D, FDG PET scan obtained 2 months after treatment shows no appreciable glucose uptake (*arrows*). On images obtained 4 months after treatment (not shown), mass had further decreased in size and density and has since remained stable.
E, Photomicrograph of mesenteric mass resected at 7 months after treatment shows gross replacement of tumor by myxoid degeneration (*light pink*) with only microscopic viable tumor (*arrows*). (H and E, ×40)

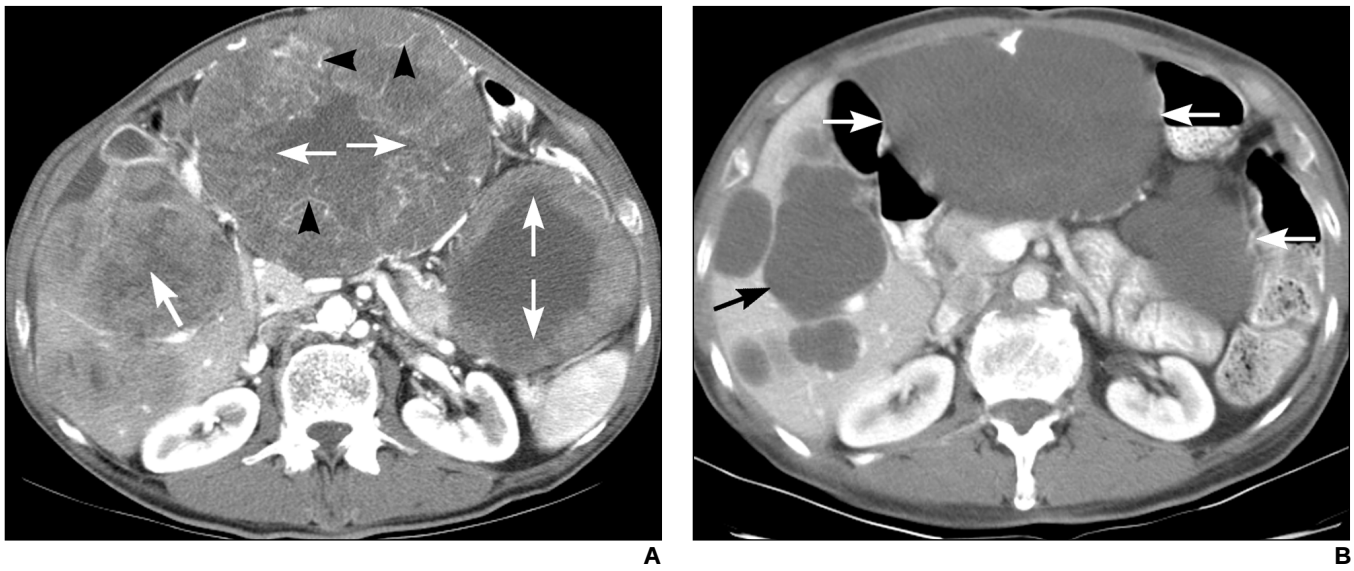

Fig. 7.—68-year-old man with primary gastrointestinal stromal tumor of stomach and recurrent disease with hepatic and peritoneal metastases.
A, Pretreatment CT scan shows large mesenteric and hepatic masses on late arterial phase image, with hyperdense tumor nodules (*arrows*) along periphery. Notice multiple prominent tumor vessels (*arrowheads*).
B, CT scan obtained 2 months after treatment shows that lesions (*arrows*) have become significantly hypodense, and peripheral tumor nodules and tumor vessels are no longer detectable.

area in tumor density measurement on CT. Also, the 1999 European Organization for Research and Treatment of Cancer criteria used in our FDG PET analysis were developed from the results of multiple small clinical studies of brain, neck, and breast tumors and colorectal metastases to the liver [16]. These criteria may not be suitable for evaluating metastatic or advanced GISTs [20].

Although we did not correlate our results with pathologic findings for all patients, a decrease in tumor density, a decrease in tumor vessels, the disappearance of the tumor nodule, and a decrease in glucose uptake suggest tumor cell death and decreased tumor cell density. In theory, changes in tumor density could be secondary to tumor necrosis, hemorrhage, and cystic or myxoid degeneration. Myxoid degeneration was observed in one of our patients who underwent surgical resection after imatinib mesylate treatment (Fig. 6), as

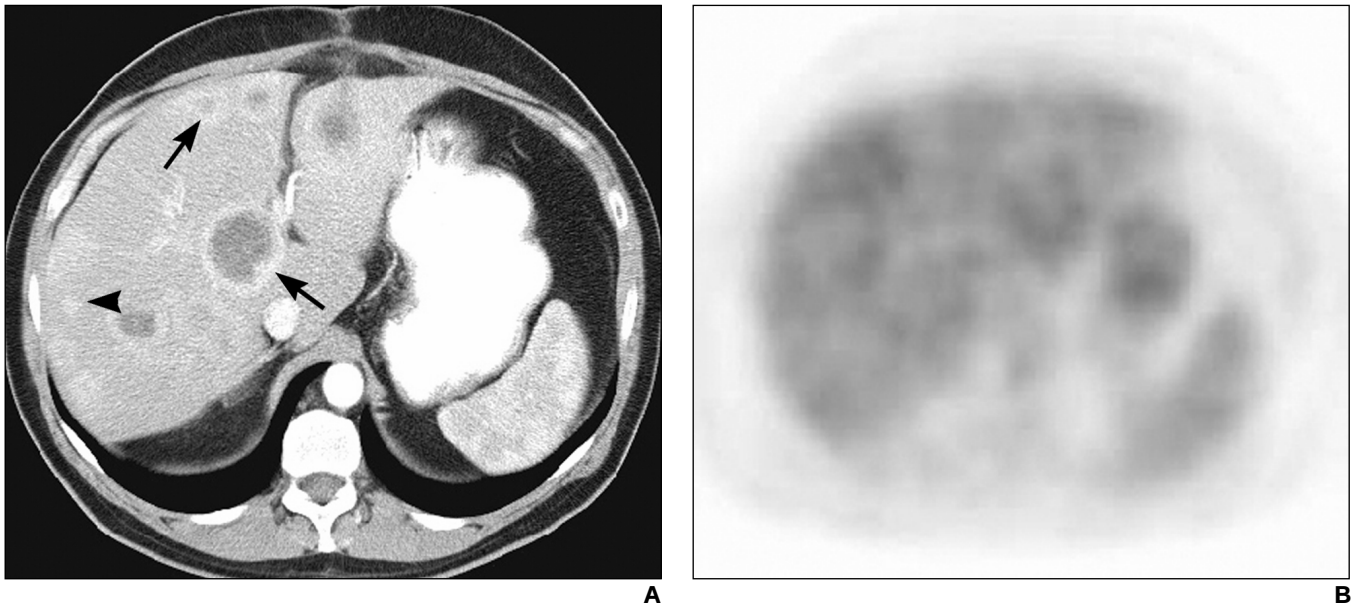

Fig. 8.—56-year-old man with newly diagnosed gastrointestinal stromal tumor of jejunum with hepatic and peritoneal metastases.
A, Pretreatment CT scan shows multiple diffuse (*arrowhead*) or rim-enhancing (*arrows*) lesions.
B, FDG PET scan obtained 3 days after **A** shows no appreciable glucose uptake.

seen in a case reported by Joensuu et al. [12]. However, the mechanism of myxoid degeneration is not clearly understood. In addition, decreases in tumor density and tumor vessels suggest that imatinib mesylate, which is known to inhibit PDGF-R [15], might have an antiangiogenic effect [21]. However, we did not investigate whether the tumors in our patients expressed PDGF-R.

One of the limitations of our study was that we measured the tumor density at only one time point on contrast-enhanced CT images; that measurement did not necessarily directly reflect the degree of enhancement. Further investigation of the degree of enhancement using both unenhanced and enhanced CT images is ongoing. Another limitation was inconsistent CT techniques (monophasic vs triphasic) and use of the time-bolus technique. However, we have shown that there were no significant differences between the use of the absolute values of tumor densities and the values of tumor densities that were normalized to those of muscles and arteries (Table 1).

Finally, radiologists should recognize a decrease in tumor density as an important CT criterion of positive tumor response to treatment in patients with GIST. The hypoattenunation of hepatic lesions on posttreatment CT should be carefully analyzed by comparing the lesions on both unenhanced and enhanced pretreatment CT images. Because of the hypervascular nature of GISTs, the metastatic liver lesions may become isoattenuating relative to the surrounding liver on portal venous phase images. This fact underscores the need for a technique that combines unenhanced and enhanced CT. For the same reason, the triphasic CT technique could increase the visibility of a tumor and tumor vessels, but its value should be evaluated further.

In conclusion, we found that FDG PET is a specific and sensitive indicator of tumor response. However, approximately 20% of lesions shown on CT did not display appreciable glucose uptake on pretreatment FDG PET images. FDG PET cannot be used to evaluate treatment response if pretreatment FDG PET showed negative results for tumor detection. Subjective evaluation using a combination of changes in the size and number of tumors, degree and extent of tumor density, and presence of enhancing nodules and tumor vessels was a better indicator than tumor density alone. Nevertheless, tumor density measurement alone is a good indicator and provides a reliable and objective means by which to monitor the tumor response quantitatively. CT technique can be critical. A combination of unenhanced and enhanced CT, possibly, using a triphasic dynamic technique, might be necessary for an accurate evaluation of tumor response. RECIST using 1D measurement of tumor size alone was an unreliable indicator for monitoring metastatic GIST during the early stage of imatinib mesylate treatment.

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Appendixes 1 and 2 appear on the next page

APPENDIX 1. Response Evaluation Criteria in Solid Tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, and National Cancer Institute of Canada [2]

1. Specific Notes for Radiologic Imaging

CT scans of the thorax, abdomen, and pelvic should be contiguous throughout the anatomic region of interest. As a rule of thumb, the minimal size of the lesion should be no less than double the slice thickness. This minimal lesion size for a given slice thickness at baseline ensures that any lesion appearing smaller on subsequent examinations will truly be decreasing in size. The longest diameter of each target lesion should be selected in the axial plane only.

2. Response Criteria: Evaluation of Target Lesions

The definitions of the criteria used to determine objective tumor response for target lesions have been adapted from the original World Health Organization handbook, taking into account the measurement of the longest diameter only for all target lesions.

- Complete response—The disappearance of all target lesions.
- Partial response—At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the sum of the longest diameter at baseline.
- Progressive disease—At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of one or more new lesions.
- Stable disease—Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the longest diameter since the treatment started.

APPENDIX 2. Definition of ^{18}F-FDG Tumor Response: 1999 Criteria by European Organization for Research and Treatment of Cancer (EORTC) PET Study Group [16]

- Progressive metabolic disease—An increase in FDG standardized uptake value (SUV) of greater than 25% within the tumor region defined on the baseline scan, a visible increase in the extent of FDG tumor uptake (20% in the longest dimension), or the appearance of new FDG uptake in metastatic lesions.
- Stable metabolic disease—An increase in FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of FDG tumor uptake (20% in the longest dimension).
- Partial metabolic response—A minimum of 15–25% in tumor FDG SUV after one cycle of chemotherapy and greater than 25% after more than one treatment cycle. Reporting needs to be accompanied by adequate and disclosed reproducibility measurements from each center. An empiric 25% was found to be a useful cutoff point, but a reproducibility analysis is needed to determine the appropriate cutoffs for statistical significance. A reduction in the extent of the tumor FDG uptake is not a requirement for partial metabolic response.
- Complete metabolic response—Complete resolution of FDG uptake within the tumor volume so that it is indistinguishable from the surrounding normal tissue.