
Studies with Positron Emission Tomography After Systemic Administration of Fluorine-18-Uracil in Patients with Liver Metastases from Colorectal Carcinoma

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Fluorouracil (FU) is the most common cytostatic agent used for chemotherapy in patients with colorectal tumors. Fifty patients with 78 hepatic metastases from colorectal tumors were examined with positron emission tomography (PET) following intravenous infusion of ^{18}F -FU. The uptake of the cytostatic agent was evaluated in normal liver parenchyma, liver metastases and the aorta. Tracer uptake was expressed with the standardized uptake value (SUV). The maximum liver activity was 11.3 SUV (mean value) with a standard deviation of 1.85 SUV. The highest activity concentrations were noted 30 min (mean value) postinjection. In comparison, the activity concentration of individual metastasis was low. Two hours after tracer injection, the mean activity in metastases was 1.3 SUV, but notable individual variation in uptake was seen. Fluorine-18 concentration values 2 hr after FU infusion were approximately 44% of the FU uptake 20 min postinfusion. Fifty-three metastases were also examined with ^{15}O -labeled water. The examination was performed to compare the uptake of the nonmetabolized tracer with FU uptake. We noted a statistically significant correlation between ^{15}O -water concentration, uptake of nonmetabolized FU 8 min after the end of the infusion and FU retention (120 min postinjection) in a subgroup of metastases. The results suggest that FU retention in different metastases is highly variable and mainly dependent on early FU uptake into tumor cells.

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The standard chemotherapeutic agent for the treatment of hepatic metastases from colorectal cancer is 5-fluorouracil (FU) (1). The metabolism of FU has been studied extensively and was recently summarized by Hull et al. (2). Kinetic data about FU have been obtained from normal tissue as well as tumors in experimental animal studies. Tissue distribution studies, which analyzed the uptake of

^{18}F -pyrimidines in different organs of AH109A tumor-bearing rats, were reported by Abe et al. (3). Shani and Wolf used an animal model to demonstrate that drug-responsive tumors have higher concentration ratios of ^{18}F -labeled FU than drug-resistant tumors (4). Although FU concentrations in the blood of humans undergoing chemotherapy have been reported (2), we are unaware of detailed data on time-dependent concentrations achieved in patients with liver metastases.

We examined patients with ^{18}F -labeled FU (12-min intravenous infusion) to obtain quantitative data on the time-activity pattern of FU and its metabolites in metastases. Data from metastases were compared against results obtained in normal liver tissue. Our primary goal was to determine maximum concentrations, time-to-maximum, 20-min (8 min after end of infusion) and 2-hr (108 min after end of infusion) tracer concentration values of FU and its metabolites. These parameters were selected because both maximum concentration and time-to-maximum are influenced by tissue metabolic activity. The 20-min values are primarily determined by intracellular uptake of nonmetabolized FU, whereas the 2-hr values were used since they are most likely to mirror the therapeutically active fraction of the infused drug.

Oxygen-15-water has been used for the measurement of regional blood flow (5,6). Herscovitch et al. used the autoradiographic technique to evaluate ^{15}O -water as a cerebral blood flow agent in an animal study (5). They showed that a linear relationship exists between true flow in a region of interest (ROI) and the tissue counts there. They emphasized that differing regional tissue counts represent relative differences in flow for the different regions of the brain. The quantitative evaluation of the perfusion in liver metastases is difficult to achieve because an accurate measurement of the input function requires blood sampling via the feeding artery. Furthermore, a model should be used that quantifies blood flow most accurately. We used an intravenous bolus injection of ^{15}O -water to assess the relative uptake of the nonmetabolized tracer in malignant lesions

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and compared the data with ^{18}F -FU kinetics in metastases. The major aim of the use of this tracer was not a quantitative evaluation of tumor perfusion, but a comparison between the uptake of a nonmetabolized and metabolized drug in order to evaluate active uptake processes.

MATERIALS AND METHODS

Fifty patients (27 female and 23 male) with liver metastases from colorectal carcinoma were studied. The standard chemotherapeutic protocol included the infusion of FU (500–1500 mg/m²/24 hr) for 5 days followed by a 3-wk interval without chemotherapy. To exclude potential effects of chemotherapy on the PET results, the patients were routinely examined with PET and ^{18}F -FU either preceding the FU therapy ($n = 20$) or at least 1 wk following the last FU application in the drug-free interval of the therapeutic cycle ($n = 30$).

All patients were referred on a routine basis. Liver metastases were diagnosed prior to referral for the PET examination. Computed tomography (CT) (Somatom DRH, Siemens Co., Erlangen, Germany) immediately preceded the PET examination and was used to identify the region of the metastasis with the greatest diameter in each patient. Only patients who had at least one metastasis identified in two contiguous CT slices (8 mm slice thickness) were included in the study, due to the limited resolution of PET and possible errors due to partial volume effects. Contrast medium was injected only when required. Skin markings were used for proper positioning during PET scanning after the image level had been determined with CT. We used identical positioning supports for both CT and PET.

A positron emission tomograph (PC2048-7WB, Scanditronix Co., Uppsala, Sweden) with two ring detectors was used for the PET examinations. The system provides for simultaneous acquisition of three slices, two primary sections (11 mm thick) and one cross section (8 mm thick). Each of the two rings (107 cm diameter) contains 512 BGO/GSO detectors (crystal size $6 \times 20 \times 30$) and provides a 52-cm field of view. The mean sensitivity for the two primary sections is 12,500 cps per $\mu\text{Ci}/\text{cm}^3$ and 17,500 cps per $\mu\text{Ci}/\text{cm}^3$ for the secondary slice. The dead time loss is 10% at 30,000 cps per slice. Spatial linearity evaluation showed that the maximum displacement from the ideal source position was less than 0.4 mm in the whole field of view. Transmission scans with more than 15 million counts per section were obtained with a rotating pin source prior to the radionuclide application in order to obtain cross sections for attenuation correction of the emission tomographic images.

Oxygen-15 was produced using the procedure described by Del Fioze et al. (7). We obtained ^{15}O -labeled water by bubbling $^{15}\text{O}_2$ through sterile physiologic saline. We injected 1184–3700 MBq ^{15}O -water prior to the ^{18}F -uracil infusion and acquired five 1-min images following radiotracer application. The last image of the series, 4–5 min after intravenous tracer injection, was used for quantitative evaluation of nonmetabolized tracer uptake in the metastases using a ROI technique.

Fluorine-18-FU was prepared by direct fluorination of uracil in acetic acid using $(^{18}\text{F})\text{F}_2$ diluted in neon (8). Quality control included HPLC. Typically, 17.5 mg ^{18}F -FU was obtained with a purity greater than 99% and a specific activity of $1.14 \cdot 10^{-5}$ Ci/ μM . Fluorine-18-FU (370–444 MBq) was given together with 500 mg unlabeled FU in a short 12-min intravenous infusion using an infusion pump (PERFUSOR segura, Braun Melsungen Co., Melsungen, Germany). Twelve 2-min images followed by seven

5-min images and six 10-min images were acquired beginning with the FU infusion for a total acquisition time of 2 hr. Appropriate skin markings were used to align the system accurately with positioning laser lights.

PET cross sections were generated using an iterative reconstruction program. The image matrix was 128×128 and interpolated to 256×256 for display in 14 patients. A larger reconstruction matrix with 256×256 image elements was used in 36 patients. The spatial resolution in a cross section was 5.1 mm using the iterative reconstruction, whereas the slice thickness was 11 mm (direct sections) and 8 mm (cross section). A 4-mm pixel was chosen for the 128×128 matrix ($n = 14$) and a 2-mm pixel was used with the 256×256 matrix in 36 patients. The transverse slices were compared to the corresponding CT images to permit secure identification of the metastasis using anatomical landmarks (e.g., upper pole of the kidney, lower part of the heart, shape of liver, spleen and gallbladder). This was followed by quantitative evaluation of the PET images using a ROI technique. ROIs were placed over the metastasis, normal liver parenchyma and the aorta. Only those metastases visible in two contiguous CT slices (8-mm thick) and identified in at least two consecutive PET slices were included in the final evaluation in order to minimize partial volume effects. The slice showing the largest metastasis diameter was used for the placement of the ROI. Because small lesions visible in only one slice were excluded from evaluation and respiration movement accounts for additional artifacts, no attempt was made to correct for partial volume effects. Time-activity data were calculated from each image series for further evaluation.

Quantitative evaluation of tracer kinetics requires the use of models. There are no accurate models available for either ^{15}O -water or ^{18}F -FU in liver metastases. The most important problem is correct measurement of the input function, which requires intra-arterial blood sampling. Therefore, we restricted quantitative evaluation to the calculation of standardized uptake values (SUV) (9):

$$\text{SUV} = \frac{\text{tissue concentration}(\text{nCi/g})}{(\text{injected dose}(\text{nCi})/\text{body weight}(\text{g}))}$$

Based on the ROIs, SUVs were calculated for each image of a FU study. The total number of counts exceeded 15 million per slice for the transmission images. The number of counts acquired for ^{18}F varied because they were dependent on tracer accumulation, organ size, attenuation and injected dose.

RESULTS

Visual inspection of early PET images may show metastases in the late phase either as defects or poorly delineated against normal liver tissue (Fig. 1). Liver parenchymal FU activity varies with time. Visual inspection proved inadequate for evaluating tracer uptake in metastases when these were viewed against background. In most of the patients, we failed to observe a clear difference in ^{18}F tumor concentrations when early and late images were compared visually.

We evaluated the normal liver tissue of 50 patients as well as 78 metastases. Furthermore, concentration values were obtained for the aorta using a ROI technique. Fluorine-18 uptake was expressed as SUVs. Time-dependent tracer concentrations are demonstrated for the aorta, nor-

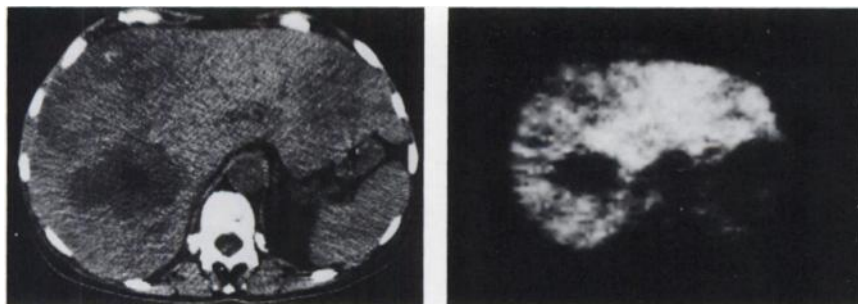


FIGURE 1. (A) CT scan of a female patient with multiple metastases in both lobes. (B) PET cross section 2 hr after intravenous FU infusion. Note the poor delineation of the metastasis in the left lobe due to tracer accumulation. Lower concentrations were observed in the other two metastases in the ventral and dorsal part of the right liver lobe. Each of the three metastases shows a different FU accumulation pattern.

mal liver parenchyma and metastases in Figure 2. The highest ^{18}F concentration for the aorta was noted 10 min after the start of the 12-min FU infusion (Fig. 2). This was followed by a rapid decrease at the end of the infusion. Maximum liver activity after infusion of the cytostatic agent was 11.3 SUV (mean value) with a standard deviation of 1.85 SUV. Time-to-maximum tracer uptake was 30 min (mean value) and ranged from 25 to 40 min after infusion began. The mean transit time was 68.2 min and the elimination half-life was 22.0 min. This is based on gamma variate curve fitting of the time-activity data from the liver parenchyma. The transit time was 83.7 min and the elimination half-life 29.9 min for liver metastases. The highest liver-to-aorta ratios were obtained 40–60 min after FU infusion (Fig. 3). The activity of individual metastases was low and relatively constant during the acquisition time after the initial distribution phase (Fig. 2). We found that the mean ^{18}F activity in metastases was one-third the concentration measured in normal liver parenchyma 120 min postinjection (Fig. 2). The metastasis-to-aorta ratios were exceeded 2.0 25–120 min after FU infusion (Fig. 3).

MRS studies have shown that FU is slowly metabolized in the tumor (10). Wolf et al. studied the kinetics of non-metabolized FU in patients with colorectal tumors and reported an elimination half-life of $1.3 \text{ hr} \pm 0.5$ (10). We

therefore used PET images 8 min after the end of the 12-min FU infusion to quantify the uptake of nonmetabolized FU into liver tissue and tumor cells. Late images, 2 hr after intravenous infusion of ^{18}F -FU, were used to estimate its therapeutically active fraction. Since the concentration of free FU in the circulation is low at this time, the evaluation of the PET images 2 hr after tracer infusion is most likely to reflect the trapped FU and/or metabolized FU. We noted a low correlation ($r = 0.64$) between the uptake of nonmetabolized FU (8 min after the end of the 12-min infusion) and late ^{18}F concentrations (120 min postinjection) in normal liver parenchyma (Fig. 4A). Fluorine-18 incorporation in metastases showed considerable variation, as seen in the differing concentration values (Fig. 4B). Cluster analysis demonstrated two groups when the 20-min and 120-min SUVs for metastases were compared (Fig. 4B). A correlation was obtained for metastases in cluster I ($n = 75$, $r = 0.89$, $p < 1\%$). The regression analysis of the 20-min and 120-min SUVs in cluster I showed that the 120-min ^{18}F concentrations were approximately 44% of the 20-min values. High early FU uptake and low late ^{18}F concentrations were noted only in three metastases which were identified by cluster II.

We were able to evaluate the uptake of nonmetabolized ^{15}O -water in 53 lesions. No significant correlation was

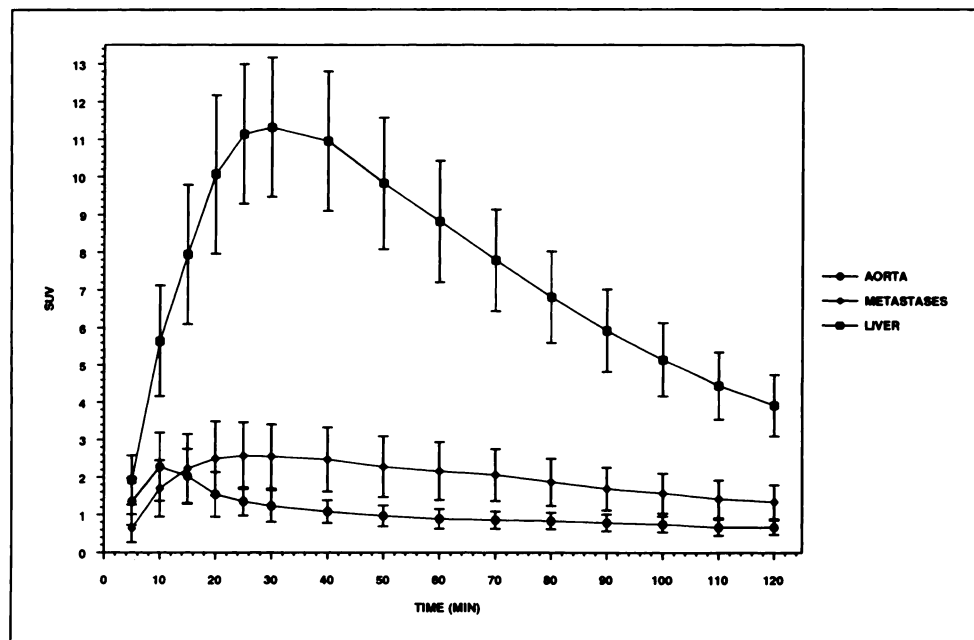
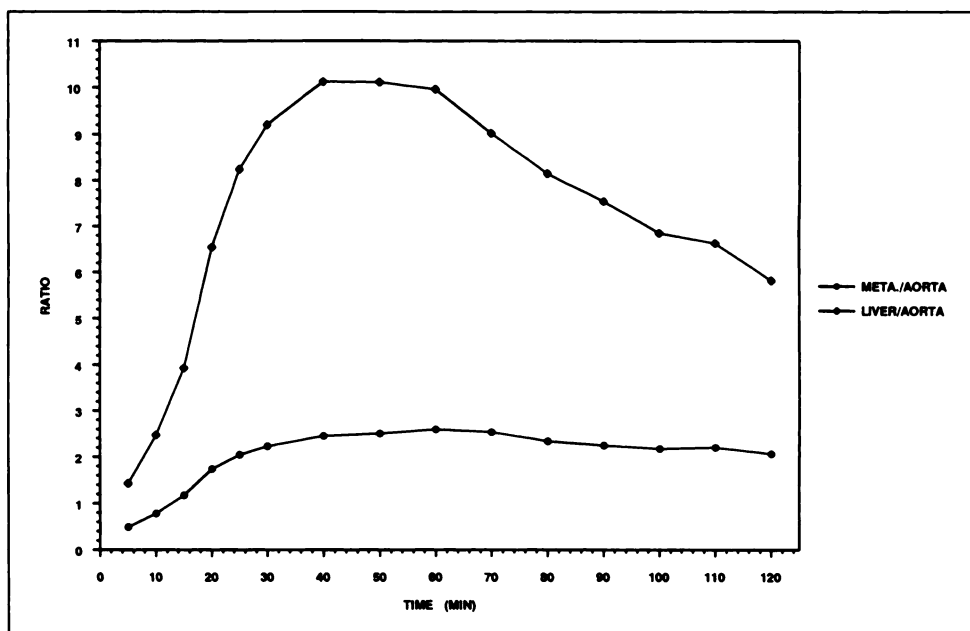


FIGURE 2. Mean ^{18}F concentrations (SUV) in normal liver parenchyma ($n = 50$), metastases ($n = 78$) and the aorta ($n = 50$) up to 2 hr after start of a 12-min FU infusion.

FIGURE 3. Liver-to-aorta and metastasis-to-aorta ratios up to 2 hr after FU infusion. The ratios were calculated from the data presented in Figure 2.



noted for ^{15}O accumulation and early FU uptake 20 min after onset of the 12-min FU infusion ($r = 0.19$, n.s., $p < 1\%$). Similar results were obtained for ^{15}O and ^{18}F concentrations 120 min after FU infusion ($r = 0.30$, n.s., $p < 1\%$). The relationship between these parameters is demonstrated in Figure 5 and two clusters were identified using the weighted average linkage method with quadratic Euclidian distances. A linear correlation ($r = 0.61$, $p < 1\%$) was noted for the data in cluster II between ^{15}O uptake values and early FU uptake concentrations, whereas no significant correlation was observed in cluster I for these parameters. In contrast, seven of ten lesions in cluster I showed uptake values exceeding 2.0 SUV 120 min after FU infusion, whereas late ^{18}F concentrations less than 2.0 SUV were measured for all lesions in cluster II. The data show that late ^{18}F concentrations (circles) are primarily determined by early FU uptake. The presence of two clusters is related to a high transport and/or low elimination of non-metabolized FU in some of the lesions.

DISCUSSION

Chemotherapy with FU has found extensive use since its introduction more than three decades ago. Depending on both the selection process and the response criteria used, the reported response rates have varied from 8% to 82% (1). Based on a literature survey, Kemeny reported that the average response rate for hepatic metastases was 23%. With individual response rates low, and population response rates highly variable, it is impossible to predict individual response rates or identify those most likely to respond to therapy. One possible approach for predicting response to FU requires radiolabeling it with ^{18}F . Fluorine-18-uracil is biochemically identical with the nonlabeled cytostatic agent FU. Therefore, PET with an ^{18}F -labeled drug gives the opportunity to determine tissue concentration of FU and its ^{18}F -labeled metabolites. Since FU uptake by a

tumor is a prerequisite for successful chemotherapy, concentration measurements of ^{18}F -uracil and metabolites in metastases may help to identify those patients who meet this first criterion of therapeutic success.

SUVs represent concentration values normalized to the injected dose and body volume. Whereas a SUV of one represents a homogenous distribution of the injected activity, accumulation of a radiolabeled tracer results in elevated SUV numbers. The mean SUV of liver metastases 2 hr after tracer injection was low (Fig. 2) and approximately one-third of the mean SUV concentration in the normal liver parenchyma. Although 41 (53%) of 78 metastases had early FU uptake values (8 min at end of the infusion) exceeding 2 SUV, late ^{18}F concentrations (120 min postinjection) higher than 2 SUV were observed only in 11 (14.1%) of the lesions (Fig. 4B). In most lesions, the high FU uptake in the early phase of the study is decreased by the efflux of FU and catabolized products out of the tumor cells. Significant differences were found when early FU uptake and late ^{18}F concentrations were compared. We were able to demonstrate a linear correlation between FU uptake values and late ^{18}F concentrations in 75 of 78 metastases (Fig. 4B). These data show that increased FU uptake in tumor cells is required in most patients to obtain high concentrations of FU that may be therapeutically effective. Although early FU uptake exceeded 6 SUV in four metastases, late ^{18}F concentrations were less than 2 SUV in three of these lesions (Fig. 4B, cluster II). This reflects a high elimination rate of FU out of the tumor cells and may represent one aspect of drug resistance.

Hull et al. found that the plasma level of FU in patients was less than $5 \mu\text{M/liter}$ 30 min after FU infusion (2). These data are comparable to our study protocol, in that 8 mg FU/kg were infused in 10 min by Hull et al., whereas we used 6.7 mg FU/kg. Chaudhuri et al. studied the degradative pathway of fluorinated pyrimidines and reported that

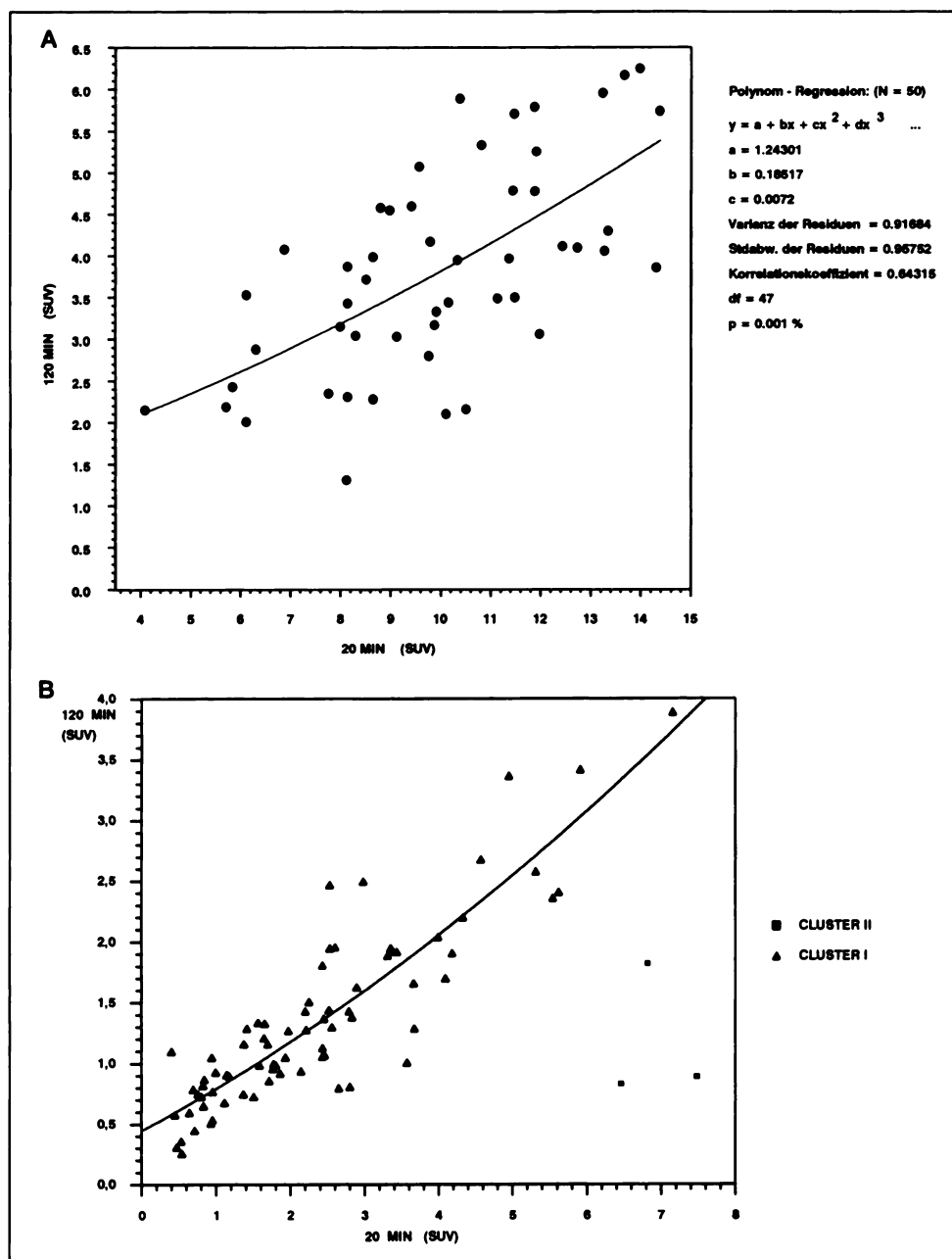


FIGURE 4. (A) Fluorine-18 concentrations ($n = 50$) in the normal liver parenchyma 20 and 120 min after onset of the 12-min FU infusion. Concentration values 8 min after the end of the FU infusion are most likely to reflect the uptake of nonmetabolized FU into the cells, whereas the late concentrations are correlated with FU retention and/or metabolites. A correlation of 0.64 was obtained for both parameters. (B) Fluorine-18 concentrations ($n = 78$) in metastases 20 and 120 min after onset of the 12-min FU infusion. Two clusters were identified using the weighted average linkage method with quadratic Euclidian distances. A correlation of 0.89 was noted for the data in cluster I ($n = 75$).

61% of the radioactivity in the tumor is represented by nonmetabolized FU even at 60 min after injection of 25 mg/kg FU in mice bearing sarcoma-180 (11). Therefore, PET images obtained 8 min after the end of the 12-min FU infusion are adequate for evaluating FU uptake in order to quantify nonmetabolized FU in tumor cells.

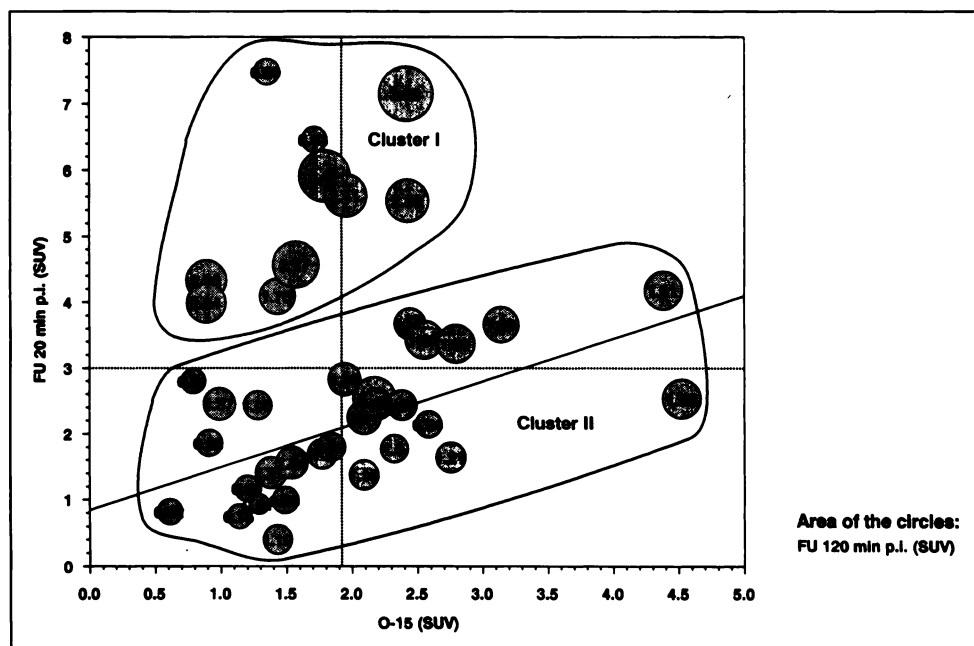
Late images obtained 2 hr after ^{18}F -uracil infusion may represent total FU metabolite concentrations and/or nonmetabolized FU. Wolf et al. studied FU kinetics up to 120 min postinjection in patients with tumors as well as in rabbits bearing VX2 tumors using ^{19}F MRS (10). The authors were able to show that there is significant trapping of nonmetabolized FU in some human tumors. The amount of trapped FU correlated with therapy outcome. These pre-

liminary data indicate that PET images 2 hr after FU infusion primarily reflect nonmetabolized FU.

No significant correlation was observed between uptake values of nonmetabolized ^{15}O -water and the 20-min and 120-min FU accumulation values (Fig. 5). Cluster analysis revealed two groups:

1. Significant correlation between ^{15}O concentration values and 20-min FU uptake values only in Cluster II (Fig. 5).
2. The highest FU concentrations 120 min postinjection were observed only for cluster I with intermediate ^{15}O concentration values (0.5–2.5 SUV) when high early FU uptake values (20 min after onset of FU infusion) were present.

FIGURE 5. Relationship between uptake of nonmetabolized ^{15}O -water, early FU uptake (8 min after the end of a 12-min FU infusion) and late ^{18}F concentrations (120 min) in 53 liver metastases. Two clusters were identified with high (>2 SUV) and low (<2 SUV) late ^{18}F concentrations. We noted a significant ($p < 1\%$) correlation coefficient ($r = 0.61$) between ^{15}O and early FU uptake only in cluster II. FU retention is mainly dependent on FU uptake.



Therefore, high systemic FU doses or regional application of a cytostatic agent to increase the local FU dose may be of limited value if early FU uptake into the cells is low. Oxygen-15-water may reflect blood volume and/or perfusion distribution in tumor tissue and provides information about “unspecific” uptake of a tracer. An increase in “unspecific” uptake, e.g., via regional infusion, may not necessarily result in high early FU uptake. Furthermore, we observed low FU retention in the presence of high early FU uptake in 3 of 78 lesions (Fig. 4B). This reflects a high efflux of FU from the metastases, resulting in low FU retention. In these patients, high dose FU therapy is not likely to improve therapy outcome. Therefore, sequential PET studies with ^{18}F -FU can be used to select those patients prior to chemotherapy.

Sequential imaging gives information about the regional kinetics of a radiopharmaceutical. The maximum liver activity of ^{18}F -FU was registered 25–40 min after the start of FU infusion. Thus, while the maximum liver activity was reached within 40 min in all 50 patients, the time-activity curves for metastases were different because they failed to show a definite maximum in most instances. Shani et al. studied FU distribution and reported a biological half-life of 0.73 hr for ^{18}F activity in the liver (12). Based on the time-activity data for the liver, we calculated a mean transit time of 68 min, a value slightly greater than the biological half-life reported by Shani. The difference may be due to the methods used to inject the tracer. Whereas Shani used a bolus injection, our data are based on examinations with an infusion technique. MRS can be used to obtain data about FU and metabolites in plasma and normal liver parenchyma (2,13,14). Hull et al. showed a monoexponential behavior of FU plasma levels at low FU doses and a shift toward biexponential behavior at high doses (2). Therefore, standard FU doses should be used for patient studies

with PET and ^{18}F -FU in order to compare ^{18}F concentration values.

An evaluation of time and ^{18}F -FU uptake in animal studies has shown that the highest ^{18}F activity was measured in various tumors 1–2 hr postinjection (15,16). Low liver activity and relatively high lesion ^{18}F uptake are sought for chemotherapy with FU in order to achieve a high probability for response. This requirement results in low contrast PET images, with respect to metastases. High liver uptake will compromise concentration measurements in metastases, especially in small lesions. Therefore, late images with the highest tumor and the lowest possible liver activity should find preferential use in patient evaluation.

It should be remembered that some fluorouracil metabolites, such as α -fluoro- β -alanine, show no significant anti-tumor activity. Therefore, the measured ^{18}F concentrations may fail to mirror the cytotoxic potency of FU metabolites. It follows that tracer uptake alone, as measured by PET, may not be predictive for therapeutic success, but therapeutic success cannot occur without uptake of the cytostatic agent. Low late ^{18}F concentration values measured in tumor tissue may indicate a low probability of success for planned or initiated chemotherapy. When high ^{18}F concentrations are noted in the tumor, the patient may have a high probability of response. Young et al. examined six patients with ^{18}F -FU (17) and was able to demonstrate that response to therapy was associated with increased ^{18}F uptake by the tumor in one patient. Four patients with low ^{18}F uptake showed no improvement, but one patient responded to polychemotherapy. Shani and Wolf attempted to predict chemotherapy response using FU distribution studies (4). Uptake of the cytostatic agent was studied in two variants of the same tumor in mice: the solid L-1210 lymphocytic leukemia tumor susceptible to FU and in a tumor line resistant to the drug. Shani obtained mean tu-

mor-to-blood ratios of 1.90 2 hr after intravenous injection of FU in the sensitive line and 0.96 in the resistant tumor. The difference was even greater 12 hr postinjection: 20.69 and 4.04 for the sensitive and resistant tumors, respectively. Wolf et al. demonstrated that response to chemotherapy is likely to correspond to FU trapping in a ^{19}F MRS study of six patients (10). These data support the hypothesis that tumor response is associated with high FU uptake, trapping and metabolism.

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