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Isolated liver perfusion: 5-year results

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Abstract. Isolated liver perfusion (ILP) for hepatic metastases of colorectal cancer with high-dose cytostatics was performed by means of a heart-lung machine at 40° C tissue temperature over 60 min. Isolation of the liver in situ is achieved with a Perfufix (B. Braun, Melsungen, FRG) double-lumen vena cava catheter and cannulation of the hepatic artery and portal vein. A total of 57 patients were submitted to ILP, eight of whom are not yet integrated into the survival curve. Fifteen of 49 patients had ILP (5-fluorouracil, 5-FU) without subsequent therapy, while in the remaining 34 cases ILP was followed by hepatic artery infusion (HAI) of 5-FU and mitomycin C (MMC). In 19 of these patients ILP was with 5-FU alone, in 15 patients MMC was added. The average total dose of 5-FU was 1000 mg, and the total dose of MMC ranged from 15 to 50 mg. ILP with 50 mg MMC was well tolerated by the parenchyma. In the ILP 5-FU/MMC group, the response rates were 62% CR and 28.5% PR, while ILP with 5-FU alone resulted in 16% CR and 79% PR. Nonresponders evidently had very poor vascularization of metastases. In the 34 patients receiving ILP and HAI, the median duration of survival was 18 months. In the subgroup of 15 patients receiving 5-FU/MMC combination in initial ILP, median survival was 22 months. Median survival of nonresponders was 7 months. At the time of writing, three patients have survived without evidence of disease for 52, 54 and 69.5 months post ILP. At the time of initial ILP these three patients had disseminated disease but no palpable liver enlargement.

Key words: Isolated liver perfusion – Hepatic arterial infusion – Hyperthermia – Liver metastases – Mitomycin C

Introduction

The technique of isolated liver perfusion (ILP) described herein was first performed in 1981 [2]. The rationale of isolated perfusion techniques for hepatic metastases of colorectal cancer is based on the poor chemosensitivity [17, 16, 23, 24] of colorectal cancer, which responds only to high drug concentrations [11]. Isolated perfusion is a means of increasing the total dose of cytotoxic drugs to an extent that is limited only by local tissue intolerance. Systemic toxicity is avoided by the complete isolation of the system. Subsequent spread of metastases from the liver to extrahepatic locations is expected to be prevented in the case of complete local response. Modifications according to the type of tumor being treated, new pharmacokinetic data and technical improvements have been continuously incorporated into the method [1, 4].

Operative procedure

Complete isolation of the liver is accomplished with a special tubing set and a double-lumen "liver perfusion catheter" (Perfufix, B. Braun, Melsungen, FRG) which is connected to a heart-lung machine (Fig. 1). The liver is exposed via an abdominal midline incision and mobilized away from the diaphragm. The hepatoduodenal ligament is then exposed and tourniquet tapes are placed around the common hepatic artery, the gastroduodenal artery and two around the portal vein for cannulation in both directions (Fig. 2). The gastroduodenal artery is then distally ligated and the entire hepatic artery dissected and collateral branches to the duodenum and stomach divided and ligated. Otherwise severe gastritis, duodenitis or ulcers may occur as a result of cytostatic infusion. In case of anatomic variations, for example of the right or left hepatic arteries, arterial cannulation is adapted to the specific situation.

The vena cava is then exposed intrapericardially through a transverse incision in the diaphragm and a tourniquet tape is placed around it (Fig. 3). Further tourniquets are placed around the vena cava above and (two) below the origin of the renal veins. The lumbar

veins entering the vena cava in this area are ligated and divided for complete isolation. Then the vena cava is temporarily occluded with two vascular clamps below the renal veins and a Perfufix double-lumen perfusion catheter is introduced through a longitudinal venotomy (Fig. 5, 6). During the cannulation procedure the liver perfusion catheter is temporarily blocked with a guide tube in order to avoid blood loss through the side openings. Just before inserting the catheter completely into the vena cava, the guide tube is withdrawn and the end of the catheter clamped until it is in its proper position in the vena cava and all tourniquets are fixed. This procedure takes about 1.5 – 2 min.

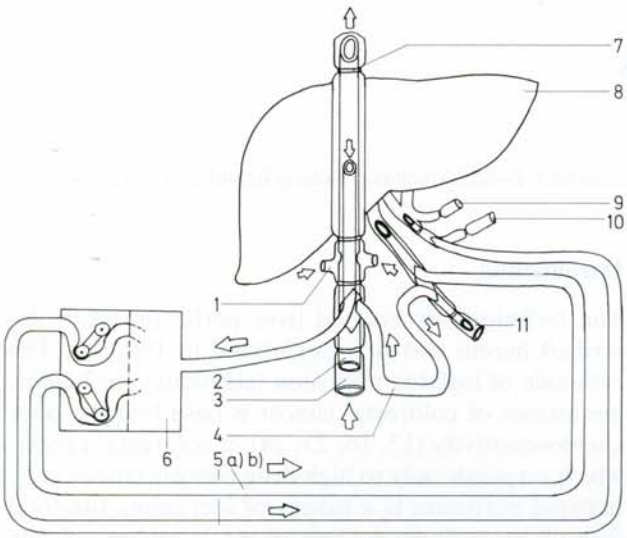


Fig. 1. Isolated liver perfusion circuit

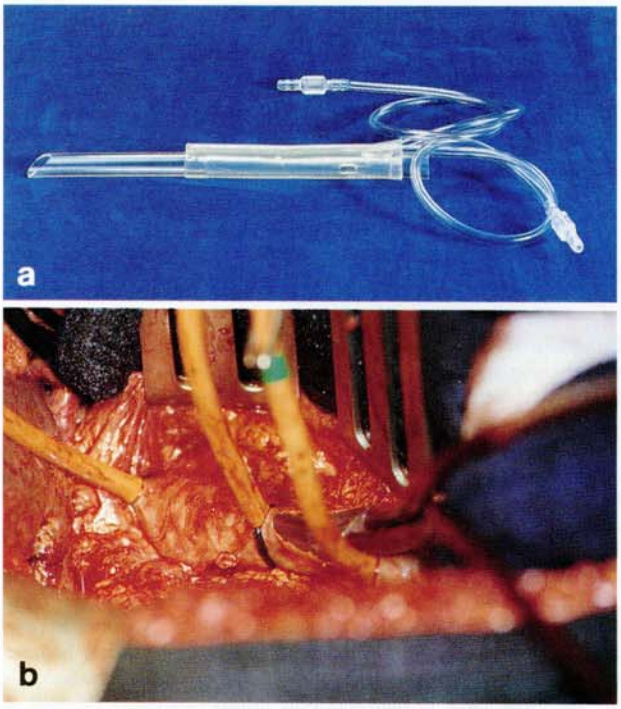


Fig. 6 a Perfufix liver perfusion catheter. **b** Perfufix catheter in vena cava

Subsequently the portal vein is cannulated in both directions (Perfex, B. Braun, Melsungen, FRG) through a transverse incision. The distal tube toward the GI tract is immediately connected with a portocaval shunt line of the Perfufix vena cava catheter in order to shunt the venous return from the GI tract to the right atrium. The proximal tube, directed toward the liver, is connected with the portal perfusion line of the heart-lung machine, and the venous hepatic return line of the perfusion catheter is connected to the venous line of the heart-lung machine. The common hepatic artery is clamped in order to avoid blood loss into the isolated perfusion system. Once the suprarenal and intrapericardial vena cava tourniquets are narrowed too, the so-called portal isolation is established and the heart-lung machine can be turned on, adapting the flow rate to the hepatic venous return.

The hepatic artery is cannulated through the gastroduodenal artery (Fig. 7). At this time the portal flow for immediate oxygenation of the liver is usually about 300 – 400 ml/min. As soon as the hepatic artery cannula is connected to the arterial line of the heart-lung machine, the hepatic artery perfusion flow rate is slowly increased to about 300 ml/min, while the portal flow is again adjusted according to the hepatic venous return. The volume level in the oxygenator should be maintained at a steady state. The high flow rates at the beginning of the perfusion are for heating up the liver parenchyma to 39.5 – 40° C; the temperature is measured with thermistor probes in both liver lobes. At this temperature blood supply to the metastases is at its optimum [25]. Blood temperature in the oxygenator has to be kept at 41.5 – 42° C. During infusion of the cytotoxic drug into the arterial line the hepatic arterial flow rate is decreased to that needed in order to achieve the desired drug plasma concentration.

After 60 min isolated cytotoxic perfusion the venous tube is cut through and the perfusate washed out. The hepatic vascular system is refilled with plasma expander and one unit of blood that is usually obtained by preoperative hemodilution [26]. For decannulation, the double-lumen catheter is first removed and the vena cava repaired with a running suture. In order to avoid ischemia in the postperfusion period the bulldog clamp is removed from the common hepatic artery. The portal vein too is repaired with a running prolene suture, and after removal of the hepatic arterial tube an Implantofix (B. Braun, Melsungen, FRG) port catheter is placed in the same position in the gastroduodenal artery (Fig. 8) for subsequent arterial infusion chemotherapy.

Fig. 2. Exposure of hepatoduodenal ligament

Fig. 3. Exposure of vena cava intrapericardially

Fig. 4. Tourniquet tapes around inferior vena cava

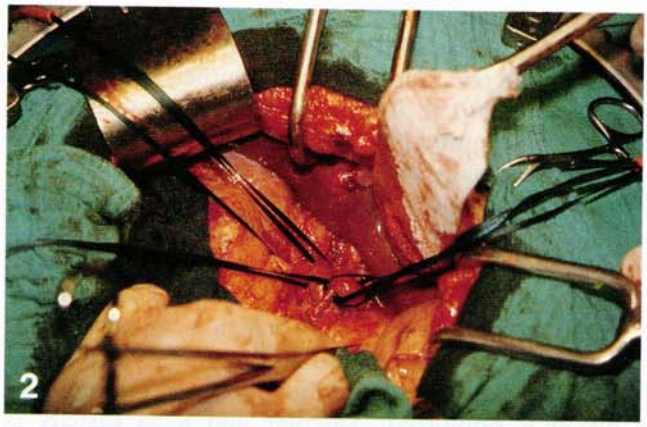
Fig. 5. Longitudinal incision of inferior vena cava

Fig. 7. Cannulated porta hepatis (from left to right: cannulation of hepatic artery, portal shunt, portal "arterial" line)

Fig. 8. Implantofix catheter in gastroduodenal artery

Fig. 9. Distribution of intra-arterially infused blue dye in small metastases and in the periphery of large metastases

Fig. 14. Inner view of a completely liquefied hepatic metastasis of colorectal cancer after ILP, with remaining vascular structures in the shell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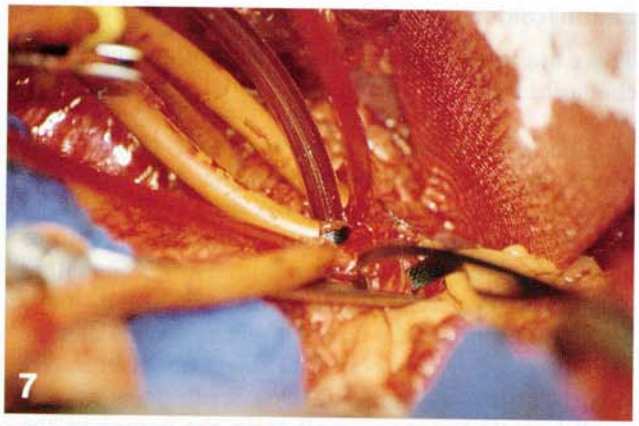
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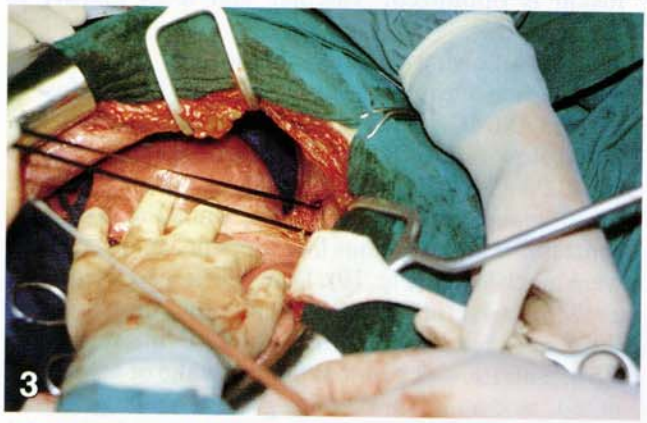
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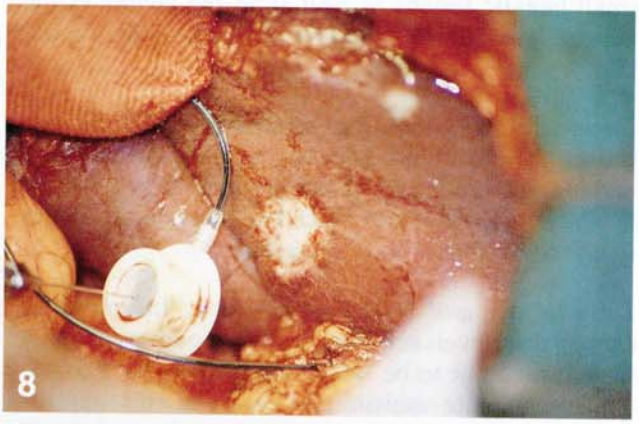
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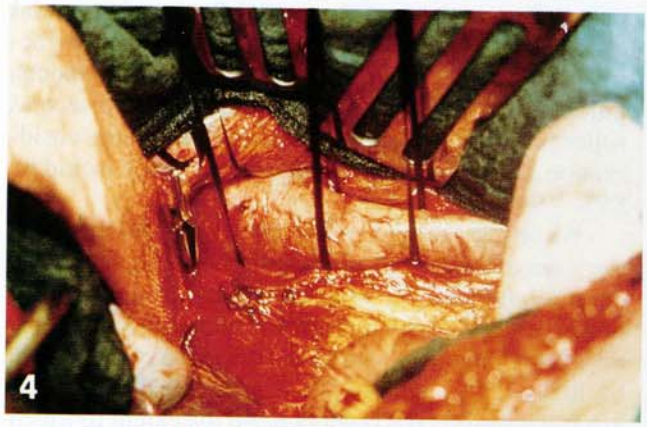
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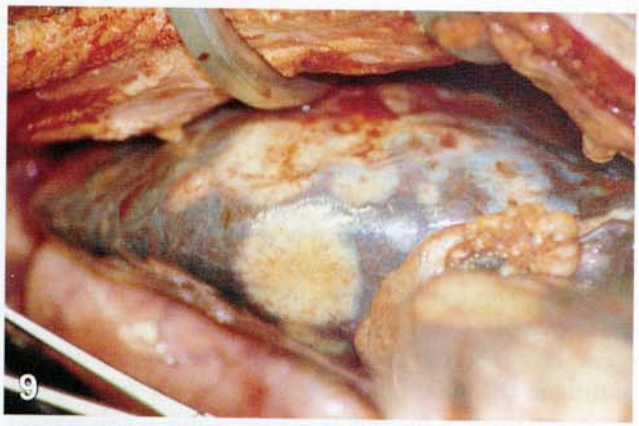
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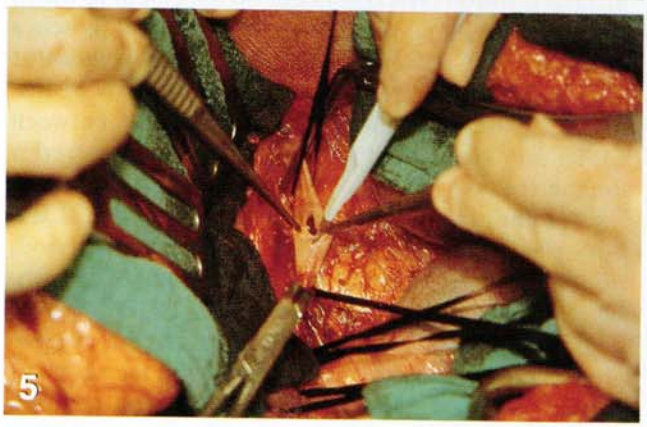
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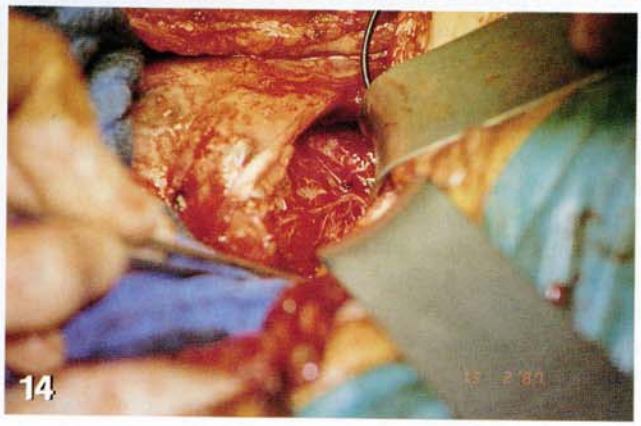
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Pharmacokinetics and dose-response relationship

There are three factors influencing response in cancer chemotherapy.

Vascularization. Vascularization of tumors has to be considered a prerequisite for response; no tumoricidal effect can be expected unless the drug is delivered to the target region. Blood supply is different in various histological types of tumor tissue. However, within one histological type small metastases usually have better vascularization than large ones. This can be demonstrated by intra-arterial injection of blue dye (Fig. 9). Measurements of drug levels in large and small hepatic lesions as well as in the center vs the periphery of metastases have confirmed this theory [5].

Chemosensitivity. Testing of chemosensitivity has proved to be useful for selecting the most potent drugs and for ascertaining which drug is likely to be effective in which tumor [17] and which local concentration has to be achieved to induce a response.

Drug dosage and local concentration. In colorectal cancer, drug levels achieved in systemic chemotherapy have turned out to be rather ineffective. As a consequence complete remission is rarely seen This supports the administration of high local doses in an isolated perfusion circuit.

There is still confusion about which mode of drug application is preferable in isolated perfusion systems: (a) bolus injection in the oxygenator, (b) fractionated or bolus injection in the arterial line or (c) infusion in the arterial line at decreased blood flow rates.

Historically, as described in isolated extremity perfusion, bolus injection in the oxygenator is the method of choice. This may be useful in the case of highly toxic drugs or very chemosensitive tumors. The disadvantages, however, might be dilution of the total amount of drug in the heated priming solution and perfusate, increased protein binding due to prolonged exposure, or degradation in case of thermoinstability of drugs (*L*-phenylalaline mustard, L-PAM). In the case of anthracyclines (adriamycin, ADM), adhesion to the plastic material of the oxygenator, heat exchanger or long tubings has been observed consistently. Thus the fraction of remaining active drug is reduced and can hardly be estimated.

Bolus injection of the total drug may result in intimal lesions followed by vascular thrombosis, as seen on increased exposure to mitomycin C (MMC), or nerve damage, observed in extremity perfusions when CDDP was given in one shot [3, 7].

It is our experience in isolation perfusion techniques that infusion of cytotoxics into the arterial line at reduced arterial blood flow permits adjustment of arterial drug concentrations at the tumor site and controll of the risk of local toxicity. Sufficient drug levels according to data from chemosensitivity testing [18] are a prerequisite for response in tumors with low chemosensitivity.

With reduction of the arterial blood flow via the roller pumps of the heart-lung machine and infusion of drug into the arterial line, the speed of infusion regulates the drug concentration and, alone, determines the necessary infusion duration. Thus the product of concentration and time (area under the curve, AUC) is predictable and the efficacy of isolated perfusion is optimized. Vascular and local toxicity is avoided.

The following example should give a better understanding of the situation: During a 30-min infusion of 50 mg MMC via the arterial ILP perfusion line at a blood flow rate of 80 – 120 ml/min drug levels of at least 20 μg MMC/ml were maintained throughout the infusion period at the target site, while the drug concentrations in the venous line (hepatic venous return) were much lower (Fig. 10). Drug levels were measured at the arterial inflow into the liver and directly from the venous return simultaneously. With this technique a concentration-dependent tissue uptake of MMC was noted, as demonstrated during the remaining 30 min of ILP. During the first 30 min of ILP, when the arterial concentrations were $>$ 20 (max. 50) μg/ml, the extraction rate was 95% – 97%. Taking the simultaneous portal flow rate of 150 – 200 ml/min via the second roller pump (at reduced hepatic outflow) into consideration, the calculated arterial/venous ration would be 85% – 94%.

When, at the end of the 30-min MMC infusion, the concentration in the arterial line decreased to 3 μg/ml and less, the arterial/venous ratio decreased to about 70%, which indicates, depending on the portal roller pump flow, a realistic decrease of extraction to 10%– 20%. Whether ILP is superior to hepatic arterial infusion (HAI) depends on the extent to which the pharmacokinetic potential is exploited. When a total dose of 15 mg MMC is injected into an oxygenator with its large dilution volume, the superiority of ILP might be only minimal. The relationship between MMC total dose, plasma levels and AUC achieved is demonstrated in Fig. 11.

Another factor that has to be considered in ILP is biliary excretion of drugs in the postoperative period, possibly causing systemic toxicity. In trial of ILP combination treatment with MMC/5-FU/CDDP, where CDDP was given as a bolus injection into the oxygenator, drug levels in the arterial line were measured at 10-min intervals. Through a biliary drain, samples were taken on 8 consecutive days for determination

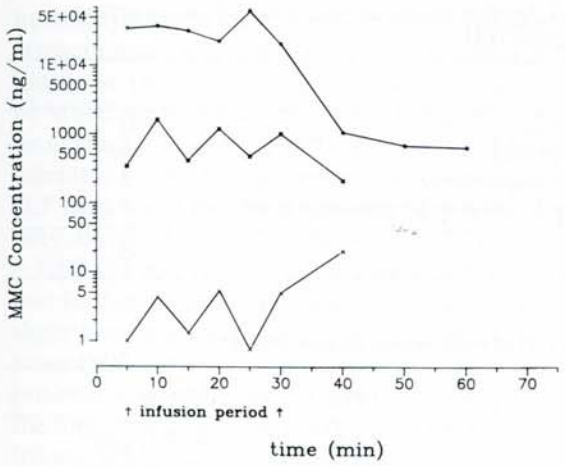

Fig. 10. MMC levels in arterial (⟜⟞) and venous (■—■) line during isolated liver perfusion (50 mg MMC, 30 min infusion in arterial perfusion line. (⟝⟞) ratio venous/arterial line)

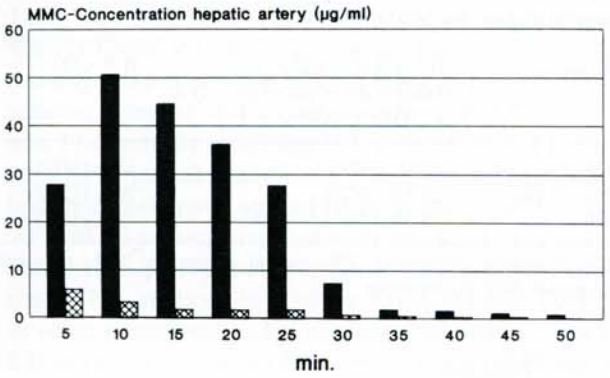

Fig. 11. Hepatic arterial drug exposure (AUC) during ILP (50 mg infusion in arterial line vs 15 mg bolus in oxygenator) ■ , 50 mg MMC; ▩ , 15 mg MMC

of biliary excretion of platinum (Fig. 12). A correlation between the total dose of CDDP adminstered in ILP and tissue uptake was also investigated. Tissue uptake is enhanced when the total dose is increased [5, 27].

Clinical cases

Fifty-seven patients with disseminated nonresectable liver metastases were submitted to ILP. Eight of these patients were not integrated into the survival curve: two had complete cannulation of the liver but were not perfused with drugs due to anesthesiologic, hypertensive and respiratory disturbances; four had MMC/5-FU, one MMC/5-FU and CDDP for hepatic metastases of colorectal carcinoma and one had CDDP and L-*PAM* for hepatic metastases of ocular melanoma. Of the remaining 49 patients, 15 had ILP with 5-FU alone without further therapy (Table 1). Three of these 15 patients died in the early postoperative period. This was in the initial phase, when ILP was being developed. Since then no further early postoperative deaths have occurred. Thirty-four patients received ILP followed by five courses of HAI with MMC/5-FU. In 19 of these 34 only 5-FU (750 – 1250 mg) was administered by ILP; in the

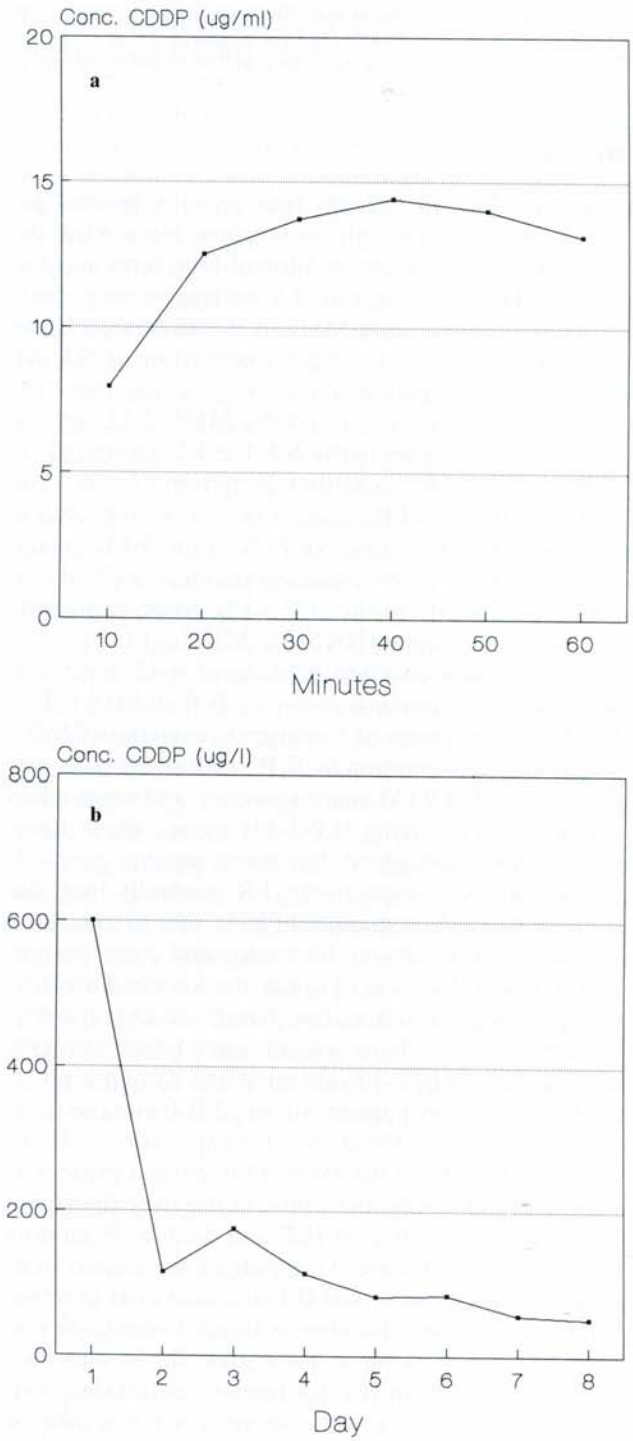

Fig. 12 a CDDP concentrations in arterial line during ILP (50 mg CDDP, bolus injection in oxygenator). **b** ILP 50 mg CDDP (biliary excretion)

remaining 15 MMC (15 – 50 mg) was added. Forty-six of 49 patients had hepatic metastases of colorectal carcinoma, two had carcinoid and one had hepatoma. The hepatoma patient and one carcinoid patient had ILP with 5-FU alone and so do not appear in the group of 34 patient that is evaluated in more detail. One carcinoid patient

had subsequent HAI and did not differ significantly from the rest of the patients, so is included. HAI maintenance therapy was performed at 4-week intervals according to the schedule shown in Table 2.

Results

In the MMC/5-FU group, four recently treated patients are considered only for response rates, while the remaining 15 are evaluated for of long-term survival as well. The advantage of ILP with increasing doses of the alkylating agent MMC is demonstrated by an increasing number of complete remissions (CR). Although the total percentage of responses is about the same in the 5-FU group and the MMC 5-FU group, the CR rate is higher in the MMC/5-FU group (62%) than in the 5-FU monotherapy group (16%). The partial remission (PR) rate, however, is only 28.5% in the MMC/5-FU group vs 79% in the 5-FU group. This indicates a dose-response relationship (Table 3), while the PR rate in the ILP 5-FU group is possibly caused by subsequent HAI with MMC/5-FU.

The median duration of survival is 18 months in the group of 34 patients receiving ILP and HAI (Fig. 13). In the subgroup of 15 patients receiving a MMC/5-FU drug combination in ILP, median survival was 22 months. ILP/HAI nonresponders and responders in the group receiving ILP 5-FU alone, where there was no CR, had about the same median survival, 7 and 8 months respectively. PR generally took the form of palpable reduction of liver size as measured by the distance between liver edge and costal margin and transient decrease of tumor markers and alkaline phosphatase, but within a few months the liver reached its former size. There was no correlation between clinical stage of liver involvement and response rate.

Forty-six of 49 patients survived ILP and the postoperative phase without major complications. There were five long-term survivors. One patient presented with a second tumor metastatic to the liver (hypernephroma) 34 months post ILP and died at 38 months due to the new disease. One patient developed local recurrence 40 months post ILP and died at 45 months. Three patients are still alive without evidence of disease and are working in their jobs 52, 54 and 69.5 months post ILP. In ILP for hepatic metastases from colorectal primary, to date there is a 6.5% rate of survival for 4.5 – 5.5 years. Long-term survivors had disseminated or central nonresectable metastatic liver involvement but no significant palpable liver enlargement.

Side effects

Generally, liver tissue damage is unexpectedly mild despite high-dose cytotoxic therapy. A transient increase of SGOT and SGPT to 100 – 200 U/l usually occurs, but normalizes within 1 week. In one of the earlier patients a prolonged ischemic interval of more than 10 min in the right liver lobe due to reconstruction of the devided accessory hepatic artery with intimal damage from the tube was noted during the decan-

Table 1. Number of patients treated by ILP with or without subsequent HAI

ILP	
With HAI	34
Without HAI	12
Died postoperatively	3
Follow-up too short for evaluation of survival	8
Total	57

Table 2. HAI maintenance therapy after ILP

Day	Drug	Dosage
1	MMC	8 – 10 mg/m^2
2 – 6	5-FU	550 mg/m^2/day
Infusion time 60 min		

Table 3. Response rates in ILP (n = 40) with MMC/5-FU, MMC/5-FU/CDDP, CDDP/L-*P*AM and 5-FU alone. Maintenance therapy in all patients: HAI (MMC/5-FU)

Response	ILP MMC/5-FU *or* MMC/5-FU/CDDP (n = 1) *or* CDDP/L-*P*AM (n = 1)	ILP 5-FU
CR	62% (13/21)	16% (3/19)
PR + MR	28.5% (6/21)	79% (15/19)
NR	9.5% (2/21)	5% (1/19)

CR, complete remission; PR, partial remission; MR, minimal response; NR, no response

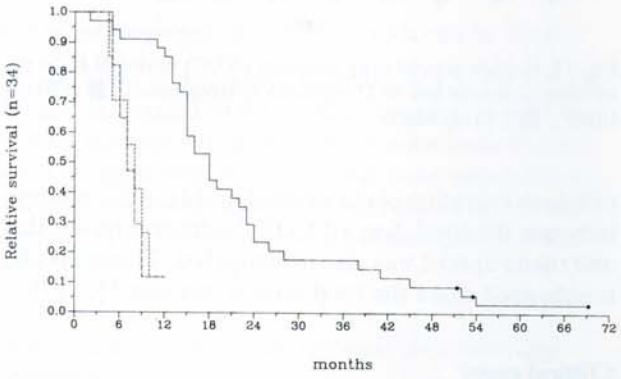

Fig. 13. ILP overall survival curves. –, *Group A*, ILP + HAI: responders, median survival time 18 months; —, *Group B*, ILP monotherapy, ILP + HAI: nonresponders, median survival time 7 months; – – –, *Group C*, ILP monotherapy: responders (no CR!), median survival time 8 months

nulation procedure followed by chemical hepatitis with transaminases above 1000 U/l and elevation of bilirubin above 10 U/l. The drugs themselves, at dose ranges of MMC up to 50 mg given in 30-min infusions with an average additional 1000-mg bolus of 5-FU are well tolerated by the liver parenchyma. Performance after ILP does not differ from that after any other laparotomy, lasting 3 to 4 h. Cholinesterase decreases to 800 – 1200 U/l and returns to normal within 1 month. In two further patients transient chemical hepatitis with slight jaundice and distinct elevation of the transaminases (600 – 900 U/l) occurred without evidence of a prolonged ischemic period, but had disappeared by the time of discharge at 2 and 3 weeks postoperatively. Biliary sclerosis was never observed following ILP alone, but occurred in one patient who had six courses of HAI with MMC/5-FU.

Extrahepatic metastases

Forty of 46 patients (87%) developed extrahepatic lesions (peritoneum, lungs, bone, brain or a combination) after treatment. These were detected after a median interval of 4 months in the ILP 5-FU group and 11.6 months following ILP with MMC/5-FU (Table 4). Peritoneal dissemination is a predominant problem in extrahepatic spread of metastases. More than 70% of all patients treated with any kind of regional chemotherapy for liver metastases, among them more than 90% of those in clinical stages III and IV [15] develop peritoneal carcinomatosis, even in the case of CR in the liver. Quite often the first manifestation of peritoneal or lymph node involvement is observed in the hepatoduodenal ligament. Metastatic invasion of the porta hepatis was diagnosed in 74% of our patients after ILP with 5-FU alone and in 20% after ILP with MMC/5-FU. This indicates less metastatic spread from the liver to other areas following initial high-dose therapy. In the course of longer follow-up there is a shift toward bone and brain metastases.

Response criteria

Liver metastases of different primaries showed different response behavior. While impressive shrinkage of liver metastases from breast cancer can commonly be observed on CT, liver metastases from colorectal cancer, even in the case of CR, more often show initial central hypodensity, indicating necrosis, and later on calcifications in the periphery or throughout the former metastases. Complete disappearance is not a rule, usually taking years, but a slight or moderate shrinkage in the case of response is commonly observed. Estimation of response from the diameter of the lesions alone is not really reliable in metastases from colorectal primaries and therefore tumor markers should be taken into consideration as a second parameter. Figure 14 gives an example of CR following ILP for liver metastases of colorectal origin. CEA had returned to normal, but on CT there were still hypodense lesions with diameters reduced by about 30%. Second-look laparotomy revealed liquefication of center and periphery with remaining small borderline vascular structures. Complete eradication of tumor tissus was confirmed histologically.

CEA is certainly a good parameter for classification of the response rate and follow-up evaluation. Even clinical stage III patients with liver enlargement and elevation of alkaline phosphatase show CR with decrease of the CEA level to normal within 4 – 8 weeks post ILP (Fig. 15), and a sudden increase precedes other evidence of intrahepatic recurrence. Second-look laparotomy or aspiration of ascites following suspicious ultrasound or CT may reveal peritoneal carcinosis, which in our patients occurred more often and earlier than pulmonary metastases. Often, disseminated microlesions in the peritoneal cavity are thought already to have been present at the time of ILP [4, 21]. Therefore a combined modality treatment should be planned in order to avoid potential locoregional overtreatment from ILP, adding intracavitary and sys-

Table 4. Manifestation of extrahepatic lesions following ILP or ILP/HAI

Method	Extrahepatic metastases	Postoperative peritoneal carcinosis
ILP (5-FU)	After 4 months	74%
ILP (5-FU/MMC) + HAI	After 11.5 months	20%

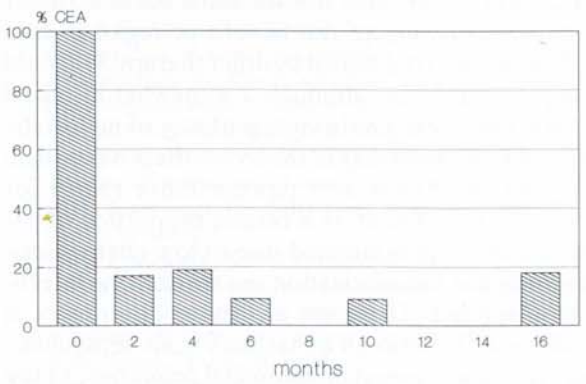

Fig. 15. Typical course of CEA in the case of immediate response to ILP

temic chemotherapy to inhibit growth of peritoneal microlesions.

Discussion

There were waves of enthusiasm for regional chemotherapy of liver metastases in the 1960s, the mid-1970s and, even more strongly in recent years, mainly supported by continuous infusion pump studies. Excitement about impressive results was followed by disappointment due to local toxicity, technical complications and the discrepancies in response rates reported by different groups [6, 10, 13, 14]. At present there is a lot of controversy about the status of regional chemotherapy in general, and there is even doubt concerning the superiority of regional therapy and the influence of local response on survival. Moreover, there is no consensus about the quality of life [12] during regional chemotherapy – depending on which drug is used – of, above all, about in which tumor and in which clinical stage [20] regional chemotherapy might be indicated. Perhaps premature conclusions have been drawn about a treatment modality that is still in a process of evolution.

Moreover, we should not forget that all new forms of cancer therapy have been controversial regarding the administered drugs, the mode of delivery, the clinical stage of the patients treated and, specifically, the tumors treated. Nevertheless during recent years some progress has been made in the understanding of regional chemotherapy (van de Velde et al., next issue) [24]. The basic questions arising now are: Has the best drug for the specific tumor been used? Is the catheter technique optimal – does the drug get to the tumor? Is there any chemosensitivity in the high dose range that can be achieved by arterial delivery? Is the suggested toxicity acceptable and can quality of life be improved?

It should be taken into account that colorectal cancer, from the point of chemosensitivity and vascularization, is certainly not the most suitable tumor in which to investigate the benefit of regional drug application unaccompanied by other therapy. It should be kept in mind that although a somewhat localized and to some extent predictable pathway of metastatic spread, for example that in the liver, offers a rationale for taking this tumor as a representative model for locoregional treatment, in a certain proportion of patients failure is programmed due to low chemosensitivity and poor vascularization, no matter which technique is applied. There are enormous differences in vascular supply between metastases from hepatoblastoma, carcinoid, breast or colorectal primaries, so the response rates should also be expected to be different. Hepatoblastomas are well vascularized and chemosensitive, so that systemic chemotherapy causes visible tumor shrinkage and intra-arterial infusion can cause complete eradication.

Metastases from colorectal primaries however – with a few exceptions – are just the opposite, and require intensive therapy and high drug levels [8, 9]. Individual cases of impressive responses have been reported using many different treatment modalities, but case reports alone do not suffice to establish a representative scale of tumoricidal potency of various methods. Favorable circumstances such as good tumor vascularization,high chemosensitivity, high tissue uptake of the infused drug and, last but not least, perfect angiographic or surgical positioning of the infusion catheter, reaching all of the tumor-bearing area, may have a positive influence on a tumor with a bad prognosis.

However, the only way to establish the real benefit of locoregional treatment modalities are randomized studies. The NCOG randomized trial comparing hepatic arterial vs systemic FUDR [13] showed a better local response and longer disease-free intervals in the intra-arterial group, but evaluation of survival data was a problem, since intra-arterial FUDR had to be stopped due to local toxicity [12]. The Kemeny study recently showed an advantage regarding survival in the group treated with intra-arterial FUDR [14].

In our experience, ILP is the most potent regimen used so far as an initial treatment for tumor mass reduction or eradication. Subsequent intra-arterial, peritoneal or systemic chemotherapy might prevent the growth of disseminated micrometastases [15]. This might be the rationale for a randomized trial of ILP plus intravenous chemotherapy vs intravenous chemotherapy alone in clinical stage I and II patients. This is supported by our preliminary ILP data, although said data relate to a relatively small number of patients. However, a disease-free long-term survival rate of as much as 6.5% has not yet been observed with any other therapeutic regimen in disseminated nonresectable liver disease.

In the early years of ILP, when patients with predominantly advanced disease were treated, the advantage over easier techniques such as HAI was only small, since peritoneal dissemination predictably terminated the clinical course [4]. If ILP prevents further spread of metastases from the liver to extrahepatic sites as seems possible, disease-free life expectancy may well be prolonged.

Taking this into consideration, our group of 46 fully documented and eight recently perfused patients is certainly too small to provide definite support for ILP. In addition, dosage and mode of drug injection were not the same in all patients.

Furthermore, the first 24 cases evaluated were all clinical stage III (70%) or stage II (30%), whereas later care was taken to select only stages I and II. Nevertheless, our data indicate that in early clinical stages with metastases confined to the liver, only ILP can bring about 3 – 5 years of disease-free survival. A crucial point in cancer chemotherapy is to use the right drug in the right patient. Although in chemosensitivity testing it looks as if, at high concentration, a few drugs were active in nearly all of the tumors, there are marked differences. It has been observed that a change of drug according to in vitro testing results causes formerly resistant tumors to suddenly respond [16, 17, 19]. Targeted chemotherapy with predictive drug testing should therefore be evaluated in prospective studies. This might be a way of further improving the CR/PR ratio in high-dose chemotherapy. In our experience with HAI alone, it is not clear whether PR, constituting the majority of responses, really does prolong life expectancy to a significant extent. Slight shrinkage of central metastases adjacent to the bile ducts, even in PR, may certainly temporarily prevent jaundice and liver failure due to biliary occlusion. The effect on survival of transient PR followed by recurrence has not yet been established in the majority of metastases located elsewhere in the liver parenchyma and in the periphery.

This again is an argument for initial high-dose ILP chemotherapy in patients with hepatic metastases of colorectal carcinoma in order to increase the CR rate in the first treatment. To obtain definite information concerning the value of regional modalities in colorectal disease, randomized trials of initial ILP followed by HAI vs systemic chemotherapy should be carried out.

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