David L. Morris
Colin S. McArdle
Gary M. Onik

Hepatic Metastases

Butterworth-Heinemann
Linacre House, Jordan Hill, Oxford OX2 8DP
A division of Reed Educational & Professional Publishing Ltd

A member of the Reed Elsevier plc group

OXFORD BOSTON JOHANNESBURG
MELBOURNE NEW DELHI SINGAPORE

First published 1996

British Library Cataloguing in Publication Data
Morris, David L.
Hepatic Metastases: Diagnosis and Management
I. Title
616.99434706

ISBN 0 7506 0879 X

Library of Congress Cataloguing in Publication Data
Hepatic metastases: diagnosis and management/[edited by] D. L. Morris, C. S. McArdle, G. M. Onik.
p. cm.
Includes bibliographical references and index.
ISBN 0 7506 0879 X
1. Liver—Cancer. 2. Colon (Anatomy)—Cancer—Complications. 3. Rectum—Cancer—Complications. 4. Metastasis. 5. Liver—Surgery. 6. Hepatic artery. I. Morris, David L. II. McArdle, C. S. (Colin Stewart) III. Onik, Gary, 1952–
[DNLM: 1. Liver Neoplasms—secondary. 2. Liver Neoplasms—diagnosis. 3. Liver Neoplasms—therapy. WI 735 H5267 1995]
RC280.L5H443
616.99'436—dc20
DNLM/DLC
for Library of Congress

95-7176
CIP

Photoset by Wilmaset Ltd, Birkenhead, Wirral
Printed in Great Britain by The Bath Press plc, Bath, Avon

10

Isolated liver perfusion

K. R. Aigner

The principle of isolation perfusion for locoregional chemotherapy was first described by Creech *et al.* in 1958 for treatment of disseminated melanoma of a limb. The concept behind this strategy is to supply extremely high drug exposure to the tumour-invaded organ while systemic toxicity is prevented or at least extremely reduced (Creech *et al.*, 1958; Stephens, 1988). The technique of isolated liver perfusion (ILP), as described herein, was first performed in 1981 (Aigner *et al.*, 1982). Due to the poor chemosensitivity of colorectal liver metastases (Link *et al.*, 1986, 1988; De Bruijn *et al.*, 1988), there seemed to be a need for an isolated procedure as a means of increasing the total dose and concentration of cytotoxic drugs to an extent that is only limited by local tissue tolerance. Complete isolation of the perfused system avoids systemic side-effects. Modifications, according to the type of tumour to be treated, technical improvements and new drugs, have been continuously incorporated into the method by our group (Aigner, 1988, 1993a) as well as other investigators (De Brauw *et al.*, 1988; Schalhorn *et al.*, 1988; Hafstroem *et al.*, 1990; Naredi *et al.*, 1992).

Perfusion technique

Complete isolation of the liver is accomplished with a special double-lumen liver perfusion catheter (Perfufix, Braun Melsungen, Germany), introduced into the vena cava, and shunting the caval blood from the lower hemibody to the right atrium (Fig. 10.1).

First the liver is exposed via a midline incision and costal retractors, and mobilized away from the diaphragm. The hepatoduodenal ligament is then exposed and tourniquet tapes are placed around the common hepatic artery, gastroduodenal artery and two around the portal vein for cannulation in both directions. The gastroduodenal artery is then distally ligated. Collateral hepatic arterial branches are dissected. In case of anatomical variations, replaced right or left hepatic arteries are ligated.

Through a transverse incision in the diaphragm the vena cava is exposed intrapericardially and secured with a tourniquet tape. Further tourniquets are placed around the vena cava above and (two) below the renal veins. The lumbar veins entering the vena cava in this area are divided and ligated. Then the patient is heparinized with 150 u/kg.

For cannulation of the vena cava through a longitudinal incision between two vascular clamps, the perfusion catheter is introduced while temporarily blocked with a central guide tube in order to avoid blood loss through the side openings. For complete introduction into the vena cava the guide is removed and the end of the catheter occluded with a strong clamp. When it is in its proper position all tourniquets are fixed.

Cannulation of the portal vein in both directions is performed through a transverse incision. The distal cannula towards the gastrointestinal tract is immediately connected with the portocaval shunt tube of the perfusion catheter. The proximal tube, directed towards

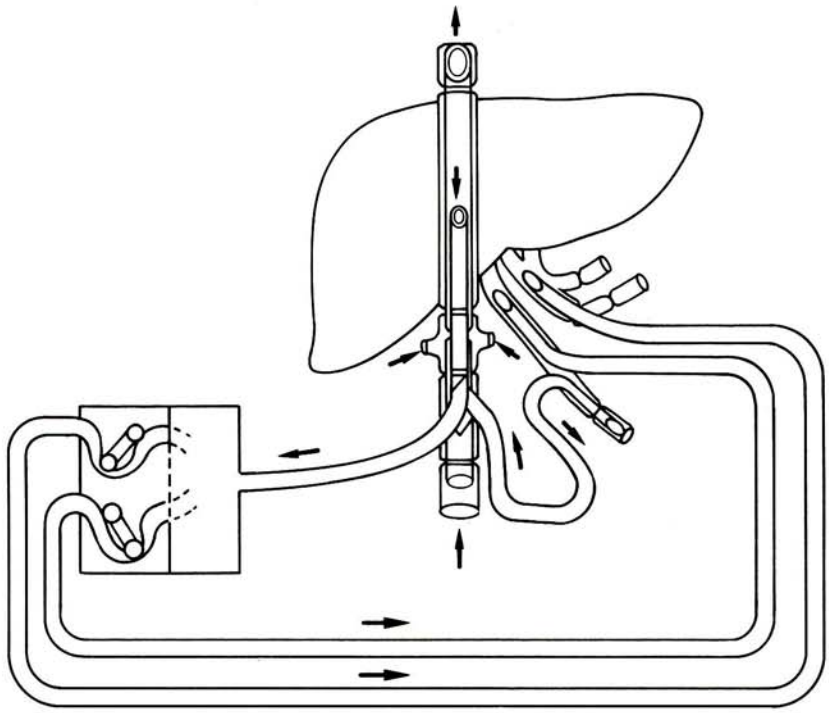

Figure 10.1 The isolated liver perfusion circuit.

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. At this time the common hepatic artery must be clamped in order to prevent systemic blood loss into the isolated perfusion circuit. 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. The flow rate is adapted to the hepatic venous return.

The hepatic artery is usually cannulated through the gastroduodenal artery. At this time the portal flow rate for immediate oxygenation of the liver is adapted to about 300–400 ml/min. During infusion of drugs into the hepatic arterial line over 15–30 min, depending on the drug used and its total dose, the blood flow in this line is kept low, at about 100 ml/min, in order to reach a high local drug concentration. The volume level in the oxygenator is maintained at a steady state, mainly regulated through the venous return and the portal flow. In cases of hyperthermic perfusion, before application of drugs, high flow rates are aimed at in both lines 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. Blood temperature in the oxygenator has to be kept at 41.5–42°C.

After 60 min of isolated cytotoxic perfusion, the venous line is cut through and the perfusate washed out. The hepatic vascular system is refilled with plasma expander and 1 unit of blood that is usually obtained by preoperative haemodilution. After decannulation the vena cava is repaired with a running suture while the bulldog clamp is already removed from the common hepatic artery. The portal vein, too, is repaired with a running Prolene suture. After removal of the hepatic arterial tube a port catheter is inserted into the gastroduodenal artery for subsequent infusion chemotherapy.

Prerequisites for optimal drug exposure and response

Quality of response is basically dependent on tumour vascularization, chemosensitivity and local drug exposure (concentration × time).

Blood supply is different in various histological types of tumour tissue: however, within one histological type small metastases are better vascularized than large ones. Measurements of drug levels in large versus small hepatic lesions as well as in the centre versus the periphery of metastases have confirmed this theory (Aigner *et al.*, 1988).

Chemosensitivity testing has proved to be useful for selecting drugs that are likely to be effective in the tumour to be treated, and to determine which concentration is required to induce an optimal response. In colorectal cancer, drug levels achieved with systemic chemotherapy have turned out to be not sufficiently active. As a consequence, complete remission is rarely seen. This supports the administration of high local concentrations in an isolated perfusion circuit. With reduction of the arterial blood flow via the roller pumps and infusion of cytotoxics 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 isolation perfusion is optimized.

An easier technique of isolation of the liver has been described recently (Aigner, 1995), where a double-balloon stopflow catheter (PfM, Cologne, Germany) with central shunts isolates the hepatic venous return. The catheter is introduced through the femoral artery. The liver is perfused selectively through the hepatic artery while the portal vein is clamped (Fig. 10.2).

Clinical cases

Overall, 57 patients with disseminated non-resectable liver metastases were submitted to ILP. Fifty-three patients had colorectal liver metastases, 1 had liver metastases from ocular melanoma and received 150 mg Cisplatinum (CDDP) and 30 mg Phenylalanine mustard (L-Pam), 2 had carcinoid and 1 had hepatoma. Fifteen colorectal cases had ILP with 1000 mg 5-fluorouracil (5-FU) alone without further therapy. Three of these patients died in the early postoperative phase when ILP was being developed. Since then, no further early post-operative deaths have occurred.

In 19 patients, which was the early group, ILP was performed with 5-FU alone. Forty patients received subsequent hepatic arterial infusion (HAI) with Mitomycin (MMC) (14 mg) and 5 × 5-FU (1000 mg). Thirty-eight of 40 had prior ILP with MMC/5-FU, 2/40 had ILP with 5-FU alone. In these 2 patients response was more impressive during subsequent HAI, which leads to the conclusion that alkylating agents should be used for perfusion. Total MMC dose was continuously increased up to 50 mg without major evidence of local toxicity. Therefore, the study has to be considered a dose-finding pilot trial, particularly since clinical stages were not uniform and consisted of 67% clearly palpable liver enlargement with elevation of the alkaline phosphatase.

Results

Response was generally estimated according to the course of tumour markers. Second-look surgery was only performed in cases where resectability of bulky lesions was to be expected while small lesions had disappeared. On these occasions it became evident that even totally necrotic colorectal metastases with normal carcinoembryonic antigen levels usually do not disappear on the computed tomographic scan – they just shrink – while histologically calcifications and connective tissue are observed. One of those patients, who had turned out to be resectable 4 weeks after ILP at second look, 5 years post-ILP had no evidence of any small lesions, but died after 6 years from myocardial infarction. Another patient presented with a second tumour 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 after 45 months. Two patients are still alive after 9.5 and 10.5 years. The median survival of the total group of 40 patients receiving ILP/HAI was 18 months.

The advantage of ILP with increasing doses of Mitomycin is demonstrated by an increasing number of complete remissions. Although the total percentage of responses is about the same in the 5-FU group and the MMC/5-FU group, the complete response rate is higher in the latter (62%) as compared with the 5-FU group (16%). The partial response rate, however, is only 28% in the MMC/5-FU group versus 79% in the 5-FU group. This indicates a clear dose–response behaviour of Mitomycin.

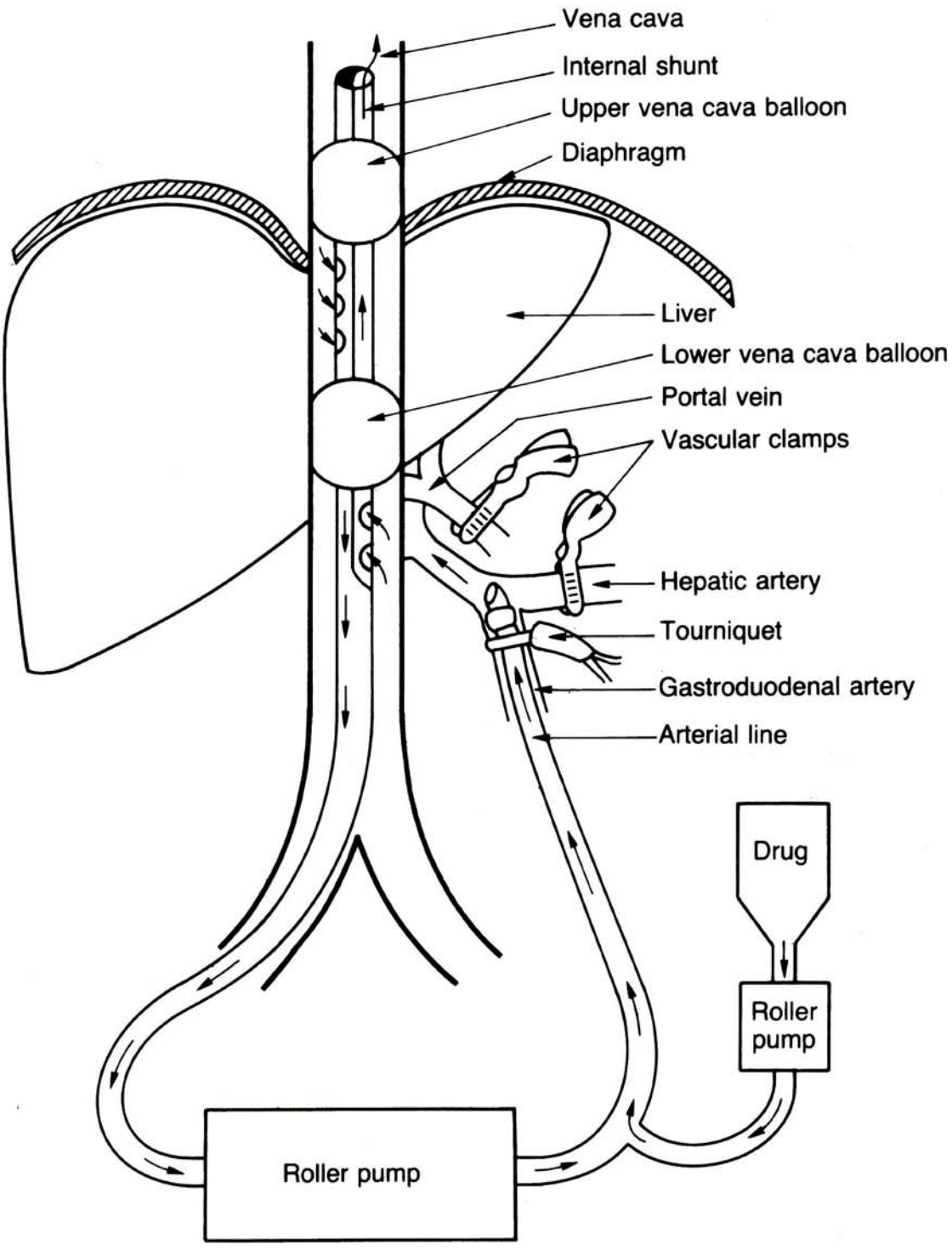

Figure 10.2 Isolated liver perfusion with a double-balloon vena cava catheter.

Table 10.1 Manifestation of extrahepatic lesions following isolated liver perfusion (ILP) or ILP/hepatic arterial infusion (HAI)

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

5-FU = 5-Fluorouracil; MMC = Mitomycin.

Side-effects

Generally, liver tissue damage is unexpectedly mild despite high-dose cytotoxic therapy. A transient increase of serum glutamic oxaloacetic and pyruvic transaminase to 100–200 u/l uusually occurs, but normalizes within 1 week. Performance after ILP does not differ from that after any other laparotomy, lasting 3–4 h. Cholinesterase decreases to 800–1200 u/l and returns to normal within 1 month. Biliary sclerosis was never observed after ILP.

Extrahepatic metastases

A total of 87% of patients developed extrahepatic lesions (peritoneum, lungs, bone, brain or a combination) after therapy at a median interval of 4 months in the ILP 5-FU group and 11.5 months following ILP with MMC/5-FU (Table 10.1). More than 70% of all patients – among them more than 90% of those in clinical stages III and IV (Khayat *et al.*, 1988) – develop peritoneal carcinomatosis, even in cases of complete response in the liver. 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 towards bone and brain metastases.

Discussion

It is evident that in resistant tumour tissue like colorectal metastases, systemic chemotherapy and even HAI fail to provide sufficient local control, since the required local drug exposure due to lack of local concentration or even poor vascularization can never be achieved (Link *et al.*, 1986, 1988; Sigurdson *et al.*, 1987; De Bruijn *et al.*, 1988). Further, it remains questionable whether a high partial response rate in liver metastases really can definitely induce prolonged life expectancy. The answer is most probably no, except in those cases of central metastases adjacent to the bile ducts, where even a partial remission with slight shrinkage of the lesion may postpone the occurrence of jaundice with consecutive liver failure due to biliary occlusion. However, this is not the rule in the majority of the patients at risk, and may certainly not influence the median survival rate of all patients. Since the main criterion is the median survival rate, and not a possibly augmented number of a few more long-term survivors in the lower part of the survival curve, it seems mandatory to investigate further treatment modalities that induce an improved complete/partial response ratio and consequently prolong median survival due to long disease-free intervals. In recent years chemoembolization, performed with the suitable drugs and embolisate, appeared to bear unexpected potential (Konno *et al.*, 1992; Stagg *et al.*, 1992; Taguchi, 1992).

However, 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 tumours treated. Nevertheless, during recent years some progress has been made in the understanding of regional chemotherapy (Pettavel *et al.*, 1984; Krementz, 1986; Wile *et al.*, 1987; Van de Velde, 1988; Ishida *et al.*, 1992; Kemeny *et al.*, 1992). The basic questions arising now are: Has the best drug for the specific tumour been used (Link *et al.*, 1986, 1988; Hafstroem *et al.*, 1990; Naredi *et al.*, 1992)? Is the catheter technique optimal – does the drug get to the tumour? Is there any chemosensitivity in the high dose range that can

be achieved by arterial delivery (Link *et al.*, 1986, 1988)? Is the suggested toxicity acceptable and can quality of life be improved? It should be taken into consideration that colorectal cancer, from the point of view of chemosensitivity and vascularization, is certainly not the most suitable tumour in which to investigate the benefit of regional drug application.

In the perfusion situation it became obvious that isolation techniques with flow reduction and possibly even hypoxia (Aigner, 1993) for further enhancement of the cytotoxic potential of melphalan and Mitomycin might provide – not yet overseeable – possibilities for further improvement of local control. The pitfall, however, that could be foreseen at the very beginning, was that, regarding the tremendous number of patients at risk, the relatively few number of tumour centres able to perform isolation techniques would never be able to cope with it. Furthermore, it became obvious in our study that only lower tumour stages are candidates for isolation perfusion, since distant metastases, first of all in the peritoneum, occur even in cases of local control in the liver. This is a challenge first, to simplify isolation perfusion techniques substantially and, second, to improve local control of peritoneal relapse. Therefore, the technically much easier and less time-consuming stopflow and above all vena cava double-balloon techniques (Aigner, 1993, 1995) for isolation of the hepatic venous return should be taken into consideration, since this can easily be achieved from the femoral access. In addition cannulation of the gastroduodenal artery and clamping of the portal vein are low-risk procedures. Immediate peritoneal lavage (Sugarbaker *et al.*, 1988), hyperthermic peritoneal perfusion (Fujimoto *et al.*, 1988, 1993) or abdominal stopflow or hypoxic perfusion may be useful adjuvants to prevent peritoneal progression, which up to now terminates all local therapeutic endeavours. To obtain definite information concerning the value of isolation perfusion for colorectal liver metastases, randomized trials of the ILP with and without adjuvant modalities should be carried out.

References

Aigner KR (1988) Isolated liver perfusion: 5-year results. *Reg. Cancer Treat.* **3**, 11–20.

Aigner KR (1993) Aortic stopflow infusion (ASI) and hypoxic abdominal perfusion (HAP) for disseminated bulky peritoneal carcinomatosis – rationale and technique. *Reg. Cancer Treat.* (suppl. 1), abstracts A4: 3.

Aigner KR (1995a) A simplifed technique for isolated liver perfusion using a vena cava double balloon catheter with central shunt. *Reg. Cancer Treat.* (in press).

Aigner KR, Walther H, Tonn JC *et al.* (1982) Die isolierte Leberperfusion mit 5-Fluorouracil (5-FU) beim Menschen. *Chirurg.* **53**, 571–573.

Aigner KR Müller H, Walther H & Link KH (1988) Drug filtration in high dose chemotherapy. In: Aigner KR, Patt YZ, Link KH & Kreidler J (eds) *Reg. Cancer Treat.* Vol. 29, pp. 261–280. Basel: Karger.

Creech OJ, Krementz ET, Ryan RF & Winblad JN (1958) Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. *Ann. Surg.* **148**, 616–632.

De Brauw LM, Van der Velde CJH, De Bruijn EA & Tjaden UR (1988) Controlled release of 5-FU ra by application of isolated liver perfusion in the treatment of hepatic metastases. *Reg. Cancer Treat.* Vol. 29, pp. 217–221. Basel: Karger.

De Bruijn EA, Slee PhThJ, Kuppen PJK *et al.* (1988) The importance of exposure time in regional chemotherapy: mitomycin C and fluoropyrimidines. *Reg. Cancer Treat.* Vol. 29, pp. 43–48. Basel: Karger.

Eggermont AMM, Van Ooijen B & Wiggers T (1992) Locoregional immunotherapy for nonresectable malignant hepatic disease. *Reg. Cancer Treat.* **4**, 227–231.

Fujimoto S, Shresta RD, Kokobun M *et al.* (1988) Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. *Ann. Surg.* **208**, 36–41.

Fujimoto S, Takakashi M, Kokobun M *et al.* (1993) Clinical usefulness of cimetidine treatment for prevention of scald injury on the peritoneo-serosal membrane in intraperitoneal hyperthermic perfusion for patients with advanced gastric cancer. *Reg. Cancer Treat.* **1**, 1–6.

Hafstroem L, Rudenstam CM, Holmberg SB, Schersten T & Ehrsson H (1990) The pharmacokinetics of melphalan in regional hyperthermic liver perfusion. *Reg. Cancer Treat.* **3**, 23–25.

Ishida H, Jurama T & Mishima Y (1992) Comparison between portal vein chemotherapy and hepatic artery chemotherapy on experimental liver micrometastases. *Reg. Cancer Treat.* **5**, 74–78.

Kemeny MM, Alava G, Oliver JM & Smith FB (1992) The use of circadian flow patterning to reduce toxicity in continuous infusions of recombinant interleukin-2. *Reg. Cancer Treat.* **4**, 260–264.

Khayat D, Le Cesne A, Weil M *et al.* (1988) Intraarterial treatment of hepatic metastasis using fluorouracil, adriamycin and mitomycin C (FAM) chemotherapeutic regimen. *Reg. Cancer Treat.* **1**, 62–64.

Konno T, Yamashita R, Oda T, Maeda H, Taguchi T & Nagamitsu A (1992) Targeting cancer chemotherapy used lipiodol as a carrier of anticancer agents for hepatocellular carcinoma. *Reg. Cancer Treat.* **5**, 110–116.

Krementz ET (1986) Regional perfusion – current sophistication. What next? *Cancer* **57**, 416–432.

Link KH, Aigner KR, Kuehn W, Schwemmle K & Kern DH (1986) Prospective correlative chemosensitivity testing in high-dose intraarterial chemotherapy for liver metastases. *Cancer Res.* **46**, 4837–4840.

Link KH, Aigner KR & Kessler D (1988) *In vitro* chemosensitivity profiles of human malignancies for high-dose (regional) chemotherapy. In: Aigner KR, Patt YZ, Link KH & Kreidler J (eds) *Reg. Cancer Treat.* Vol. 29, pp. 28–42. Basel: Karger.

Naredi P, Holmberg SB, Hafstroem L, Heath DD, Shalinsky DR & Howell SB (1992) Pharmacokinetics of cisplatin in an isolated liver perfusion system in humans. *Reg. Cancer Treat.* **4**, 254–257.

Pettavel J, Leyvraz S & Douglas P (1984) The necessity for staging liver metastases and standardizing treatment-response criteria. The case of secondaries of colo-rectal origin. In: Van de Velde CJH & Sugarbaker PH (eds) *Liver Metastasis*. pp. 154–168. Dordrecht: Nijhoff.

Schalhorn A, Peyerl G & Denecke H (1988) Pharmacokinetics of 5-fluorouracil during isolated liver perfusion. *Reg. Cancer Treat.* **1**, 21–27.

Sigurdson ER, Ridge JA, Kemeny N & Daly JM (1987) Tumor and liver drug uptake following hepatic artery and portal vein infusion. *Clin. Oncol.* **5**, 1836–1840.

Stagg RJ, Venook AP, Chase JL, Frye JW, Ring EJ & Hohn DC (1992) Chemoembolization of primary and metastatic liver tumors. *Reg. Cancer Treat.* **5**, 53–57.

Stephens FO (1988) Why use regional chemotherapy? Principles and pharmacokinetics. *Reg. Cancer Treat.* **1**, 4–10.

Sugarbaker PH, Cunliffe W, Belliveau JF *et al.* (1988) Rationale for perioperative intraperitoneal chemotherapy as a surgical adjuvant for gastrointestinal malignancy. *Reg. Cancer Treat.* **1**, 66–79.

Taguchi T (1992) A comparative randomized study on the treatment of primary and secondary liver tumors with intraarterial chemotherapy with or without degradable starch microspheres (DSM) (Spherex). *Reg. Cancer Treat.* **5**, 117–120.

Van de Velde CJH, de Brauw LM, Sugarbaker PH & Tranberg K (1988) Hepatic artery infusion chemotherapy: rationale, results, credits and debits. *Reg. Cancer Treat.* **1**, 93–101.

Wile AG, Kar R, Cohen RA, Jakowatz JG & Opfell RW (1987) The pharmacokinetics of cisplatin in experimental regional chemotherapy. *Cancer* **59**, 695–700.