

Comparison of Changes in Tumor Metabolic Activity and Tumor Size During Chemotherapy of Adenocarcinomas of the Esophagogastric Junction

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We evaluated the temporal relationship between chemotherapy-induced changes in tumor glucose use and tumor size.

Methods: Twenty patients with adenocarcinoma of the esophagogastric junction (AEG) were studied by ¹⁸F-FDG PET and CT scans before neoadjuvant chemotherapy, 14 d after the initiation of therapy, and 4 wk after the completion of therapy.

Results: The relative change in ¹⁸F-FDG uptake was more than 2 times larger than the decrease in tumor size at all time points ($P < 0.01$). At 14 d after the initiation of chemotherapy, there was no correlation between the reduction in ¹⁸F-FDG uptake and tumor wall thickness. The change in ¹⁸F-FDG uptake after 14 d of therapy was significantly correlated with the reduction in tumor size after the completion of therapy. **Conclusion:** In AEG, changes in tumor metabolism are a more sensitive parameter for assessing the effects of chemotherapy than are changes in tumor size. Early changes in metabolic activity predict the subsequent reduction in tumor size.

Key Words: CT; ¹⁸F-FDG PET; esophageal cancer; therapy monitoring

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In the treatment of locally advanced adenocarcinoma of the esophagogastric junction (AEG), neoadjuvant chemotherapy can improve the outcome of patients who respond to preoperative therapy compared with surgical treatment alone. However, the prognosis for patients who do not respond to preoperative therapy seems to be even worse than that for patients treated by surgery alone (1–4). Initial

reports have indicated that effective chemotherapy causes a rapid decrease in tumor ¹⁸F-FDG uptake in esophageal cancer and AEG and that ¹⁸F-FDG PET can differentiate between eventually responding and nonresponding tumors within 2 wk after the initiation of chemotherapy and after the end of chemotherapy (5–8). It is a common assumption that morphologic imaging techniques can assess changes in tumor size not before 8–12 wk of chemotherapy. However, to our knowledge the time course of changes in tumor size during chemotherapy has not been systematically studied so far. Therefore, it is not clear whether metabolic changes actually precede the reduction in tumor size. Knowledge about changes in tumor size during chemotherapy is also of importance for the interpretation of ¹⁸F-FDG PET scans because part of the measured reduction of tracer uptake during chemotherapy could be caused by a reduction in tumor size resulting in an underestimation of the true ¹⁸F-FDG uptake because of partial-volume effects (9). The goals of this study were therefore to evaluate the time course of tumor metabolic activity measured by ¹⁸F-FDG PET and tumor size measured by multislice CT (MSCT) and to analyze whether there is a correlation between early changes in ¹⁸F-FDG uptake and changes in tumor size.

MATERIALS AND METHODS

Patients

PET and CT scans for 20 consecutive patients who underwent PET and CT for assessment of tumor response as part of phase II studies evaluating neoadjuvant chemotherapy of AEG were analyzed in this study. The sample size of 20 patients was based on the following power calculation. In a previous study, we had observed that ¹⁸F-FDG uptake of AEGs decreased by $31\% \pm 27\%$ (mean \pm SD) within 2 wk after the initiation of chemotherapy (7). The present study was designed to detect with 80% power that the decrease in tumor ¹⁸F-FDG uptake was at least 20 percentage

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TABLE 1
Patient Characteristics and Changes in Tumor Wall Thickness and in Tumor ^{18}F -FDG Uptake

Patient	Sex*	Age (y)	Tumor ^{18}F -FDG uptake (SUV)			Tumor wall thickness (mm)		
			Baseline	After 2 wk	Preop	Baseline	After 2 wk	Preop
1	F	56	9.2	5.0	2.3	16	18	7
2	M	52	11.7	4.4	2.7	27	19	9
3	M	67	12.4	9.9	NA	14	18	13
4	M	52	3.7	1.9	1.7	23	21	21
5	M	62	5.6	5.4	4.2	19	14	16
6	M	53	16.8	8.5	2.1	21	19	10
7	F	42	8.3	5.5	3.2	16	15	15
8	M	73	6.7	5.8	NA	14	13	14
9	M	61	4.9	2.9	2.6	40	31	21
10	F	44	5.3	4.2	4.2	17	16	13
11	M	65	3.4	2.1	1.9	17	10	9
12	M	60	5.6	4.7	NA	13	19	15
13	M	60	6.7	5.4	3.6	21	19	14
14	M	71	6.3	3.2	NA	22	15	19
15	M	62	7.1	3.6	NA	15	14	14
16	M	70	4.7	3.5	3.0	10	9	10
17	F	59	8.5	5.7	4.0	38	43	22
18	M	66	6.2	3.8	4.3	17	17	15
19	M	50	13.4	5.3	2.6	34	25	11
Mean \pm SD		59 \pm 8.7	7.7 \pm 3.6	4.8 \pm 2.0	3.0 \pm 0.9	20 \pm 10	19 \pm 9	14 \pm 5

*Four women and 15 men.

Preop = preoperative; NA = not applicable.



points larger than the change in tumor diameter. Under these assumptions, 20 patients are needed to detect this difference in a paired *t* test at a significance level of $P = 0.05$. Sample size calculations were performed with the PS program (10). In the first phase II study from which patients were recruited ($n = 10$), all patients underwent 2 cycles of preoperative chemotherapy. In the second study ($n = 10$), treatment was changed on the basis of the findings of the ^{18}F -FDG PET scan (11). Patients with a decrease in tumor ^{18}F -FDG uptake of at least 35% after 2 wk of chemotherapy (metabolic responders) underwent 2 full courses of chemotherapy. In contrast, chemotherapy was stopped and the tumor was resected in metabolic nonresponders (<35% decrease in ^{18}F -FDG uptake).

In both studies, inclusion criteria consisted of the presence of biopsy-proven adenocarcinoma of the distal esophagus (AEG I) or cardia (AEG II), with or without local lymph node metastases and without distant metastases (tumor stage T3 NX M0 or T4 NX M0) (7). Patients were treated with 2 cycles of platinum-based combination chemotherapy (each with a duration of 36 d) as described previously (7). The study protocol was approved by the Ethics Committee of the University of Technology, Munich, Germany, and written informed consent was obtained from every patient. Patient characteristics are summarized in Table 1.

PET Imaging

An ^{18}F -FDG PET scan was performed for each patient before the initiation of preoperative chemotherapy and 14 d after the initiation of chemotherapy. In 14 patients, a third PET scan 3–4 wk after the completion of chemotherapy (13–14 wk after the initiation of chemotherapy, immediately before surgery) was performed.

Patients fasted for at least 6 h before PET to minimize blood glucose and insulin levels and to ensure standardized metabolism in all patients. Blood glucose levels were measured before each PET examination. All measured values were less than 150 mg/dL and showed no significant changes during chemotherapy. Static emission images (20 min) of the tumor region were acquired 40 min after intravenous injection of 300–370 MBq of ^{18}F -FDG by use of an ECAT EXACT PET scanner (CTI/Siemens). After the emission scan, transmission measurements were performed for attenuation correction. Images were reconstructed iteratively with an attenuation-weighted ordered-subset expectation maximization algorithm (8 iterations, 4 subsets) and then smoothed in 3 dimensions with a 4-mm gaussian filter. Quantitative image analysis was performed by 1 specialist in nuclear medicine who had more than 2 y of experience in PET imaging and who was not provided with clinical information concerning the patients.

Circular regions of interest (ROIs) with a diameter of 1.5 cm (corresponding to 10 pixels) were manually placed over the tumor at the site of maximum ^{18}F -FDG uptake in the baseline scan. In the following PET scans, the ROIs were placed in the same positions as in the baseline study. Standardized uptake values (SUVs) normalized to patient body weight were calculated from the average activity values in the ROIs. On the basis of previously described criteria (12), patients were excluded if tumor ^{18}F -FDG uptake was too low for quantitative analysis. The length of the tumor in coronal slices was measured by 1 observer. For these measurements, the images were scaled to the maximum ^{18}F -FDG uptake of the tumor tissue and displayed on a computer screen by use of an inverted gray scale. With these standardized display settings, the

extent of the tumor was determined visually. Measurements were performed on a Sun Workstation (Sun Microsystems) running ECAT 7.1 software (CTI/Siemens).

CT

For all patients, MSCT was performed before the initiation of preoperative chemotherapy, 14–17 d after the initiation of chemotherapy, and directly before surgical resection (13–14 wk after the initiation of chemotherapy, 3–4 wk after the completion of chemotherapy).

Patient preparation included the oral administration of 500 mL of water directly before the scan, followed by an injection of 40 mg of *N*-butylscopolamine intravenously to dilate the esophagus and stomach. After intravenous administration of 120–150 mL of iodine contrast agent (Imeron 300; Altana) at a flow rate of 3 mL/s, a VolumeZoom Scanner (Siemens) was used to perform a CT scan of the thorax and upper abdomen in the late arterial enhancement phase (delay of 30 s) and then a scan of the abdomen in the portal venous phase. The following scan parameters were used: tube voltage, 120 kV; tube current, 180 mAs; collimation, 4×1 mm; slice thickness, 1.25 mm; and reconstruction increment, 0.8 mm. Images were sent to a Leonardo Workstation (Siemens) for further analysis. The maximum wall thickness was measured in the axial plane at the same height for each examination; the maximum length of the tumor was measured in the coronal reconstructed images. Images were analyzed by 1 resident in radiology who had more than 2 y of experience in CT and who was unaware of any clinical information concerning the patients as well as the results of the ^{18}F -FDG PET scan. For measurement of the size of the tumor, a soft-tissue window was used to display the CT images on the computer screen (center, 50 Hounsfield units; width, 350 Hounsfield units). Tumor extent was assessed visually by taking into account the regional wall thickness of the esophagus as well as contrast enhancement. Measurements were performed on the Leonardo Workstation with standard Syngo Software tools (Siemens).

Statistical Analysis

Statistical analyses were performed with the StatView program (SAS Institute Inc.). Quantitative values were expressed as mean \pm 1 SE (SEM) or mean \pm 1 SD. Intra- and interindividual comparisons of absolute values and changes in tumor ^{18}F -FDG uptake and tumor wall thickness were performed with Wilcoxon signed rank or paired *t* tests and Mann–Whitney tests, respectively. Correlations between quantitative parameters were evaluated by linear regression analysis. All statistical tests were performed at the 5% level of statistical significance.

RESULTS

Time Course of ^{18}F -FDG Uptake, Tumor Length, and Tumor Wall Thickness

One tumor showed only low ^{18}F -FDG uptake at the baseline examination in comparison to the surrounding tissue (SUV, 3.7) and therefore was excluded from further analysis. All other tumors ($n = 19$) showed intense ^{18}F -FDG uptake, with a mean SUV at baseline of 7.7 (SD, 3.6). At 14 d after the initiation of chemotherapy, the SUV decreased significantly to 4.8 (SD, 2.0) (relative change, -35% ; SD, 16% ; $P < 0.01$) (Fig. 1). At the preoperative scan (13–14 wk after the initiation of chemotherapy, di-

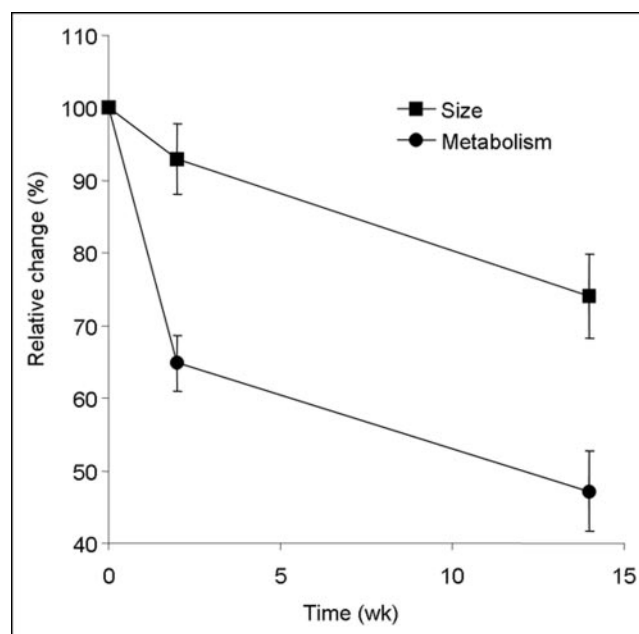


FIGURE 1. Time course of changes in tumor ^{18}F -FDG uptake and tumor wall thickness. Error bars denote 1 SEM.

rectly before surgery), there was a further significant decrease in the SUV to 3.0 (SD, 0.9) (relative change, -53% ; SD, 21% ; $n = 14$; $P < 0.01$ for a comparison with the baseline scan and the first follow-up scan) (Fig. 1). Maximum tumor SUVs showed similar changes during therapy. The maximum SUVs at the time of the first, second, and third PET scans were 8.8 (SD, 3.9), 5.3 (SD, 2.2), and 3.6 (SD, 1.1), respectively. The corresponding relative changes were -38% (SD, 18% ; from the first scan to the second scan) and -55% (SD, 23% ; from the first scan to the third scan). Therefore, only the mean SUVs were used for further analysis.

The mean tumor length in ^{18}F -FDG PET at baseline was 64 mm (SD, 19). At 14 d after the initiation of chemotherapy, the length decreased significantly to 57 mm (SD, 19 mm) (relative change, -9% ; SD, 10% ; $P < 0.01$). After the completion of chemotherapy, the tumor length in ^{18}F -FDG PET decreased further to 41 mm (SD, 10) (relative change, -34% ; SD, 20% ; $P < 0.01$ for a comparison with the length at the time of the second PET scan).

The mean tumor wall thickness at baseline was 20 mm (SD, 10). At 14–17 d after the initiation of chemotherapy, the mean wall thickness was 19 mm (SD, 9) (relative change, -4% ; SD, 20% ; $P = 0.23$) (Fig. 1). After the completion of chemotherapy, the mean tumor wall thickness decreased significantly to 14 mm (SD, 5) (relative change, -26% ; SD, 27% ; $P = 0.0075$) (Fig. 1). The mean tumor length in CT was 85 mm (SD, 18) at baseline and showed no significant decrease at 14–17 d after the initiation of chemotherapy (84 mm; SD, 20) (relative change, -1% ; SD, 6% ; $P = 0.6$). At the preoperative scan, there was a significant decrease in the mean tumor length to 71 mm (SD, 23) (relative change, -16% ; SD, 16% ; $P < 0.01$).

The relative decrease in the SUV at 14 d after the initiation of chemotherapy and after the end of chemotherapy was significantly higher than the corresponding decrease in tumor wall thickness ($P < 0.01$, as determined by paired t tests or Wilcoxon tests) (Fig. 1). Figure 2 shows an example of a tumor with a marked decrease in ^{18}F -FDG uptake after 2 wk of therapy but no apparent change in size.

Correlation Among ^{18}F -FDG Uptake, Tumor Length, and Tumor Wall Thickness

At 14 d after the initiation of chemotherapy, there was no correlation between the reduction in the SUV and changes in tumor wall thickness ($r^2 = 0.16$, $P = 0.05$) (Fig. 3A) or tumor length ($r^2 = 0.08$, $P > 0.5$). Similarly, there was no correlation between changes in tumor length as measured by PET and CT ($P > 0.5$). In contrast, there was a significant correlation between early changes in tumor ^{18}F -FDG uptake and the reduction in tumor size after the completion of therapy ($r^2 = 0.38$, $P = 0.005$) (Fig. 3B). Changes in tumor length after 2 wk of therapy showed no significant correlation with the reduction in tumor wall thickness after the completion of therapy ($r^2 = 0.18$, $P = 0.05$).

Metabolic changes at 2 wk after the initiation of chemotherapy also were significantly correlated with the reduction in metabolic activity after the completion of therapy ($r^2 = 0.63$, $P = 0.0007$) (Fig. 4A). In contrast, early changes in tumor wall thickness ($r^2 = 0.20$, $P = 0.05$) (Fig. 4B) or length ($r^2 = 0.005$, $P = 0.35$) did not predict a reduction in tumor size after the completion of therapy.

DISCUSSION

This study demonstrates that chemotherapy causes a decrease in tumor ^{18}F -FDG uptake that precedes a reduction in tumor size. Tumor ^{18}F -FDG uptake decreased significantly by 35% at 2 wk after the initiation of chemotherapy; at the same time, there was only a minimal decrease in tumor wall thickness as measured by MSCT. Furthermore, the decrease in tumor ^{18}F -FDG uptake at 2 wk after the initiation of therapy was significantly correlated with a reduction in tumor size after the completion of chemotherapy, indicating that early quantitative metabolic changes predicted subsequent morphologic tumor responses. In contrast, measurements of tumor size by CT and tumor length by CT and PET after 2 wk of therapy were not significantly correlated with a reduction in tumor size after the completion of therapy.

It is generally assumed that a reduction in tumor metabolic activity precedes morphologic changes in tumor tissue. However, very few data in the literature actually confirm this hypothesis. Wahl et al. (13) reported for 11 patients with breast cancer that changes in ^{18}F -FDG uptake during chemohormonotherapy were not accompanied by a decrease in tumor size as measured by conventional mammography. To our knowledge, no systematic studies have compared changes in ^{18}F -FDG uptake with measurements of tumor size by MSCT. Changes in tumor size early in the course of treatment could significantly affect the measurement of activity concentrations by PET. In this situation, the measured activity concentrations would become smaller because of

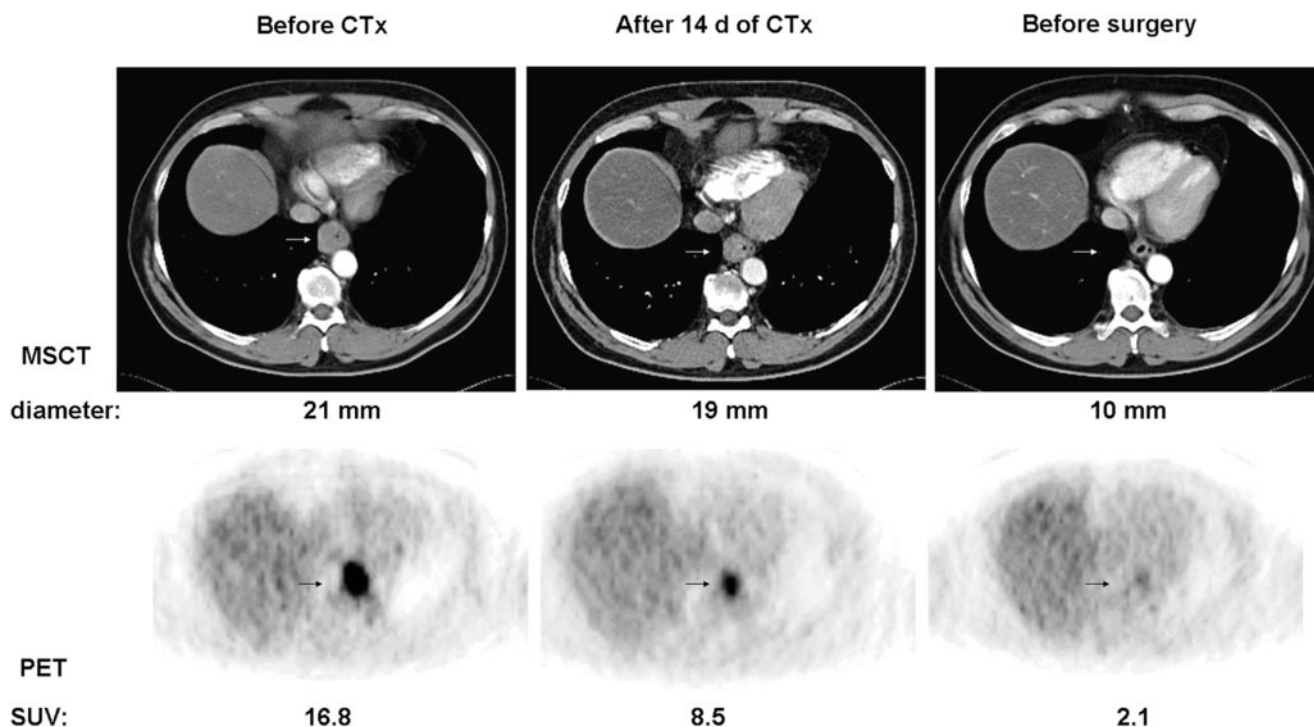


FIGURE 2. MSCT and ^{18}F -FDG PET in patient before chemotherapy (CTx), after 14 d of therapy, and before surgery. Tumor size (arrow) was almost unchanged in MSCT after 14 d of therapy but showed significant decrease after completion of therapy. However, ^{18}F -FDG uptake by tumor after 14 d of therapy showed distinct decrease and was reduced to background levels in scan before surgery.

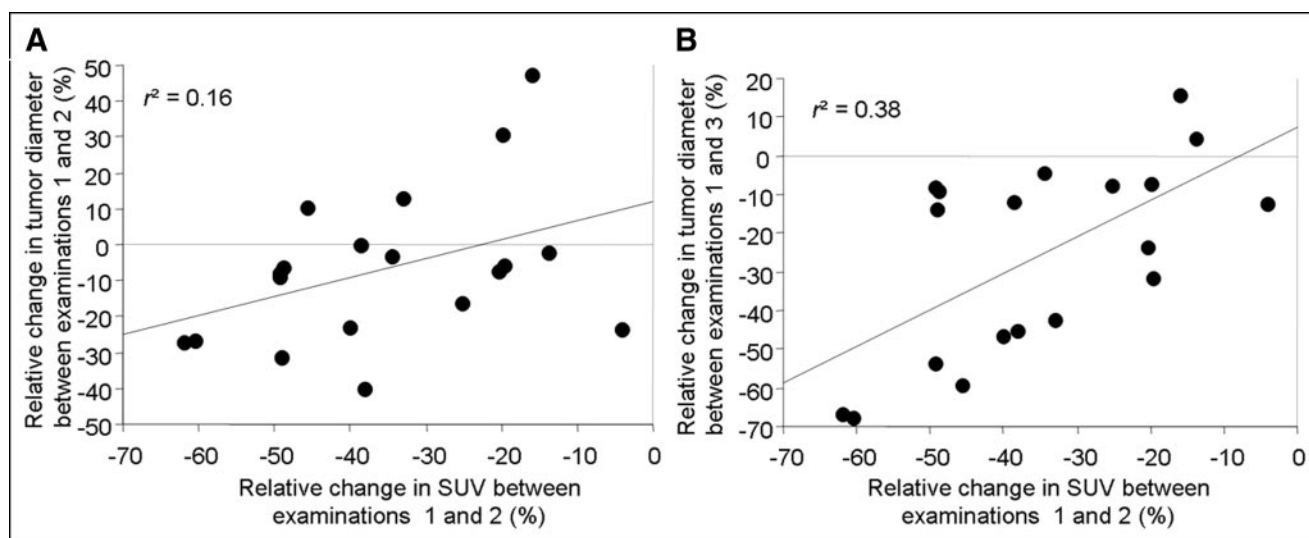


FIGURE 3. Correlation between early changes in ^{18}F -FDG uptake and early (A) and late (B) changes in tumor size.

partial-volume effects, even if the true activity concentrations were unchanged. Thus, the effect of treatment on tumor metabolism would be overestimated by PET imaging. Kessler et al. (14) and Brix et al. (15) developed a model for calculating recovery coefficients (RCs) for spheres of various diameters. This model is similar to the design of our study, because most esophageal tumors have a long cranio-caudal extension compared with their diameter and, in a first approximation, resemble cylinders. For a cylinder with a diameter of 20 mm (the mean tumor wall thickness before therapy in the present study), a ratio between the concentration of the cylinder and the concentration of the background of 4.0 (corresponding to the ratio of the tumor SUV to the background SUV in the present study), and a spatial resolution of the reconstructed images of 12 mm, the RC

was 90%. Under the same conditions, the RC for a 19-mm cylinder (corresponding to the mean tumor wall thickness after 14 d of therapy) was 88%. Although there were some variations in wall thickness changes on a per-patient basis (Table 1), most patients had only minor reductions in tumor wall thickness. The average RCs at the baseline and at the first and second follow-up scans were 84% (SD, 13%), 80% (SD, 13%), and 70% (SD, 15%), respectively. Therefore, it can be concluded that partial-volume effects cannot explain the 35% decrease in ^{18}F -FDG uptake after 2 wk of therapy. This conclusion is further corroborated by the lack of correlation between changes in ^{18}F -FDG uptake and tumor wall thickness ($r^2 = 0.16$).

The following limitations of this study should be noted. Because of the small number of patients included in this

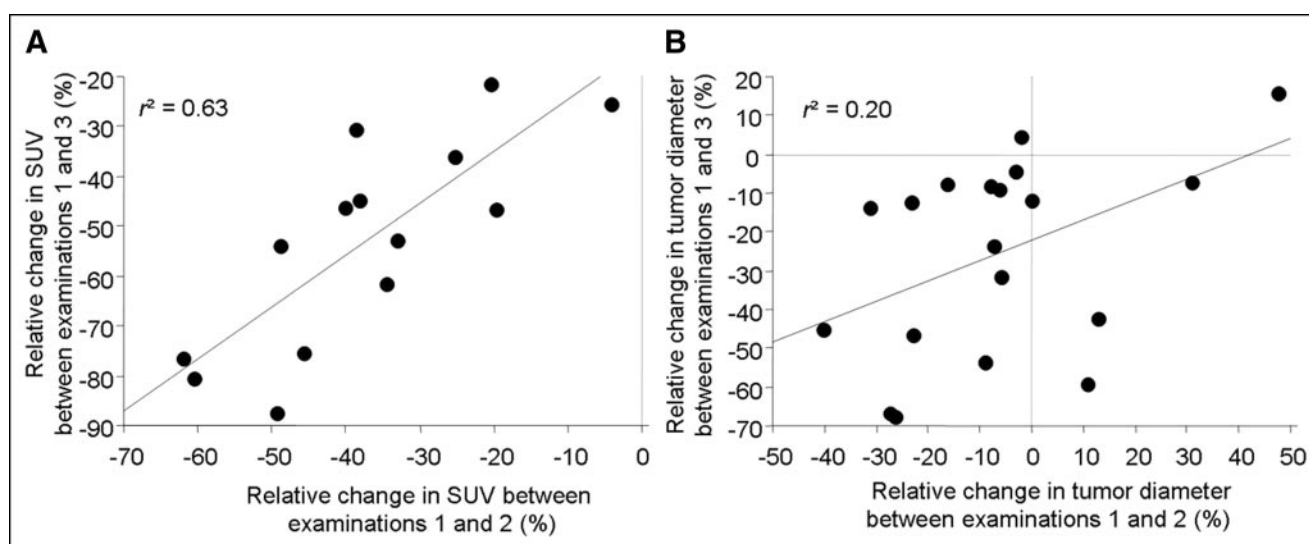


FIGURE 4. Relationship between early and late changes in tumor metabolism and size. (A) Correlation between early and late changes in tumor metabolism. (B) Correlation between early and late changes in tumor size.

study, no attempt was made to calculate the sensitivity and specificity of ^{18}F -FDG uptake or CT for the prediction of a histopathologic response (only 3 patients were histopathologically classified as responders in this study). Only wall thickness and length, not the volume of the tumor, were measured in this study. Detailed volumetric measurements may provide a more sensitive way to assess tumor response by CT. However, accurate techniques for measuring tumor volume in AEGs have not been established so far.

CONCLUSION

This study demonstrates that metabolic changes during chemotherapy actually precede a significant reduction in tumor size. This finding supports the concept that quantitative assessment of tumor metabolism by ^{18}F -FDG PET is a more sensitive test for monitoring tumor response than are size measurements with anatomic imaging modalities.

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