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Hepatic arterial infusion chemotherapy for unresectable confined liver metastases: prediction of systemic toxicity with the application of a scintigraphic and pharmacokinetic approach

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Abstract *Purpose*: The incorrect positioning of the arterial Port-a-Cath or the presence of anatomic or functional hepatic arteriovenous shunting may explain the occurrence of systemic toxicity of hepatic arterial infusion of floxuridine in patients with liver metastases. The aim of our study was to predict the occurrence of systemic toxic effects from this treatment using a scintigraphic and pharmacokinetic approach. *Methods*: A group of 26 patients were studied. Before treatment, Tc-99m-labelled macroaggregated albumin arterial perfusion scintigraphy was performed to verify the correct positioning of the catheter, to evaluate the percentage of pulmonary uptake of the tracer, reflecting intrahepatic arteriovenous anatomic shunting, and to qualitatively assess the perfusion pattern of the metastases with respect to the normal liver parenchyma (SPECT images). Hepatic arteriovenous functional shunting was assessed through the bioavailability of intraarterially administered D-sorbitol. Treatment was then started and systemic toxic effects were evaluated according to WHO recommendations. *Results*: No correlation was found between anatomic shunting (≤10% in all patients) and systemic toxicity of treatment. The 9 patients with hypoperfused metastases experienced a significantly lower level of toxic effects (1 low-grade toxicity and 8 no toxicity) than the 17 with hyperperfused metastases (6 high-grade toxicity, 5 low-grade and 6 no toxicity; $\chi^2 = 7.170$, $P = 0.028$). Functional shunting was significantly different in patients with high-grade, low-grade and no toxicity (46.5 ± 19.9%, 15.8 ± 12.7% and 16.5 ± 10.3%, respectively; $P < 0.001$ by analysis of variance). Moreover, functional shunting was significantly greater only in patients with hyperperfused metastases who developed high-grade toxicity. *Conclusions*: A protocol combining scintigraphic and pharmacokinetic methods is of value in the individual patient in assessing the risk of high-grade systemic toxicity during hepatic arterial infusion of floxuridine. A flow-chart used in our ongoing prospective study for the evaluation of patients undergoing regional chemotherapy for liver metastases is included.

Key words Perfusion imaging · Regional chemotherapy · Secondary liver neoplasms · Sorbitol · Systemic toxicity

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Introduction

Hepatic arterial infusion (HAI) chemotherapy with floxuridine (FUDR) has recently been reevaluated for the treatment of confined unresectable liver metastases owing to the higher responses which can be achieved using this kind of therapy compared with conventional systemic chemotherapy [2, 17, 18, 19, 22], and to the availability of a minimally invasive procedure for placing a hepatic arterial Port-a-Cath [31, 32, 33]. Moreover, the pharmacokinetics of FUDR administration show that direct infusion of the chemotherapeutic agent into the hepatic artery should be the best way to avoid or minimize adverse systemic toxic effects, since negligible amounts of the drug would be expected to reach the systemic circulation [6, 8, 9, 10, 27, 28]. Nonetheless, in some patients, the occurrence of high, and in some instances life-threatening, gastrointestinal toxicity during HAI chemotherapy requires the permanent or temporary withdrawal of the treatment.

To explain the occurrence of toxic effects of HAI chemotherapy [7, 15, 20], previous studies have focused

on the presence of a newly formed arterial network in case of liver metastases [1, 5, 21], and on the subsequent formation of hepatic arteriovenous shunting. Hepatic arteriovenous shunting can be quantified by a nuclear technique, using technetium-99m-labelled macroaggregated albumin (Tc-99m-MAA) injected into the catheter [15], which provides an "anatomical" view of possible drug escape, or by using a safe molecule having similar kinetic features to FUDR, which provides a "functional" view of possible drug escape.

Our study was therefore aimed at evaluating the ability of an anatomical approach (Tc-99m-MAA arterial perfusion scintigraphy) [4, 13, 30] and a functional approach (the bioavailability of intraarterially administered D-sorbitol) to predict the occurrence of systemic toxicity of HAI chemotherapy with FUDR. We also tried to determine the possible additional contribution to clinical evaluation of the application of both approaches in the individual patient.

Patients and methods

Patients

The study group comprised 26 consecutive noncirrhotic patients (14 males, 12 females; mean age 58 years, range 32–82 years), submitted for implantation of an arterial Port-a-Cath for regional chemotherapy of liver metastases, of whom 20 had liver metastases from colorectal carcinoma, 2 from breast carcinoma, 2 from gastric carcinoma, 1 from pancreatic carcinoma and 1 from esophageal carcinoma. None of them had extrahepatic metastases or major alterations of liver function. For each patient a contrast-enhanced computed tomography (CT) scan of the liver was performed before implantation of the arterial catheter.

The arterial Port-a-Cath was placed in the hepatic artery using a minimally invasive approach via transaxillary access [32, 33], with the embolization of the gastroduodenal artery performed to avoid misperfusion. The correct positioning of the catheter was achieved with the aid of a contrast agent by noting the diffusion of the agent to all sections of the liver.

All patients gave their informed consent to the study, which was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Methods

Before the beginning of regional chemotherapy all patients were first evaluated by Tc-99m-MAA arterial perfusion scintigraphy. Then, 2 to 4 days later, the bioavailability of intraarterially administered D-sorbitol was determined in each patient.

Tc-99m-MAA arterial perfusion scintigraphy

Perfusion scintigraphy with intraarterial infusion of Tc-99m-MAA (20–50 μm diameter; 37 MBq), was performed in two consecutive steps. In the first step, with the patient in a supine position under a gamma camera, the catheter was gently flushed by the operator with 10 to 20 ml isotonic saline and then 37 MBq (1 mCi) of Tc-99m-MAA in 2 ml saline was slowly injected manually through the gripper (Hüber needle) of the catheter. The catheter was then again flushed slowly with 10 to 20 ml isotonic saline. In the second step, images were acquired with a two-head gamma camera (VARICAM ELSCINT) with a high resolution collimator and the acquisition window set at 140 keV. The study was accomplished with two total-body scans acquired in the anterior and posterior projections (1024×256 matrix).

Pulmonary uptake of Tc-99m-MAA, an index of "anatomic" intrahepatic arteriovenous shunt rate (AIHAVS), was calculated as follows:

$$\mathrm{AIHAVS} = \frac{\sqrt{\text{total counts in lung in anterior projection}}}{\sqrt{\text{total counts in the body in anterior projection}}} \times \frac{\sqrt{\text{total counts in lung in posterior projection}}}{\sqrt{\text{total counts in the body in posterior projection}}} \times 100$$

Once the correct positioning of the Port-a-Cath had been verified by planar imaging (distribution of Tc-99m-MAA to liver parenchyma only), all patients were submitted to single photon emission computed tomography (SPECT) of the liver anatomical area. SPECT and CT imaging were then independently compared by three nuclear physicians in order to qualitatively determine the distribution pattern of Tc-99m-MAA in liver metastases with respect to normal liver parenchyma [12]. In this way patients were classified into two subgroups: those in whom MAA was mainly distributed to the metastases (hyperperfused metastases) and those in whom MAA was mainly distributed to normal liver parenchyma (hypoperfused metastases).

Bioavailability of intraarterially administered D-sorbitol

Each patient was evaluated on two consecutive days and the tests were performed during fasting and bed rest. On the first day, after collection of a basal blood sample, a pyrogen-free 1.5% solution of D-sorbitol in water was directly administered into the hepatic artery through the Port-a-Cath, using a peristaltic infusion pump, at a constant rate of 60 ml/h for 3 h, in order to reach a steady-state condition. Just before the end of the infusion, blood was collected from a brachial vein. On the second day, a basal blood sample was collected and a pyrogen-free 3% solution of D-sorbitol in water was administered via a peripheral vein using an infusion pump at a constant rate of 60 ml/h for 3 h. Just before the end of the infusion, blood was taken from the contralateral arm.

The concentration of D-sorbitol in each blood sample was determined using an enzymatic spectrophotometric method [3] by an automated procedure on a clinical chemistry multiparametric autoanalyzer (HITACHI 911, Boehringer Mannheim, Germany). The original method of the commercial kit for D-sorbitol determination (code 670057, Boehringer Mannheim, Germany) was modified according to the features of the autoanalyzer, as follows: serum samples were deproteinized by centrifugation on Microcon-30 Amicon and reconstitution of the reagents was adapted to the autodispenser of the instrumentation [11].

Net steady-state D-sorbitol concentrations in peripheral blood after intraarterial (C_{ia}) and intravenous (C_{iv}) infusions were calculated by subtracting the respective basal concentration from the concentration in the sample taken at the end of the infusion. Arterial bioavailability of D-sorbitol (the percentage of D-sorbitol directly administered into the hepatic artery that reached the systemic circulation, an index used to evaluate functional arteriovenous shunting), indicated as B, was calculated as follows:

$$B = \frac{C_{ia} \times D_{iv}}{C_{iv} \times D_{ia}} \times 100$$

where D_{ia} and D_{iv} are the doses of D-sorbitol intraarterially and intravenously infused, respectively.

The day after this functional evaluation patients started intraarterial regional chemotherapy, following the schedule [16, 19] FUDR 0.3 mg/kg per day + dexamethasone 2 mg/day + leucovorin 15 mg/m^2 per day (as a continuous 24-h infusion through the Port-a-Cath device) for 14 days, repeated four times, every 21–28 days. Systemic toxicity of this treatment was evaluated in accordance with the WHO recommendations for grading of acute and subacute toxic effects of chemotherapy [29].

At the end of the four cycles of HAI chemotherapy, all patients were resubmitted to contrast-enhanced CT of the liver to evaluate the response: "responders" were those patients in whom CT imaging revealed no changes (NC) or more than 50% reduction of liver metastases (PR) or complete regression of disease (CR) and "nonresponders" those in whom progression of the disease (PD) was documented.

During the treatment 12 of the patients studied (46%) developed toxicity, six high-grade toxicity (one bleeding gastric ulcer and five grade III diarrhea) and six low-grade toxicity (four antral gastritis, one grade I diarrhea and one grade I mucositis). The remaining 14 patients (54%) did not develop any toxicity. The evaluated parameters are shown in Table 1.

Results

In the studied patients the percentage of pulmonary uptake of Tc-99m-MAA injected into the Port-a-Cath (an index of AIHAVS) ranged from 1% to 10% (3.6 ± 2.4% mean ± SD), and no correlation was found between the value of pulmonary uptake and the toxic effects of the treatment. Indeed, as shown in Table 2, AIHAVS (mean ± SD) in patients who developed high-grade, low-grade and no toxicity, was 3.75 ± 3.06%, 4.25 ± 2.59% and 3.26 ± 2.13%, respectively ($P = 0.706$ by analysis of variance).

On the basis of the distribution pattern of Tc-99m-MAA to liver metastases with respect to normal liver parenchyma, we identified 9 patients (with hypoperfused metastases) in whom MAA was mainly distributed to normal liver parenchyma and 17 patients (with hyperperfused metastases) in whom MAA was mainly distributed to the metastases. Table 3 shows that none of the patients with hypoperfused metastases developed high-grade toxicity, only one patient developed low-grade toxicity (one of nine, 12%) and eight patients (eight of nine, 88%) did not develop toxicity. In contrast, six patients with hyperperfused metastases developed high-grade toxicity (6 of 17, 35%), five developed low-grade toxicity (5 of 17, 29%), and six did not develop toxicity (6 of 17, 35%; $\chi^2 = 7.170$, $P = 0.028$). No significant differences concerning Tc-99m-MAA distribution pattern were found between responders and nonresponders ($\chi^2 = 0.058$, $P = 0.81$; Table 4).

In the patients studied, bioavailability of intraarterially administered D-sorbitol varied widely, ranging from 4% to 72% (23.3 ± 18.3% mean ± SD). In relation to the systemic toxicity of the treatment, the bioavailability of D-sorbitol (mean ± SD) was 46.5 ± 19.9%, 15.8 ± 12.7% and 16.5 ± 10.3%, respectively, in those experiencing high-grade, low-grade and no toxicity ($P < 0.001$ by analysis of variance). Statistical analysis using the Student-Newman-Keuls' test showed significant differences between patients who developed high-grade toxicity and other groups, whereas no significant differences were found between patients developing low-grade and no toxicity (Table 2).

Table 5 shows the values of bioavailability of D-sorbitol in patients with hyperperfused and hypoperfused liver metastases grouped according to systemic toxicity of treatment. Finally, no correlation was found

Table 1 Evaluated parameters in the studied patients (*AIHAVS* "anatomic" intrahepatic arteriovenous shunt, *hyper* hyperperfused metastases, *hypo* hypoperfused metastases, *NC* no change, *PD* progression of disease, *PR* partial response, *CR* complete response)

Patient no.	Sex	Age (years)	Primary	AIHAVS (%)	D-sorbitol bioavailability (%)	Tc-99m-MAA distribution pattern	Toxicity	Response
1	M	60	Colon	2.5	67	Hyper	Diarrhea III	NC
2	F	57	Colon	2.5	20	Hyper	None	PD
3	F	59	Colon	2.5	26	Hyper	Diarrhea III	NC
4	F	75	Colon	2.5	72	Hyper	Bleeding ulcer	PD
5	M	43	Colon	2.5	46	Hyper	None	PR
6	F	69	Esophagus	2.5	14	Hypo	Diarrhea I	PR
7	M	59	Colon	2.5	18	Hypo	None	PR
8	F	48	Colon	2.5	10	Hypo	None	PD
9	M	66	Pancreas	7.5	17	Hyper	Mucositis II	PD
10	M	61	Colon	10.0	51	Hyper	Diarrhea III	PD
11	F	32	Colon	7.5	5	Hyper	Antral gastritis	CR
12	F	62	Breast	2.5	8	Hypo	None	NC
13	F	45	Breast	2.5	13	Hyper	Antral gastritis	PR
14	M	46	Colon	7.5	10	Hyper	None	PR
15	F	58	Colon	2.5	24	Hypo	None	PR
16	M	61	Colon	2.5	34	Hyper	Diarrhea III	PR
17	M	59	Colon	2.5	29	Hyper	Diarrhea III	NC
18	F	82	Stomach	2.5	4	Hyper	None	PD
19	M	66	Stomach	1.5	16	Hyper	None	PD
20	M	58	Colon	3.7	40	Hyper	Antral gastritis	NC
21	M	70	Colon	1.0	21	Hypo	None	NC
22	F	70	Colon	1.8	6	Hyper	Antral gastritis	PR
23	M	63	Colon	4.1	13	Hypo	None	NC
24	F	40	Colon	8.5	20	Hypo	None	PR
25	M	57	Colon	2.4	10	Hypo	None	PD
26	M	52	Colon	3.1	11	Hyper	None	NC

Table 2 AIHAVS and bioavailability of D-sorbitol in patients who developed high-grade, low-grade and no toxicity. Values are mean ± SD

Toxicity	*n*	AIHAVS (%)	D-sorbitol bioavailability (%)
High grade	6	3.75 ± 3.06	46.5 ± 19.9*
Low grade	6	4.25 ± 2.59	15.8 ± 12.7
None	14	3.26 ± 2.13	16.5 ± 10.3
P-value[a]		0.706	< 0.001

* $P < 0.05$ vs low toxicity and vs none; Student-Newman-Keuls' test

[a] By analysis of variance

Table 3 Relationship between Tc-99m-MAA distribution pattern and systemic toxicity of HAI chemotherapy (*hyper* hyperperfused metastases, *hypo* hypoperfused metastases)

Systemic toxicity	Tc-99m-MAA distribution pattern		
	Hyper	Hypo	Total
High grade	6	0	6
Low grade	5	1	6
None	6	8	14
Total	17	9	26

$\chi^2 = 7.170$; $P = 0.028$

Table 4 Relationship between Tc-99m-MAA distribution pattern and response to regional chemotherapy (*hyper* hyperperfused metastases, *hypo* hypoperfused metastases)

	Tc-99m-MAA distribution pattern		
	Hyper	Hypo	Total
Responders	11	7	18
Nonresponders	6	2	8
Total	17	9	26

$\chi^2 = 0.058$; $P = 0.810$

Table 5 Bioavailability of D-sorbitol in patients with hyperperfused (*hyper*) and hypoperfused (*hypo*) liver metastases, grouped according to systemic toxicity of treatment. Values are mean ± SD

Systemic toxicity	Hyper		Hypo	
	n	D-sorbitol bioavailability (%)	*n*	D-sorbitol bioavailability (%)
High grade	6	46.5 ± 19.8	0	–
Low grade	5	16.2 ± 14.2	1	14
None	6	17.8 ± 14.8	8	15.5 ± 6.0

Table 6 Bioavailability of D-sorbitol in responders and nonresponders. Values are mean ± SD

	n	D-sorbitol bioavailability (%)
Responders	18	21.1 ± 16.5
Nonresponders	8	28.1 ± 22.2

$P = 0.378$, Student's *t*-test

between the response to therapy and the bioavailability of D-sorbitol (Table 6). Indeed the bioavailability of D-sorbitol (mean ± SD) was 21.1 ± 16.5% in responders (18 patients) and 28.1 ± 22.2% in the nonresponders (8 patients) ($t = -0.898$; $P = 0.378$, Student's *t*-test).

Discussion

The rationale for HAI of FUDR in the treatment of patients with unresectable confined liver metastases is based on the fact that liver metastases are mainly perfused by arterial vessels [1, 5, 21] so that high concentrations of drug can be achieved in tumor tissue, and on the very high hepatic extraction of FUDR that results in very low concentrations of drug at extrahepatic sites [6, 9, 10, 28]. Systemic toxicity of this kind of treatment is thus likely due to extrahepatic misperfusion or to the partial escape of the drug from first-pass liver extraction. Reasons for this can be incorrect positioning of the tip of the catheter or the presence of neoplastic tissue associated with arterial intrahepatic vascular alterations that prevent hepatic extraction of FUDR.

The correct positioning of the intraarterial catheter can be verified using the nuclear technique. In accordance with previously reported data [4, 12, 13, 14, 30], we evaluated the correct positioning of the Port-a-Cath by slow injection of 37 MBq of Tc-99m-MAA through the catheter. These tracer particles range from 20 to 50 μm in diameter and are held in the first arteriolar-capillary bed encountered. When nuclear planar imaging showed distribution of the tracer to the liver area only, without evidence of other abdominal structures, the catheter was judged as well positioned and the therapy was started.

With the possibility of misperfusion excluded, the toxic effects of the chemotherapy have to be the result of escape of drug from liver extraction. This escape can be explained by either the presence of AIHAVS with leakage of the drug from the vicinity of the tumor to the systemic circulation or the presence of neoplastic cells unable to extract FUDR as efficiently as hepatocytes, combined with a distribution pattern of arterial blood flow in the liver leading to a functional arteriovenous shunting (i.e. patients with arterial blood flow mainly distributed to liver parenchyma rather than to metastases and vice versa).

The evaluation of Tc-99m-MAA pulmonary uptake showed an AIHAVS (mean ± SD) of 3.6 ± 2.4% (range 1–10%) and no correlation was found between the value of pulmonary uptake and the toxic effects of the treatment (Table 2). However, in our patients, the low levels of pulmonary uptake (maximum 10%) and the lack of correlation between AIHAVS and toxicity indicate that systemic toxicity of regional chemotherapy with FUDR is probably not due to AIHAVS.

Therefore the shunt effect to which FUDR is subjected can be affected by the perfusion pattern of liver metastases [28]. Comparing contrast-enhanced CT scanning of the liver with SPECT imaging enabled the

perfusion pattern of neoplastic nodules to be qualitatively evaluated. In the case of hypoperfused liver metastases, the drug will be mainly distributed to normal liver parenchyma rather than to neoplastic tissue, so that its hepatic extraction will be higher, and its expected systemic toxic effects lower. As expected, the percentage of patients who did not develop systemic toxicity was significantly greater amongst those with hypoperfused liver metastases than amongst those with hyperperfused tumors. Specifically, in the group with hypoperfused liver metastases there were no cases of high-grade toxicity and the only patient who developed toxicity, experienced a grade I diarrhea (compared with six patients who developed high-grade toxicity and five patients who developed low-grade toxicity in the group with hyperperfused liver metastases). These results are shown in Table 3.

To indirectly evaluate the functional escape of FUDR, we used the determination of the bioavailability of intraarterially administered D-sorbitol. The use of D-sorbitol in the assessment of hepatic vascular alteration and functional liver plasma flow in liver diseases is well established [23, 24, 25, 26]. D-sorbitol is a safe, natural compound, and is easy to measure in blood samples. Its first-pass hepatic extraction is almost complete and, when a steady-state infusion technique is employed, it shows first-order elimination kinetics over a wide range of doses. In other words, liver blood flow is the main limiting factor for D-sorbitol extraction. That is, when D-sorbitol is administered intraarterially, the greater the proportion of the D-sorbitol dose that does not reach functioning hepatocytes, the greater is its systemic bioavailability. As previously described by Ensminger et al. [10], the kinetic features of FUDR are quite similar to those of D-sorbitol. It is extracted by hepatocytes more efficiently than by tumor cells and, in normal liver parenchyma, its hepatic extraction is almost complete in one pass. Indeed, when patients were grouped according to the systemic toxicity of the treatment, those who developed high-grade toxicity had a bioavailability of D-sorbitol significantly greater than those who developed low-grade or no toxicity (Table 2). It is worth noting that the bioavailability of D-sorbitol was significantly greater only in patients with hyperperfused metastases who developed high-grade systemic toxicity (Table 5). This finding explains the importance of the determination of the percentage of escape of D-sorbitol in the prediction of the occurrence of severe toxic effects in patients with hyperperfused metastases.

In conclusion, our results show that in patients with liver metastases who undergo the implantation of a hepatic arterial Port-a-Cath for HAI of FUDR, both nuclear and pharmacokinetic approaches previously described can be of value in predicting the occurrence of systemic toxicity from the therapy. A further study is ongoing to evaluate the efficacy of a combined scintigraphic and pharmacokinetic protocol (Fig. 1) in avoiding high-grade systemic toxic effects of this therapy. Once the correct positioning of the Port-a-Cath has been verified by Tc-99m-MAA arterial perfusion scintigraphy, SPECT imaging is performed. Patients with hypoperfused liver metastases receive a standard treatment schedule. In patients with hyperperfused liver metastases the bioavailability of intraarterially administered D-sorbitol is determined, and the dose of FUDR is adapted to the D-sorbitol bioavailability in order to avoid high-grade systemic toxicity while maintaining the dose-intensity.

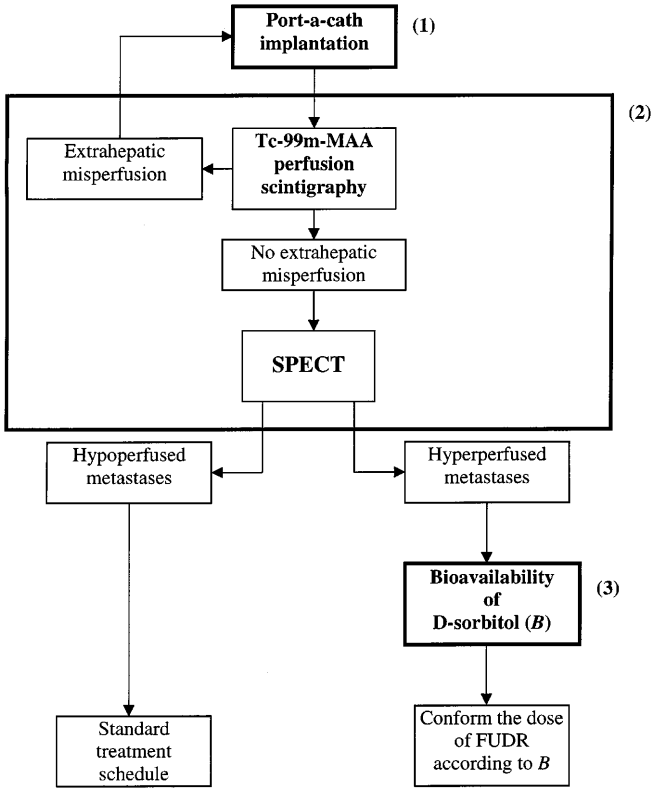

Fig. 1 Flow chart used in our ongoing prospective study for the evaluation of patients undergoing HAI chemotherapy with FUDR for unresectable confined liver metastases. After the implantation of the Port-a-Cath (1), Tc-99m-MAA perfusion scintigraphy is performed and, if the catheter is found to be positioning correctly, a SPECT image of the liver anatomical area is acquired during the same session without additional tracer injection (2). In the case of hyperperfused liver metastases, the bioavailability (*B*) of intraarterially administered D-sorbitol is determined (3) and the dose of FUDR is adjusted accordingly

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