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Perfusion of Colorectal Liver Metastases and Uptake of Fluorouracil Assessed by $H_2{}^{15}O$ and [^{18}F]Uracil Positron Emission Tomography (PET)

P. Hohenberger, L.G. Strauß, B. Lehner, S. Frohmüller, A. Dimitrakopoulou and P. Schlag

Perfusion and fluorouracil (FU) accumulation were assessed using positron emission tomography (PET) with $H_2{}^{15}O$ and ^{18}FU in 36 patients with colorectal liver metastases. The tracers were injected intravenously and via the hepatic artery. Standard uptake values (SUV) were calculated using a region of interest (ROI) technique. The perfusion of non-tumorous liver tissue was similar after intravenous (i.v.) and intra-arterial (i.a.) assessment [mean of 2.67 (s = 0.61) and 2.2 (s = 0.45)]. Metastases were found to be hypoperfused compared to normal liver tissue after i.v. examinations [mean 1.73 (s = 0.77)]; i.a. injections revealed greater perfusion in metastases [mean 6.41 (s = 5.47)]. Single metastases showed up to 10 times greater perfusion with the i.a. injection route than with the i.v. one. However, lesions with no change or lower perfusion were also observed. Generally, accumulation of ^{18}FU in metastases after i.v. infusion was less than after i.a.. Correlation of i.v. perfusion and uptake was moderate ($r = 0.54$, $P = 0.0001$); i.a. correlation was only slightly better ($r = 0.61$, $P = 0.008$). Perfusion as measured by $H_2{}^{15}O$-PET does not generally predict uptake of ^{18}FU in colorectal liver metastases. To measure FU uptake using PET and ^{18}F seems to be the most accurate method. It would allow one to identify individual patients with considerably greater accumulation of ^{18}FU following i.a. administration who should profit from a cross-over to intrahepatic chemotherapy.
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INTRODUCTION

5-FLUOROURACIL (5-FU) uptake by colorectal liver metastases is of predictive value regarding response to chemotherapy [1]. Positron emission tomography (PET) with [^{18}F]uracil (^{18}FU) as a non-invasive method allows one to assess the accumulation of FU in a region of interest and thus may help to select patients for treatment and to individualise chemotherapy [2].

It is the subject of scientific controversy as to whether perfusion of colorectal liver metastases is associated with response to subsequent chemotherapy [1, 3–5]. Angiographic methods, scintiscan with Tc-99m sulphur colloid or Tc-99m macroaggregated albumin (MAA), and single photon emission computed tomography (SPECT) have been used to assess perfusion of liver lesions [1, 6–8]. These methods are limited due to colloidality of contrast media, capillary occlusion by use of MAA, or sum effects of scintiscan.

Daly *et al.* reported that capillary obstruction by microspheres resulted in an increased FUdR uptake by the tumour and subsequently resulted in improved response rate to intra-arterial chemotherapy [1, 9].

Using radiolabelled water ($H_2{}^{15}O$), PET may allow one to examine the perfusion of the liver more accurately. It provides a cross-sectional image of small regions of interest. In combination with PET using ^{18}FU, it enables one to measure perfusion and FU accumulation within a single lesion.

It was the aim of this study to investigate whether the perfusion of colorectal liver metastases would be a predictor of FU uptake and whether this influence would depend upon the route of administration.

PATIENTS AND METHODS

Patients

36 patients were entered into the study and underwent PET investigation. All patients had colorectal liver metastases proven by biopsy, either ultrasonographically guided or at laparotomy.

20 patients were examined after intravenous (i.v.) application of drugs by either a central or peripheral venous catheter.

In 16 patients intra-arterial (i.a.) examinations were performed using a catheter system (Infuse-a-port®, Infusaid Co., Norwood, Massachusetts, U.S.A.) implanted into the gastroduodenal artery for chemotherapy as described previously [10]. Postoperatively, a Tc-99m-MAA perfusion scan was performed to ensure the complete hepatic distribution of drugs instilled via the port. These patients underwent PET evaluations by the i.a. and i.v. route.

PET investigations

For assessment of perfusion 3.7 GBq of $H_2{}^{15}O$ were injected as a bolus via the hepatic arterial or i.v. catheter system. PET data acquisition consisted of five takes per min for 5 min and started 5 min after having finished i.a. injection or 10 min after having finished i.v. application. At that time an equal distribution within the blood could be expected.

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There was a minimum interval of 2 weeks between intravenous and intra-arterial examinations.

To evaluate the uptake of FU, 444 MBq radiolabelled ^{18}FU were mixed with 500 mg of 5-FU to simulate therapeutic dosages. The mixture was infused using the same application as described for the perfusion studies. Infusion time was 12 min for both routes of administration. PET data acquisition started at the beginning of the infusion for 120 min, providing 60–75 takes. Initially [0–25 min post injection (p.i.)], data acquisition time was 2 min per image, afterwards (25–60 minutes p.i.) it was 5 min, thereafter (61–120 minutes p.i.) it was 12 min.

Data acquisition was performed by a PET scanner (Scanditronix Co. PC 2048-7WB, technical details as described elsewhere [11]). We evaluated the data using a 'region of interest technique' (ROI). ROI of liver metastases were located and marked by computer tomography (CT) scan of the liver that had been performed immediately prior to the PET investigation. The size of metastatic nodules was at least 1.5 cm (detection on two CT-scan slices with 8 mm steps). The semiquantitative data on accumulation of the tracer were calculated as 'standardised uptake values' (SUV), which relates activity found in the tissue to the dose injected and the subject's mass (SUV = cmp found per g tissue : cmp injected per g subject mass). This method has been evaluated for a number of species to calculate biological tissue distributions or relative concentrations of radiotracers [12]. A SUV of 1 indicates a homogenous distribution of the tracer in the body, higher numbers represent accumulation.

Another ROI was placed within a cross-section of the aorta to check the amount of circulating ^{18}FU. In accordance with other authors, it could be shown that this concentration was negligible two hours p.i., and that there was only a small vascular component within the tissue ROI [13]. Therefore, the SUV 2 h p.i. was taken to determine the accumulation of ^{18}FU in liver tissue and metastases.

Statistical methods

Means, standard deviations, medians and ranges for perfusion and uptake values were calculated.

The relationship between arterial and venous perfusion and accumulation of ^{18}FU was examined by calculating respective correlations (Spearman's rank correlation coefficient (r) [14]), and probabilities for correlation (P values) were estimated. All statistical calculations were performed with the SAS statistics package (Jubelsoft) on an IBM main frame computer at the German Cancer Research Center.

RESULTS

Perfusion of non-tumorous liver tissue

Perfusion values of liver tissue not affected by tumour were similar after i.v. and i.a. assessment. Mean SUV for i.v. measurements (n = 56) was 2.67 (s = 0.61) with a median of 2.62 (range 1.52–3.86). Intra-arterial examination (n = 22) resulted in a mean SUV of 2.2 (s = 0.45) with a median of 2.12 (range 1.31–2.86), as shown in Fig. 1.

Perfusion of metastases after i.v. application of $H_2{}^{15}O$ (Fig. 1)

Sixty metastases were examined. Perfusion measurements resulted in a mean value of 1.73 SUV (s = 0.77), the median value was 1.66 (range 0.22–3.62). Thus, colorectal liver metastases were hypoperfused compared to normal liver tissue.

Perfusion of metastases after i.a. application (Fig. 1)

Twenty-three metastases were investigated after i.a. injection of $H_2{}^{15}O$. Mean perfusion was 6.41 SUV (s = 5.47), the median value was 4.65 (range 0.8–22.9). Compared with i.v. measurements, after i.a. injection, perfusion of metastases is generally 3–4 times greater. Compared to non-tumorous liver tissue examined i.a., mean perfusion of metastases was three times greater.

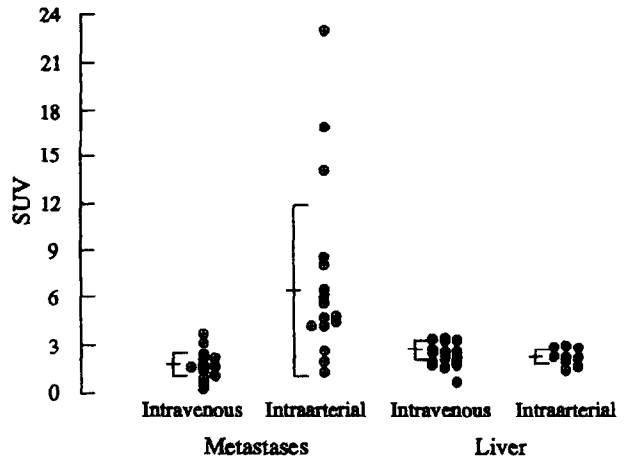

Fig. 1. Perfusion of normal liver tissue and colorectal metastases after i.v. and i.a. application of $H_2{}^{15}O$; mean values and standard deviation are given.

Comparison of the perfusion of metastases after i.v. and i.a. examinations (Fig. 2)

In 22 metastases the perfusion could be determined after i.v. and i.a. application of $H_2{}^{15}O$. There was only a weak correlation between i.v. and i.a. perfusion of metastases (r = 0.26, P = 0.27, F = 9.37, df = 20). While individual metastatic lesions showed a perfusion up to 10 times greater on the i.a. pathway when compared with i.v. injection, other lesions showed no difference or even lower arterial perfusion values (Fig. 2).

Comparison of perfusion and ^{18}FU accumulation on i.v. route (Fig. 3)

The mean ^{18}FU accumulation after i.v. infusion was 1.36 SUV (s = 0.76); the median was calculated as 1.15 (range 0.37–3.5). The degree of correlation was rather low, but statistically significant with r = 0.54 (P = 0.0001, F = 15.5, df = 56).

Five metastases showed ^{18}FU accumulation of 2.5 SUV or

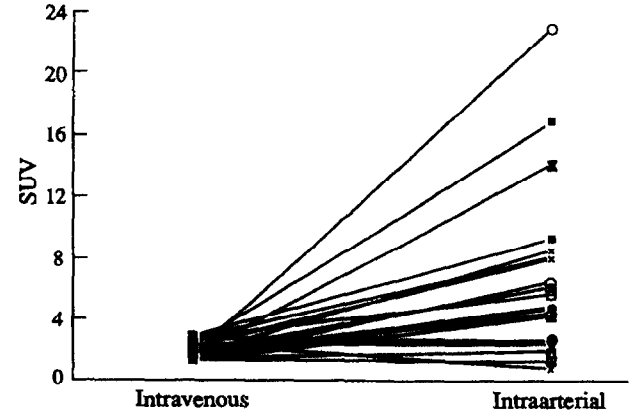

Fig. 2. Corresponding uptake values of perfusion in metastases after i.v. and i.a. administration.

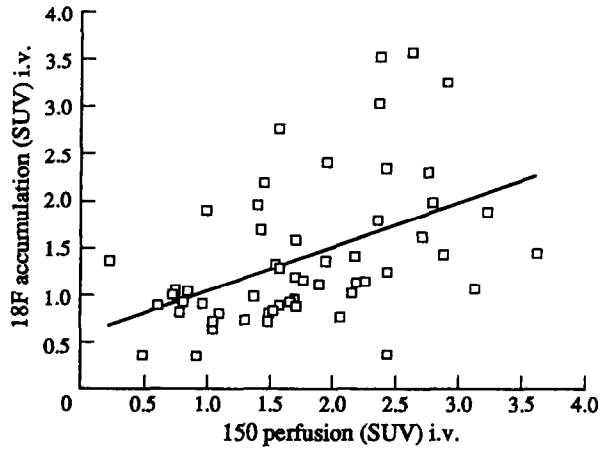

Fig. 3. Correlation of perfusion and [^{18}F]uracil accumulation in colorectal liver metastases after i.v. administration (r = 0.54, P = 0.0001).

more and four out of these had perfusion values exceeding the mean + s ranging from 2.4 to 3.0. Looking at 10 metastases with a perfusion of 2.5 (x + s) or more, six had ^{18}F accumulation values of less than 2.0, ranging from 1.1 to 1.95.

Comparison of perfusion and ^{18}FU accumulation on i.a. route (Fig. 4)

Though the perfusion of metastases was much greater (factor 3–4) with i.a. injection, the accumulation of ^{18}FU showed only a tendency towards a greater uptake. The mean was 1.76 (s = 1.13), and the median 1.29 (range 0.54–5.03). Again, the relationship between perfusion and accumulation showed a moderate but statistically significant correlation (r = 0.61, P = 0.008, F = 12.2, df = 21).

Six metastases showed increased accumulation of an ^{18}FU of 2.5 SUV or more, and four out of these lesions had perfusion values of 8 or more. However, one metastasis was measured with an ^{18}FU concentration of 3.4 based on a perfusion index of 0.81 only. Looking at metastases with a perfusion of 7.2 or more (SUV of double the maximum of i.v. measurements) three out of six lesions showed ^{18}FU accumulations of 2.5 or more.

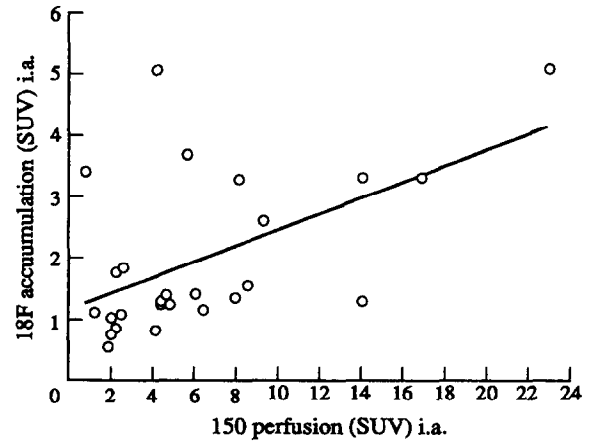

Fig. 4. Correlation of perfusion and [^{18}F]uracil accumulation in colorectal liver metastases after intra-arterial administration (r = 0.61, P = 0.008).

DISCUSSION

Chemotherapeutic treatment of colorectal liver metastases is unsatisfactory due to the lack of active substances. Response rates reported for 5-FU are low [15]; for 5-FU/leucovorin higher response rates are reported but no survival advantage could be demonstrated after a longer follow-up period [16]. For intra-arterial 5-FU or FUdR therapy response rates are reported to reach 60%. However, no survival benefit could be proven in randomised trials [17, 18]. Some patients may profit from crossing-over from i.v. to i.a. treatment in case of progression without extrahepatic disease [19].

Prerequesites for cytotoxic activity of fluoropyrimidines are: transport to the tumour, uptake of the drug, accumulation, and metabolism to anabolites [20]. Several attempts have been made to investigate these different steps required for response.

Kim *et al.* examined the vascularity of colorectal hepatic metastases by contrast angiography. They reported that tumours with good perfusion had improved prognosis after intra-arterial chemotherapy and hepatic artery ligation [3]. Kaplan *et al.* [4] used radionuclide angiography with Tc-99m-MAA and were able to predict the response in 10 out of 11 patients with good nuclide flow. Later, Daly reported an excellent prognostic significance of Tc-99m-MAA scans to predict response to intra-arterial FUdR treatment [1]. 16 out of 31 patients expected to have high uptake of FUdR due to good perfusion of their metastases subsequently responded to treatment. In another 15 patients with low FUdR uptake 1 patient only developed tumour remission. The result was highly significant with a P-value of 0.006, sensitivity and specificity were calculated to be 91% and 77%, respectively.

However, Lehner *et al.* pointed out that neither by angiogram nor by MAA-scintiscan was it possible to discriminate responders from non-responders prior to treatment. There was no correlation between tumour vascularity and response to 5-FU or survival [5]. Angiography is of limited value in the assessment of liver metastases perfusion, because the colloidality of contrast media does not allow examination of the microcirculation at the border of the metastatic lesion, where the main nutritional blood flow is located. The MAA-scintiscan, however, is based on the occlusion of the capillary bed and assesses the sum of Tc-99m activity over the whole liver in planar scans. Advantageously, PET using $H_2{}^{15}O$ represents perfusion and distribution of the body water, which might correspond better with the blood perfusion (since blood contains 60% water). ^{18}F and ^{15}O are positron emitting isotopes; their biological behaviour is equivalent to that of ^{19}F and ^{16}O [21, 22]. PET enables one to determine relative tissue concentration of labelled metabolites in a cross-sectional image analogous to CT scans [22]. This allows measurement of the perfusion and accumulation of ^{18}FU within the same region of interest. Prior to our investigations, [^{13}N]glutamate and ^{81}Kr had been used to assess the perfusion of liver lesions. However, the extremely short half-life of ^{81}Kr did not allow measurement of the arterial perfusion [23]. PET with [^{13}N]glutamate gave improved perfusion measurements of individual liver lesions in contrast to Tc-99m-MAA, but due to the large blood pool of glutamine, measurements of amino acid uptake by liver cells were not possible [24].

Our investigations demonstrated that the liver shows twice the perfusion rate of the whole body with SUV ranging from 2.2 to 2.6. There is no significant difference in perfusion after i.v. and i.a. assessment. In i.v. examinations, liver metastases of colorectal cancer seem almost always to be less perfused in i.v. examinations than surrounding normal liver tissue. This is in

accordance with the results of contrast angiography and scintiscan [3–5]. However, $H_2{}^{15}O$ given i.a. showed a very high perfusion, which in some metastases reached up to 10 times the i.v. values. Similar results are reported by CT-scan examinations with contrast media given i.a. [25]. Additionally, PET scans provide perfusion values that allow one to quantify and compare data after different routes of administration and in different regions of interest. This seems to be advantageous compared to judgements of "hypo-", "iso-", and "hyperperfusion" resulting from conventional methods.

The mechanism why perfusion of metastases should work as a prognostic factor for response to chemotherapy is due to the fact that it should predict uptake of cytostatic drugs, not only fluoropyrimidines [1], but also cisplatinum and others [26]. On the other hand, few studies compare the perfusion and the uptake of cytostatic drugs by tumour tissues at different routes of administration with the response to chemotherapy [1, 27].

In resection specimens of colorectal liver metastases it could be shown that the metastases:liver ratio of accumulated FUdR significantly correlated with the perfusion of the metastases [9]. The ratio, however, ranged from 0.09 to 1.1 and was much lower than in our determinations using PET. It has to be considered that the tissue concentrations of FUdR were determined by the use of microspheres and immediately after the end of the infusion [9]. Therefore, the drug accumulation might have been determined prior to the optimum time which is reported to be about 90 min p.i. [13, 28].

Sigurdsson *et al.* intraoperatively administered FUdR together with Tc-99m-MAA via the hepatic artery and the portal vein. They did not find significant differences between FUdR levels in normal liver tissue. However, after intra-arterial injection, the mean tumour drug levels were 10–15 times higher than after injection into the portal vein. Interestingly, the drug levels of FUdR correlated with tumour blood flow; drug levels and perfusion measured by MAA correlated well for the i.a. route ($r = 0.86$), but only weakly for application via the portal vein ($r = 0.58$). No examinations after systemic injection were reported. The authors described a heterogeneity of perfusion and subsequent uptake of FUdR despite homogenous gross appearance of liver perfusion scans [29].

Finan *et al.* examined tissue concentrations of fluorinated products in specimens obtained surgically after 5-FU bolus injections 48 h prior to the operation. They were not able to correlate concentrations in plasma, normal and metastatic tissue and concluded that levels of 5-FU are due to cellular activity rather than due to the handling of the drug [27].

In our examinations the correlation between perfusion and accumulation of ^{18}FU after i.v. injection was poor ($r = 0.54$); these data are comparable to those of the intraportal route reported by others [29]. However, after i.a. injection the degree of correlation in our patients was moderate only ($r = 0.61$) which is in disagreement with the data mentioned above [29]. But our data are in accordance to clinical observations that intrahepatic 5-FU chemotherapy is not generally superior to the i.v. route, as could be shown in randomised trials [17, 18].

No general advantage of the i.a. route of administration could be demonstrated by PET examination. This is due to the fact that an improved perfusion does not always result in increased uptake of the drug. A perfusion of SUV of 14 goes with an ^{18}FU in the range of 1 to 3 and a ^{18}FU-SUV of 3–5 may be reached at perfusion SUV ranging from 1 to 22. Therefore manipulation of tumour perfusion alone may not be advantageous for the patient.

However, PET examinations allow measurement of the perfusion and the accumulation of ^{18}FU within regions of interest, and may thus help to identify patients who have a significantly improved activity of ^{18}FU with the i.a. application. These patients might profit from a cross-over to intrahepatic chemotherapy in case of progression under systemic treatment. PET to examine the uptake of 5-FU is accurate only when measuring the accumulation of ^{18}FU directly. To determine the tumour perfusion in order to get information on FU uptake results in data with low prognostic significance. ^{18}FU PET will be very helpful in individualising chemotherapy and in avoiding implantation of intrahepatic catheter systems to patients in whom a response to treatment cannot be expected.

Also, it has to be considered that PET detects all intratumoral ^{18}F containing metabolites, and that it is not possible to distinguish between cytotoxic anabolites, non-metabolised 5-FU, or inactivated catabolites. Furthermore, it has still to be determined to what extent perfusion is necessary for uptake of drugs and to what extent uptake is necessary for metabolism of 5-FU to cytotoxic anabolites [30]. PET examinations will be of value in answering these questions during the planning and observation of treatment effects.

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An Evaluation of Photodynamic Therapy in the Management of Cutaneous Metastases of Breast Cancer

Seema A. Khan, Thomas J. Dougherty and Thomas S. Mang

A series of 37 patients with cutaneous metastases of breast carcinoma were treated with photodynamic therapy (PDT) to the chest wall; decreasing doses of photofrin II and increasing light doses were used in order to test drug/light dose reciprocity and determine the lowest effective dose of photofrin II. 5 patients (13.5%) achieved a complete response, 13 (35.1%) demonstrated partial responses and 19 (51.4%) showed no benefit. The extent and type of recurrent disease were strong determinants of the likelihood of response. Minimal and nodular disease responded well to PDT (5/5 complete responses); partial responses were seen in 11/20 (55%) of patients with disease of moderate extent. No patient with extensive erythema derived any benefit (0/5), and only 2/12 (17%) patients with advanced nodularity showed a partial response. Reductions in photofrin dose to 0.75 mg/kg with reciprocal increases in light dose to 182 J/cm^2 did not impair treatment efficacy.
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INTRODUCTION

LOCALLY RECURRENT breast cancer may range in extent from completely asymptomatic skin nodularity to a debilitating encuirasse lesion. Photodynamic therapy (PDT) has emerged as a new form of locally cytotoxic treatment which may have some utility in the local control of this problem. The principle underlying PDT involves excitation of tissue-bound photosensitiser by light, resulting in the production of singlet oxygen, with subsequent cell death [1]. The photosensitiser being used in clinical trials today is photofrin, a purified form of the original hematopophyrin derivative, which consists of about 80% of the porphyrin oligomers selectively retained by tumours [2, 3]. Photofrin is injected intravenously and is retained in malignant tissue and many normal tissues, including skin. It has been shown that there is at least three times more porphyrin in neoplastic skin lesions than in surrounding normal skin [4, 5].

In addition to the photodynamic effect, another property of

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