

Hyperthermic intraperitoneal chemoperfusion in the treatment of locally advanced intra-abdominal cancer

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Background: Surgical treatment of intra-abdominal cancer is often followed by local recurrence. In a subgroup of patients, local recurrence is the sole site of disease, reflecting biologically low-grade malignancy. These patients might, therefore, benefit from local treatment. Recently, debulking surgery followed by hyperthermic chemoperfusion has been proposed in the treatment of locally advanced or recurrent intra-abdominal cancer. This paper reviews the rationale and assesses the currently accepted indications for and results of this novel treatment.

Methods: A systematic web-based literature review was performed. Information was also retrieved from handbooks, congress abstracts and ongoing clinical trials.

Results: A growing body of experimental evidence supports the use of hyperthermia combined with chemotherapy as an adjunct to cytoreductive surgery. Randomized clinical trials are available to support its use in the treatment and prevention of peritoneal carcinomatosis following resection of pathological tumour stage pT₃ or pT₄ gastric cancer; several other phase III trials are ongoing. Numerous phase I and II trials have reported good results for various other indications, with acceptable morbidity and mortality rates. Case mix, limited patient numbers and absence of a standardized technique are, however, a drawback in many of these series.

Conclusion: For a subgroup of patients with peritoneal cancer without distant disease, debulking surgery followed by hyperthermic chemoperfusion may offer a chance of cure or palliation in this otherwise untreatable condition. This novel therapy should, however, be considered experimental until further results from ongoing phase III trials become available.

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Introduction

Despite seemingly curative surgery, 20–30 per cent of patients with gastrointestinal cancer will develop some form of locoregional recurrence as the sole site of cancer recurrence^{1,2}. Locoregional recurrent cancer causes significant morbidity and may give rise to secondary metastatic disease, and this group of patients with biologically low-grade disease might, in theory, benefit from local treatment. The same holds true for patients suffering from stage III epithelial ovarian cancer and primary abdominal mesothelioma, diseases that remain confined to the peritoneal surfaces during most of their natural history. Traditionally, locoregional cancer recurrence with widespread peritoneal implantation has been difficult to treat, most patients undergoing palliative procedures or no surgery at all. Although intraperitoneal chemotherapy has been used alone or after surgery, taking advantage of the presence

of a peritoneal–plasma barrier, its clinical efficacy is moderate³. Recently, cytoreductive surgery followed by hyperthermic intraperitoneal chemoperfusion (HIPEC) has been described for both the treatment and prevention of locoregional cancer spread from various origins, a management plan based on the experimentally noted synergism between hyperthermia and several antineoplastic drugs. The method was first applied clinically in 1980 by Spratt *et al.*⁴, who treated a patient with pseudomyxoma peritonei. Since then, a growing number of reports has attracted considerable interest in this therapy. This paper reviews the biological and clinical rationale for HIPEC, and its clinical outcome.

Methods

A literature search was performed using a web-based search engine (Web of Science, Institute for Scientific

Information, Philadelphia, Pennsylvania, USA). With 'hyperthermia or hyperthermic' and 'surgery or surgical' combined in a Boolean search, 646 articles from 1988 to 2000 were retrieved. Relevant papers were selected and checked for references relating to experimental work. Further information was retrieved from handbooks, congress and meeting reports, and communication from researchers active in the field of hyperthermia.

Hyperthermia alone

The tumoricidal properties of hyperthermia have been recognized since ancient times. The observation of spontaneous tumour regression in patients with hyperpyrexia led to the first clinical application of hyperthermia, which consisted of injection of pyrogenic substances in patients suffering from sarcoma⁵. The biophysical effects of hyperthermia are incompletely understood, but probably include membrane protein denaturation, increased neovascular permeability, and perturbation of multimolecular complexes such as the insulin receptor^{6–10}. Tumour cell inactivation is time and temperature dependent, and starts at 40–41°C. At temperatures above 43°C exponential inactivation of tumour cells occurs for most rodent cell lines, resembling the effect of ionizing radiation. Human tumour cell lines may be more sensitive to mild hyperthermia (41–42°C) than rodent cell lines¹¹.

The sensitivity of solid tumours to hyperthermia is probably due to a susceptible microenvironment with low pH, low oxygen tension, low glucose and loss of adaptive vasodilatation in response to heat¹². The cytotoxic effects of hyperthermia are modified by the phenomenon of thermotolerance and by genetic variability. Thermotolerance describes the observation that cells preheated at mild temperature become resistant to subsequent exposure at the same temperature. This resistance is accompanied by the synthesis of heat-shock proteins, and can be overcome by very prolonged heating or by heating to high temperature¹³. This threshold temperature seems to be higher for human cell lines (44°C), and this has to be taken into account when planning multiple hyperthermia treatments. Heat-resistant clones have been described *in vitro*, and probably exist also in human solid tumours¹⁴. These subpopulations may, however, be of limited clinical importance.

Hyperthermia with chemotherapy

Both experimentally and clinically, the antitumoral effect of various chemotherapeutic drugs is enhanced by hyper-

Table 1 Pharmacokinetic data on combined chemotherapy and hyperthermia

Reference	Year	Product	AUCp/AUCb
Jacquet <i>et al.</i> ¹⁵	1998	Doxorubicin	83
Pestieau <i>et al.</i> ¹⁶	1998	Gemcitabine	12
Bartlett <i>et al.</i> ¹⁷	1997	Cisplatin	14
Bartlett <i>et al.</i> ¹⁷	1997	TNF	4854
Van Goethem <i>et al.</i> ¹⁸	1997	Mitomycin C	38

AUC, area under the concentration–time curve in perfusate (AUCp) and blood (AUCb). The AUC is calculated by integrating the concentration curve over time and reflects the total amount of drug present in perfusate or blood. TNF, tumour necrosis factor

thermia (Table 1). This observation is explained by an increase in cell membrane permeability, altered active drug transport and altered cell metabolism^{7,19}. Moreover, hyperthermia decreases tumour tissue interstitial fluid pressure, enhancing convection-driven macromolecular drug delivery²⁰. A possible disadvantage of the addition of hyperthermia is the induction of multidrug resistance gene (*MDR1*) expression, resulting in the multidrug-resistant phenotype. In the clinical setting, however, this risk has been shown to be minimal²¹. Most clinical experience with hyperthermic chemoperfusion has involved mitomycin C (MMC) or platinum compounds.

MMC is commonly used in the treatment of gastrointestinal cancer, usually in combination with other drugs. *In vitro*, MMC administration to hypoxic tumour cells at 43°C results in a 40-fold increase in cell killing compared with the same concentration at 37°C²². Pharmacokinetic analysis of hyperthermic MMC has demonstrated a mean area under the concentration–time curve peritoneal: plasma ratio of 23.5²³. Furthermore, rapid absorption with resulting high tissue levels of MMC has been reported following intraperitoneal administration²⁴.

Platinum compounds are widely used in the treatment of epithelial ovarian cancer. *In vitro*, thermal enhancement has been demonstrated for cisplatin, carboplatin, oxaliplatin and lobaplatin^{25–27}. The hyperthermia-enhanced activity of cisplatin is explained by the following mechanisms. First, there is increased DNA alkylation, increased turnover to active metabolites and increased activity at low pH (pH less than 6.5)^{28,29}. Second, there is an increased production of free oxygen radicals³⁰. Finally, cellular cisplatin resistance is reduced by hyperthermia^{31,32}.

Other drugs that exhibit synergism with hyperthermia in cytotoxicity cell line assays include tumour necrosis factor (TNF) α ^{33,34}, interleukin 1 α ³⁵, angiogenesis inhibitors³⁶, bleomycin³⁷, doxorubicin¹⁵, carboplatin³⁷, irinotecan³⁸, ifosfamide³⁹, gemcitabine⁴⁰ and vinblastine⁴¹.

Table 2 Overview of centres with reported clinical use of hyperthermic intraperitoneal chemoperfusion in the treatment of peritoneal carcinomatosis

Country	No. of centres
USA	7
Canada	1
Brazil	1
Australia	1
Japan	4
China	2
Korea	1
France	2
Belgium	2
Greece	2
UK	1
The Netherlands	1
Switzerland	1
Norway	1
Germany	1
Italy	1
Spain	1
Total	30

Hyperthermia with radiotherapy

Several randomized clinical studies have clearly demonstrated that hyperthermia and radiotherapy act synergistically on tumour tissue^{42,43}. This synergism is explained by two phenomena observed in animal experiments. First, hyperthermia is cytotoxic to cells in an environment with low partial pressure of oxygen and pH⁴⁴. Second, hyperthermic treatment at mild temperatures induces reoxygenation of tumour cells, rendering them more sensitive to the effects of radiation therapy (in a rat tumour model)⁴⁵. At higher temperatures (over 43°C) the opposite happens; tumour oxygenation is reduced to a greater extent than with radiation alone, probably owing to heat-induced damage to tumour capillaries⁴⁶.

Clinical experience

Hyperthermia alone or as part of multimodal treatment has been applied clinically in cancer therapy for more than two decades. Examples include locoregional treatment of breast cancer recurrence, advanced neck node metastases and superficial melanoma metastases⁴⁷⁻⁴⁹. Local heating is usually delivered by microwave, radiofrequency, laser or ultrasound equipment. The delivery of hyperthermia to the peritoneal surfaces by closed perfusion of a heated solution was first described in a clinical situation in 1980⁴. Since that time, a growing number of centres in Europe, the USA and Asia have reported use of the technique (Table 2).

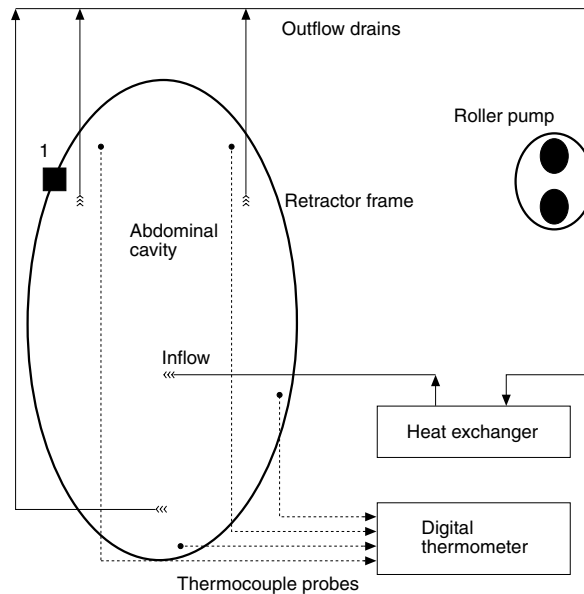


Fig. 1 Schematic representation of the open continuous perfusion technique. Following cytoreduction, the abdominal wall is sutured to a retractor frame fixed on the operating table (1). The frame itself is covered by a plastic sheet with a small slit accommodating the surgeon's hand. A Tenckhoff-type inflow catheter is placed centrally, and multiperforated outflow drains are placed in the left and right subdiaphragmatic space and pelvis. Continuous perfusion is established with a roller pump. Thermocouple probes are placed in the vicinity of the drains; central temperature is monitored with oesophageal or pulmonary artery catheter probes. Cytotoxic drug is added to the perfusate once a temperature of 41.5–44°C is reached. Perfusion is performed over 90 min. Perfusate is continuously distributed throughout the peritoneal cavity manually

Continuous peritoneal perfusion technique

Closed circuit techniques have been described for isolated chemoperfusion of the liver, the kidney, the lung, the limb and the peritoneum⁵⁰⁻⁵⁴. The technique of continuous hyperthermic peritoneal perfusion is illustrated schematically in Fig. 1. Considerable variation exists in the various descriptions of different technical aspects of HIPEC. Generally, following cytoreduction, one or more Tenckhoff-type inflow catheters and three multiperforated outflow drains are placed, together with temperature probes; chemotherapy is added to the perfusate (usually peritoneal dialysis solution) once a temperature of 41.5–44°C is reached inside the abdomen. Perfusion may be performed following temporary closure of the abdomen, or with an open abdomen technique in which the abdomen is covered with a plastic sheet and drug vapour is evacuated to protect the operating room personnel. Proponents of the

latter technique claim better drug distribution by continuous manipulation of the abdominal organs. Closed perfusion, on the other hand, has the advantage of permitting an increase in intra-abdominal pressure that might lead to increased convection-driven drug penetration of macromolecular agents such as TNF- α ^{20,55,56}. Consensus is lacking about the optimal target temperature. Intra-abdominal temperatures ranging from 41 to 44°C have been described; owing to the demonstrated dose-effect curve of hyperthermia a target temperature of at least 43°C seems advisable.

Intestinal anastomoses are usually constructed after the perfusion in order to facilitate uniform distribution of heat and drug. The influence of intraperitoneally administered chemotherapy and heat on anastomotic healing is a concern. In animal studies, anastomotic healing is impaired by intraperitoneal MMC, but not by 5-fluorouracil, at normal temperature^{57,58}. Local hyperthermia in itself has no adverse effects on rat anastomotic healing⁵⁹. When combined with preoperative irradiation, however, hyperthermia has been shown to increase anastomotic complications in a rat model⁶⁰.

Toxicity

Extensive cytoreduction followed by HIPEC is associated with considerable rates of morbidity and mortality, and the potential risks of the procedure must be weighed carefully against any potential benefit. In a recent analysis of morbidity and mortality rates following HIPEC with MMC in 60 patients with disseminated colorectal cancer, the postoperative mortality rate was 5 per cent⁶¹. Complications were noted in 35 per cent of patients, and consisted mainly of anastomotic leak (six), bowel perforation (five) and grade III or IV haematological toxicity (four). In a multivariate analysis, the occurrence of death or complications was associated with the duration of surgery and intra-abdominal temperature, but not with MMC dose. In a recently published randomized trial comparing surgery alone with surgery followed by HIPEC in patients with gastric cancer, postoperative morbidity did not differ between the groups⁶². Postoperative morbidity and death may, therefore, relate mainly to the extent and duration of surgery, and not to the hyperthermic perfusion itself.

Epithelial ovarian cancer

Most patients with ovarian cancer are diagnosed with stage III or IV disease; surgical debulking followed by platinum/paclitaxel-based adjuvant therapy has become the accepted treatment. However, long-term survival is achieved in only 10–20 per cent of patients with stage III disease⁶³. Since

ovarian epithelial cancer rarely spreads systemically, locoregional chemotherapy might benefit these patients. A large Intergroup trial randomized 654 stage III patients with optimal residual disease (defined as largest nodule 2 cm or less after cytoreduction) to intraperitoneal cisplatin plus intravenous cyclophosphamide or intravenous cisplatin plus intravenous cyclophosphamide⁶⁴. Intraperitoneal therapy was associated with a significantly improved median survival (49 *versus* 41 months) and fewer toxic side-effects. The results of this trial have, however, not substantially altered clinical practice. First, the study was initiated in 1986, before the availability of paclitaxel. Second, somewhat counterintuitively, survival was not dependent on the extent of residual tumour mass. In a subsequent Gynecologic Oncology Group trial, 523 patients were randomized to intravenous cisplatin/paclitaxel or high-dose carboplatin followed by intraperitoneal cisplatin plus intravenous paclitaxel. The recently presented preliminary results demonstrated a significant increase in recurrence-free survival (28 *versus* 22 months), without improvement in overall survival⁶⁵. Paclitaxel administered intraperitoneally has an excellent pharmacokinetic and activity profile in phase I and II trials^{66,67}. On the basis of these results, a further Gynecologic Oncology Group trial currently randomizes optimal stage III patients either to intravenous cisplatin/paclitaxel or intravenous paclitaxel plus intraperitoneal cisplatin plus intraperitoneal paclitaxel.

A clear disadvantage of intraperitoneal chemotherapy is the limited penetration into tumour nodules larger than 5 mm⁶⁸. Both in animal experiments and humans, cisplatin has been shown to penetrate much deeper under hyperthermic conditions^{27,69}. Several phase I trials of concurrent intraperitoneal platinum compounds and hyperthermic perfusion have, therefore, been initiated. Researchers from the National Cancer Institute of the USA⁷⁰ found no toxicity associated with cisplatin perfusion for 90 min at 41–43°C and at a dose of 300 mg/m². Further dose escalation was abandoned in favour of the addition of TNF- α to the regimen. The same authors investigated hyperthermic perfusion with high-dose carboplatin in small-volume residual ovarian cancer. Although systemic drug absorption appeared to be unpredictable, carboplatin was safely administered at a dose of 800 mg/m². No adverse effects on bowel function, wound healing or anastomotic healing were noted in this small study⁷¹. Pharmacokinetic data from another phase I trial investigating intraperitoneal cisplatin with hyperthermia revealed a peritoneal:plasma concentration ratio of 15, which is lower than that reported with normothermic intraperitoneal cisplatin⁷². This difference was probably due to increased drug absorption by the addition of hyperthermia. Penetration depth of cisplatin, as measured by DNA adduct formation, was at least 3–5 mm

Table 3 Clinical results of hyperthermic chemoperfusion for treatment or prevention of peritoneal carcinomatosis following resection of gastric cancer

Reference	Year	n	Survival (%)		P
			Surgery alone	Surgery + HIPEC	
Hamazoe <i>et al.</i> ⁷⁸	1994	82	52	64	n.s.
Yonemura <i>et al.</i> ⁷⁹	1995	160	28	50	0.052¶
Kim ⁸⁰	1996	52	46	50	n.s.
Sayag-Beaujard <i>et al.</i> ⁸¹	1999	42*	—	41‡	—
Fujimoto <i>et al.</i> ^{62†}	1999	141	49§	62§	0.04

*Patients with peritoneal carcinomatosis present at surgery. †Prospective randomized controlled trial. Five-year survival rates are shown unless otherwise indicated; ‡3-year and §8-year rates. ¶A significant survival advantage was noted in a subset of stage III patients. HIPEC, hyperthermic intraperitoneal chemoperfusion; n.s., not significant

and higher than that in buccal cells of the same patients. Intraperitoneal carboplatin with deep hyperthermia generated by external radiofrequency probes has also been studied, but intraperitoneal temperature goals could not be reached because of patient intolerance⁷³.

In conclusion, chemotherapy can play a small but important role in a subgroup of patients with ovarian cancer who have small-volume residual or recurrent stage III disease. Whether the pharmacodynamic advantage of hyperthermic drug administration will translate into a clinical benefit must be addressed by randomized controlled trials.

Gastric cancer

Locoregional treatment failure is common following resection of gastric cancer, and is explained by both early mural and lymphatic spread, and by peritoneal seeding of exfoliated cells. Lymphatic spread reflects systemic disease, and locoregional treatment alone does not alter long-term survival in this circumstance. This is illustrated by the recent trials comparing standard with extended (D₂) gastrectomy, which did not find a survival advantage associated with more extended lymphadenectomy^{74,75}. Macroscopic or microscopic peritoneal spread is present in 40 per cent of patients with stage II and III disease, and is associated with a significant survival disadvantage^{76,77}.

This observation led several Japanese authors to investigate the usefulness of adjuvant hyperthermic chemoperfusion following pathological tumour stage pT₃/pT₄ gastric cancer resection (Table 3). In most of these series, HIPEC was used as a preventive measure with the aim of eradicating microscopic peritoneal implants. A recently published randomized trial investigated the use of prophylactic hyperthermic perfusion with MMC following curative resection of stage II and III gastric cancer⁶². Both the peritoneal recurrence rate and long-term survival were

significantly improved in the surgery plus HIPEC group; the postoperative morbidity rate (3 per cent) was not increased. Interestingly, the hepatic recurrence rate was no different between the groups, despite the fact that during HIPEC treatment the liver is exposed to MMC. Although the number of patients treated was small, the results of this trial favour further study of the use of this form of adjuvant treatment.

Colorectal cancer

Next to the liver, the peritoneal surfaces are the most common site for cancer recurrence after 'curative' colorectal cancer resection. Local peritoneal recurrence occurs in as many as 50 per cent of patients with colorectal cancer after resection^{2,82}. Peritoneal cancer spread from a colorectal origin has long been regarded as untreatable, and inflicts substantial suffering on the patient. The importance of locoregional therapy is especially relevant in rectal carcinoma, where optimal surgical technique (total mesorectal excision) encompassing possible lateral tumour spread is known to improve local recurrence rates dramatically⁸³. In theory, adjuvant intraperitoneal chemotherapy may be beneficial in certain groups of patients with colorectal cancer, provided that maximal surgical cytoreduction is possible. Such groups would be those after resection of advanced (pT₃, pT₄) disease, those having resection of recurrent peritoneal disease, and those with a perforated cancer, positive peritoneal cytology or accidental tumour spillage⁸⁴.

The possible role of intraperitoneal chemotherapy in resected high-risk colorectal cancer has been highlighted in a recent randomized trial⁸⁵. In this study, combined intravenous plus normothermic intraperitoneal adjuvant therapy resulted in a 43 per cent reduction in mortality rate in comparison to intravenous chemotherapy alone in resected stage III colon carcinoma. Fujimoto *et al.*⁸⁶

Table 4 Clinical results of hyperthermic chemoperfusion for peritoneal carcinomatosis of colorectal origin

Reference	Year	n	Product	Median survival (months)
Yonemura <i>et al.</i> ⁸⁸	1999	106	Cisplatin + MMC + etoposide	—
Cho <i>et al.</i> ⁸⁹	1999	56	Cisplatin	—
Bartlett <i>et al.</i> ⁹⁰	1998	27	Cisplatin + TNF	—
Ma <i>et al.</i> ⁹¹	1997	10	Cisplatin	—
Stephens <i>et al.</i> ⁹²	1996	13	Cisplatin	—
Kober <i>et al.</i> ⁹³	1996	25*	MMC or cisplatin	11
Loggie <i>et al.</i> ⁹⁴	1997	39	MMC	33†
Mansvelt <i>et al.</i> ⁹⁵	1997	28	MMC	9
Fujimura <i>et al.</i> ⁹⁶	1999	25	MMC or cisplatin	48
Gilly <i>et al.</i> ⁹⁷	1999	18	MMC or cisplatin	—
Jähne and Piso ⁹⁸	1998	48	Cisplatin	28

*Includes 12 ovarian cancers. †For patients without ascites at surgery. MMC, mitomycin C; TNF, tumour necrosis factor

performed HIPEC following primary resection of rectal cancer in 14 patients. When compared with a control group, the local recurrence rate was significantly improved. Moreover, positive peritoneal cytology was present before surgery in six of the 14 patients treated with HIPEC, but in none of these patients after the procedure. In patients with peritoneal carcinomatosis of colorectal origin, cytoreduction and intraperitoneal normothermic chemotherapy resulted in excellent survival in a large retrospective series⁸⁷. Clinical variables associated with long-term survival were appendiceal origin, grade 1 histology, complete cytoreduction, lymph node-negative disease and volume of cancer present before surgery. Cytoreduction followed by HIPEC in the treatment of peritoneal carcinomatosis of mainly colorectal origin has been reported in numerous phase I and II trials. Most of these studies suffer from methodological flaws, such as inclusion of different primary tumour types, absence of clearly defined endpoints and small patient numbers (Table 4). Generally, long-term survival rates of 25–30 per cent are described in groups of patients who undergo complete cytoreduction. Significant prognostic factors include completeness of cytoreduction, lesion size, lesion distribution and tumour histology^{99–101}. In an analysis of 18 patients who had second-look surgery following initial debulking with HIPEC, completeness of cytoreduction, both at the initial procedure and at the time of second look, proved to be of prognostic significance¹⁰².

Results from controlled randomized trials are awaited to establish the role of HIPEC in colorectal cancer. A prospective phase III trial comparing intravenous chemotherapy plus cytoreduction plus HIPEC with intravenous therapy alone, in patients with peritoneal carcinomatosis of colorectal origin, was initiated recently at the Netherlands Cancer Institute with promising interim results (F. A. Zoetmulder, personal communication)¹⁰³.

Primary peritoneal mesothelioma and sarcoma

Peritoneal mesothelioma is a locally aggressive disease that is relatively unresponsive to systemic chemotherapy. Given its tendency to remain confined to the peritoneal surfaces, intraperitoneal chemotherapy has attracted some interest in the treatment of this disease. Intraperitoneal normothermic cisplatin has resulted in a 59 per cent response rate, but relapse is rapid in most patients¹⁰⁴. Recently, the results of hyperthermic chemoperfusion with cisplatin for primary peritoneal mesothelioma were reported by researchers at the National Cancer Institute in the USA. Median progression-free survival in 18 patients was 26 months, with a 2-year survival rate of 80 per cent. Ascites disappeared in nine of ten patients after operation¹⁰⁵.

Conclusion

Peritoneal carcinomatosis is generally considered to be an incurable condition. However, a growing body of both experimental and clinical evidence supports the therapeutic and prophylactic use of HIPEC in patients without systemic disease. Level I evidence (from at least one randomized controlled trial) is available on the use of this technique in the prevention and treatment of peritoneal carcinomatosis of gastric origin. Numerous phase I and II trials have been published on primary and metastatic peritoneal carcinomatosis of diverse origin. Owing to the small number of patients and the case mix in these trials, few definitive conclusions may be drawn at this time. However, there is a clear need for well structured randomized trials to establish the role of this promising technique in the treatment of peritoneal carcinomatosis. Many surgeons may not be familiar with the use of hyperthermia as an adjunct to

surgery; the authors hope that this article will stimulate their interest.

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