

Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy

Arjen J. Witkamp, Eelco de Bree, Andres R. Van Goethem and Frans A. N. Zoetmulder

Department of Surgical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands

Background: In recent years surgical cytoreduction followed by intra-operative hyperthermic intraperitoneal chemotherapy (HIPEC) was introduced as treatment modality in patients with peritoneal surface malignancy. In the current review the rationale for this approach, the prerequisites and the different techniques used are discussed.

Methods: A literature search through PubMed was performed.

Results: Pharmacokinetic studies have shown an important dose advantage for intraperitoneal versus intravenous application. Hyperthermia enhances the penetration of cytostatic drugs into tumour tissue and also shows synergism with various cytostatic drugs. The penetration depth of drugs into tissue is limited, therefore HIPEC can only be effective in patients with minimal residual disease after (aggressive) surgery. HIPEC can be conducted in various ways, without clear proven advantage of one method over the others. Local complications after this combined treatment approach are mainly surgery related. Intra-peritoneal chemotherapy may cause systemic toxicity, dependant on the drug used. In randomised studies cytoreductive surgery followed by HIPEC has proven its value in the prevention of peritoneal dissemination in gastric cancer. Phase II data on HIPEC in peritoneal carcinomatosis of colorectal origin and pseudomyxoma peritonei are promising, but randomised studies are still not available.

Conclusion: Aggressive surgical cytoreduction and HIPEC in patients with peritoneal surface malignancy has a clear rationale and seems to have clinical value. © 2002, Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Peritoneal surface malignancy has always been a major problem in cancer management. Surgery alone can never be complete at microscopic level and in gastrointestinal cancers systemic chemotherapy has only limited value. Residual or recurrent disease will occur in almost all cases and patients usually die of

gastrointestinal malfunction and cachexia. In recent years it has been emphasised that peritoneal seeding can be understood as regional spread, comparable to lymph node metastases. This means that it is a poor prognostic sign, but no proof for distant metastases. This provides a rationale for regional therapy, as effective regional control will postpone death in most cases and possibly cure some of the patients. Intra-operative heated chemoperfusion of the abdominal cavity was introduced in the prevention and treatment of peritoneal surface malignancy in the early eighties. The current report reviews the literature concerning the rationale and techniques of this treatment option in the treatment of peritoneal

Correspondence to: F.A.N. Zoetmulder MD PhD, Department of General Surgery, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam. Tel.: +31/20 512 2550; Fax: +31-20 512 2554; E-mail: fzoet@nki.nl

metastases with a main emphasis on gastrointestinal tract cancers. A literature search was performed through PubMed (United States National Library of Medicine) using hyperthermia, hyperthermic, intraperitoneal, chemotherapy, colorectal cancer, gastric cancer and pseudomyxoma peritonei as keywords, using English language only.

INTRAPERITONEAL CHEMOTHERAPY

In most cases peritoneal metastases from primary gastrointestinal tract cancer are relatively resistant to intravenous cytotoxic drugs with a clear dose-effect relation, but with the effective dose exceeding the toxic dose. Intraperitoneal administration of cytotoxic drugs can increase the local exposure with less systemic toxicity compared to intravenous administration. An additional advantage is that the blood drainage of the peritoneal surface through the portal vein to the liver provides an increased exposure of potential hepatic micro metastases to intraperitoneally administered cytotoxic drugs. The concept of intraperitoneal chemotherapy is not new. Already in 1955 Weissberger *et al.* reported the treatment results of intraperitoneal nitrogen mustard in 7 patients with ovarian cancer (1). However, most of the early reports on the clinical use of intraperitoneal chemotherapy failed to produce a clear survival benefit in patients with peritoneal surface malignancy. It was not until 1978 that Dedrick and his co-workers took a more studied look at the pharmacokinetic favours of intraperitoneal chemotherapy (2). They found that hydrophilic cytotoxic drugs can maintain a significant concentration gradient along the peritoneal-plasma barrier, with high intraperitoneal concentrations, when added in the abdominal cavity in large volumes (3). However, they also emphasised that the most limiting factor in the clinical use of intraperitoneal chemotherapy is the restrictive penetration depth of the used drugs in tumour tissue (probably 1–3 mm). Dedrick's findings are confirmed by more recent studies in ovarian cancer (4–6). It is now generally accepted that the only patients that will possibly benefit from intraperitoneal chemotherapy are patients with minimal residual disease after surgery.

SURGERY

The aim of cytoreductive surgery before intraperitoneal chemotherapy is to obtain complete resection of macroscopic tumour and the complete lysis of pre-existent intra-abdominal adhesions in order to create an optimal exposure to intraperitoneal drugs. Often

complete removal of all macroscopic tumour is not possible. Most groups consider intraperitoneal therapy only useful if residual tumour nodules are smaller than 3 mm, in view of recorded drug penetration depth. The importance of cytoreductive surgery on survival has already been studied in ovarian cancer (7,8). However, it was Sugarbaker who developed a specific surgical procedure which made it possible to perform large peritonectomy procedures with the use of Electro-surgery in order to obtain maximal cytoreduction in peritoneal carcinomatosis (9). He described six different peritonectomy procedures which can be performed separately or all together: Greater omentectomy-splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy-cholecystectomy with stripping of the omental bursa, pelvic peritonectomy with sleeve resection of the sigmoid colon and antrectomy. Using this cytoreductive technique combined with an aggressive approach towards affected intra-abdominal organs makes it possible to create an optimal situation for intraperitoneal chemotherapy in most patients. When surgical cytoreduction is performed in advance of intra-operative intraperitoneal chemotherapy, bowel reconstruction after resections is usually postponed till after the chemotherapy perfusion in order to minimise the risk of tumour cell seeding at anastomotic sites. Sugarbaker also developed an objective method to score the presence and size of macroscopic tumour in 13 different abdominal regions (Peritoneal Cancer Index) before and after cytoreductive surgery (10). This Peritoneal Cancer Index is based on the natural route of tumour implantation and is an important help in estimating the likelihood of complete cytoreduction in peritoneal surface malignancy. The use of this scoring system should be encouraged in the surgical treatment of peritoneal carcinomatosis because it prevents unnecessary surgery in high risk patients, thus decreasing postoperative morbidity. In The Netherlands Cancer Institute a simplified version of the Peritoneal Cancer Index is used which contains seven abdominal regions (small pelvis, ileocolic, omentum and transverse colon, small bowel and mesentery, subhepatic, subdiaphragm left and subdiaphragm right).

HYPERTHERMIA

True clinical hyperthermia is defined as the use of temperatures of 41°C and higher. The scientific basis for the use of hyperthermia in malignancy is multifactorial. Hyperthermia itself has a direct cytotoxic effect caused by impaired DNA repair, denaturation of proteins, induction of heat-shock proteins which

TABLE I Interaction between hyperthermia and cytotoxic drugs that are used during HIPEC procedures (69). Although enhancement of penetration depth should theoretically apply for all drugs, this has only been proved for cisplatinum

	Synergism	Non cell-cycle specific
Mitomycin C	yes (linear $\geq 39^{\circ}\text{C}$)	yes
Cisplatinum	yes (linear $\geq 39^{\circ}\text{C}$)	yes
Melphalan	yes (linear $\geq 39^{\circ}\text{C}$)	yes
Mitroxantrone	yes (linear $\geq 39^{\circ}\text{C}$)	yes
Bleomycin	yes (threshold $\geq 42^{\circ}\text{C}$)	yes
Doxorubicin	yes (threshold $\geq 42^{\circ}\text{C}$)	yes
Taxanes	no	yes
5-FU	no	no

may serve as receptors for natural killer-cells, induction of apoptosis and inhibition of angiogenesis (11,12). The cytotoxic effect of hyperthermia is not only temperature dependent, but is also related to the exposure time and the time-relation to other therapies. Furthermore hyperthermia also shows a synergism with certain cytotoxic drugs (Table 1). Increased cell-membrane permeability at higher temperatures, can increase drug uptake by tumour tissue (13). Pharmacokinetics of these drugs can also be affected by altered active drug transport and cell metabolism. This synergism can already occur at temperatures as low as $39\text{--}41^{\circ}\text{C}$ (mild hyperthermia) in some cytotoxic drugs as cisplatinum, ifosfamide, melphalan and mitomycin C (13). Besides this synergistic effect hyperthermia can also diminish the systemic toxicity of some drugs (e.g. doxorubicin and cyclophosphamide) by increasing their alkylation and/or excretion (14).

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

In the late 1970s Spratt *et al.* began experiments in dogs in which they tried to combine hyperthermia and continuous perfusion of the abdominal cavity, in order to find a selective local treatment option for peritoneal carcinomatosis (15). They created a model that was based on the earlier findings of the direct cytotoxic effect of hyperthermia, the synergism between hyperthermia and cytotoxic drugs and the pharmacokinetic advantage of intraperitoneal chemotherapy. Five dogs were treated with a continuous 2 h perfusion of the abdominal cavity at 41°C without direct toxicity and a quick and homogeneous distribution of the added drug over the peritoneal cavity. This finally resulted in the first intra-operative heated intraperitoneal chemotherapy (HIPEC) perfusion in a human being with pseudomyxoma peritonei in

February 1979 (16). After surgical debulking of the macroscopic tumour mass, the abdominal cavity was perfused with a cell cycle non-specific agent (thiotepa) directly postoperative during 1 h at 42°C . Five days postoperatively, this was followed by a cell cycle specific agent (methotrexate), which was administered during hour. No major complications or toxicity was recorded. In the following years other authors developed different clinical perfusion models for intra-operative HIPEC in respectively pseudomyxoma peritonei, colorectal- and gastric cancer.

DIFFERENT PERFUSION TECHNIQUES

Peritoneal expansion

In early reports the HIPEC procedure was performed during the early postoperative phase, as described by Spratt (15,16). However, experiments with blue dye showed that intraperitoneal fluid distribution was not optimal, probably due to early postoperative adhesions and the development of preferential intraperitoneal pathways for perfusion fluid as soon as the abdomen is closed (17). Therefore, peritoneal expansion is applied in most centers to optimise exposure of the intra-abdominal organs and the parietal peritoneum to the perfusate. This can be achieved by different methods (Figure 1). Sugarbaker introduced the so called coliseum technique (18). The skin of the abdomen is attached to a retractor ring, which is placed above the laparotomy wound. The abdominal cavity is covered with a plastic sheet with a small opening in the centre allowing entrance for the surgeon's hand to stir the abdominal contents, resulting in a better exposure of the seroperitoneal surfaces and a more uniform distribution of drug and heat. Yonemura and his co-workers were the first to introduce a 'peritoneal access devise' to achieve optimal peritoneal expansion (19,20). This expander is made of a transparent acrylic cylinder, which is fitted in the laparotomy wound. Creating peritoneal expansion according this technique makes it possible to add large volumes of perfusion fluid allowing the small bowel to float in the cavity expander. A major advantage of the two previously described techniques is that they create a controlled distribution of fluid, heat and cytotoxic drugs. Disadvantages, however, are heat loss through the open laparotomy wound and more important, possible leakage of drugs thus creating a health risk for the operating theatre staff. Another disadvantage in the use of the peritoneal expander might be that small parts of the parietal peritoneum are not fully exposed thus creating a risk area for tumour recurrence (21).

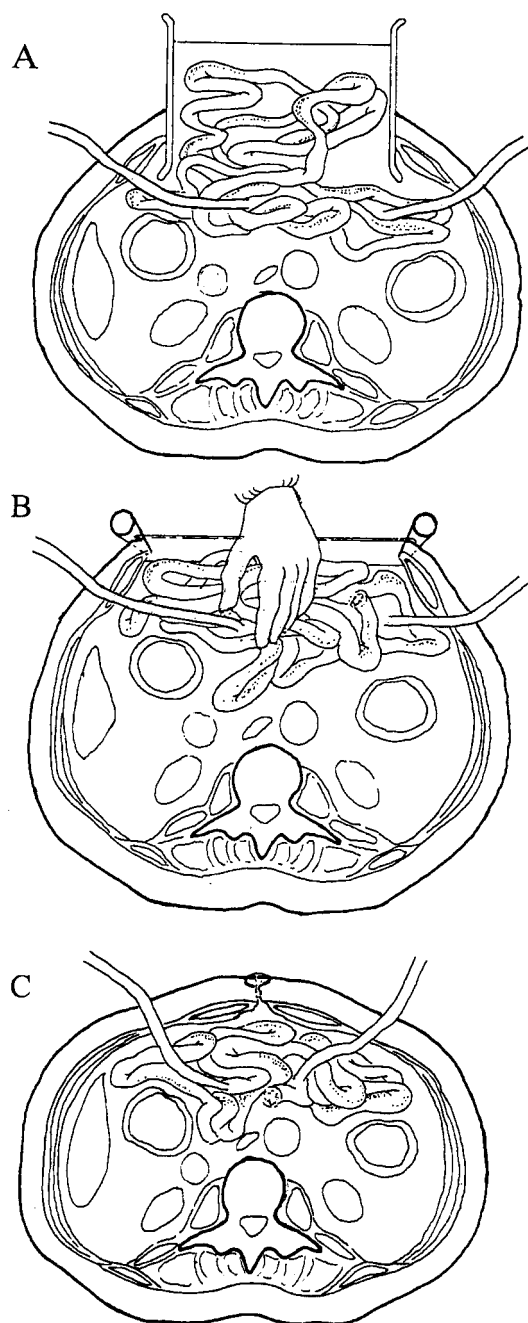


Figure 1 Cross-section through the abdomen during intra-operative HIPEC procedures using different peritoneal expansion techniques: A = coliseum technique, B = with the use of a peritoneal cavity expander and C = with closed abdomen.

Fujimoto and Koga both developed separately from each other a perfusion system in which the abdomen is closed during perfusion by a running suture of the skin (22,23). This way the whole peritoneal surface is exposed and it prevents drug spillage and heat loss. This technique also provides the possibility of increasing the abdominal pressure by adding large volumes of perfusion fluid (up to 9 L) which might

lead to increased drug penetration of macromolecular agents (24). The latter has only been proved in a rat model using doxorubicin (25). However, homogeneous distribution of the perfusion fluid with a closed abdomen remains very uncertain (17,21). Other attempts to promote the distribution of the perfusion fluid include external massage of the abdomen and an increased flow rate of perfusion fluid (26,27).

Perfusion models

Another difference in perfusion techniques is the use of an open versus a closed perfusion model. Most centers use a curled Tenckhoff inflow catheter (placed centrally in the abdomen or at the site of highest risk for recurrence) and two or more outflow catheters (placed in the subdiaphragmatic space and in the lower pelvis) to obtain a continuous flow of perfusion fluid equally distributed throughout the abdominal cavity. These catheters are inserted through separate stab incisions in the abdominal wall. When both the inflow and outflow catheters are connected to a perfusion pump, fluid filter and heat exchanger, a closed circuit is formed (26). In an open perfusion model the outflow catheters are connected to a separate compartment, thus preventing re-use of perfusion fluid (23). The advantage of the closed model is that it creates more control over the whole perfusion system and that it is easier to maintain adequate hyperthermia of the perfusion fluid. Disadvantage is the theoretical possibility of re-introduction of tumour cells into the abdominal cavity.

Hyperthermia control

There is no consensus yet on the optimal temperature during HIPEC procedures. As pointed out above, synergism between various cytotoxic drugs and hyperthermia starts at a temperature of 39°C but is stronger at higher temperatures. On the other hand, at temperatures above 43°C this synergism seems to decrease in most cytotoxic drugs (13) and the small bowel toxicity of heat increases above 43°C. Another problem in the use of hyperthermia during perfusion is the development of thermotolerance due to the activation of heat shock proteins at temperatures of around 43°C during short exposure time (30 min or less) (11). Hyperthermia $\leq 43^\circ\text{C}$ itself appears to have no influence on the complication rate in HIPEC procedures (28). Most groups perfuse therefore at temperatures between 41 and 43°C for 60 min or longer. Temperature probes are attached to the in- and

outflow catheters in the abdominal cavity and to the heat exchanger to control the distribution of heat. In The Netherlands Cancer Institute the intraperitoneal temperature control at multiple locations (subdiaphragmatic left and right, small pelvis and centrally in the abdominal cavity) are used as main help to register the fluid distribution. Insufficient perfusion in an area of the abdomen will very quickly result in a drop of temperature. However, manual stirring of the abdominal contents during perfusion leads to an homogeneous heat (and thus fluid) distribution. A probe in the oesophagus or larynx monitors the core temperature in order to prevent malignant hyperthermia of the patient.

CHOICE OF DRUG AND PHARMACOKINETICS

The pharmacokinetic advantage of intraperitoneal chemotherapy is the most important rationale for HIPEC in peritoneal surface malignancy. The movement of large molecular drugs from the intraperitoneal cavity to the systemic compartment of the body is much slower than the clearance of drugs from the systemic compartment. This principle creates a concentration gradient over the peritoneal-plasma barrier, strongly in favour of the intraperitoneal concentration after intraperitoneal drug administration. Stripping of large surfaces of the peritoneum as common in peritonectomy procedures does not alter this phenomenon (29). Rubin *et al.* showed that removal of intra-abdominal viscera also has no effect on the effectiveness of the peritoneal-plasma barrier (30). It has to be noted that for the treatment of free intraperitoneal tumour cells high intraperitoneal drug concentrations seems of main importance. However, for invasive peritoneal tumour deposits it is more important to achieve high drug concentrations in superficial tissue bordering the peritoneal cavity. Therefore, high intraperitoneal/plasma drug concentration ratios are not automatically associated with higher efficacy, but may even be undesirable if it

means that no drug has entered the target tumour residues.

Cytotoxic drugs used

For use during HIPEC procedures drugs should fulfil the following criteria: they have to be of large molecular weight and be water-soluble, they must be rapidly cleared from the systemic circulation and their effectiveness must be enhanced by (mild) hyperthermia. Non cell-cycle specific drugs are preferred because they are cytotoxic after even a relatively short exposure time. Table 1 shows commonly used chemotherapeutic agents that meet these criteria. Although 5-fluorouracil has been widely used in postoperative intraperitoneal chemotherapy, it is not an ideal drug for HIPEC procedures because it does not exhibit synergy with hyperthermia and its cytotoxicity is cell-cycle dependent.

Pharmacokinetics and dosage

Both clinical and pre-clinical studies have shown the pharmacokinetic advantage of HIPEC. High intraperitoneal drug concentrations can be obtained in HIPEC procedures in combination with relatively low plasma concentrations (31–39). This is also found when the area under the time concentrations curve (AUC) is used as more exact measure of total drug exposure. However, comparison between the different studies regarding pharmacokinetics is difficult because of the difference in drugs, dosage and perfusion techniques used. Most clinical experience in HIPEC procedures is gained with mitomycin C (MMC) and platinum containing therapy. With MMC, peritoneal-plasma concentration ratio's up to 28 are described (32), while rapid absorption leads to high tissue levels (35). Tables 2 and 3 show various pharmacokinetic studies in MMC and cisplatin in HIPEC procedures. It appears that higher abdominal temperatures lead to higher peritoneal/plasma

TABLE 2 MMC pharmacokinetics during HIPEC

Study	n	Dose	Abdomen	Mean i.p. temp.	Perfusion time	i.p. t _{1/2} (min)	MMC _{max} pe/pl	AUC pe/pl
Loggie (56)	7	20 mg/L	closed	40.5°C (inflow)	120 min	97 min. (± 31)	27	–
Fujimoto (32)	21	10 mg/L	closed	45°C (outflow)	118 (± 17) min	–	28	–
Beaujard (39)	83	10 mg/L	closed	42°C	90 min	–	20	–
Panteix (35)	18	10 mg/L	closed	42°C	90–120 min	–	24	–
Fernandez-Trigo (26)	10	5–10 mg/L	closed	41–43°C	120 min	58 (± 13) min.	–	22
Jacquet (42)	18	10 mg/L	open	41–43°C	120 min	58 (± 10) min	–	23.5
Neth. Cancer Institute	118	18 mg/L	open	40–41°C	90 min	–	25	13

TABLE 3 Cisplatin pharmacokinetics during HIPEC

Study	n	Dose	Abdomen	Mean i.p. temp.	Perfusion time	i.p. $t_{1/2}$ (min)	MMC] _{max} pe/pl	AUC pe/pl
Stephens (70)	13	86.4 mg	closed	40.6°C	120 min	48 (± 14)	–	6.9 (± 3.6)
van de Vaart (36)	5	108 mg	open	41.5°C	90 min	–	15	–
Ma (37)	9	300 mg	closed	41°C	90 min	30	13	21

concentration- or AUC-ratios. In some of the reported studies the plasma AUC is only calculated for the duration of the perfusion, while in other studies the AUC is calculated for the first 24 h during and after perfusion. The duration of perfusion seems to have no influence on the peritoneal/plasma ratios. In most of the reported studies intraperitoneal drug half-life is 90 min or less. This finding pleads for a perfusion time of 90 min or less, or a divided drug administration, in order to maintain effective intraperitoneal drug concentrations. When MMC is used, higher ratios are reached compared to cisplatin. DNA-adduct measurements after HIPEC procedures with cisplatin have shown that penetration of cisplatin in tissue is significantly improved when compared to normothermic intraperitoneal therapy (36,40). There are no data on the penetration depth of MMC after intraperitoneal use. However, therapeutic MMC concentrations are found in the urothelium, lamina propria and even the muscle layer of the bladder after intravesical instillation therapy, suggesting the penetration of at least a few millimetres (41). Different dose schedules are described. Most authors dose per litre volume of perfusion fluid (mg/L) (32,38,42). Other studies use a dosage based on body surface (mg/m²) (43) or a combination of both (mg/m²/L) (44). The latter seems the most accurate because the total volume of perfusate used can differ significantly between individuals. There are few reports on the maximum tolerated dose of cytotoxic drugs in HIPEC procedures (45). In our own institution we have performed HIPEC procedures with MMC in colorectal carcinoma and pseudomyxoma peritonei at different dose levels. We used 15, 25, 35 and 40 mg/m². Pharmacokinetic analysis showed that the best peritoneal-plasma AUC ratio was at 35 mg/m². Unacceptable systemic toxicity occurred at 40 mg/m² (i.e. grade IV leucocytopenia), finally resulting in two postoperative deaths. Therefore 35 mg/m² MMC was chosen as standard dose in HIPEC procedures in The Netherlands Cancer Institute.

COMPLICATIONS

The combination of aggressive surgical cytoreduction and HIPEC is associated with a relatively high

morbidity rate. Complications that occur may arise as a result from the surgical procedure, hyperthermia or the intraperitoneal chemotherapy. There is a wide variation in reported morbidity (0–39%) and mortality rates (0–20%), regardless of indication, technique and cytotoxic drug used (23,24,39,46–50).

Surgical complications

The major surgical complications described include mainly bowel perforations, anastomotic leakage and fistula formation. Also bile leakage, pancreatitis, postoperative bleeding, wound dehiscence, deep vein thrombosis and pulmonary embolism, pneumothorax, cardiovascular arrest and ischaemic cerebral damage are reported. It is often difficult to separate complications related to surgery from those that are related to intraperitoneal chemotherapy or heat. Most of the described major complications appear to be related to the aggressive surgical procedure. The number of previous laparotomies, duration of surgery, number of peritonectomy procedures, number of visceral resections and number of suture lines are associated with major morbidity (49). Fumagalli *et al.* found that MMC impairs the healing of suture lines, resulting in an increased anastomotic leakage after HIPEC with MMC in rats (51). Randomised studies in gastric cancer have shown no clinical proof for this (19,23,52,53). Bowel perforations are probably caused by surgical trauma of the bowel surfaces, possibly enhanced by thermal and chemotherapeutic damage (46,54,55). However, by using a control group that was treated with intra-operative normothermic intraperitoneal chemotherapy, Shido *et al.* showed that hyperthermia itself does not cause peritoneal damage when used in HIPEC procedures.

Systemic toxicity

Systemic toxicity includes renal failure in cisplatin perfusions and grade III and IV hematologic toxicity in MMC perfusions. Renal failure after HIPEC is generally reversible, however postoperative death due to severe renal failure has been described (56). There is also a case report of

anaphylactic reaction after intraperitoneal chemotherapy with cisplatin (57). Bone marrow suppression resulting in leucocytopenia and thrombocytopenia is clearly a result of the intraperitoneal chemotherapy and is dose and drug (MMC) related (49,55). Interestingly, the nadir of bone marrow suppression after HIPEC with MMC is <2 weeks post-operatively, while the nadir after systemic MMC is 4–6 weeks after administration (38). The haemolytic-uraemic-syndrome (HUS), which sometimes occurs after intravenous MMC or cisplatin administration, is not described after HIPEC procedures.

SURVIVAL AFTER HIPEC

Most clinical experience with aggressive surgical cytoreduction in combination with HIPEC has been gained in gastric cancer, pseudomyxoma peritonei and peritoneal carcinomatosis from colorectal origin (see Table 4). Other positive results have been reported in intraperitoneal mesothelioma, sarcomatosis and advanced ovarian cancer (37,58–60). An important prognostic factor in most studies reporting survival is the completeness of cytoreduction achieved during surgery. Unfortunately there are no reliable data on the influence of drug dosage on

survival. Aggressive surgical cytoreduction followed by HIPEC appears to be an effective treatment in peritoneal carcinomatosis from gastric origin, resulting in an improved survival rate (61). At this time randomised data on survival after HIPEC are only available from studies in which HIPEC was used as prophylactic adjuvant treatment during primary surgery for high-risk gastric cancer (47,62,63). These studies show that survival in high risk gastric cancer can be improved by using HIPEC as adjuvant treatment (see Table 5). Phase II data on colorectal cancer and pseudomyxoma peritonei are promising (43,50,64–68). Randomised studies in colorectal cancer are now awaited. In The Netherlands Cancer Institute a randomised phase III trial is now in progress to investigate the value of cytoreductive surgery and HIPEC in peritoneal carcinomatosis from colorectal origin. First results of this study will be available by the end of 2001.

CONCLUSIONS

Aggressive cytoreductive surgery followed by intra-operative HIPEC has recently been introduced in the treatment of peritoneal surface malignancy. Pharmacokinetic studies have shown a clear dose

TABLE 4 Results regarding survival after extensive surgical cytoreduction and HIPEC in patients with pseudomyxoma peritonei and peritoneal carcinomatosis of colorectal and gastric origin. Not included are (randomised) studies on the prevention of peritoneal dissemination of gastric cancer. (* = Follow-up for whole group of treated patients, not specified for colorectal carcinoma)

Study	Year	Tumour site	n	Median follow-up	Survival
Sugarbaker (65)	1999	appendix carcinoma	161	–	2 years 50%, 5 years 30%
Schneebaum (64)	1996	colorectal carcinoma	15	10 months	NED in 1 patient, all alive
Loggie (68)	2000	colorectal carcinoma	38	27* months	2 years 39%, 3 years 24%
Cavaliere (66)	2000	colorectal carcinoma	14	30* months	2 years 64%
Witkamp (50)	2000	colorectal carcinoma	29	38 months	2 years 45%, 3 years 23%
Elias (67)	1997	colorectal carcinoma	23	12* months	2 years 40%
Witkamp (43)	2000	pseudomyxoma peritonei	46	12 months	3 years 81%
Sugarbaker (65)	1999	pseudomyxoma peritonei	224	–	5 years 80%
Fujimoto (61)	1997	gastric cancer	48	–	3 years 42%, 5 years 31%
Yonemura (71)	1999	gastric cancer	83	–	5 years 11%
Beaujard (39)	2000	gastric cancer	23	–	1 year 48%, 2 years 33%

TABLE 5 Results of randomised studies regarding HIPEC as adjuvant prophylactic treatment in high risk (stage III, TNM classification) gastric cancer

Study	Year	no. of patients surgery alone	no. of patients surgery + HIPEC	5 years survival surgery alone	5 years survival surgery + HIPEC
Yu (62)	1998	81	78	18.4%	49.1%
Ikeguchi (63)	1995	39	33	44%	66%
Fujimoto (47 [†])	1999	70	71	49% [‡]	62% [‡]

[†]Both low-risk and high risk patients included; [‡]8 years survival.

advantage for HIPEC versus systemic chemotherapy. The prerequisites for HIPEC are minimal residual disease after surgery and the absence of extra-abdominal metastases. The expansion of the abdominal cavity during perfusion is applied to optimise drug exposure. Various drugs can be used, but most experience has been gained with mitomycin C and cisplatin. Local complications after HIPEC are mainly surgery related, while systemic toxicity is caused by the intraperitoneal chemotherapy. The latter is dose and drug dependent. Randomised studies have shown that HIPEC reduces the risk of peritoneal recurrence when used during primary surgery in high-risk gastric cancer. Phase II data on the use of HIPEC in the treatment of pseudomyxoma peritonei and peritoneal metastases from gastric and colon cancer are promising. Randomised studies are now awaited.

ACKNOWLEDGEMENT

The authors would like to thank P.J. Tanis MD for his illustrations.

REFERENCES

- Weissberger AS, Levine B, Storaasli JP. Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. *JAMA* 1955; **159**: 1704–1707.
- Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1978; **62**: 1–9.
- Jones RB, Myers CE, Guarino AM *et al.* High volume intraperitoneal chemotherapy (“belly bath”) for ovarian cancer. Pharmacologic basis and early results. *Cancer Chemother Pharmacol* 1978; **1**: 161–166.
- Howell SB, Zimm S, Markman M *et al.* Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. *J Clin Oncol* 1987; **5**: 1607–1612.
- Alberts DS, Liu PY, Hannigan EV *et al.* Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996; **335**: 1950–1955.
- Ozols RF, Gore M, Tropé C *et al.* Intraperitoneal treatment and dose-intense therapy in ovarian cancer. *Ann Oncol* 1999; **10**: 59–64.
- Griffiths CT, Parker LM, Fuller AF Jr. Role of cytoreductive surgical treatment in the management of advanced ovarian cancer. *Cancer Treat Rep* 1979; **63**: 235–240.
- Eisenkop SM, Friedman RL, Wang HJ. Secondary cytoreductive surgery for recurrent ovarian cancer. A prospective study. *Cancer* 1995; **76**: 1606–1614.
- Sugarbaker PH. Peritonectomy procedures. *Ann Surg* 1995; **221**: 29–42.
- Sugarbaker PH, Ronnet B, Archer A *et al.* Pseudomyxoma peritonei syndrome. *Adv Surg* 1996; **30**: 233–280.
- Christophi C, Winkworth A, Muraliharan V, Evans P. The treatment of malignancy by hyperthermia. *Surg Oncol* 1999; **7**: 83–90.
- Dahl O, Dalene R, Schem BC, Mella O. Status of clinical hyperthermia. *Acta Oncol* 1999; **38**: 863–873.
- Storm FK. Clinical hyperthermia and chemotherapy. *Radiol Clin N America* 1989; **27**: 621–627.
- Bull JMC. An update on the anticancer effects of a combination of chemotherapy and hyperthermia. *Cancer Res* 1984; **44**: 4853s–4856s.
- Spratt JS, Adcock RA, Sherrill W, Travathen S. Hyperthermic peritoneal perfusion system in canines. *Cancer Res* 1980; **40**: 253–255.
- Spratt JS, Adcock RA, Muskovin M *et al.* Clinical delivery system for intraperitoneal hyperthermic chemotherapy. *Cancer Res* 1980; **40**: 256–260.
- Averbach AM, Sugarbaker PH. Methodologic considerations in treatment using intraperitoneal chemotherapy. *Cancer Treat Res* 1996; **82**: 289–309.
- Sugarbaker PH. Management of peritoneal-surface malignancy: the surgeon’s role. *Langenbecks Arch Surg* 1999; **384**: 576–587.
- Fujimura T, Yonemura Y, Muraoka K *et al.* Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomised controlled study. *World J Surg* 1994; **18**: 150–155.
- Yonemura Y, Fujimura T, Fushida S *et al.* Hyperthermochemotherapy combined with cytoreductive surgery for the treatment of gastric cancer with peritoneal dissemination. *World J Surg* 1991; **15**: 530–536.
- Elias D, Damia E, Puizillout J *et al.* Thermic homogeneity and standardization of intraperitoneal chemohyperthermia for peritoneal carcinomatosis. *Reg Cancer Treat* 1996; **9**: 54–59.
- Fujimoto S, Shrestha R, Kokobun M *et al.* Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. *Ann Surg* 1988; **36**–40.
- Koga S, Hamazoe R, Maeta M *et al.* Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin-C. *Cancer* 1988; **61**: 232–237.
- Tsiftis D, de Bree E, Romanos J *et al.* Peritoneal expansion by artificially produced ascites during perfusion chemotherapy. *Arch Surg* 1999; **134**: 545–549.
- Jacquet P, Stuart OA, Chang D, Sugarbaker PH. Effects of intra-abdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration. *Anticancer Drugs* 1996; **7**: 596–603.
- Fernandez-Trigo V, Stuart OA, Stephens AD *et al.* Surgically directed chemotherapy: heated intraperitoneal lavage with mitomycin C. *Cancer Treat Res* 1996; **81**: 51–61.
- Otani S, Maeta M, Oka A *et al.* Long term survival of 5 years following initial surgery for gastric cancer and simultaneous disseminated peritoneal metastasis. *Surg Today* 1995; **25**: 959–961.
- Shido A, Ohmura S, Yamamoto K *et al.* Does hyperthermia induce peritoneal damage in continuous hyperthermic peritoneal perfusion. *World J Surg* 2000; **24**: 507–511.
- Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. *Cancer Treat Res* 1996; **82**: 53–63.
- Rubin J, Jones Q, Planch A, Bower JD. The minimal importance of hollow viscera to peritoneal transport during peritoneal dialysis in the rat. *Am Soc Artif Intern Organs Transact* 1988; **34**: 912–915.
- Ceelen WP, Hesse U, de Hemptinne B, Pattyn P. Hyperthermic intraperitoneal chemoperfusion in the treatment of locally

- advanced intra-abdominal cancer. *Br J Surg* 2000; **87**: 1006–1015.
32. Fujimoto S, Shrestha RD, Kokobun M *et al.* Pharmacokinetic analysis of mitomycin C for intraperitoneal hyperthermic perfusion in patients with far-advanced or recurrent gastric cancer. *Reg Cancer Treat* 1989; **2**: 198–202.
33. Nicoletto MO, Padrini R, Galeotti F *et al.* Pharmacokinetics of intraperitoneal hyperthermic perfusion with mitoxantrone in ovarian cancer. *Cancer Chemother Pharmacol* 2000; **45**: 457–462.
34. Jacquet P, Averbach A, Stuart OA *et al.* Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. *Cancer Chemother Pharmacol* 1998; **41**: 147–154.
35. Panteix G, Guillaumont M, Cherpin L *et al.* Study of the pharmacokinetics of mitomycin C in humans during intraperitoneal chemotherapy with special mention of the concentration in local tissues. *Oncology* 1993; **50**: 366–370.
36. van de Vaart PJM, Van der Vange N, Zoetmulder FAN *et al.* Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. *Eur J Cancer* 1998; **34**: 148–154.
37. Ma GY, Bartlett DL, Reed E *et al.* Continuous hyperthermic peritoneal perfusion with cisplatin for the treatment of peritoneal mesothelioma. *Cancer J Sci Am* 1997; **3**: 174–176.
38. Loggie BW, Fleming RA. Complications of heated intraperitoneal chemotherapy and strategies for prevention. 1996; 221–233.
39. Beaujard AC, Glehen O, Caillot JL *et al.* Intraperitoneal chemohyperthermia with mitomycin C for digestive tract cancer patients with peritoneal carcinomatosis. *Cancer* 2000; **88**: 2512–2519.
40. Los G, van Vucht MJ, Pinedo HM. Response of peritoneal solid tumors after i.p. chemohyperthermia treatment with cisplatin or carboplatin. *Br J Cancer* 1994; **69**: 235–241.
41. Wientjes MG, Badalament RA, Wang RC *et al.* Penetration of mitomycin C in human bladder. *Cancer Res* 1993; **53**: 3314–
42. Jacquet P, Averbach A, Stephens AD *et al.* Heated intraoperative intraperitoneal mitomycin C and early postoperative intraperitoneal 5-fluorouracil: pharmacokinetic studies. *Oncology* 1998; **55**: 130–138.
43. Witkamp AJ, de Bree E, Kaag MM *et al.* Extensive surgical cytoreduction and intra-operative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei. *Br J Surg* 2001; **88**: 458–463.
44. Cavaliere F, Di Filippo F, Botti C *et al.* Peritonectomy and hyperthermic antitumor perfusion in the treatment of peritoneal carcinomatosis. *Eur J Surg Onc* 2000; **26**: 486–491.
45. Steller MA, Egorin MJ, Trimble EL *et al.* A pilot phase I trial of continuous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer. *Cancer Chemother Pharmacol* 1999; **43**: 106–114.
46. Jacquet P, Stephens AD, Averbach AM, Chang D, Ettinghausen SE, Dalton RR, Steves MA, Sugarbaker PH. Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. *Cancer* 1996; **77**: 2622–2629.
47. Ikeguchi M, Kondou A, Oka A *et al.* Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. *Eur J Surg* 1995; **161**: 581–586.
48. Yonemura Y, Ninomiya I, Kaji M *et al.* Prophylaxis with intraoperative chemohyperthermia against peritoneal recurrence of serosal invasion-positive gastric cancer. *World J Surg* 1995; **19**: 450–455.
49. Stephens AD, Alderman R, Chang D *et al.* Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. *Ann Surg Oncol* 1999; **6**: 790–796.
50. Witkamp AJ, de Bree E, Kaag MM *et al.* Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis from colorectal origin. *Eur J Cancer* 2001 (in press).
51. Fumagalli U, Trabucchi E, Soligo M *et al.* Effects of intraperitoneal chemotherapy on anastomotic healing in the rat. *J Surg Res* 1991; **50**: 82–87.
52. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomised controlled study. *Cancer* 1994; **73**: 2048–2052.
53. Fujimoto S, Shrestha R, Kokobun M *et al.* Positive results of combined therapy of surgery and intraperitoneal hyperthermic perfusion for far-advanced gastric cancer. *Ann Surg* 1990; **212**: 592–596.
54. Sayag-Beaujard AC, Francois Y, Glehen O *et al.* Intraperitoneal chemohyperthermia with mitomycin C for gastric cancer patients with peritoneal carcinomatosis. *Anticancer Res* 1999; **19**: 1375–1382.
55. Witkamp AJ, Muller SH, de Bree E *et al.* Impact of mitomycin-C kinetics on surgical complications after hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol* 2000; **26**:
56. Loggie BW, Fleming RA. Complications of heated intraperitoneal chemotherapy and strategies for prevention. *Cancer Treat Res* 1996; **82**: 221–233.
57. Özgüroglu M, Demir G, Demirelli F, Mandel NM. Anaphylaxis from intraperitoneal infusion of cisplatin: a case report. *Am J Clin Oncol* 1999; **22**: 172–173.
58. de Bree E, Christodoulakis M, Tsiftis D. Malignant peritoneal mesothelioma treated by continuous hyperthermic peritoneal perfusion chemotherapy. *Ann Oncol* 2000,
59. Eilber FC, Rosen G, Forscher C *et al.* Surgical resection and intraperitoneal chemotherapy for recurrent abdominal sarcomas. *Ann Surg Oncol* 1999; **6**: 645–650.
60. Van der Vange N, van Goethem AR, Zoetmulder FAN *et al.* Extensive cytoreductive surgery combined with intraoperative intraperitoneal perfusion with cisplatin under hyperthermic conditions (OVHIPEC) in patients with recurrent ovarian cancer: a pilot study. *Eur J Surg Onc* 2000,
61. Fujimoto S, Takahashi M, Mutou T *et al.* Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. *Cancer* 1997; **79**: 884–891.
62. Yu W, Whang I, Suh I *et al.* Prospective randomised trial of early postoperative intraperitoneal chemotherapy as an adjuvant to resectable gastric cancer. *Ann Surg* 1998; **228**: 347–354.
63. Fujimoto S, Takahashi M, Mutou T *et al.* Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 1999; **85**: 529–534.
64. Schneebaum S, Arnold MW, Staubus A *et al.* Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. *Ann Surg Oncol* 1996; **3**: 44–50.
65. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999; **6**: 727–731.
66. Cavaliere F, Perri P, Di Filippo F *et al.* Treatment of peritoneal carcinomatosis with intent to cure. *J Surg Oncol* 2000; **74**: 41–44.

67. Elias D, Dubé P, Blot F *et al.* Peritoneal carcinomatosis treatment with curative intent: the Institut Gustave-Roussy experience. *Eur J Surg Onc* 1997; **23**: 317–321.
68. Loggie BW, Fleming RA, McQuellen RP *et al.* Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin. *Am Surgeon* 2000; **66**: 561–568.
69. Rietbroek RC. Hyperthermia in combination with chemotherapy: from laboratory bench to bedside. 1996, 13–37.
70. Stephens AD, Belliveau JF, Sugarbaker PH. Intraoperative hyperthermic lavage with cisplatin for peritoneal carcinomatosis and sarcomatosis. *Cancer Treat Res* 1996; **81**: 15–30.
71. Yonemura Y, Fujimura T, Nishimura G *et al.* Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. *Surgery* 1996; **119**: 437–444.