Noninvasive Monitoring of Tumor Metabolism Using Fluorodeoxyglucose and Positron Emission Tomography in Colorectal Cancer Liver Metastases: Correlation With Tumor Response to Fluorouracil

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Purpose: **To investigate and measure the metabolism of colorectal cancer liver metastases using 18F-fluorodeoxyglucose positron emission tomography (FDG PET), before and during the first month of chemotherapy. The findings were compared with tumor outcome conventionally assessed using changes in tumor size.**

Patients and Methods: **Patients with colorectal cancer liver metastases were treated with fluorouracil (5FU) as a protracted venous infusion (300 mg/m^2/d), with or without interferon-α 2b for two 10-week blocks separated by a 2-week break. Before and at 1 to 2 and 4 to 5 weeks on treatment, FDG PET scans were performed. Patients fasted, were injected intravenously with FDG (50 to 100 MBq), and scanned using a large-area positron camera; the image data was processed such that regions of interest could be identified. The results were expressed as a ratio of FDG uptake in the tumor and normal liver (T:L) or as a semiquantitative standardized uptake value (SUV). These measures were compared with the tumor dimensions measured on a computed tomographic (CT) scan performed at 12 weeks from commencement of chemotherapy.**

Results: **Twenty patients were studied; however, two did not have assessable liver metastases. Objective partial responses were observed in 11 of 18 patients. A total of 27 metastatic lesions were assessable. Pretreatment T:L ratios and SUVs did not correlate with tumor response, although response was associated with lower 1- to 2-week (1.84 *v* 2.17; $t = 2.667$; $P < .02$) and 4- to 5-week (1.36 *v* 2.28; $t = 5.02$; $P < .001$) T:L ratios, and 4- to 5-week (3.57 *v* 4.95; $t = 2.492$; $P < .05$) SUVs. Expressed as a percent of the baseline values of the T:L ratio, responding lesions had a greater reduction in metabolism (67% *v* 99%; $t = 7.53$; $P < .001$). The 4- to 5-week T:L ratio was able to discriminate response from nonresponse both in a lesion-by-lesion and overall patient response assessment (sensitivity 100%; specificity 90% and 75%, respectively).**

Conclusion: **Positron emission tomography used to evaluate the uptake of FDG in tumors yields data that correlate with the antitumor effect of chemotherapy in patients with liver metastases from colorectal cancer.**

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POSITRON EMISSION tomography (PET) is a functional imaging technique with increasing clinical application, particularly in the fields of neurology and cardiology. However, its use in oncology is less well developed. Because the current PET camera technology is limited to a smaller field of view, it is better suited to the study of areas such as the brain and heart, but less so to the study of cancer, which may be at several different sites.

The PET studies performed in gastrointestinal malignancy have been performed predominantly in patients with colorectal cancer using 18F-fluorodeoxyglucose (FDG). They have been designed to investigate a variety of clinical situations ranging from diagnosis and preoperative staging to predicting relapse and response to treatment.[1-3]

Okazumi et al[4] investigated 35 patients with a variety of secondary and primary hepatobiliary tumors, and compared the results with 12 individuals with normal liver and 10 with cirrhosis of the liver. Using dynamic scanning, they were able to determine the rate constants ($k_1 - k_4$) for a three-compartment model. Normal and cirrhotic liver showed an initial accumulation of FDG, followed by a rapid reduction until a plateau at approximately 60 minutes. Comparative data in tumors revealed a gradual increase to a plateau at 60 minutes. The FDG uptake for hepatocellular tumors fell into three categories: lower, equal, or higher than liver uptake. Metastatic lesions and cholangiocarcinoma showed higher levels than liver at 60 minutes, while two hemangiomas showed similar uptake to the surrounding liver.

Nagata et al[2] studied 17 patients with primary or metastatic liver lesions who received transcatheter arterial em-

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bolization, hyperthermia, and radiotherapy. The investigators found a correlation between the changes in FDG uptake and tumor marker response, but not with measurements made by computed tomographic (CT) scan. They commented that this form of treatment may often result in no change in tumor size but in tumor density.

In a study of patients with recurrent colorectal carcinoma treated with radiotherapy, 21 had FDG PET scans before and after treatment; however, a significant correlation between palliative benefit and FDG reduction was demonstrated in only 50% of patients.[5] The investigators postulated that an inflammatory response to radiotherapy may have given increased FDG uptake values. They suggested deferring post-treatment PET evaluation for at least 6 months.

Investigators at the Institute of Cancer Research, The Royal Marsden Hospital, and the Rutherford Appleton Laboratories have developed a multiwire proportional chamber PET camera (MUP-PET) with a large field of view for cancer studies.[6,7] Using this camera, we undertook a study of patients with liver metastases from colorectal cancer who were being treated in a phase III trial to examine protracted venous infusion fluorouracil (5FU) with or without interferon-α. The study was designed to monitor the metabolism of liver metastases using FDG before and at different times during the first month of chemotherapy.

PATIENTS AND METHODS

Patients and Chemotherapy

The study population for this investigation was limited to any patient who was being treated for colorectal cancer liver metastases in a randomized clinical trial comparing protracted infusion 5FU with or without interferon-α, the results of which are reported in the literature.[8] Because of the limited sensitivity of the PET camera, only patients with liver metastases $\geq$ 3 cm were eligible for this protocol. Patients were not considered eligible if they lived at a significant distance from the study facility (The Royal Marsden Hospital) because it was inconvenient to travel for extra scan visits. The study protocol was approved by the Royal Marsden Hospital Committees for Clinical Research and Ethical Review. Written informed consent from the patient was also required before study entry.

Tumor Response Evaluation

Patients had their metastatic lesions measured using CT or magnetic resonance imaging (MRI) scans before treatment and at 12-week intervals after commencement of chemotherapy. These scans were brought forward if disease progression was clinically evident and chemotherapy was to be stoppped. The World Health Organization (WHO) criteria for objective response were used.[9] Response evaluation was performed prospectively by a radiologist without knowledge of the PET data. Evaluation of the PET data was prospective and performed before the 12-week CT evaluation.

PET Imaging Protocol

PET scans were performed before chemotherapy and again at 1 to 2 weeks and 4 to 5 weeks after starting treatment. The MUP-PET camera was used to scan the patients. The camera consists of two opposed multiwire proportional chambers mounted on a rotating gantry, functioning as a large-area detector with a field of view 30 cm in the axial direction and 40 cm in the other directions. The spatial resolution of this system using a point source in air is 0.6 cm. Details of the specifications of the camera and its performance relative to other systems have been described previously.[6,7] Patients fasted for 6 hours before an intravenous (IV) injection of FDG (50 to 100 MBq). The FDG was synthesized at the Clinical PET Centre, St Thomas' Hospital (London, United Kingdom).[10] The patient was positioned in the camera with the center of the field of view at the xiphisternum and then scanned for approximately 20 minutes (1 to 1.5 million coincident events), starting no earlier than 45 minutes after the FDG IV injection (mean, 55 $\pm$ 10 minutes (1 SD); range, 45 to 99 minutes). Blood was drawn just before the FDG injection and at the end of the scan for subsequent plasma glucose evaluation.

PET Image Analysis

The raw data were back-projected to form a three-dimensional image containing 64^3 voxels of 0.216 cm^3 volume. The image was corrected for attenuation and scatter at the back-projection stage using an algorithm based on measurements using a 25- $\times$ 10-cm phantom producing scatter representative of that within a patient. The image was then deconvolved with a three-dimensional, experimentally measured, point spread function. Images were displayed in a series of 24 transverse section slices taken through the central 15 cm of the axial field of view (ANALYSE; Mayo Clinic, Rochester, MN), and region of interest (ROI) analysis was performed to determine the mean count per voxel in the designated region in the tumor or liver.[11] ROIs containing 4 $\times$ 4 voxels (of 0.216-cm^3 volume) were placed so that over a series of three to four contiguous slices, the maximum area of intensity of the tumor was sampled, while the liver ROIs were placed in a similar fashion so as to avoid contamination from tumor tissue. The ROI data were processed in two ways: as a standard uptake value (SUV) and as a tumor-to–normal liver ratio (T:L). The SUV is an estimate of the FDG concentration in the ROI, standardized to body weight. For this semiquantitative estimate of FDG, the calibration factor used was calculated from the results obtained after scanning a 25-cm diameter, 10-cm long phantom uniformly filled with a known activity of FDG. The SUV is unitless assuming the density of the tissue scanned is the same as that of the water suspending the injected FDG. The alternative method of data presentation is as the image ratio of the mean tumor and normal liver tissue count from the ROI data. Because this is a nonquantitative relative estimate, no calibration factor, patient weight, or injected dose data is required.

Statistics

The means of tumor SUV and T:L values were calculated with 95% confidence intervals (CI), while differences in these means were compared using the t test (two-tailed). Least squares linear regression was used to compare these metabolic indices with other physiologic and pathologic variables.

RESULTS

Patient Characteristics

Patients in this investigation were taken from a randomized trial examining protracted infusion 5FU with or

Table 1. Study Characteristics

	5FU	5FU + IFN	Total
No. of patients	11	9	20
No liver metastases	1	1	2
Incomplete data			
No CT assessment*	1	1	2
No PET assessment†	1	1	2
Complete CT and PET data	8	6	14
Response rate (CR + PR)‡	6/10	5/8	11/18
Assessable lesions studied	18	9	27
Responding lesions	10/18	6/9	16/27

Abbreviation: IFN, interferon.

*One patient had progressive disease in the primary site requiring surgery, after which he refused further CT assessment of 2 measurable liver lesions. Another patient developed subacute bowel obstruction from progressive peritoneal disease and was started on second-line chemotherapy before CT evaluation of 2 measurable liver lesions.

†One patient with 2 measurable liver lesions violated the fasting instructions just before the pretreatment PET scan. Another presented for the on-treatment PET scans only to be cancelled on 2 occasions because of FDG production failure and MUP-PET software problems. The patient was unwilling to have further scans rescheduled.

‡Includes the 2 patients with extrahepatic tumor progression mentioned above and the 2 patients who were assessable for response by CT but not by PET. One other patient with 3 discrete liver metastases was found to have a differential response, namely a 50% reduction in tumor area in one lesion, and a > 25% increase in the others (categorized as overall progressive disease).

without interferon-α.[8] Details of study characteristics are listed in Table 1. Two patients were given a pretreatment PET scan before a CT scan, based on surgical evaluation of the presence of liver metastases; however, the subsequent CT scan showed neither patient had measurable metastases. One patient who was randomized to receive 5FU alone subsequently withdrew consent before starting because of concerns about managing an indwelling central venous line. He was therefore treated with 5FU 425 mg/m^2/d IV plus folinic acid 20 mg/m^2/d IV for days 1 through 5 each month and continued to be observed in the PET study. To increase the information from this group, patients with multiple assessable metastases had all lesions studied, enabling a lesion-by-lesion evaluation of PET and CT. This approach allowed for the study of a patient with a differential tumor response. There were more lesions assessable in the 5FU arm than the 5FU-interferon arm (18 in 10 patients *v* nine in eight patients). Five lesions in the 5FU-interferon arm and one in the 5FU arm were not assessable with PET because of their close proximity to heart or kidney. The patients' overall tumor response rate (complete response [CR] + partial response [PR]), using the WHO guidelines,[9] was 11 of 18 (61%; 95% CI, 38 to 84), with no significant differences observed between the arms. The tumor response rate in the overall patient population from this study (n = 125) was 31% (95% CI, 19 to 45) with 5FU and 24% (95% CI, 12 to 36) with 5FU plus interferon.[8]

Plasma Glucose, Patient Weight, and Scan Time

Because of the assumption that variations in the fasting plasma glucose level will not significantly affect the uptake of FDG, the SUV (liver and tumor) and T:L value were compared with this variable in a linear regression analysis. The plasma glucose was expressed as an average of the values obtained from the samples taken at the time of FDG injection and at the end of the PET scan. One patient with non–insulin-dependent diabetes mellitus had consistently increased plasma glucose levels with each scan, whereas two other patients had slightly raised values during one of their scans. There was no detectable correlation with plasma glucose and liver SUV (r = .0749; P = .6), tumor SUV (r = −.0761; P = .49), or T:L (r = −.1426; P = .23). Patient weight is used in the SUV calculation assuming a linear correlation with the FDG volume of distribution and weight. Comparison of pretreatment SUV and T:L with patient weight using linear regression should therefore reveal no correlation; however, this was not the case for tumor SUV (r = −.4889; P = .007) or T:L (r = −.5418; P = .0024). Liver SUV did not correlate with patient weight (r = .25; P = .083). Although there has been an adjustment for the physical decay of FDG, the biological decay may vary, depending on the time from its injection to the scan. However, there were no correlations between the time from FDG injection to the midpoint of the scan and the pretreatment liver SUV (r = .1074; P = .67), the tumor SUV (r = −.1665; P = .39), or the T:L (r = −.1131; P = .56).

Pretreatment SUV and T:L Data

The mean pretreatment values were as follows: liver SUV 2.53 (95% CI, 2.24 to 2.82); tumor SUV 5.65 (95% CI, 5.08 to 6.22); and T:L ratio 2.25 (95% CI, 2.04 to 2.46). Regression analysis showed a significant positive linear correlation between pretreatment tumor SUV and pretreatment liver SUV (r = .781; P < .0001); thus, it is improbable the T:L activity will be influenced by varying levels of injected activity.

Effects of Interferon-α on SUV Data

Because the observed reduction in plasma 5FU clearance with the addition of interferon-α may be because of an alteration in hepatic blood flow,[12] it is possible that

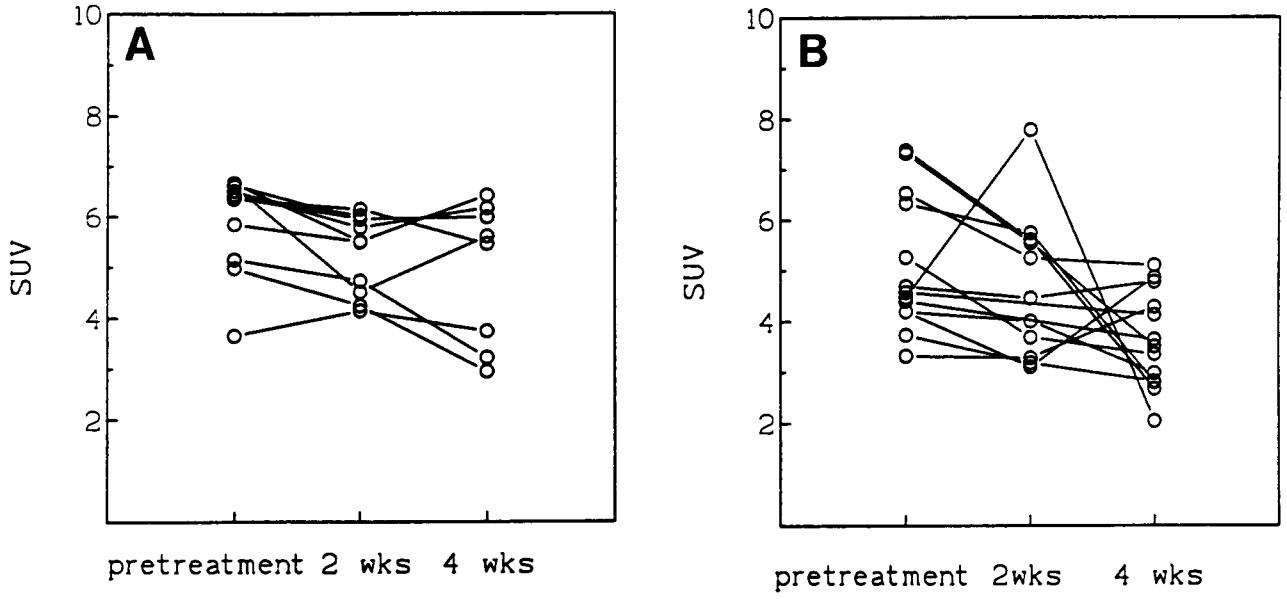

Fig 1. SUV in nonresponding (A) and responding (B) tumors.

interferon-α may also modify delivery and therefore uptake of FDG in the liver. To assess this possibility, the liver SUVs were plotted according to whether interferon-α was received. There were no significant differences in the liver SUVs with interferon-α addition either at 2 weeks (t = .497; P = .626) or 4 weeks (t = .316; P = .757).

FDG SUV Versus Tumor Response

The tumor SUVs plotted by tumor response are shown in Fig 1. Mean pretreatment SUVs for responding tumors (5.15; 95% CI, 4.26 to 6.04) and nonresponding tumors (5.93; 95% CI, 5.29 to 6.57) were not different (t = 1.605; $P > .1$). The mean SUVs at 1 to 2 weeks for responding and nonresponding tumors were 4.69 (95% CI, 3.72 to 5.66) and 5.32 (95% CI, 4.81 to 5.83), respectively (t = 1.28; $P > .2$). At 4 weeks, the mean responding tumor SUV was 3.57 (95% CI, 2.94 to 4.2), and nonresponding tumor SUV was 4.95 (95% CI, 3.77 to 5.13) (t = 2.492; $P < .05$). There were three lesions in the responding group that had an overall increase in uptake values by 4 weeks and two lesions in the nonresponding group that had a marked reduction by that time. The two nonresponding lesions that had a reduced SUV at 4 weeks were in a patient who had an unknown quantity of the FDG injection extravasate at the time of this study; therefore, the FDG dose used in the calculation of the SUV is likely to be an overestimate, and could account for this finding. However, there was no identifiable problem with the injection of FDG in the two patients with the three responding lesions that had increasing SUVs.

FDG T:L Ratio Versus Tumor Response

Figure 2 shows the T:L ratio in responding and nonresponding tumors before and at 1 to 2 and 4 to 5 weeks of treatment. Mean pretreatment T:L ratios for responding tumors (2.05; 95% CI, 1.9 to 2.2) and nonresponding tumors (2.27; 95% CI, 2.03 to 2.51) were not different (t = 1.76; $P > .05$). The mean T:L ratios at 1 to 2 weeks for responding and nonresponding tumors were 1.84 (95% CI, 1.6 to 2.08) and 2.17 (95% CI, 2.04 to 2.30), respectively (t = 2.667; $P < .02$). The mean T:L ratio in the responding and nonresponding groups at 4 to 5 weeks were 1.36 (95% CI, 1.87 to 2.69) and 2.28 (95% CI, 1.87 to 2.69), respectively (t = 5.02; $P < .001$). Linear regression showed a positive correlation between two-dimensional tumor reduction and T:L at 4 weeks (r = .4581; P = .05). All tumors that responded to chemotherapy had a reduction in the T:L ratio by 4 to 5 weeks; however, four tumors initially had a marked increase in T:L ratio at 2 weeks before reducing to become the lowest of the 4- to 5-week values. Expressed as a percent of the pretreatment value, the mean T:L ratio at 4 to 5 weeks for responding lesions (67%; 95% CI, 60 to 74) was significantly lower than for nonresponding lesions (99%; 95% CI, 93 to 105) (t = 7.53; $P < .001$). Using a 15%

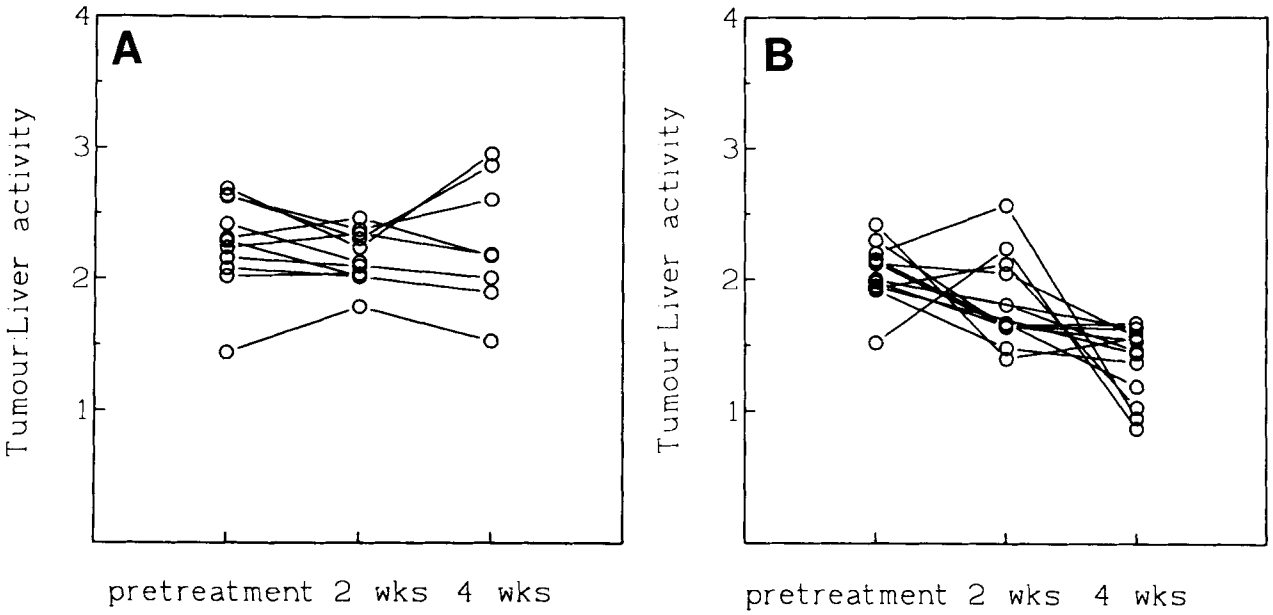

Fig 2. Tumor-to-normal liver ratios in nonresponding (A) and responding (B) tumors.

reduction in the pretreatment T:L ratio by 4 to 5 weeks in a comparison with tumor response, a correlation can be demonstrated with a sensitivity of 100% and specificity of 90% (Table 2).

Patient Outcome and FDG Uptake

Application of the findings from individual tumors to the overall patient response is complicated by the presence of multiple and potentially independently responsive lesions in some cases. An example shown in Fig 3 is that of a patient with three lesions in the liver. With chemotherapy, the 4- to 5-week PET scan showed reduced metabolism in one lesion but not in the other two. The 12-week CT scan showed that the lesion with reduced metabolism responded while the other two did not. If the mean 4- to 5-week T:L ratio for a patient's lesions is taken and applied to the same 15% reduction criterion, the results (Table 3) remain consistent (100% sensitivity; 75% specificity). The patient with a differential tumor response accounted for the lower specificity, with a mean T:L reduction greater than 15% at 4 to 5 weeks. There were no patients who responded but failed to reduce their tumor T:L by ≥ 15%.

Table 2. Lesion-by-Lesion Tumor Response Compared With a Reduction in the 4-Week Ratio of Tumor to Normal Liver Activity

	≥ 15% Reduction	< 15% Reduction
PR	13	0
No response	1	9

NOTE. 100% Sensitivity; 90% specificity.

DISCUSSION

This study was designed to investigate the use FDG PET in the evaluation of changes in tumor metabolism at various stages of cytotoxic treatment and to compare these changes with tumor outcome. In the first instance, it was considered that a study of this type should conduct a lesion-by-lesion analysis to obtain a more specific comparison of the data. The advantage of this approach was demonstrated by the patient whose liver metastases underwent a differential response. However, a disadvantage is that a collection of metastases in one patient may be more likely to respond or progress in unison and are therefore not independent. This consideration is less important when using the biologic tracer FDG, because it is a nonspecific marker of tumor cell viability, rather than, eg, labeled thymidine, which in addition to giving an indication of DNA turnover, may also indicate variations in thymidine salvage de novo or in response to different treatments and is therefore more prone to be confounded by coincidental biologic parameters.[13] The observation that a reduction in the T:L ratio by ≥ 15% at 4 to 5 weeks compared with the pretreatment value correlates with response assessed at 12 weeks using CT, indicates that this method may be applicable to patients in this and possibly other clinical set-

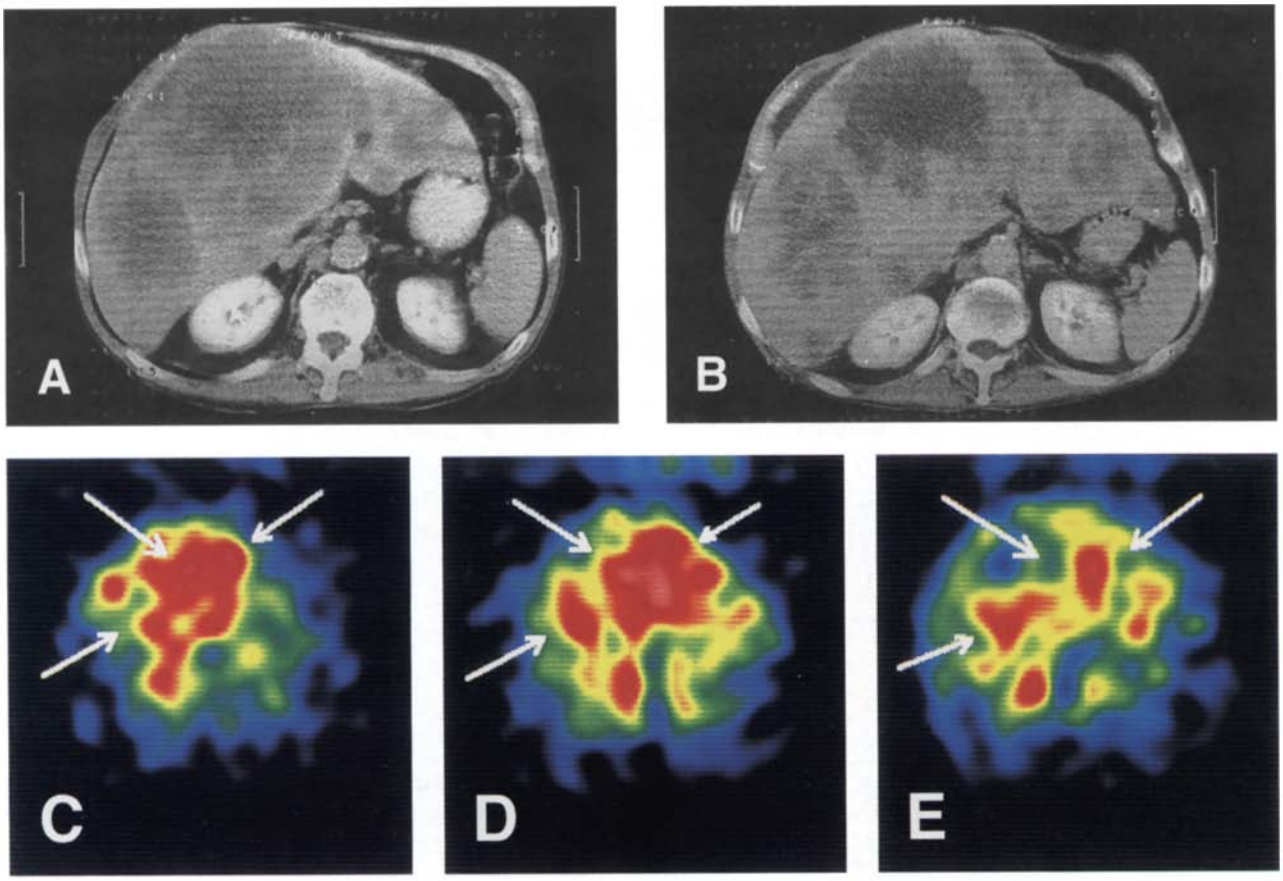

Fig 3. An example of a patient with a tumor that is showing a differential response to chemotherapy. CT scans were performed pretreatment (A) and at 12 weeks on treatment (B). PET scans were performed pretreatment (C), at 2 weeks (D) and at 1 month on treatment (E). Metastases are indicated by arrows in the PET scans. The CT scan shows progression of metastatic tumor in the left and right margins of the liver while responding in the central lesion. The PET scans show a reduction in the metabolism in the central lesion with no reduction and some increase in the adjacent metastases.

tings. Because a CT scan was not performed at 4 weeks, it is theoretically possible that the PET data do not represent an earlier marker of response, but that it parallels objective response and that all of these patients had achieved such a response at the time of the 4- to 5-week PET scan. It is not possible to address this specifically using the current study design; however, some of these patients were involved in a pilot study developing localization techniques for ^{19}F magnetic resonance spectroscopy and had sequential studies at 2 and 4 weeks that included an MRI scout scan. Direct comparison with the pretreatment CT scans is not valid; however, there were no significant changes in tumor size between 2 and 4 weeks on MRI in any patient.

Table 3. Overall Tumor Response for a Patient Compared With the 4-Week Ratio of Tumor to Normal Liver Activity

	≥ 15% Reduction	< 15% Reduction
PR	9	0
No response	1	3

NOTE. 100% Sensitivity; 75% specificity.

The criteria for PR using the WHO guideline[9] requires a ≥ 50% reduction in the sums of the products of the largest tumor dimension and its widest perpendicular, in the absence of a greater than 25% increase in any existing lesion or the development of a new lesion. When applying the PET results to this format, it is clear that there may be false-positive responses if the impact of any responding T:L values is greater than the impact of any nonresponding or progressing value in any one patient. However, a false-positive response in this setting may be a function of the shortcomings of the current criteria based on tumor size and that the biologic significance of a mean reduction in the activity of multiple lesions may indicate a short-term symptom advantage for the patient who may

be experiencing an overall reduction in tumor load, although at some time the nonresponding and eventually the responding areas will all progress and the patient will deteriorate.

Although the mean 4- to 5-week SUVs were significantly lower in responding lesions than in nonresponding lesions, the SUV was not as reliable as the T:L (Figs 1 and 2). This is indicative of the problems of introducing extra measurement variables when trying to establish a semiquantitative method. In one of the nonresponding patients, there was a problem calculating the exact dose administered because of extravasation of some of the FDG at the time of IV injection. Because the original dose was the only measure that could be used in the calculation and the measured count was lower because of the inadequate injection, this most likely led to an underestimate of the liver and tumor SUV. This problem did not affect the T:L because it is purely a ratio of the observed radioactivity in the two ROIs; therefore, injected activity is irrelevant. The two patients with responding tumors and an increasing SUV at 4 weeks are more difficult to explain in the absence of an injection error in the pretreatment scan. The pretreatment normal liver SUV in both of these patients was approximately 50% of the value observed at 4 weeks, suggesting that an error in the calculation of the dose administered may be affecting both liver and tumor SUV. Another possibility is that a competing organ may have, for some reason on that occasion, taken up a greater proportion of the injected FDG dose, leaving less for the liver and tumor. One of these patients was noted to have an unduly high myocardial FDG uptake (more so than any other patient studied in this series), while the other patient (among three others) had a high renal uptake. Both of these observations were present only in the pretreatment scan.

Potential confounding factors for SUV calculation were examined using linear regression analysis. From these studies, it appeared that the fasting blood sugar and the time to scanning did not have any impact on the SUV. Although plasma glucose and insulin levels do alter FDG uptake in various tissues, this is thought to be minimal in the fasting euglycemic patient.[14] When planning the timing of the scans, it was initially considered that 45 to 60 minutes from the time of FDG injection was an appropriate period for both tumor and liver FDG levels to have plateaued. This was based on data from normal brain studies (45 to 60 minutes)[15] and colorectal liver metastasis studies ($\leq$ 60 minutes based on extrapolation from published time-activity curves).[4] A subsequent study of 68 scans in 47 patients[14] suggested a good correlation ($r = .91$; $P < .0001$) between the fractional rate of tracer uptake from Patlak plots and SUVs at 60 minutes for a range of tumor types. Hamberg et al[16] recently reported the results of a study examining this issue. In eight patients with non–small-cell lung cancer, they found that the FDG SUV (or dose-uptake ratio) plateau in these tumors was not reached by 90 minutes in the majority of scans both before and after treatment. The average time to reach 95% of the plateau SUV in pretreatment scans was 298 $\pm$ 42 minutes (range, 130 to 500) and in posttreatment scans was 154 $\pm$ 31 minutes (range, 65 to 240). They calculated that because the time-activity curve is increasing more steeply in the pretreatment scans and less steeply in the posttreatment scans, probably because of a treatment-induced reduction in glycolytic rates, there will be an underestimate of the change with treatment when based on 60-minute data. The timing of scans in relation to the FDG injection needs further investigation to determine the impact on the utility of the clinical method, although it did not appear to be a major factor in this study.

One potential confounding factor, patient weight, did correlate with the SUV, although in the absence of any significant weight change during the period of study, this factor would not cause a problem when comparing serial studies in a single patient. The reason for this correlation may be twofold. First, the body distribution of (water soluble) FDG may be underestimated in heavy patients with a low ideal body mass, thus increasing the dose available to the liver and tumor relative to the measured weight and resulting in a lower SUV.[17] Second, the calibration factor used a scatter correction, which is based on measurements from a 25-cm diameter by 10-cm–long phantom. If the patient's cross-sectional dimensions are larger or smaller than the phantom used, there could be an increase in the error of the measurement. This factor is currently under further investigation.

An area in which FDG PET is relatively limited compared with CT is in the spatial resolution of small lesions. This effect also compromises the ability to study lesions that lie in close proximity to areas of high FDG activity, such as the myocardium and kidney— a problem that is not uncommon considering the proximity of these organs to the liver. However, it is noteworthy that the MUP-PET system used in this study has only modest sensitivity (2- to 3-cm lesions) and spatial resolution compared with conventional PET scanners (1- to 1.5-cm lesions).[18] The study was designed to account for the specifications of the MUP-PET camera by excluding lesions less than 3 cm and those not separable from cardiac or renal activity.

This ensured that the biologic end points were being tested without potential confounding from technical factors caused by sensitivity. The findings of the study should be interpreted in the light of the limitations of this particular PET scanner, with the knowledge that most conventional PET scanners have a superior sensitivity and spatial localization and are therefore more likely to be a feasible instrument for clinical application.

The observation that at 1 to 2 weeks some responding tumors had a significant increase in the T:L value before ultimately reducing by 4 to 5 weeks, is of considerable interest both in planning future studies and in understanding the mechanisms of tumor resolution. It has been suggested that the macrophage infiltration in tumors accounts for some of its metabolic activity.[19] Intuitively, an increased macrophage infiltration will occur with a greater tumor cell kill and may ultimately indicate a better tumor outcome. The four patients in this study who demonstrated an increase in the 1- to 2-week T:L ultimately had the lowest 4- to 5-week T:L of the group. To evaluate the prognostic significance of this early "flare" phenomenon would require a study of significantly larger size; however, it is clear from these data that there is a correlation between 4- to 5-week T:L value and tumor response, which should be prospectively validated in a specifically designed protocol.

Although the results presented in this pilot study show a correlation between tumor response and FDG activity, further definition of the applicability to this and other clinical situations is needed. For the application of this technique to the management of patients with colorectal liver metastases, it would have to demonstrate an ability to predict not just objective tumor response but overall palliative outcome and patient survival. We believe that with state-of-the-art PET scanners, this is a worthwhile area of research to pursue because of the potential savings in costs, both in terms of toxicity to the patient and in dollar terms to the health resource. Beyond evaluation of early response of colorectal liver metastases, FDG-PET has great potential for application to a variety of clinical investigational settings, including the following: early prediction of preoperative treatment response (or ultimate outcome) in patients with non–small-cell lung cancer, rectal cancer, breast cancer, or gastro-esophageal tumors; drug interaction (modulation and scheduling) studies in which the FDG activity changes can be compared with different interventions, perhaps giving indications of positive or negative synergy; phase I studies in which heavily pretreated tumors may show no objective response to a drug (however, a clearer anticancer profile could be achieved by comparing plasma drug levels to the changes in tumor FDG activity); tumor staging; and re-evaluation of residual masses. The PET methodology and the appropriate positron-emitting nuclide can also be used to conduct in vivo studies of tracer amounts of labeled drug.

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