

**Immuno-chemoembolization in the treatment of  
disseminated colorectal liver metastases  
– comparison between two treatment  
schedules**

**Presented by Herwart Müller, Vlastimil Valek**

**Department of oncologic surgery,  
Carl von Hess – Hospital, Hammelburg, Germany**

**Dept. of radiology,  
Masaryk University, Brno, Czech Republic**

Correspondence to :

Dr. Herwart Müller  
Dept. of surgical oncology  
Carl von Hess – hospital  
97762 Hammelburg / Germany  
e-mail : H.Mueller@Klinik-Hammelburg.de

## **Abstract**

**Introduction:** Regional chemotherapy, delivered via the hepatic artery, may significantly increase tumour response rates in patients with colorectal liver metastases. However, survival is limited by extra hepatic disease progression. In order to achieve high local response rates and also inhibit extra hepatic tumour progression we have developed a novel therapeutic approach for patients with metastases confined to the liver called immuno-chemoembolization.

**Material and method:** In a prospective, comparative, but not randomised trial 103 patients with inoperable, disseminated colorectal liver metastases were treated by two different regimen of immuno-chemoembolization. Group A : intraarterial circadian administered 5-FU infusion 1400 mg/m<sup>2</sup> plus iv. Leucovorin 100 mg/m<sup>2</sup> plus GM-CSF 150 µg (day 1+2) combined with chemoembolization with 23 mg/m<sup>2</sup> Melphalan plus Lipiodol and Gel-foam (day 3). Group B: short time ia. infusion of 5-FU 550 mg/m<sup>2</sup> (day 1-4) plus GM-CSF 150 µg (day 1+2) combined with chemoembolization with 23 mg/m<sup>2</sup> Melphalan plus Lipiodol and Gel-foam (day 3). Most of these patients have had prior systemic chemotherapy (59/103).

**Results:** 103 pts. (62 male/ 41 female) with a medium age of 59,9 and a medium KI of 88.5 were treated with 447 cycles of immuno-chemoembolisation ( Group A 299, Group B 148 cycles). Side effects did occur in all patients, mainly consisting of upper abdominal pain lasting for 1-4 days and vomiting grad 1 or 2. Systemic side effects were mild and transient with a very low rate of leucocytopenia. Due to the use of chemoembolization with Lipiodol response criteria had to be changed in comparison to WHO criteria leading to the following responses in Group A: CR 6%, PR 45%, MR 18%, SD 18%, NR 13% and Group B CR 3%, PR 37%, MR 19%, SD 27%, NR 16% corresponding to a remission rate of 51 % vs. 40%. Time to progression was 8 months in both groups and median survival has not been reached after 27 months in group A and 17 months in Group B. (p = 0.0095). Interestingly there was no statistical significant difference between chemo naive patients and patients treated with prior systemic therapy.

**Conclusion:** Immuno-chemoembolization combined with two-day circadian application of 5-FU is an effective tool in the treatment of disseminated colorectal liver metastases. Response rate and survival are very encouraging and should be confirmed in randomised trials. This treatment schedule is very effective as second-line therapy in this tumour entity.

## ***Introduction***

Colorectal cancer is one of the most common forms of cancer in developed countries. A recent report of mortality from cancer in the European Union between 1955 and 1994 showed that mortality rates from intestine cancer is about 15 per 100.000 for women, and 19 per 100.000 for men (1). Liver is the most frequent site of metastasis. At the time of diagnosis, 20 % of the patients have synchronous liver metastases (2,3), and 25 – 30 % of patients with initially localised tumours will develop liver metastases in the three following years (4). Moreover, metastases defined to the liver are a frequent situation, since two thirds of the patients with liver metastases have no evidence of extra-hepatic disease (3).

Surgery is the only curative treatment of colorectal liver metastases, providing a five-year survival rate between 25 and 45 % (5,6). However, curative surgical resection of liver metastases is possible in less than 20 % of all cases with colorectal cancer (6,7).

In patients with colorectal liver metastases hepatic tumour burden, performance status and site of primary tumour are regarded as important prognostic factors (8,9). In the past 20 years standard first-line chemotherapy regimens have been based on fluoropyrimidines, but tumour response rates with bolus intravenous 5-fluorouracil (5-FU) alone are only about 10 % and reported median survival rarely exceed one year (10). Several experimental approaches have been developed to increase the efficacy of fluoropyrimidines, including the biomodulation of 5-FU by Leucovorin or Methotrexat and the administration of 5FU by continuous intravenous infusion (11,12,13). During last years several new drugs have shown potent efficacy against colorectal carcinoma such as Oxaliplatin, Irinotecan or Ralitrexate (14,15,16).

An effective alternative can be the administration of chemotherapeutic agents via hepatic artery. The rationale for hepatic arterial infusion is that the liver has a dual blood supply. Established hepatic metastases derive their blood supply largely from the hepatic artery, whereas normal liver cells derive most of their blood supply from the portal vein (17). Infusion of chemotherapy directly into hepatic artery thus exposes the metastases to high drug concentrations, while sparing normal liver tissue. Most chemotherapeutic drugs have steep dose – response curves such that increased response rates are achieved with higher dose regimens. Attempts to increase systemic doses of 5-FU, however, have led to unacceptable toxicity.

Prospective, randomised trials for patients with unresectable liver metastases have reported response rates ranging from 42 to 62 % in the groups given arterial infusion, as compared with rates of 10 to 21 % in the groups treated with systemic chemotherapy (18-23).

**Table 1: Randomised trials of regional vs. systemic chemotherapy for colorectal liver metastases**

Reference	Year	No.pts.	Response %		med. Survival		p-value
			Systemic	Regional	Systemic	Regional	
Grage	1979	61	23	34	13	10	n.s.
Kemeny	1987	162	20	50	12	17	n.s.
Chang	1987	64	17	62	15	22	n.s.
Hohn	1989	143	10	42	16	17	n.s.
Martin	1990	69	21	48	11	13	n.s.
Rougier	1992	163	9	43	11	15	0.03
Allen-Mersh	'94	100	-	-	8	15	0.03

This study was undertaken to test the feasibility and antitumour activity of two different intra-arterial regimens dealing with regional immuno-chemotherapy. These schedules consist three different steps of therapy:

- Intra-arterial infusion of 5-Fluorouracil in two different application forms with or without intravenous infusion of Leucovorin
- The intra-arterial infusion of Granulocyte-Macrophage-Colony-Stimulating-Factor (GM-CSF)
- Chemoembolization of the hepatic artery with Melphalan as cytostatic drug and Lipiodol plus Gelfoam as embolizing substances

Levi et al. has shown the efficacy, of chronomodulated application of 5-FU leading to an increase in response rate combined with a reduction in rate of side effects (24,25). The possible reduction in side effects combined with this special infusion form gives way for the combination with other cytostatic drugs and application forms. Here it seems sensible for the use of chemoembolization - an application form, which has a low rate of systemic side effects with respect to bone marrow depression and dysfunction of gastrointestinal tract (26,27).

Introducing a vascular occlusion agent combined with cytostatic drugs into hepatic artery, which results in a dual ischemic and cytotoxic insult in the tumour infiltrated area, performs chemoembolization. In addition to that, vascular occlusion results in the prolongation of transit time through the vascular bed of the tumour, with increasing exposure time between the chemotherapy and the tumour cells.

Baxevanis et al. could improve immunologic parameters in patients treated with second-line chemotherapy for gastrointestinal tumours by using a systemic application of GM-CSF (28). In our study we used GM-CSF intraarterially in order to mobilise intrahepatic immunocells like dendritic cells or natural killer cells and to improve immunologic parameters as well.

In this study we wanted to show the feasibility and efficacy of these regimens in the treatment of inoperable, disseminated colorectal liver metastases. Study endpoints were response rate and overall survival.

## **Methods**

All patients had histological confirmed colorectal adenocarcinoma with unresectable liver metastases. All patients were required to give informed consent. Adequate performance status (Karnofsky – index > 50) and haematological (granulocyte count > 2000 / $\mu$ l, platelet count > 100.000 / $\mu$ l), hepatic (bilirubin < 3.0 mg/dl) and renal (creatinin < 2.0 mg/dl) function without other concomitant, active medical illness was required to enter the study. Patients received a minimum of two treatments with treatment free interval of 4 weeks.

Prior treatment, celiac and in most cases mesenteric angiography was performed to define vascular anatomy and confirm portal vein patency. With a selective catheter via the celiac axis the proper hepatic artery was intubated. In some cases a micro catheter was advanced coaxial into the right or left hepatic artery.

After correct placement of this catheter GM-CSF was applied over 60 minutes in a dosage of 150  $\mu$ g on day 1 and 2 for both therapeutic regimen. Thereafter a circadian infusion of 5-FU with an infusion time of 24 hours in Group A (day 1 + 2) or a short time infusion of 1 hour in Group B (day 1-4) was started. In addition Leucovorin was given intravenously in a dosage of 100 mg / m<sup>2</sup> in Group A.

On the last day of therapy the chemoembolization was carried out after control of correct catheter position. Chemoembolization regimen consisted of 5 ml of contrast medium mixed with 5 ml Lipiodol plus 40 mg Melphalan. After injection a small amount of Gel-foam was applied in order to cause a temporary occlusion of arterial blood flow. At the day of chemoembolization all patients were pre-hydrated with 2000 ml Ringer-solution and were treated with a sufficient amount of painkillers as well as sedatives. Laboratory workup, including a complete blood count and chemistry measurement, were obtained on the first and third day after treatment as well as weekly after hospital discharge.

### **Three-day schedule - Group A**

Day 1	GM-CSF 150 µg. 5-Fluorouracil 2500 mg 100 mg Leucovorin iv.	ia. ia.	over 60 min. over 24 hours circadian applied over 60 min.
Day 2	GM-CSF 150 µg. 5-Fluorouracil 2500 mg application 100 mg Leucovorin iv.	ia. ia.	over 60 min. over 24 hours circadian over 60 min.
Day 3	40 mg melphalan plus 5 ml Lipiodol plus Gel-foam as microembolization		

### **Five day schedule – Group B**

Day 1	GM-CSF 150 µg. 5-Fluorouracil 1000 mg	ia. ia.	over 60 min. over 60 min.
Day 2	GM-CSF 150 µg. 5-Fluorouracil 1000 mg	ia. ia.	over 60 min. over 60 min.
Day 3	5-Fluorouracil 1000 mg	ia.	over 60 min.
Day 4	5-Fluorouracil 1000 mg	ia.	over 60 min.
Day 5	40 mg melphalan plus 5 ml Lipiodol plus Gel-foam as microembolization		

Responses were assessed by radiological evaluation with computer tomography and by measurement of tumor markers, if positive. Complete Response (CR) was defined as the complete disappearance of all tumour signs combined with normalization in tumour-markers. A radiological Partial response (PR) was measured as a decrease in the lesion density in at least 75 % of the lesion consistent with necrosis or a 25 % decrease in size of the lesions without development of concomitant lesions. A tumour-marker response was measured by a 50 % or greater decrease from baseline value.

## **Results**

All 103 patients included in this study had progressive disease and disseminated not operable liver metastases. 62 of these patients were male and 41 female with medium age of 59,9 years. All patients fulfilled entrance criteria of this study and medium Karnofsky – index was 88.5 ranging between 50 and 100 (median 90). 59 of these patients had been treated previously by some kind of systemic therapy as an adjuvant therapy after primary large bowel resection or for therapy of liver metastases.

**Table 2: therapeutic schedules in patients treated with systemic chemotherapy previously (59 pts.)**

<b>Prior systemic therapy</b>	<b>Pts.</b>
5-Fluorouracil, folinic acid	38
5-Fluorouracil, folinic acid, Dexamethason	2
5-Fluorouracil, Levamisol	5
Regional Chemotherapy	4
5-Fluorouracil, Adriamycin, Mitomycin	1
Ardalan- scheme	5
Mitomycin, 5-FU, Bendamustin	1
5-Fluorouracil, Tomudex	1
5-Fluorouracil, Mitomycin	1
5-Fluorouracil, Oxaliplatin	1

**Table 3 : Systemic side-effects in group A 66 pts, 299 cycles**

<b>WHO -</b>	<b>grad 1</b>	<b>grad 2</b>	<b>grad 3</b>	<b>grad 4</b>
Bilirubin	5,7 %	0,7 %	-	-
Alk. phosphatase	20,1 %	12,7 %	2,7 %	0,3 %
GOT	19,0 %	15,7 %	8,0 %	7,7 %
Anemia	12,7 %	3,7 %	1,0 %	0,3 %
Leucocytopenia	3,0 %	0,7 %	-	0,7 %
thrombocytopenia	0,3 %	-	0,3 %	0,3 %
Creatinin	0,3 %	-	-	-
Fever	21,0 %	18,7 %	-	-
Vomiting	12,0 %	28,1 %	1,7 %	-
Pain	9,0 %	14,7 %	-	-
Cardiac insufficiency	-	-	0,7 %	-
Allergy	-	1,3 %	2,0 %	-
Diarrhoea	0,3 %	1,0 %	-	-
Consciousness	-	0,3 %	-	-
Lung function	-	-	-	-
Obstipation	-	-	-	-
Thrombosis	-	0,3 %	1,0 %	-

**Table 4: Systemic side effects in group B 37 patients, 148 cycles**

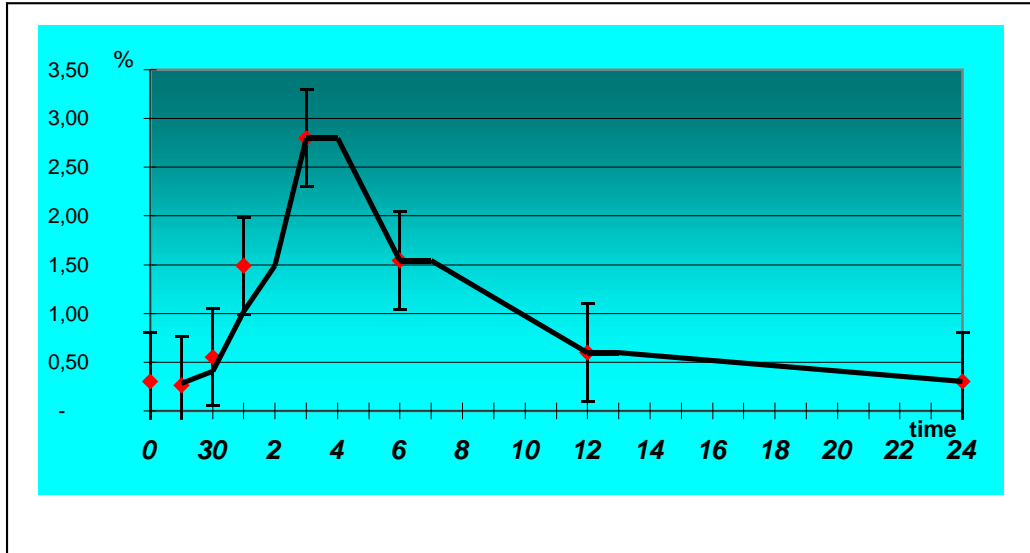
<b>WHO -</b>	<b>grad 1</b>	<b>grad 2</b>	<b>grad 3</b>	<b>grad 4</b>
Bilirubin	8,1 %	1,4 %	-	0,7 %
Alk. phosphatase	26,4 %	9,5 %	0,7 %	1,4 %
GOT	21,6 %	20,9 %	8,8 %	4,7 %
Anemia	14,2 %	8,8 %	-	-
Leucocytopenia	-	-	-	-
Thrombocytopenia	-	0,7 %	-	-
Creatinin	-	-	-	-
Fever	16,9 %	27,7 %	-	-
Vomiting	2,7 %	25 %	-	-
Pain	8,1 %	9,5 %	-	-
Cardiac insufficiency	-	-	-	-
Allergy	-	1,4 %	0,7 %	-
Diarrhoea	0,7 %	1,4 %	0,7 %	-
Consciousness	-	-	-	-
Lung function	-	-	-	0,7 %
Obstipation	-	-	-	0,7 %
Thrombosis	0,7 %	1,4 %	-	-

447 cycles of immuno-chemoembolization have been done in these 103 patients (medium 4.34 cycles) with 299 cycles in 66 pts. in group A (medium 4,53 cycles ) and 148 cycles in 37 pts. in group B (medium 4,0 cycles). Side effects did occur in most of the patients, mainly consisting of upper abdominal pain lasting for 1 –4 days, as well as fever and vomiting. Other systemic side effects were rare and transient not exceeding WHO grad 2. Especially there was a negligible rate of bone marrow depression in both groups of patients.

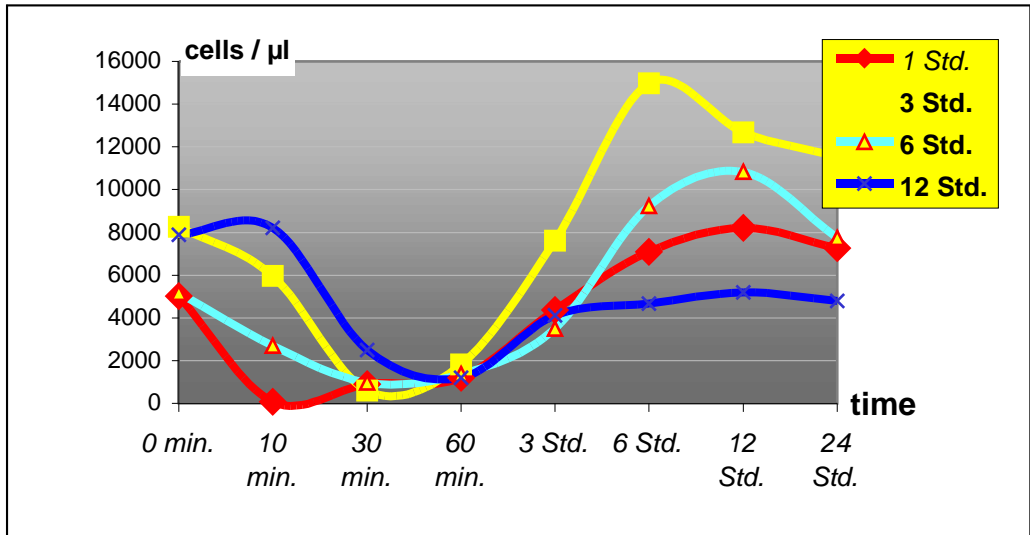
An elevation in liver enzymes especially alkaline phosphatase and glutamat-oxalat-transferase (GOT) has to be stated in both treatment groups. In a few cases special therapy dependent side effects like gastroduodenal ulceration (6) or cholecystitis (5) had to be stated. There were also a few cases with catheter related complications like a partial thrombosis of hepatic artery (7) and one case with severe cardiotoxicity. All these complications could be treated conservatively.

Comparing the rate of side effects for both treatment groups no difference in rate of side effects or the profile was noted. Both regimens are combined with an acceptable rate of side effects, but an effective anti-emetic regimen is necessary.

In 10 patients we have measured dendritic cells in peripheral blood using a monoclonal antibody against CD 84+ cells (Fig.1). There was a steep increase in value of this cell fraction starting during GM-CSF infusion with a peak concentration after 3 hours. The value of dendritic cells has been normalised 24 hours later. Measuring count of neutrophil granulocytes there were severe changes after infusion of 150 µg GM-CSF (Fig. 2). These changes were dependent to the infusion time of GM-CSF.



**Fig.1 Value of dendritic cells (CD 84+) in peripheral blood caused by GM-CSF infusion 150  $\mu$ g given over 60 minutes**



**Fig. 2 Value of neutrophil granulocytes in peripheral blood during GM-CSF infusion 150  $\mu$ g given over 1,3,6 and 12 hours**

Using the above mentioned response criteria, which are different to WHO-criteria we have seen the following response rates:

Response	Group A 66 pts.	Group B 37 pts.
Complete	4 6 %	1 3 %
Partial	30 45 %	14 37 %
Minor	12 18 %	7 19 %
Stable disease	12 18 %	9 25 %
Progression	8 13 %	6 16 %

Table 5: Response rates

Overall remission rate was 51 % in Group A and 40 % in Group B. Actual median observation time is 39 months lasting from 5 to 53 months. Time to progression was 8 months and median survival has not been reached after 27 months in Group A and 17 months in Group B. This difference was statistically significant at a p-value of 0.0095 (Wilcoxon-test).

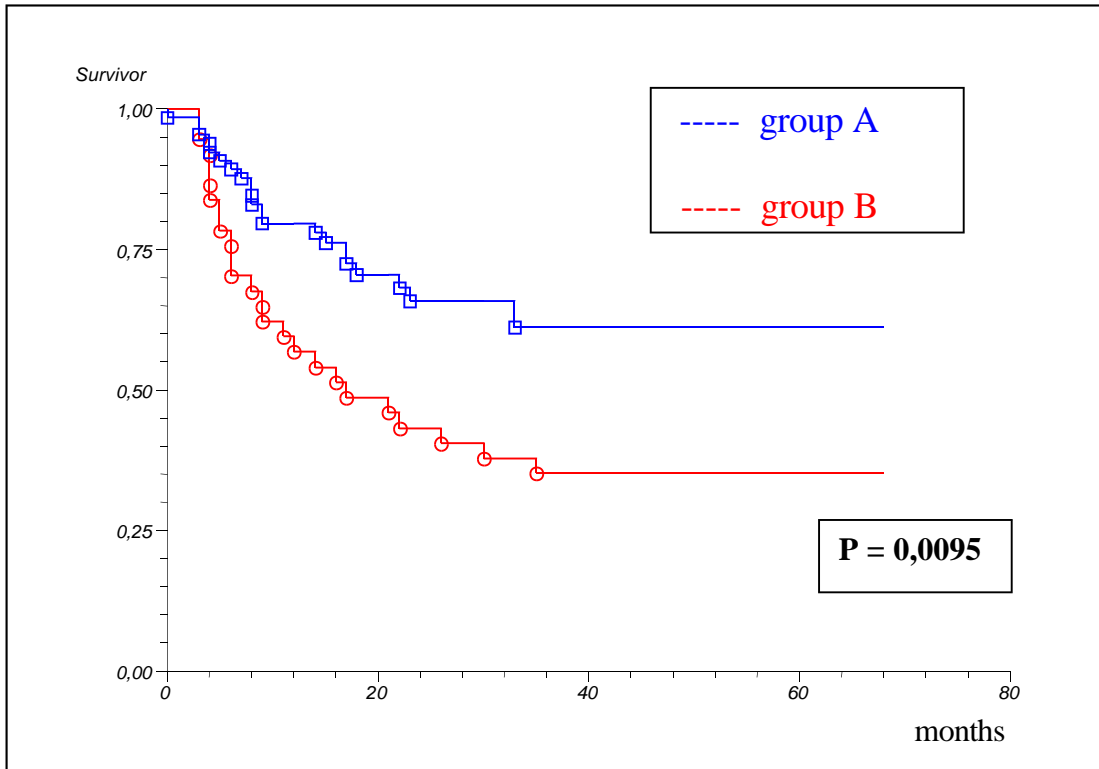


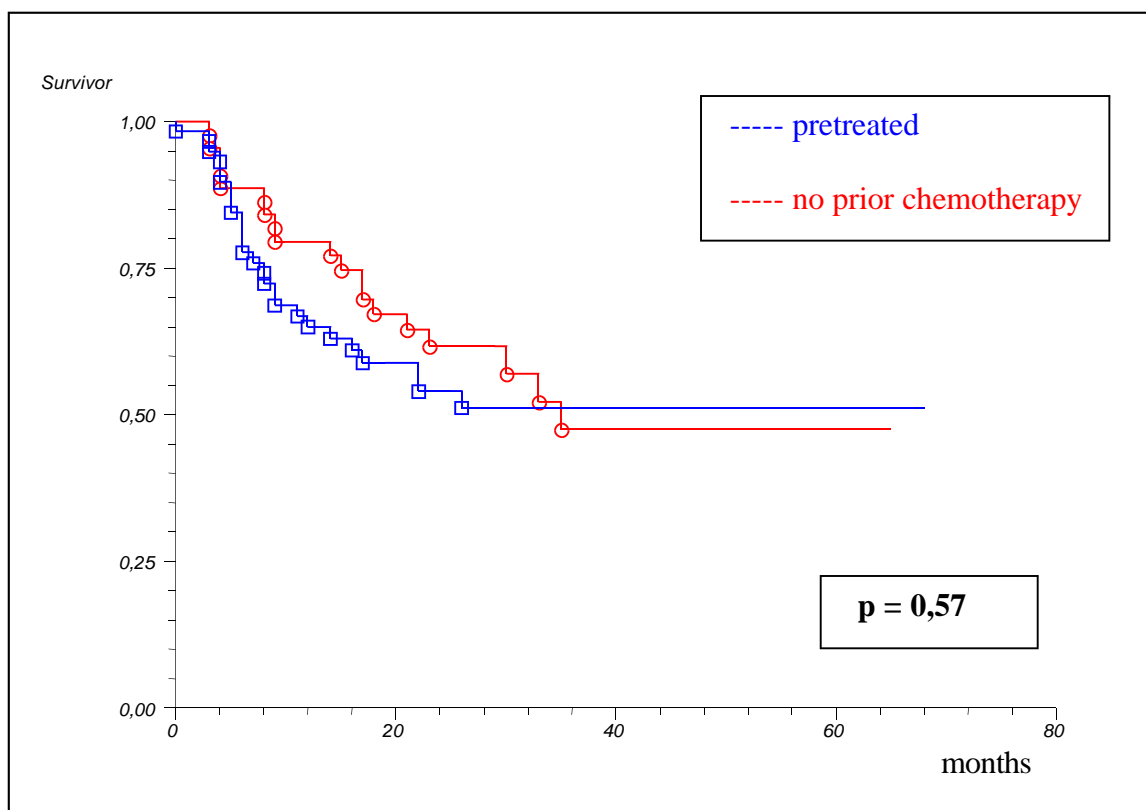
Fig. 3 Kaplan – Meier – curve of 103 patients treated with two different therapeutic regimen

Looking for determinants of outcome we have searched for the effect of pain status and general condition at study entry as well as the positive or negative influence of prior systemic chemotherapy.

According to Edmonton staging system 83/103 patients did not have any kind of pain from their tumour disease at study entry. 12 patients were in stage I and in stage II. 7 patients had severe pain treatable only by morphine derivates (29). Median survival was 14 months only for the group of patients with any kind of pain. Median survival time has not been reached after 25 months for the group of patients without any tumour related pain. This difference was marginal statistically significant at a p-value of 0.083.

According to Karnofsky staging system 37/103 patients have had an Index of 100, 30 KI 90, 23 KI 80, 11 KI 70 and one a KI 60 and KI 50 each. Comparing survival rate of patients in good general condition with a KI of 80 – 100 with patients in reduced condition there was a dramatic difference with 9 months in the latter group and more than 23 months in the other group. Due to the small number of patients this difference was not statistically significant. ( p-value 0.62, Wilcoxon-test)

59 of these patients had been treated previously by some kind of systemic therapy as an adjuvant therapy after primary large bowel resection or for therapy of liver metastases. Interestingly there was no statistical difference in median survival time for the pre-treated group of patients (59 pts, more than 24 months) and the group without prior therapy (44 pts, 35 months). (Wilcoxon-test, p-value 0.57 ).



**Fig.4 Kaplan – Meier – curve of all patients dependent to prior systemic chemotherapy (chemo naive 44 pts. pre-treated 59 pts.)**

## **Discussion**

Although colorectal carcinoma is potentially curable in approximately 70 % of patients, it remains a therapeutic challenge because as many as 33 % of patients who undergo radical surgery and almost 50 % of patients overall will die of metastatic disease (30). Sixty percent of patients with metastatic colorectal cancer develop liver metastases during the course of their disease; in half of these patients the liver is the only or predominant site of involvement (31,32).

Hepatic arterial chemotherapy consistently yields higher response rates than does systemic therapy; however, approximately half of the patients do not achieve a major response. One potential way to improve the results of treatment is the further increase in local drug concentrations combined with a transient flow reduction by use of chemoembolisation.

Kato et al. first described Chemoembolization in 1981 (33). The procedure consists of an intraarterial infusion of chemotherapy combined with embolisation of the vascular supply to the tumour. The conjunction of the two treatments has theoretical benefits beyond those offered by either treatment given alone. In addition to the ischemic damage caused by the embolisation and the cytotoxicity yielded by the chemotherapy, vascular occlusion results in the prolongation of transit time through the vascular bed of the tumour, with increasing exposure time between the chemotherapy and the tumour cell (34). Furthermore, it has been shown that anoxic damage increases vascular permeability, promoting further chemotherapy agent infiltration into the tumour (34). Cytotoxic effect on the vessel wall may result in an irritant vasculitis, causing further occlusion and ischemia. (34). Free-radical injury may compound the toxicity to the tumour during the phase of reperfusion. It should be noted that, although the combination of techniques may result in increased local toxicity, systemic toxicity is minimized by the metabolism of the drug during its first passage through the liver (35).

This low rate of systemic side effects induced by chemoembolisation of the liver, especially the low rate of bone marrow depression gives way for the combination with other more systemic chemotherapeutic interventions. In this study a combination with intraarterial application of 5-Fluorouracil in two different application forms was used – short time infusion and continuous circadian infusion (11,12,13,36).

In order to activate immunosystem on one hand and to prevent any severe bone marrow depression on the other hand an intraarterial application of Granulocyte-Macrophage-colony-stimulating-factor (GM-CSF) was added to that protocol. The use of intraarterial GM-CSF had a strong influence on toxicity profile of this regional chemotherapeutic regimen. Due to mobilisation of immune competent cells shown by the results of our investigations (Fig.1 / 2), rate of systemic side effects are low with more or less no leucocytopenia and thrombocytopenia. This can be dependent to the fact that GM-CSF does have effects more than the stimulation of medullary cells (37,38). GM-CSF will lead to:

- a stimulation, mobilisation and differentiation of dendritic cells  
an increase in antigen presentation and endocytotic activity of monocytes and macrophages

- an increase in cytotoxic activity of Kupffer cells
- an increase in expression of IL-2 and TNF  $\alpha$

If the intraarterial infusion of GM-CSF will lead not only to a mobilization of dendritic and other immunocompetent cells, but also to a specific activation of the immunosystem is under investigation.

The comparison of both treatment groups has shown no difference in toxicity profile and range and number of side effects. In both groups there was a high rate of embolisation induced gastrointestinal and systemic side effects such as nausea and vomiting, upper abdominal pain and fever for some days after application. These effects are manageable by use of painkillers, effective anti-emetic treatment and cortisone therapy. The rate of catheter and application induced side effects were low contributing to refinements in technique of hepatic arterial chemotherapy administration during the last 10 years.

Using a circadian continuous application of 5-FU in combination with systemic application of Leucovorin response rate could be increased by 10 % up to 51 %. This was combined with an increase in acceptability of the therapeutic regimen, because of the shortening in bed stay. This increase in regional efficacy was combined with an statistical significant survival benefit, leading to a median survival of more than 35 months for untreated patients, 33 months for patients in treatment group A and a 2- year and 3-year survival rate of 66 resp. 61 %.

57 % of all patients in this study have had prior systemic chemotherapy as treatment of her liver metastases or as adjuvant therapy. Interestingly there was not statistical significant difference between chemo naive and pre-treated patients in our study. This means that immuno-chemoembolization lead to the same efficacy, if prior systemic chemotherapy has been done or not. But we have to keep in mind that most of our patients were treated with the newer agents like oxaliplatin or irinotecan.

For these patients refractory to standard therapy or progressing after tumour resection plus adjuvant therapy, there is at present no standard recommended second-line treatment. During last decade several new treatment options have been established in second-line therapy of liver metastases of colorectal origin such as immuno-chemotherapy or several new cytostatic drug combinations (Tab.6)(36,39-47). Nevertheless no definite regimen has been established for second – line therapy in these patients, when systemic chemotherapy as first option has failed. Several phase II trials dealing with this problem could not show any benefit in terms of response or survival. The studies of Adenis et al. (1995), Barni et al. (1993) or Perez et al. (1998) haven't shown any response or improvement in survival by using different regimens such as Interferon plus Interlukin-2 or Interferon plus 5-FU (41,42,44).

In contrast to these negative trials some other trials from the last three years have shown promising results using new cytostatics such as Irinotecan or Oxaliplatin. Data given by Mitry et al. (1998) or Maindrault – Goebel et al. (1999) as well as Van Cutzem et al. (1999) have given relevant data from prospective randomised trials about effective systemic chemotherapy as second –line treatment of inoperable colorectal liver metastases leading to median survival time of around 10 months (14 –16). Nevertheless response rates were disappointing not exceeding 25 %.

Author	Year	Pts.	Cytostatics	Resp.	TTP	Survival
<b>Adenis</b>	1995	17	ARA-C, CDDP	0 %	-	-
<b>Barni</b>	1993	15	IFN, IL-2	0 %	-	-
<b>Maindrault</b>	1999	60	Oxaliplatin, 5-FU, LV	27 %	5.3 Mon	10.8 Mo
<b>Mitry</b>	1998	279	Irinotecan vs. BSC	-	-	9.2 Mo
<b>Mitry</b>	1998	260	Irinotecan vs. 5-FU	-	-	10.8 Mo
<b>Palmieri</b>	1991	20	MTX, 5-FU	10 %	3.5 Mon	7 Mon
<b>Perez</b>	1998	34	IFN, 5-FU	6 %	3 Mon	5 Mon
<b>Seitz</b>	1998	24	MMC, 5-FU	29 %	7.5 Mon	10 Mon
<b>Van Cutzem</b>	1999	267	Irinotecan vs. 5-FU	-	4.2 Mon	-
<b>Zaniboni</b>	1996	31	MTX, 5-FU	6.6 %	-	5 Mon
<b>Zaniboni</b>	1995	21	Etoposid	0 %	-	-

**Table 6: Studies about second-line therapy in colorectal cancer**

In comparison to these data in the literature response rate in our own trial is nearly doubled with 51 %. But we have to take into account that we have used response criteria different to usually used WHO – criteria. This change in response criteria is dependent to the use of microembolization with Lipiodol plus Gel-foam and it's influence on the results of diagnostic evaluation using computer tomography (CT-scan). The implementation of Lipiodol particles into vascular bed of the tumour will change the results of CT-scan. Shrinkage of liver metastases is not of the same extent compared with changes after systemic chemotherapy (48). This fact is dependent to embolising effect leading to a break down of vascular system and resulting in a central necrosis and severe desmoplastic and fibrotic reaction.

Comparing data from the literature with our own data given in this prospective trial than it becomes evident that regional immuno-chemotherapy can lead to an increase in response rate and survival. But we have to take into account that this is a non-randomised trial and that these patients have had tumour spreading defined to the liver only. These facts will have severe influence into outcome of patients and results of this trial. Further randomised trials have to be undertaken to confirm these encouraging data.

## References

1. Levi F, Lucchini F, La Vecchia C, Negri E ; Trends in mortality from cancer in the European Union, 1955 – 1994 *Lancet* 1999, 354 : 742-3
2. Kune GA, Kune S, Field B et al. Survival in patients with large bowel cancer : A population based investigation from Melbourne colorectal cancer study. *Dis Colon Rectum* 1990 ; 33 (11) : 938 – 46
3. Faivre J, Rat P, Arveux P. Epidemiologie des metastases hepatiques des cancer de colon. In: Nordlinger B. Jaeck D (eds.) *Traitments des metastases hepatiques des dancers colorectaux*, Paris Springer Verlag; 1992 : 2 –9
4. Cohen MC, Minsky BD, Schilsky RI. Cancer of the colon. In Devita VT, Hellman S, Rosenberg SA (eds.) *Cancer; Principles and Practice in oncology*, 5<sup>th</sup> edition, Philadelphia, PA: JB Lippincott 1993; 1144 – 97
5. Nordlinger B, Guiguet M, Vaillant JC et al. Surgical resection of colorectal carcinoma metastases of the liver; *Cancer* 1996, 77: 1254 – 62
6. Cady B, Jenkins R, Steele GD Jr et al. Surgical margin in hepatic resection for colorectal metastases. A critical and improvable determinant of outcome. *Ann Surg* 1998; 227: 566-71
7. Fong Y, Cohen AM, Fortner JG, et al. Liver resection on colorectal metastases *JCO* 1997, 15 (3): 938-46
8. Pougier P, Milan C, Lazorthes F et al. Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer: Foundation Francaise de Cancerologie Gigestive. *Br J Surg* 1995; 82: 1397 – 1400
9. Stangl R, Altendorf-Hofmann A, Charnley RM et al. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994; 343: 1405 – 10
10. Thirion P, Wolmark N, Haddad E, et al. Survival impact of chemotherapy in patients with colorectal metastases confined to the liver: A re-analysis of 1458 non-operable patients randomised in 22 trials and 4 meta-analyses *Ann Oncol* 1999; 10: 1317-20
11. Advanced Colorectal Cancer Meta-Analyses Project. Modulation of 5-fluorouracil by leucovorin in patients with advanced colorectal cancer: Evidence in terms of response rate. *J Clin Oncol.* 1992; 10: 896-903
12. Advanced Colorectal Cancer Meta-Analyses Project. Meta-Analyses of randomised trials testing biochemical modulation of 5-fluorouracil by Methotrexat in metastatic colorectal cancer *J Clin Oncol* 1994; 12: 960 – 969
13. Meta-Analysis Group in Cancer. Efficacy of intravenous continuous infusion of 5-fluorouracil compared with bolus administration in advanced colorectal cancer *J Clin Oncol* 1998; 16: 301-8
14. Mitry, E., Ducreux, M., and Rougier, P. Second-line irinotecan chemotherapy in the treatment of metastatic colorectal cancers: phase III trials. *Bull Cancer.* 1998 Dec; Spec No: 38-42.
15. Van Cutsem, E. and Blijham, G. H. Irinotecan versus infusional 5-fluorouracil: a phase III study in metastatic colorectal cancer following failure on first-line 5- fluorouracil. V302 Study Group. *Semin Oncol.* 1999 Feb; 26(1 Suppl 5): 13-20.

16. Maindrault-Goebel, F.; Louvet, C.; Andre, T.; Carola, E.; Lotz, J. P.; Molitor, J. L.; Garcia, M. L.; Gilles-Amar, V.; Izrael, V.; Krulik, M., and de Gramont, A. Oxaliplatin added to the simplified bimonthly leucovorin and 5- fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. *Eur J Cancer*. 1999 Sep; 35(9):1338-42
17. Ackerman NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumour growth. *Surgery* 1974; 75: 589-96
18. Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma – A randomized trial. *Ann Intern Med* 1987; 107; 459 – 65
19. Hohn DC, Stagg RJ, Freidman MA et al. A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group Trial *J Clin Oncol* 1989; 7; 1646-54
20. Chang AE, Schneider PD, Sugarbaker PH et al. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases *Ann Surg* 1987; 206; 985 –93
21. Martin JK, O’Connell MJ, Wiegand HS et al. Intra-arterial floxuridine vs. Systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial *Arch Surg* 1990; 125; 1022-7
22. Rougier P, Laplanche A, Huguier M et al. Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial *J Clin Oncol* 1992; 10; 1112-18
23. Allen-Mersh TG, Earlam S, Fordy C et al. Quality of life and survival with continuous hepatic artery floxuridine infusion for colorectal liver metastases *Lancet* 1994;344; 1255-60
24. Levi, F. Cancer chronotherapy. *J Pharm Pharmacol*. 1999 Aug; 51(8):891-898.
25. Focan, C.; Levi, F.; Kreutz, F.; Focan-Henrard, D.; Lobelle, J. P.; Adam, R.; Dallemagne, B.; Jehaes, C.; Markiewicz, S.; Weerts, J.; Bismuth, H.; Jasmin, C., and Misset, J. L. Continuous delivery of venous 5-fluorouracil and arterial 5- fluorodeoxyuridine for hepatic metastases from colorectal cancer: feasibility and tolerance in a randomized phase II trial comparing flat versus chronomodulated infusion. *Anticancer Drugs*. 1999 Apr; 10(4):385-92.
26. Porta, C.; Moroni, M.; Nastasi, G.; Bobbio-Pallavicini, E., and Barazzoni, G. Utility of embolization of chemoembolization as second-line treatment in patients with advanced or recurrent colorectal carcinoma. *Cancer*. 1995 Jun 1; 75(11):2782-4.
27. Tellez C, Benson AB, Lyster MT, et al. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of literature *Cancer* 1998; 82: 1250-59

- 28 Baxevanis, C. N.; Tsavaris, N. B.; Papadhimitriou, S. I.; Zarkadis, I. K.; Papadopoulos, N. G.; Bastounis, E. A., and Papamichail, M. Granulocyte-macrophage colony-stimulating factor improves immunological parameters in patients with refractory solid tumours receiving second-line chemotherapy: correlation with clinical responses. *Eur J Cancer*. 1997 Jul; 33(8):1202-8.
- 29 Walker, P.; Watanabe, S., and Taube, A. The Edmonton Staging System. *J Pain Symptom Manage*. 1996 Nov; 12(5):269.
- 30 Schulman KA, Yabroff KR : Measuring the cost –effectiveness of cancer care. *Oncology* 1995, 9: 523 – 533
- 31 Kemeny N, Golbey R. A chemotherapeutic approach to colorectal carcinoma. In: Stearns MR, jr (editor) *Neoplasms of the colo, rectum and anus 1<sup>st</sup> ed.* New York : Wiley and Sons, 1980: 155-68
- 32 Kemeny N, Seiter K. Treatment options for patients with metastatic colorectal cancer In: Niederhuber JE (editor) *Current therapy in oncology. 1<sup>st</sup> ed.*m St.Louis: Mosby-Year Book, Inc. 1993: 447-57
- 33 Kato T, Nemoto R, Mori H, Takahashi M, Tamakawa Y, Harada M Arterial chemoembolisation with misroencapsulated anticancer drug. An approach to selective cancer chemotherapywith sustained effects *JAMA* 1981;245:1123-7
- 34 Wallace S, Carrasco CH, Chrsagavej C, Richli WR, Wright K, Gianturco C, Hepatic artery infusion and chemoembolisation in the management of the liver. *Cardiovasc Intervent Radiol* 1990;13:153-60
- 35 Collins JM. Pharmacologic rationalw for regional drug delivery. *J Clin Oncol* 1984;2(5):498-504
- 36 Falcone, A.; Allegrini, G.; Lencioni, M.; Pfanner, E.; Brunetti, I.; Cianci, C.; Galli, C.; Masi, G.; Antonuzzo, A., and Conte, P. Protracted continuous infusion of 5-fluorouracil and low-dose leucovorin in patients with metastatic colorectal cancer resistant to 5- fluorouracil bolus-based chemotherapy: a phase II study. *Cancer Chemother Pharmacol*. 1999; 44(2):159-63.
- 37 Marty M, Extra JM *Fundamentals: what is GM-CSF ?* in : Marty M (editor ) *Manual of GM.CSF .* Blackwell science, Berlin 1996, 17-23
- 38 Honkoop AH, Hoekman K, Wagstaff J et al. Continuous infusion or subcutaneous injection og granulocyte-macrophage-stimulating factor : increased efficacy and reduced toxicity when given subcutaneously *Br J Cancer* 1996; 74: 1132 - 36
- 39 Fordy, C.; Glover, C.; Davies, M. M., and Allen-Mersh, T. G. Hepatic arterial floxuridine as second-line treatment for systemic fluorouracil-resistant colorectal liver metastases. *Br J Cancer*. 1998 Oct; 78(8):1058-60.
- 40 Hartmann, J. T.; Harstrick, A.; Daikeler, T.; Kollmannsberger, C.; Muller, C.; Seeber, S.; Kanz, L., and Bokemeyer, C. Phase II study of continuous 120 h infusion of mitomycin C as salvage chemotherapy in patients with progressive or rapidly recurrent colorectal cancer. *Anticancer Drugs*. 1998 Jun; 9(5):427-31.

- 41 Adenis, A.; Carlier, D.; Darloy, F.; Pion, J. M.; Bonnetterre, J., and Demaille, A. Cytarabine and cisplatin as salvage therapy in patients with metastatic colorectal cancer who failed 5-fluorouracil + folinic acid regimen. French Northern Oncology Group. *Am J Clin Oncol.* 1995 Apr; 18(2):158-60.
- 42 Barni, S.; Lissoni, P.; Ardizzola, A.; Vigore, L.; Vezzo, R.; Rescaldani, R., and Tancini, G. Immunotherapy with low-dose subcutaneous interleukin-2 plus beta- interferon as a second-line therapy for metastatic colorectal carcinoma. *Tumori.* 1993 Oct 31; 79(5):343-6.
- 43 Palmieri, G.; Gridelli, C.; Airoma, G.; Pepe, R.; Incoronato, P.; Caponigro, F., and Bianco, A. R. Second-line chemotherapy of advanced colorectal cancer with sequential high-dose methotrexate and 5-fluorouracil. *J Chemother.* 1991 Feb; 3(1):55-60.
- 44 Perez, J. E.; Lacava, J. A.; Dominguez, M. E.; Rodriguez, R.; Barbieri, M. R.; Romero Acuna, L. A.; Romero Acuna, J. M.; Langhi, M. J.; Amato, S.; Marrone, N.; Ortiz, E. H.; Leone, B. A.; Vallejo, C. T.; Machiavelli, M. R., and Romero, A. O. Biomodulation with sequential intravenous IFN-alpha2b and 5- fluorouracil as second-line treatment in patients with advanced colorectal cancer. *J Interferon Cytokine Res.* 1998 Aug; 18(8):565-9.
- 45 Seitz, J. F.; Perrier, H.; Giovannini, M.; Capodano, G.; Bernardini, D., and Bardou, V. J. 5-Fluorouracil, high-dose folinic acid and mitomycin C combination chemotherapy in previously treated patients with advanced colorectal carcinoma. *J Chemother.* 1998 Jun; 10(3):258-65.
- 46 Zaniboni, A.; Labianca, R.; Martignoni, G.; Barni, S.; Vinci, M.; Vaghi, M.; Pirovano, M.; Facendola, G.; Marini, G., and Luporini, G. Sequential methotrexate and 5-fluorouracil as second-line chemotherapy for advanced colorectal cancer patients pretreated with 5-fluorouracil and leucovorin: a GISCAD study. *J Chemother.* 1996 Feb; 8(1):82-4.
- 47 Zaniboni, A.; Labianca, R.; Pancera, G.; Barni, S.; Frontini, L.; Marini, G., and Luporini, G. Oral etoposide as second-line chemotherapy for colorectal cancer: a GISCAD study. *Gruppo Italiano Studio Carcinomi Apparato Digerente. J Chemother.* 1995 Jun; 7(3):246-8.
- 48 Dworkin MJ, Burke D, Earlam S et al. Measurement of response to treatment incolorectal liver metastases *Br J Cancer* 1995; 71: 873-76