EVIDENCE BASE AND PRINCIPLES OF MANAGEMENT OF PERITONEAL METASTASES: A CHRONOLOGY

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MedStar Health

Peritoneal Surface Oncology Group International
PSOGI

No disclosures

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HOPSCOTCH CONGRÈS

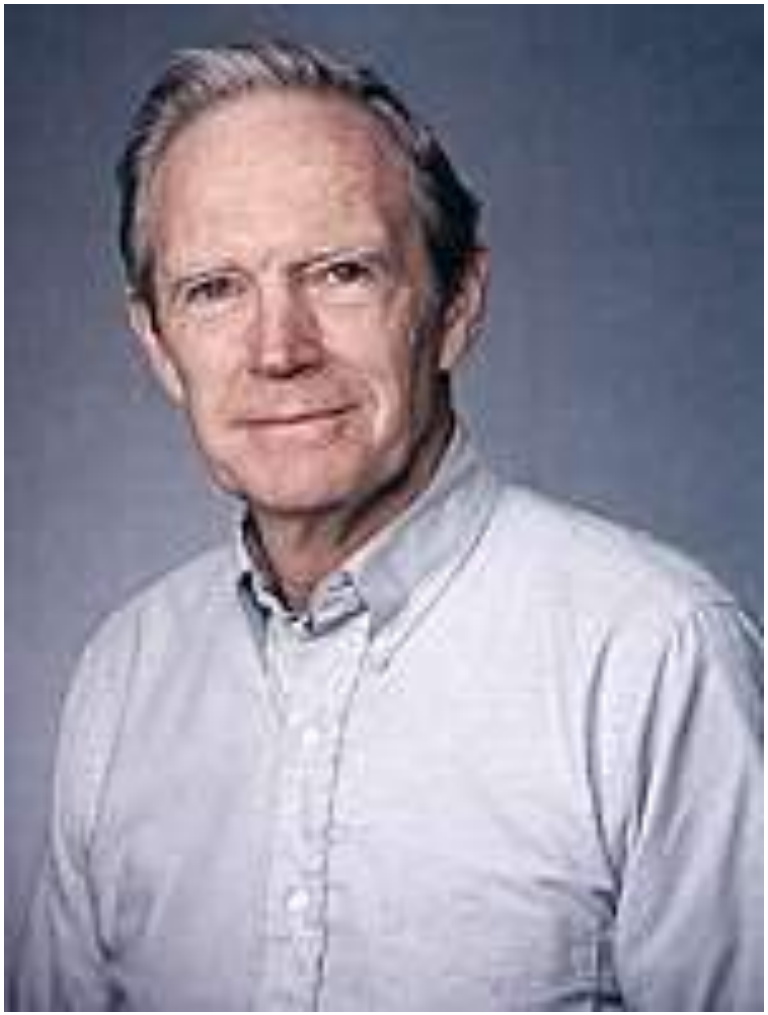
Peritoneal Surface Oncology PSOGI Group International

Pharmacokinetic Rationale for Peritoneal Drug Administration in the Treatment of Ovarian Cancer

Robert L. Dedrick, Charles E. Myers, Peter M. Bungay, Vincent deVita, Jr.
National Institutes of Health, Bethesda, MD, *Cancer Treat Rep,* 1978

Abstract: Evidence from the peritoneal dialysis literature suggests that the peritoneal permeability of a number of hydrophilic anticancer drugs may be considerably less than plasma clearance. Pharmacokinetic calculations indicate that such drugs administered ip in large volumes are expected to maintain a significantly greater concentration in the peritoneal space than in the plasma. This concentration difference offers a potentially exploitable biochemical advantage in the treatment of patients with presumed microscopic residual ovarian cancer confined to the peritoneal cavity.

(First proposal for improved outcome with intraperitoneal chemotherapy administration)



Robert L. Dedrick
Bethesda, MD

Hyperthermic Oncology: Current Biology, Physics and Clinical Results

J. L. Meyer, D. S. Kapp, P. Fessender, G. H. Hahn
Stanford University School of Medicine, Stanford, CA
Pharmac. Ther. Vol. 42, pp. 251-288, 1989

Abstract: For the practicing oncologist, the interest in hyperthermia centers around three aspects. First of all, even mildly elevated temperatures by themselves are cytotoxic to cells. Secondly, hyperthermia increases the rate of inactivation by X-irradiation. Third, the cell-killing effect of many anti-cancer drugs is vastly enhanced at elevated temperatures.

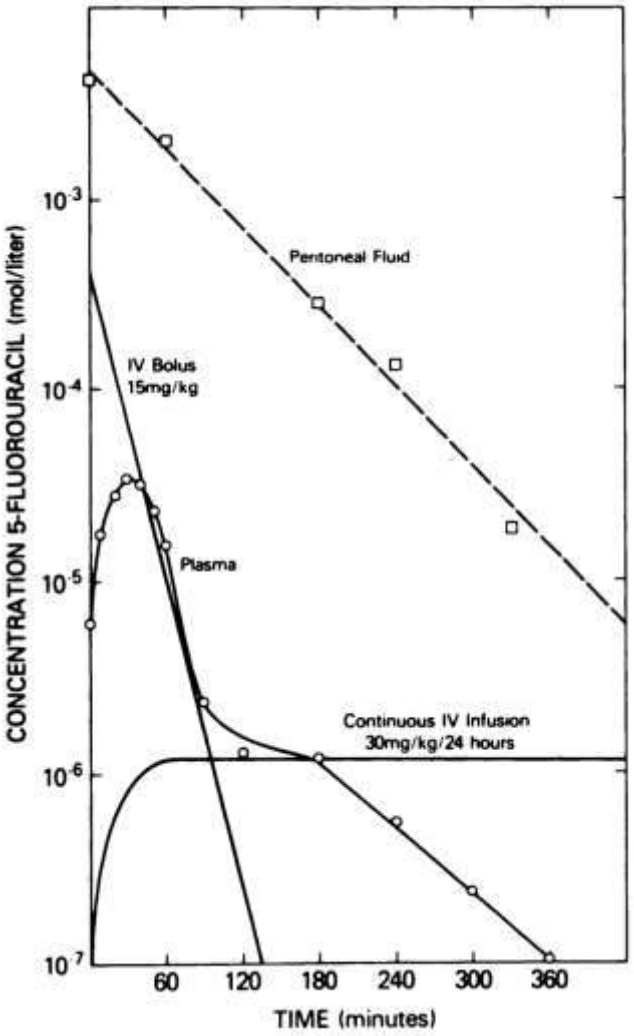
Phase I Pharmacological Studies of 5-Fluorouracil Administered Intraperitoneally

James L. Speyer, Jerry M. Collins, Robert L. Dedrick, Murray F. Brennan, Alan R. Buckpitt, Harold Londer, Vincent T. DeVita, Jr., Charles E. Myers
National Institutes of Health, Bethesda, MD, *Cancer Research*, March 1980

Abstract: A Phase I study was conducted of 5-fluorouracil administered i.p. in a 2-liter volume of 1.5% peritoneal dialysis solution. The drug was administered via Tenckhoff peritoneal dialysis catheters to ten patients with tumors confined to the i.p. space. There was no local toxicity. Dose-limiting toxicity included pancytopenia and mucositis as a dialysis administered for eight consecutive 4-hr exchanges (32 hours). 5-Fluorouracil concentrations were measured by high-pressure liquid chromatography. Peritoneal fluid concentrations decline in a first-order fashion with a half-life of 1.6 hr. Plasma levels are substantially lower than are peritoneal fluid levels. Mean 4-hr peritoneal fluid concentration was 298 times the simultaneously measured plasma levels. We conclude the i.p. route is a relatively safe way to deliver high concentrations and large amounts of drug to the i.p. cavity with a significant pharmacological advantage over conventional routes of administration.

(First intraperitoneal chemotherapy in patients)

Pharmacokinetics of 3 different types of 5-fluorouracil administration



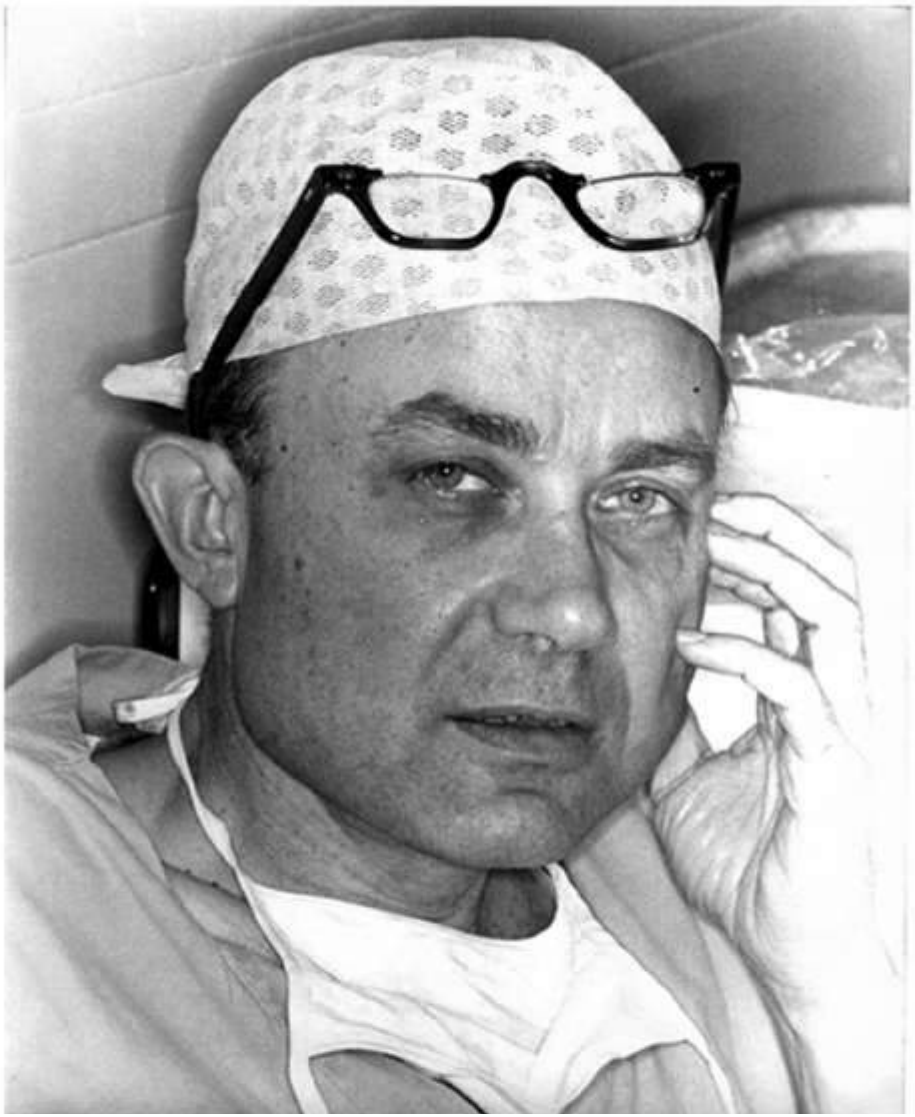
Speyer et al., 1980

Intraperitoneal Hyperthermic Treatment of Implanted Peritoneal Cancer in Rats

Man H. Shiu and Joseph Fortner
Memorial Sloan-Kettering Cancer Center, New York, *Cancer Research*, 1980

Abstract: The feasibility and efficacy of treating peritoneal cancer implants by applying heat to the peritoneal surfaces were studied in inbred Buffalo A rats given i.p. injections of Morris hepatoma 5123TC tumor cells. Heat was delivered to the peritoneum by contact with a heated physiological salt solution in the peritoneal cavity. A treatment temperature of 43.3 ± 0.3° was maintained for 30 min. Treatment was after tumor implantation to simulate clinical conditions of surgically spilled cancer cells (4 hours), established microscopic cancer implants (4 days), and macroscopic cancer implants (23 days). A statistically significant improvement in survival was observed in Groups I and II compared with sham-treated control animals; 58% of the heat-treated animals were cured. Only a slight but statistically insignificant improvement was noted in Group III. These observations indicate that i.p. surface heat treatment of peritoneal implanted cancer is feasible and effective.

(First intraperitoneal hyperthermia)



Joseph Fortner, 1921 – 2007

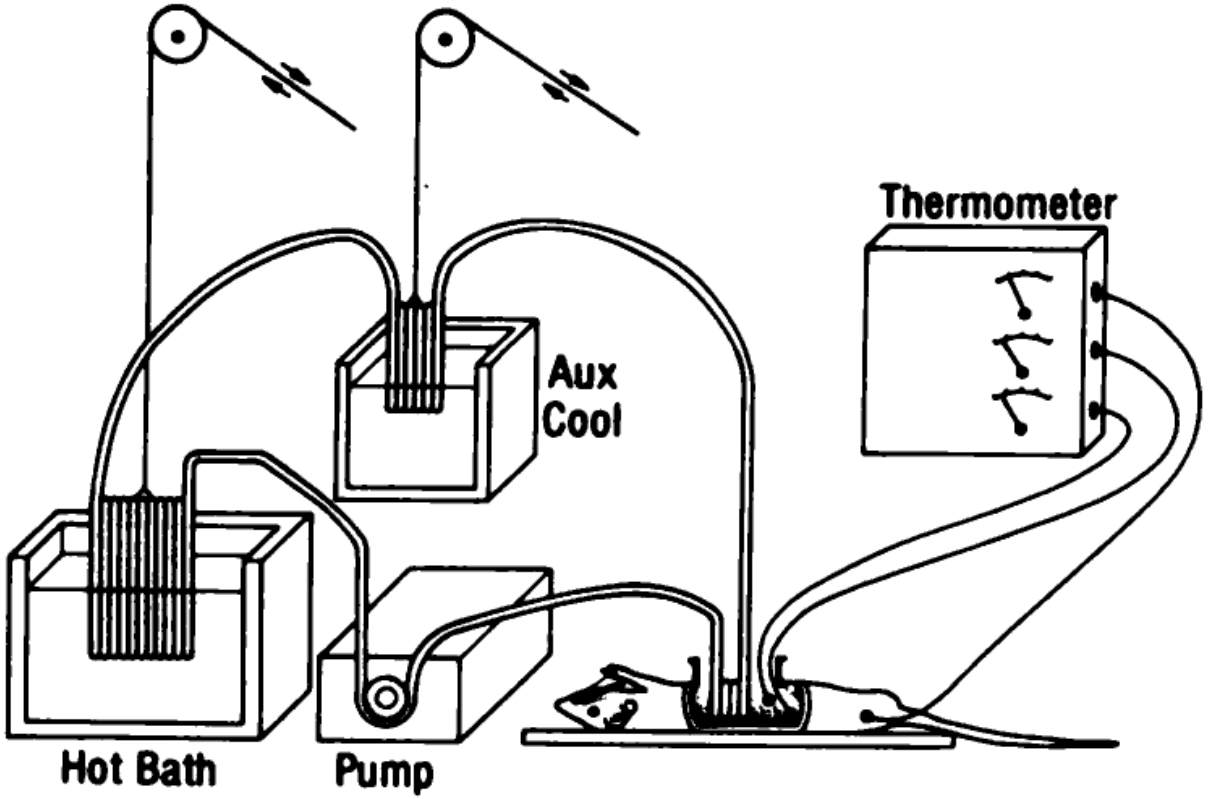
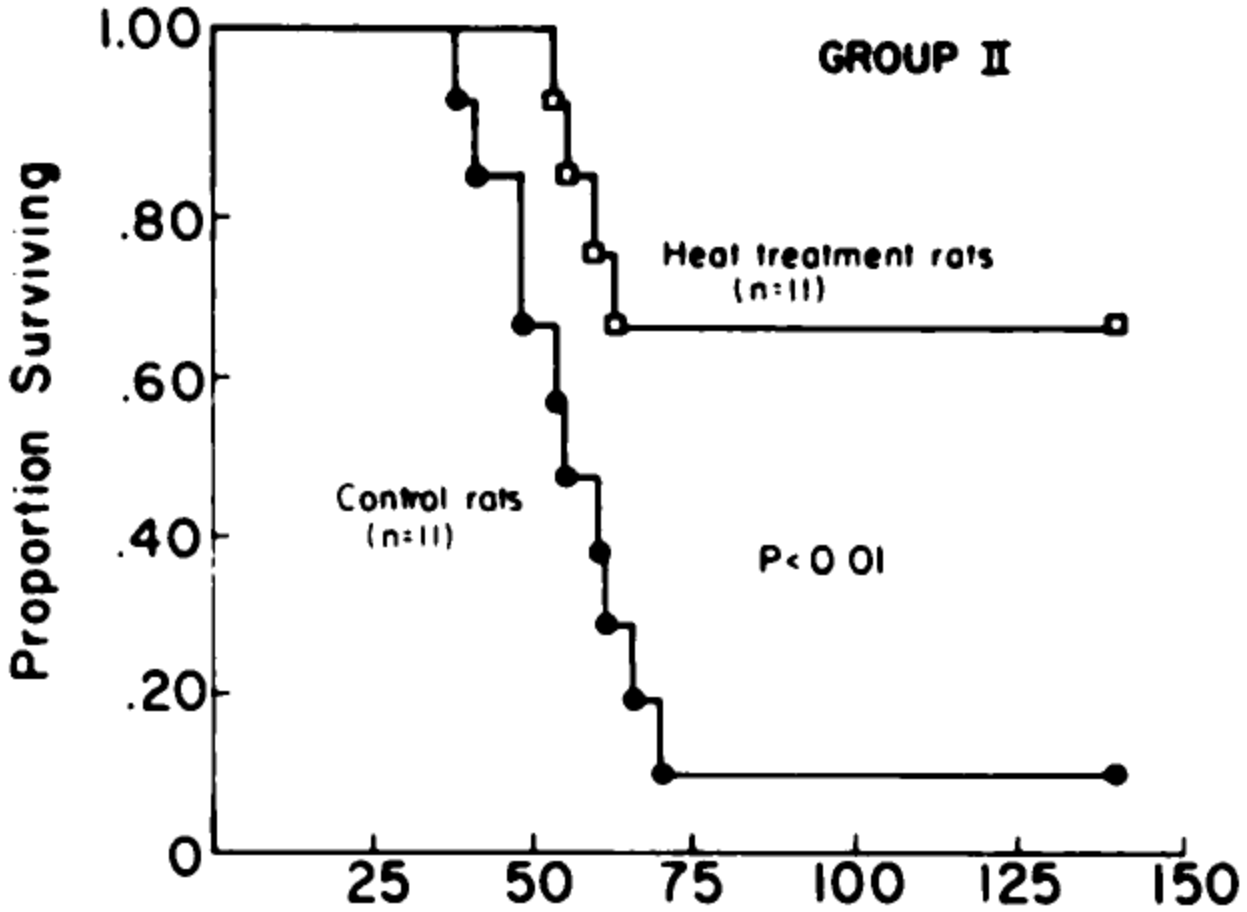


Chart 1. Schematic drawing of heat delivery system. A roller pump drives a closed system of fluid from the hot bath to the rat's peritoneal cavity which is filled with a physiological salt solution. The stainless steel coils serve as heat exchangers. The auxiliary cooling coil (*Aux Cool*) is used to prevent overshooting of the temperature whenever it tends to occur.

Shiu MH, Fortner JG. Cancer Research, 1980

Intraperitoneal Hyperthermia



Survival of rats after i.p. heat treatment at 43.3 ± 0.3° for 30 min. On Day 0, the rats received an i.p. injection of 0.5 to 1.0 x 10^8 cells of Morris hepatoma (5123TC). Heat treatment was given 4 to 5 days after tumor implantation.

Shiu MH, Fortner JG. Cancer Research, 1980

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Clinical Delivery System for Intraperitoneal Hyperthermic Chemotherapy

John S. Spratt, Robert A. Adcock, Marie Muskovin, William Sherrill, John McKeown
University of Louisville, Louisville, KY, *Cancer Research*, February 1980

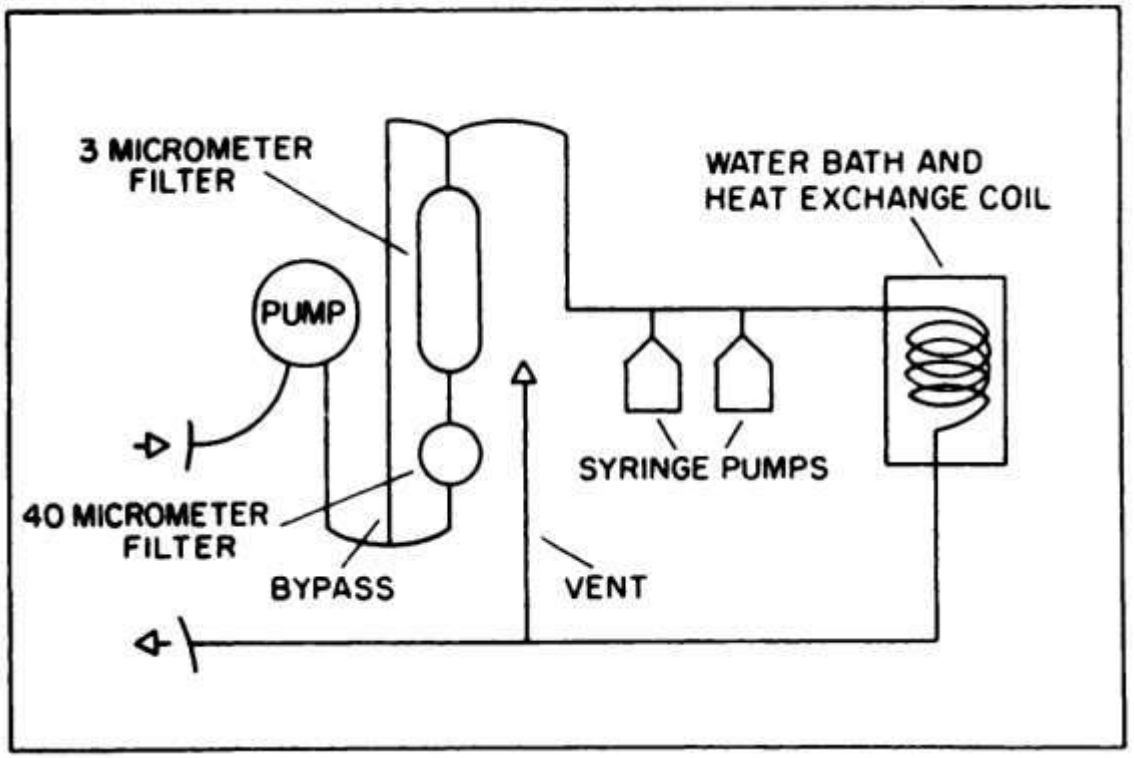
Abstract: A 35-year-old man was treated for pseudomyxoma peritonei by surgery and by thermal infusion and chemotherapy with a machine designed specifically for the treatment of cancers of serosal surfaces. After extensive abdominal resection and closure, the patient's peritoneal cavity was instilled with 2.5 liters of 5% lactated Ringer's solution. He was then attached to hyperthermic perfusion system which elevated the i.p. temperature by warming (to 42°) and recirculating the effusion solution. When the 42° i.p. temperature was attained (after 1.5 hr), chemotherapy was added (methotrexate) to the recirculating effusion. A second procedure followed 8 days later. Hyperthermic perfusion was tolerated well and was evaluated as safe for intracavitary cancer treatment.

(First HIPEC in a patient)

John L. Spratt
Louisville, KY

First Description of a HIPEC Machine

Palta JR. Design and Testing of a Therapeutic Infusion Filtration System. M. S. Thesis
University of Missouri, Columbia, MO, 1977



Spratt et al., 1980

Tottori University

Fusion of Knowledge and Practice

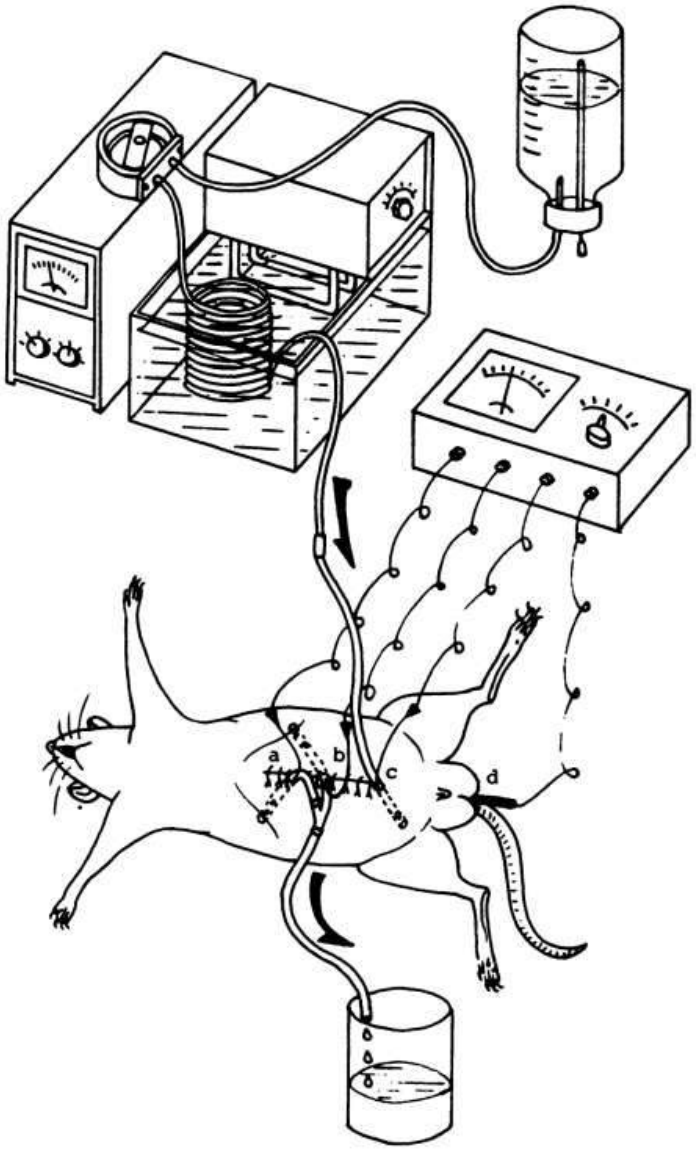
Treatment of Implanted Peritoneal Cancer in Rats by Continuous Hyperthermic Peritoneal Perfusion in Combination with an Anticancer Drug

Shigemasa Koga, Ryuichi Hamzoe, Mihio Maeta, Norio Shimizu, Hirotomo Kanayama, Yukio Osaki, Tottori University, Yonago, Japan, *Cancer Research*, May 1984

Abstract: To study the feasibility of combined hyperthermic and anticancer drug treatment for peritoneal cancer, we devised a continuous hyperthermic peritoneal perfusion system in combination with mitomycin C. The model uses i.p.-transplantable rat ascites hepatoma 100B cells. Hyperthermic peritoneal perfusion alone or combined with mitomycin C was performed after i.p. inoculation of the tumor cells into rats. In rats treated with combined peritoneal perfusion (41.5°)and mitomycin C, the mean survival times were significantly prolonged as compared to those of rats treated with peritoneal perfusion at 41.5° alone. Our results suggest that combined hyperthermic peritoneal perfusion and mitomycin C treatment may represent a therapeutic and prophy lactic treatment for peritoneal metastasis after gastric cancer surgery in humans.

(First HIPEC in an animal model)

Shigemasa Koga
Yonago, Japan



Koga et al., 1984

Table 2

Survival data after CHPP

Hyperthermic treatment with or without MMC	Time (days) after inoculation	Mean survival time (days)	No. of survivors at 60 days		%	
Group 1 (37.0°)	1 ($n = 5$)	14.4	0		0	
	5 ($n = 7$)	17.3	0		0	
	10 ($n = 4$)	16.0	0		0	
Group 2 (41.5°)	1 ($n = 9$)	19.9	0		0	
	5 ($n = 8$)	18.6	0	1	0	4.2
	10 ($n = 7$)	>24.3	1		14.3	
Group 3 (42.5°)	1 ($n = 8$)	>51.5	2		25.0	
	5 ($n = 4$)	−14.8	0	2	0	16.7
	10					
Group 4 (41.5° + MMC, 1 mg/kg)	1 ($n = 7$)	>98.9	2		28.6	
	5 ($n = 10$)	>56.3	2	8	20.0	29.6[a]
	10 ($n = 10$)	>102.8	4		40.0	
Group 5 (MMC, 1 mg/kg)	1 ($n = 5$)	>19.4	0		0	
	5 ($n = 5$)	>18.8	0		0	
	10 ($n = 5$)	>18.6	0		0	
Control group (tumor cell inoculation only)		17.6	0		0	

[a] Significant difference from Group 2 ($p < 0.05$; χ^2 test).

Koga et al., 1984

Prospective, Randomized Trial of Intravenous Versus Intraperitoneal 5-fluorouracil in Patients with Advanced Primary Colon or Rectal Cancer

Paul H. Sugarbaker, Fred J. Gianola, James C. Speyer, Robert Wesley, Ivan Barofsky, Charles E. Meyers, *Surgery*, 1985;98:414-421

Abstract: No new chemotherapy agents have been developed recently that present hope for improving survival in patients with colon or rectal cancer. We undertook this study to investigate a new route of administering an old drug, 5-fluorouracil (5-FU). Sixty-six patients with advanced primary colon or rectal cancer were randomized to receive 12 cycles with increasing dosages of intravenous (IV) or intraperitoneal (IP) 5-FU; the mean follow-up time was 3 years. Two of 10 patients had recurrent peritoneal carcinomatosis when treated with IP 5-FU; 10 of 11 patients treated with IV 5-FU developed peritoneal implants ($p<0.003$). The incidence of serious complications was the same, but hematologic toxicity and hepatic toxicity were significantly reduced in patients who received IP 5-FU. The natural history of surgically treated disease was changed by reducing the incidence of peritoneal carcinomatosis but time to relapse and survival was not improved. If 5-FU is given to patients with gastrointestinal malignancy, the IP route should be strongly considered.

(First randomized trial of intraperitoneal chemotherapy and first use of second-look surgery to evaluate peritoneal metastases treatments)

Malignant Pseudomyxoma Peritonei of Colonic Origin: Natural History and Presentation of a Curative Approach to Treatment

Paul H. Sugarbaker, Kenneth Kern, Ernest Lack, National Institutes of Health, Bethesda, MD, *Dis Colon Rectum*, 1987;30:772-779

Abstract: 14 patients underwent radical procedures in an attempt to surgically remove all gross disease from the abdomen. All patients had relief from bulky intra-abdominal tumors. Six cycles of intraperitoneal 5-FU and three doses of mitomycin C were used following cytoreductive surgery. Five of seven patients with complete resection are disease-free following staging by celiotomy with two- to four-year follow-up. This new treatment strategy, designed to cure some patients with pseudomyxoma peritonei, has given favorable results in a disease that previously had a uniformly lethal outcome.

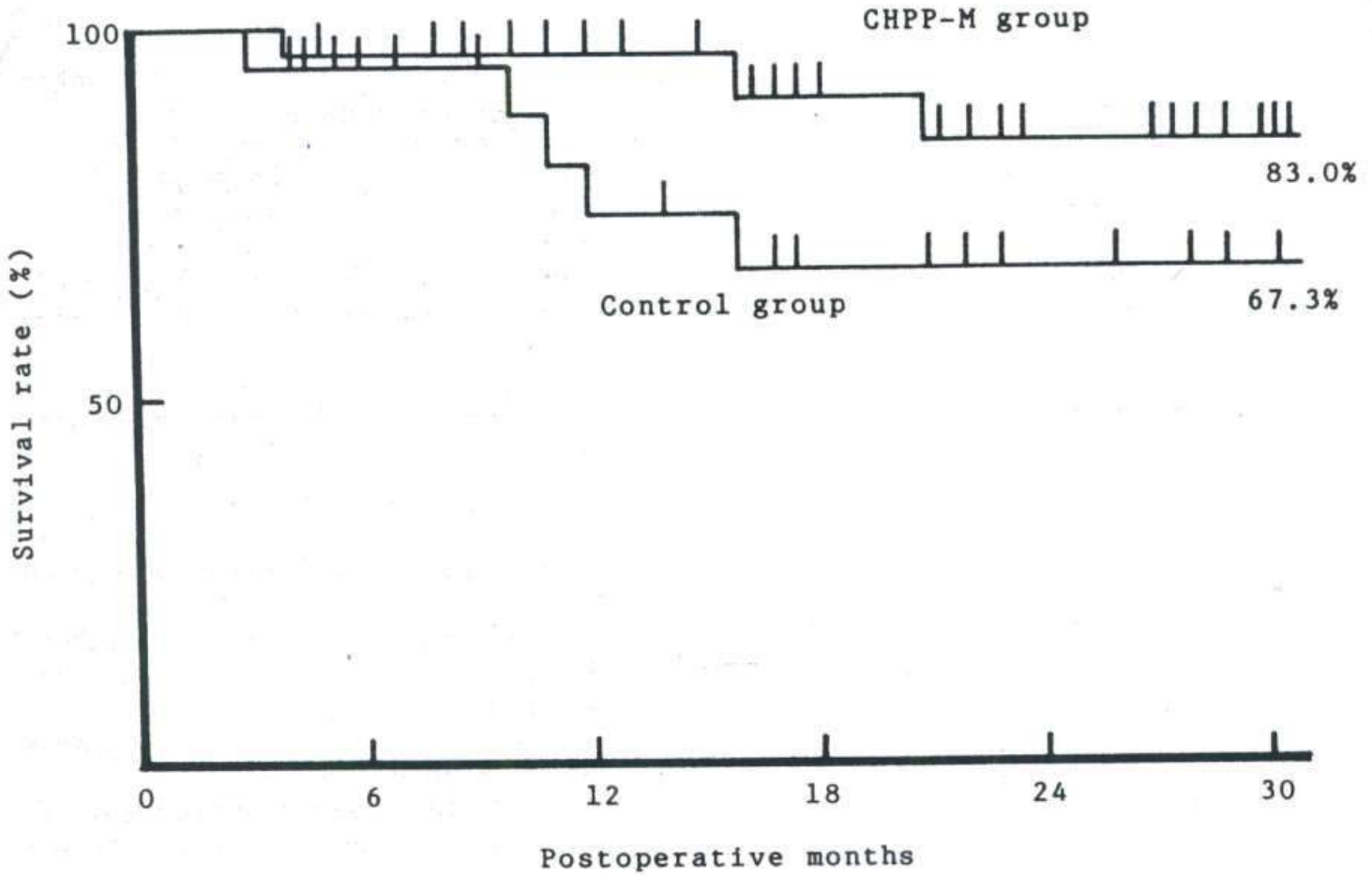
(First series of pseudomyxoma peritonei patients treated by CRS and long-term intraperitoneal chemotherapy)

Prophylactic Therapy for Peritoneal Recurrence of Gastric Cancer by Continuous Hyperthermic Peritoneal Perfusion with Mitomycin C

Shigemasa Koga, Ryuichi Hamzoe, Mihio Maeta, Norio Shimizu, Atsunobu Murakami, Toshiro Wakatsuki, Tottori University, Yonago, Japan, *Cancer*, January 1988

Abstract: Continuous hyperthermic peritoneal perfusion (CHPP) with a solution that contains mitomycin C (CHPP-M) has been clinically introduced as a prophylactic treatment for peritoneal recurrence of gastric cancer with serosal invasion. Two studies, each with a treated and a control group, were performed. In the random control study the survival rate (83%) of patients in the treated group (n = 26) was also higher than that (67.3%) of those in the control group (n = 21) in the 30 months that followed gastric surgery. However, there was no significant difference. These results indicate that CHPP-M is a simple, safe, and readily available prophylactic therapy for peritoneal recurrence that may follow gastric cancer surgery.

(First prevention trial with HIPEC)



Koga et al., 1988

Positive Results of Combined Therapy of Surgery and Intraperitoneal Hyperthermic Perfusion for Far-advanced Gastric Cancer

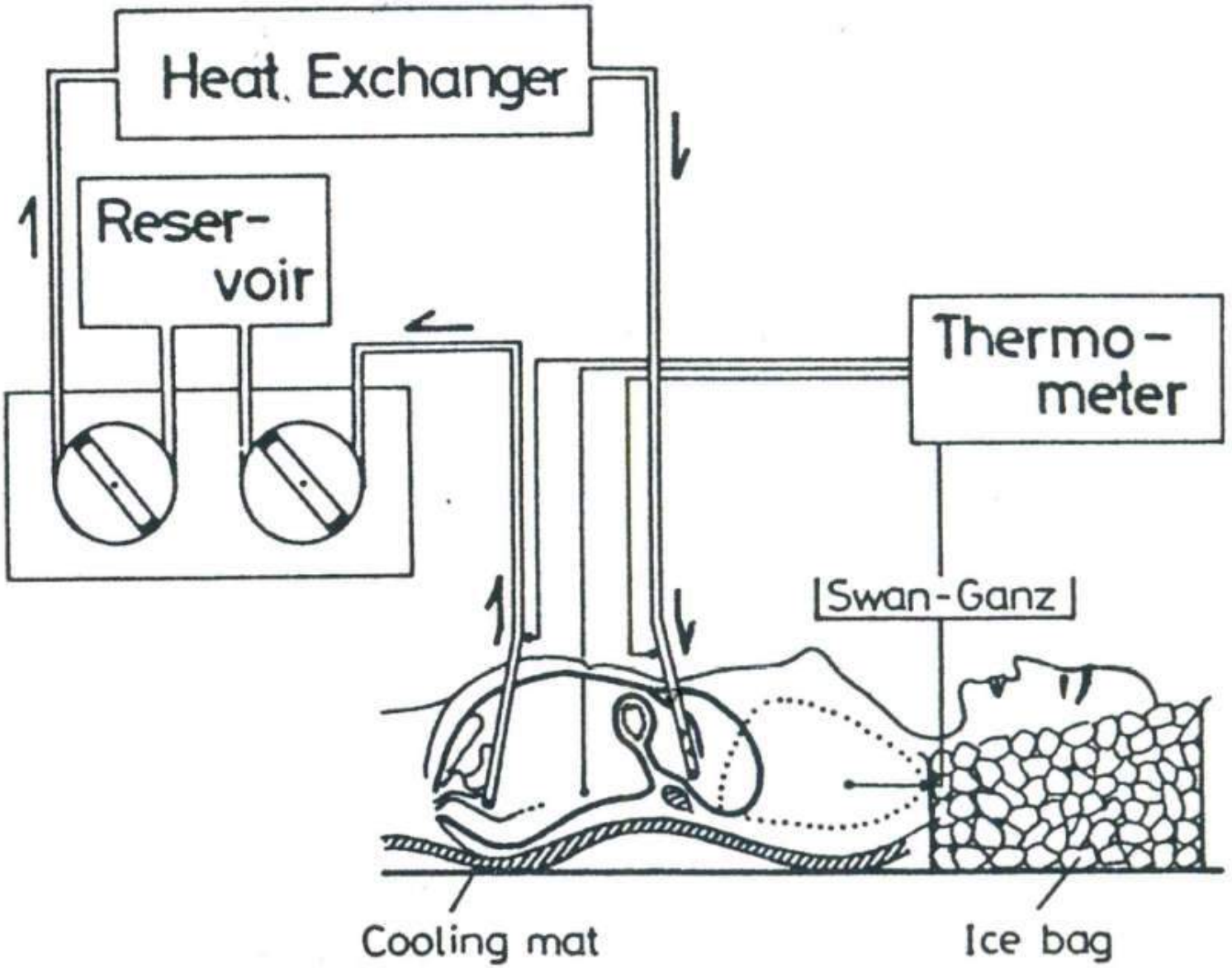
Shigeru Fujimoto, Ram Dhoj Shrestha, Masashi Kokubun et al., Chiba, Japan

Ann Surg, 1988

Abstract: Intraperitoneal hyperthermic perfusion (IPHP) was used for far-advanced gastric cancer, particularly with peritoneal seeding. The 30 patients given IPHP lived longer than the 29 patients not given IPHP (p = 0.001), with a 1-year survival rate of 80.4% in the former group compared to 34.2% in the latter. Survival time of patients with peritoneal seeding not given IPHP had a 6-month survival rate of 57.1%, whereas 20 patients given IPHP had 1- and 2-year survival rates of 78.7% and 45.0%, respectively; here the difference was significant (p = 0.001). During this IPHP temperatures at the inflow point and in Douglas' pouch were maintained at 45.0 to 47.3°C and 43.6 to 45.1°C. Thus this combined therapy offers the promise of extended survival for patients with far-advanced gastric cancer.

(First treatment trial with HIPEC)

Shigeru Fujimoto
Chiba, Japan



Fujimoto et al., 1988

Continuous Hyperthermic Peritoneal Perfusion (CHPP) for the Treatment of Peritoneal Dissemination in Gastric Cancers and Subsequent Second-Look Operation

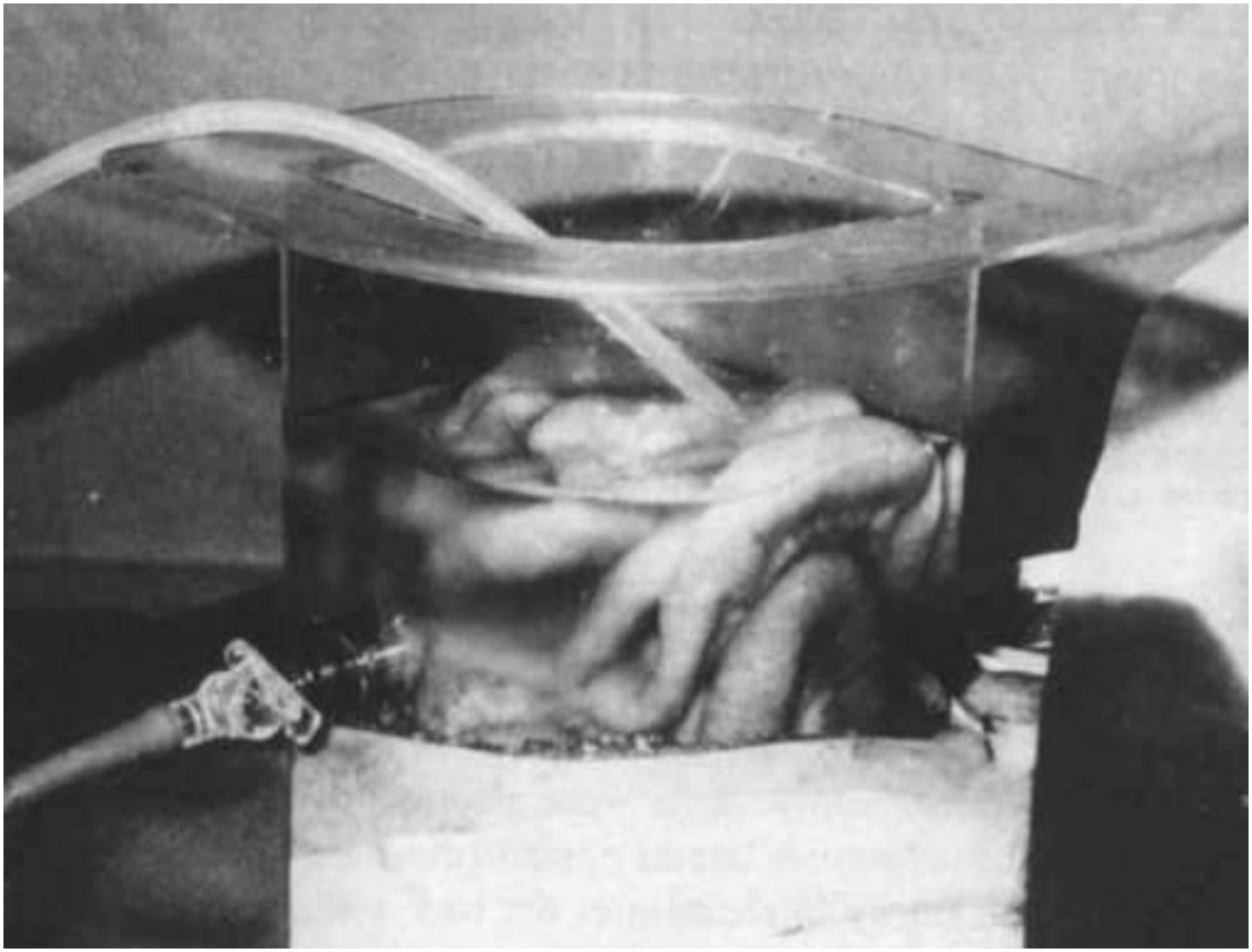
Takashi Fujimura, Yutaka Yonemura, Sachio Fushida, et al., Kanazawa, Japan

Cancer, 1990

Abstract A total of 31 patients with gastric cancer showing peritoneal dissemination received continuous hyperthermic peritoneal perfusion (CHPP) in combination with the administration of cisplatin (CDDP) and mitomycin C (MMC). The authors developed a new special device named the peritoneal cavity expander (PCE) for sufficient perfusion and direct temperature measurement in the peritoneal cavity. Twelve of 31 patients who had received CHPP during the initial operation underwent second-look operation (SLO). Among 12 patients who received SLO complete response (CR) was observed in four patients, partial response (PR) in one. Two-year survival rate of the complete and partial responders was 50%, which was significantly higher than 0% of the other responders. These results supported that CHPP was well tolerated and effective for the treatment of patients with peritoneal dissemination in gastric cancer.

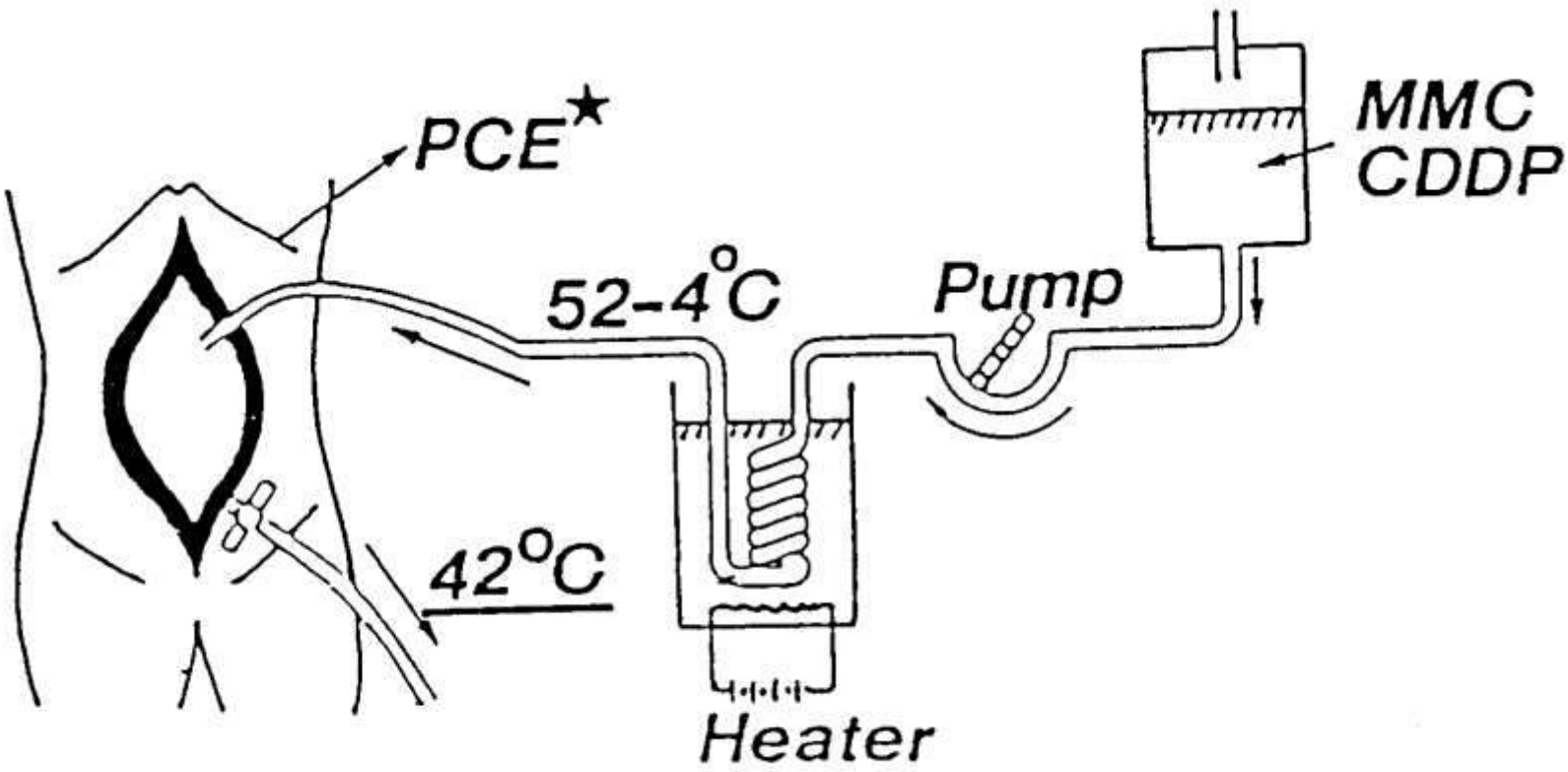
(First multi-drug HIPEC protocol, results evaluated by second-look surgery)

Yutaka Yonemura
Osaka, Japan



(Peritoneal cavity expander was first open and manually distributed HIPEC)

Yonemura et al., 1990



★PCE; Peritoneal Cavity Expander

Yonemura et al., 1990

Intra-Peritoneal Chemo-Hyperthermia (CHIP): a New Therapy in the Treatment of Peritoneal Seedings

Francois N. Gilly, Annie C. Sayag, Pierre Y., Carry, et al., Centre Hospitalier Lyon-Sud, Lyon, France

Int Surg, 1991

Abstract: After an experimental study in dogs, authors report a new therapeutic device for peritoneal seedings (Intra-Peritoneal Chemo-Hyperthermia) and their preliminary results in five patients. They observed no mortality and no morbidity with this protocol using Mitomycin as antimitotic and hyperthermia as sensibilisation agent. This new technique means important technological and time investment but preliminary results appear to be encouraging and authors intend to standardize the present apparatus in order to go on using this device and obtain more experience.

(First standardized HIPEC apparatus, the Cavitherm)

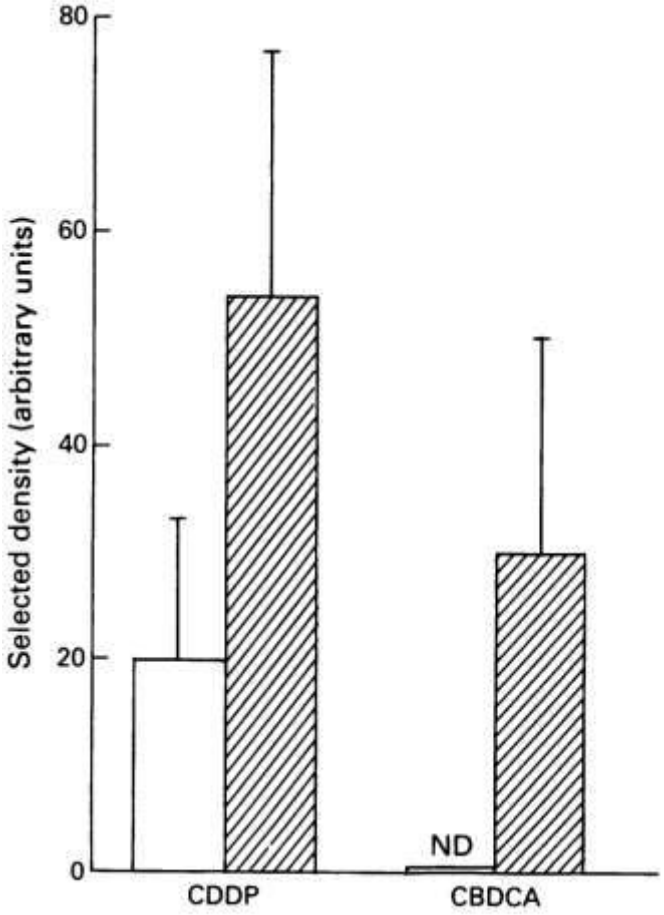
Francois Gilly
Lyon, France

Response of Peritoneal Solid Tumours After Intraperitoneal Chemohyperthermia Treatment with Cisplatin or Carboplatin

G. Los, M. J. van Vugt, H. M. Pinedo

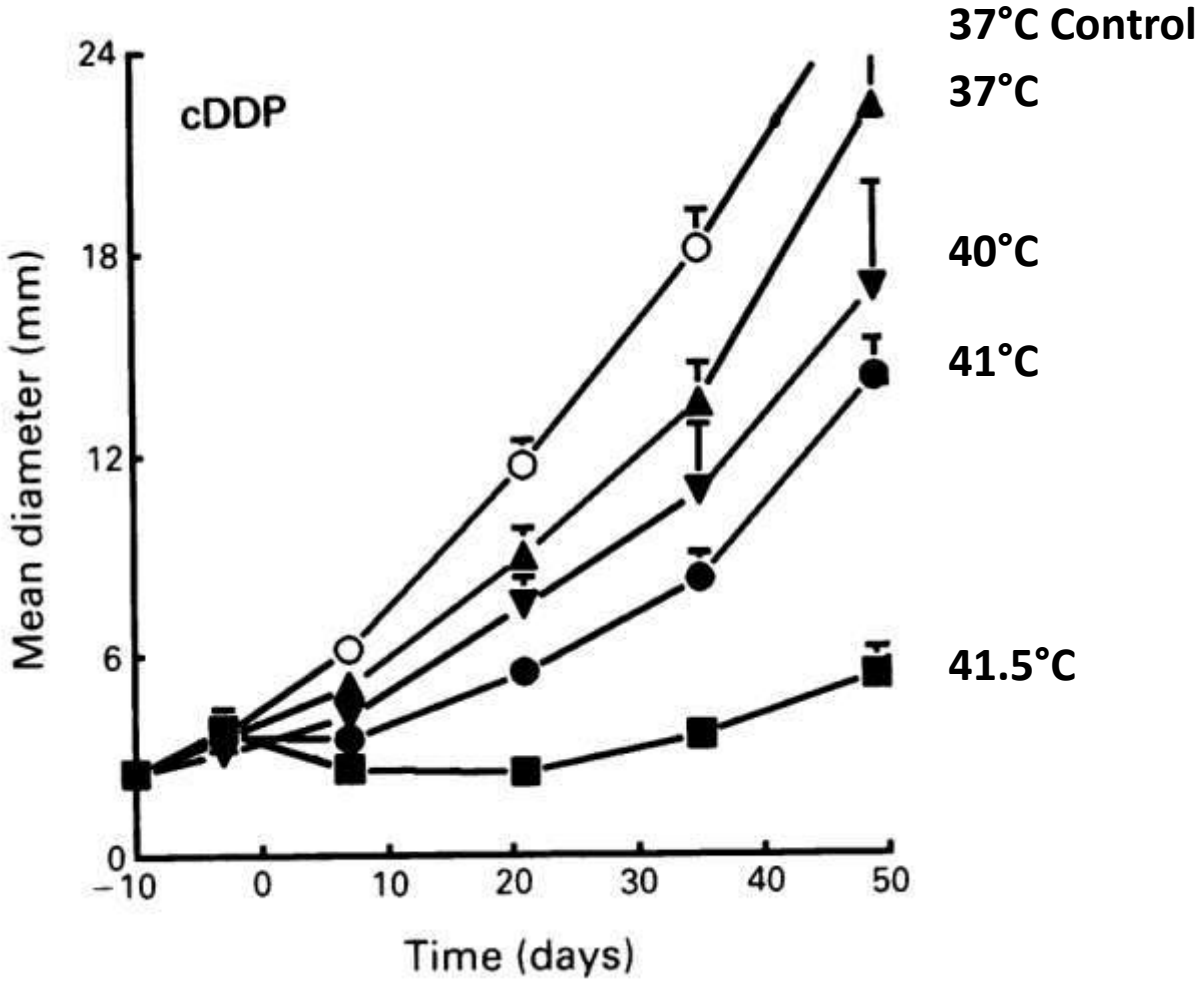
Br J Cancer, 1994

Abstract: The combination of heat and chemotherapy was studied in an intraperitoneal tumour model. The chemo-hyperthermia treatment resulted in more cDDP or CBDCA DNA adducts in peritoneal tumours after the combined treatment than after chemotherapy alone. I.p. chemotherapy combined with regional hyperthermia led to an increase in tumour growth delay (TGD) after increasing the temperature to 41.5 degrees C for cDDP and CBDCA (by 40 days for cDDP, 22 days for CBDCA). These data were in agreement with the in vitro findings, i.e. that higher temperatures led to increased cytotoxicity.



Nuclear staining density in peritoneal tumour sections (2 im) after normothermic (unshaded bar) or hyperthermic (shaded bar) treatment with i.p. cDDP (3.5 mg kg-') or CBDCA (30 mg kg-').

Los et al., 1994



Growth delay of peritoneal tumours after i.p. treatment with cDDP

Los et al., 1994

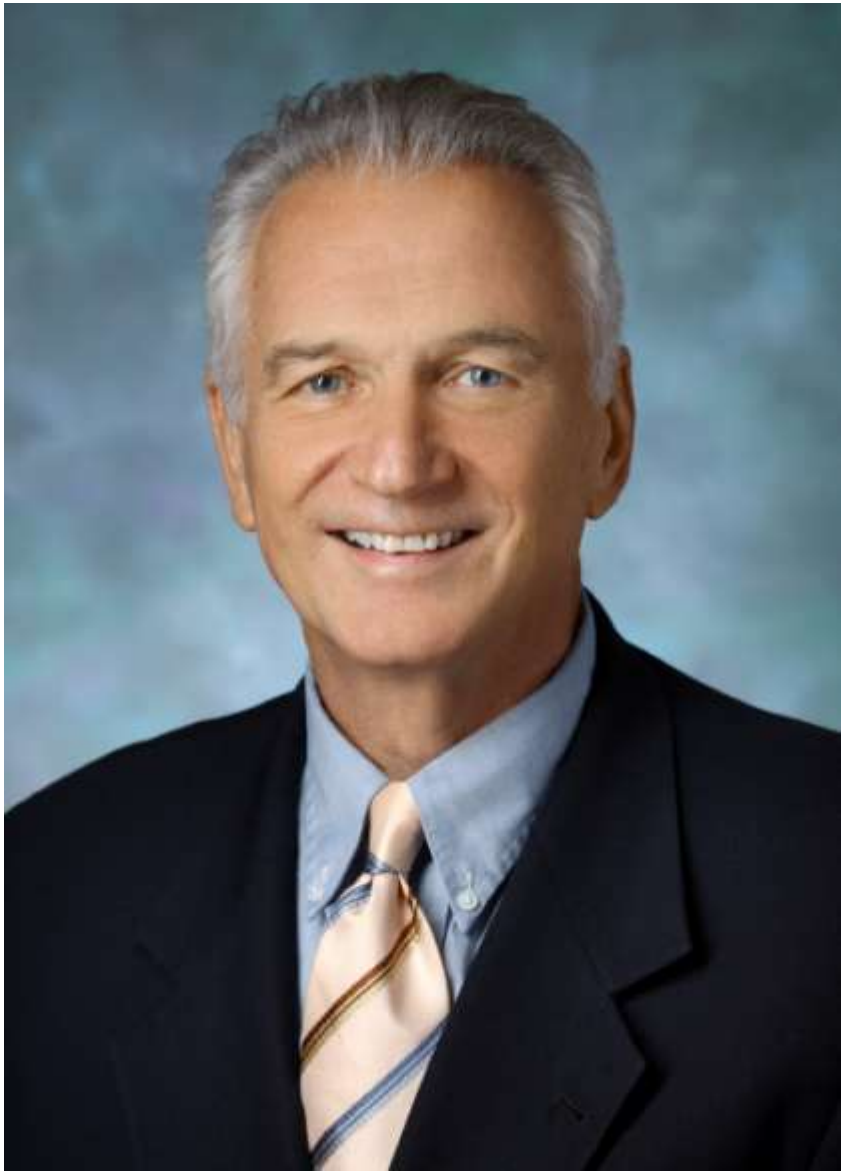
Peritonectomy Procedures

Paul H. Sugarbaker, Washington, DC

Ann Surg, January 1995

Abstract: Decisions regarding the treatment of cancer depend on the anatomic location of the malignancy and the biologic aggressiveness of the disease. Some patients may have isolated intra-abdominal seeding of the malignancy of limited extent or of low biologic grade. The cytoreductive approach may require six peritonectomy procedures to resect or strip cancer from all intra-abdominal surfaces. Peritonectomy procedures and preparation of the abdomen for early postoperative intraperitoneal chemotherapy were described to achieve long-term, disease-free survival in selected patients with peritoneal carcinomatosis.

(First formal presentation of peritonectomy procedures)



Paul H. Sugarbaker
Washington, DC

Prognostic Features of 51 Colorectal and 130 Appendiceal Cancer Patients with Peritoneal Carcinomatosis Treated by Cytoreductive Surgery and Intraperitoneal Chemotherapy

Paul H. Sugarbaker, Kathleen A. Jablonski, Washington, DC

Ann Surg, February 1995

Abstract: A treatment plan to be used in patients with peritoneal carcinomatosis was devised and tested as a Phase II study. The authors used cytoreductive surgery and intraperitoneal chemotherapy (CRS + EPIC) to treat 181 consecutive patients with peritoneal carcinomatosis. There were 51 patients with colorectal cancer and 130 patients with appendiceal cancer. Mean follow-up is 24 months. Clinical features that showed prognostic significance included appendiceal versus colorectal primary tumors (p=0.0001), grade 1 versus grades 2 and 3 histopathology (p=0.0003), complete versus incomplete cytoreductions (p=0.0001), lymph node-negative versus lymph node-positive primary tumors (p=0.0001), and volume of peritoneal carcinomatosis present preoperatively for colon cancer (p=0.0006). Features with no statistical prognostic significance included preoperative tumor volume for appendiceal cancer, age, sex, number of cycles of chemotherapy, operative time, complications, blood loss, and institution providing treatment.

(First clinical data to show importance of prognostic indicators)

Current Methodologies for Clinical Assessment of Patients with Peritoneal Carcinomatosis

Pierre Jacquet, Paul H. Sugarbaker, Washington, DC

J Exp Clin Cancer Res, 15, 1, 1996

Abstract: Peritoneal carcinomatosis is a common evolution of gastrointestinal cancers. The prognosis of patients with such disease is dependent upon pre-operative and post-operative variables. CT scan of the abdomen and the pelvis represents the adequate standardized radiologic exam for pre-operative evaluation of tumor volume and location in the peritoneal cavity. It may provide information regarding the selection of patients for complete cytoreduction surgery. Clinical factors like the extent of prior surgical procedures, the grade of the primary tumor, and the mucin content of peritoneal implants may also help to select patients for adequate treatment approach. Several intra-operative factors including the cancer distribution into the peritoneal cavity and the completeness of surgery need to be prospectively recorded by the surgeon in order to assess quantitatively their impact on the prognosis of patients with peritoneal carcinomatosis. This review provides standardized methodologies in the assessment of these clinical variables.

(First collection of prognostic indicators – tumor histology, CT-PCI, PCI, CC score, PSS)

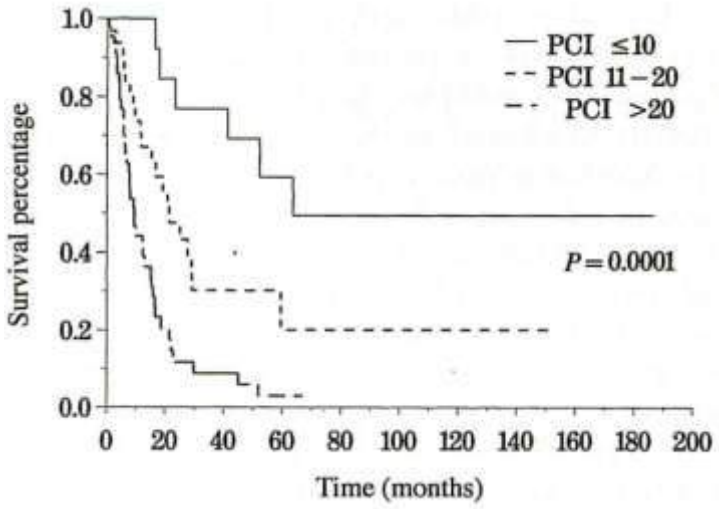
Successful Management of Microscopic Residual Disease in 100 Patients with Carcinomatosis from Large Bowel Cancer

Paul H. Sugarbaker, Washington, DC

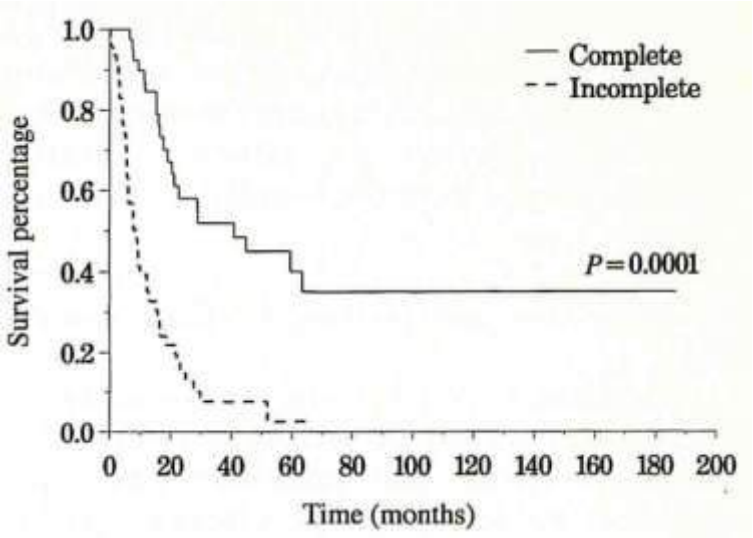
Cancer Chemother Pharmacol, 1999

Abstract: Peritonectomy procedures allow the removal of all visible peritoneal carcinomatosis with acceptable surgical morbidity (25%) and mortality (1.5%) rates. Heated intraoperative intraperitoneal chemotherapy using mitomycin C, in addition to early postoperative intraperitoneal 5-fluorouracil, can eradicate microscopic residual disease in the majority of patients. The peritoneal cancer index must be used in the selection of patients who may benefit. The completeness of the cytoreduction score is the most powerful prognostic indicator in this group of patients. The surgeon must be aware that there are no long-term survivors unless complete cytoreduction occurs.

(Confirmed prognostic indicators for colon cancer)



Survival of patients with peritoneal carcinomatosis from colon or rectal cancer by peritoneal cancer index.



Survival of patients by complete (CC-0 and CC-1 versus incomplete (CC-2 and CC-3) cytoreduction.

Sugarbaker et al., 1999

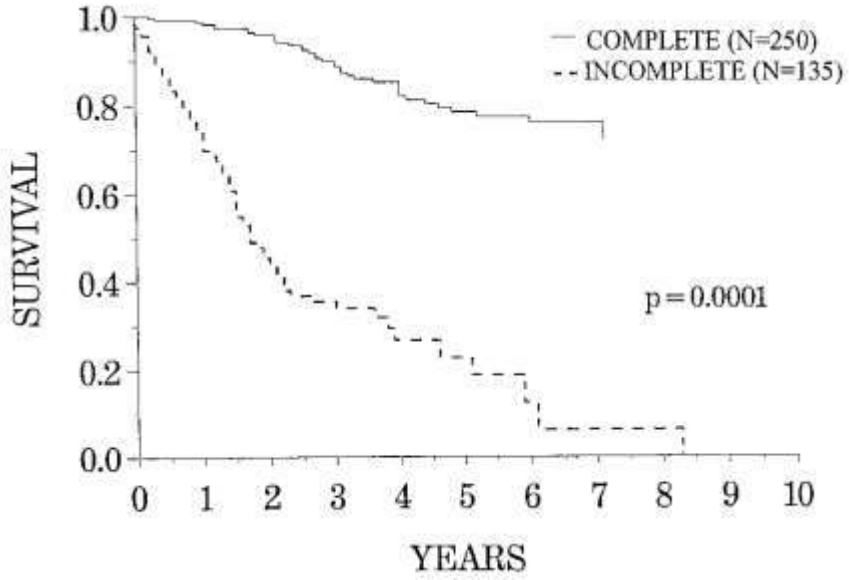
Results of Treatment of 385 Patients with Peritoneal Surface Spread of Appendiceal Malignancy

Paul H. Sugarbaker, David Chang, Washington, DC

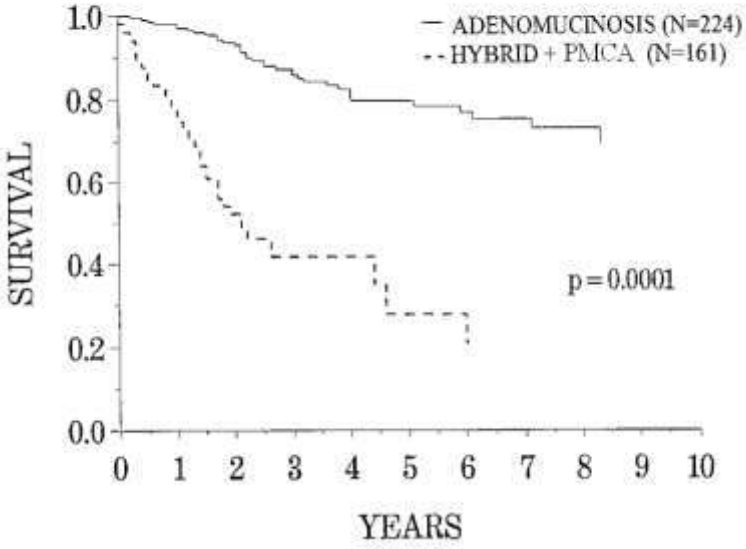
Ann Surg Oncol, 1999

Abstract: The intraperitoneal chemotherapy was given in the perioperative period, starting with mitomycin C at 12.5 mg/m^2 for males and 10 mg/m^2 for females. For patients whose pathology showed adenomucinosis, intraperitoneal chemotherapy was limited to treatment in the operating theater with heated mitomycin C. Patients with mucinous adenocarcinoma or pseudomyxoma/ adenocarcinoma hybrid had, in addition to mitomycin C, five consecutive days of intraperitoneal 5-fluorouracil at 650 mg/m^2 instilled in 1–1.5 liters of 1.5% dextrose peritoneal dialysis solution.

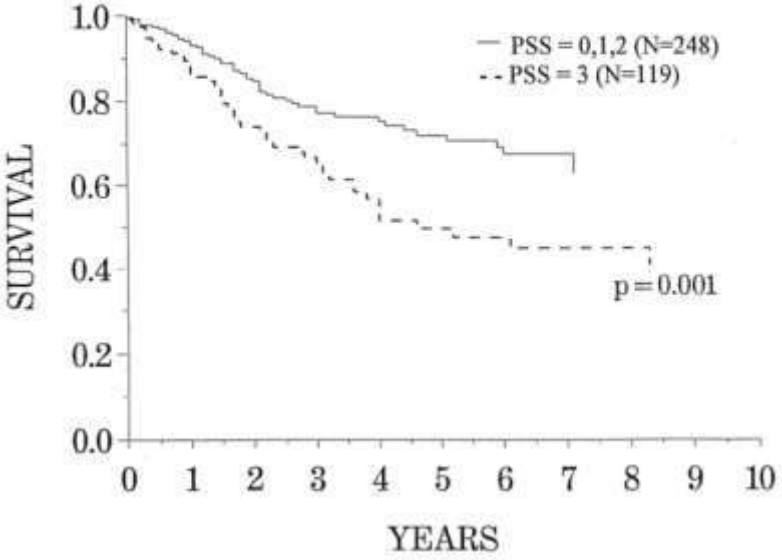
(Confirmed prognostic indicators for appendiceal cancer)



PERITONEAL SURFACE MALIGNANCY – APPENDIX
SURVIVAL BY HISTOLOGY



PERITONEAL SURFACE MALIGNANCY – APPENDIX
SURVIVAL BY PRIOR SURGICAL SCORE



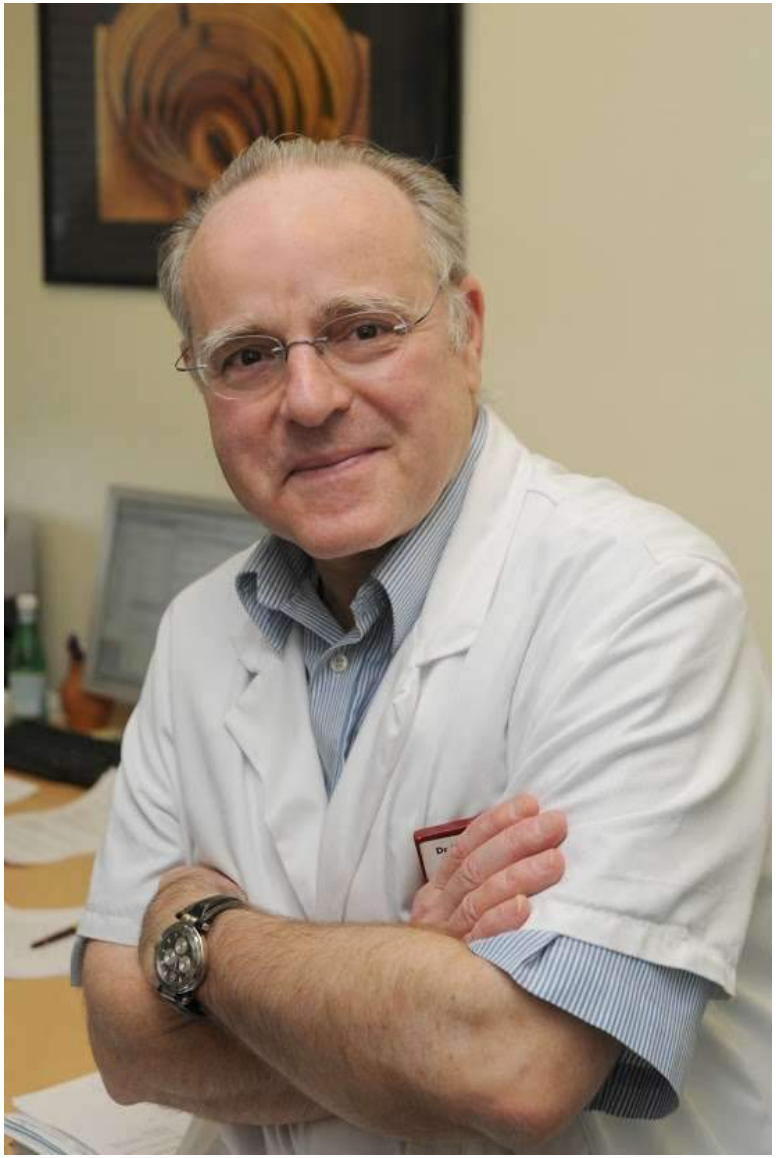
Sugarbaker and Chang, 1999

Treatment of Liver Metastases with Moderate Peritoneal Carcinomatosis by Hepatectomy and Cytoreductive Surgery Followed by Immediate Post-operative Intraperitoneal Chemotherapy: Feasibility and Preliminary Results

Dominique Elias, Pierre Dube, Sylvie Bonvalot, et al., Institut Gustave Roussy, Cancer Center Hospital, Villejuif, France, *Hepato-Gastroenterology*, 1999

Abstract: Peritoneal carcinomatosis (PC) discovered during hepatectomy is usually a contraindication to resection. A potentially efficient treatment of PC is the resection of the macroscopic disease and the treatment of the residual microscopic disease with immediate post-operative intraperitoneal chemotherapy (IPIC) (before the entrapment of cancer cells inside the fibrin deposit which rapidly cover the injured tissues). Twelve patients with liver metastases and moderate PC from miscellaneous origins, underwent: 1) hepatectomy (9 of them were major hepatectomies); 2) complete cytoreductive surgery of the PC resecting between 20 and 150 nodules; and, 3) IPIC, for 5 days, according to histology. There was no mortality. Preliminary results concerning survival are promising with 7 patients without recurrent disease. When a minimal or moderate PC is discovered during laparotomy for liver resection of metastases, the combination of hepatectomy with complete cytoreductive surgery of the peritoneal disease, followed with IPIC is logical and feasible. This aggressive treatment is well tolerated although the frequency of biliary leakage seems to be higher than that after standard hepatectomy. No recurrence of the peritoneal disease was detected and survival results are very promising.

(Confirmed treatments possible for peritoneal and liver metastases)



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Villejuif, France

Peritoneal Carcinomatosis from Non-Gynecologic Malignancies: Results of the EVOCAPE 1 Multicentric Prospective Study

Babek Sadeghi, Catherine Arvieux, Olivier Glehen, et al., Centre Hospitalier Lyon-Sud, Lyon, France

Cancer, 2000

Abstract: Peritoneal carcinomatosis (PC) is a common evolution of digestive cancer, associated with a poor prognosis. Three hundred seventy patients with PC from non-gynecologic malignancies were followed prospectively: the PC was of gastric origin in 125 cases, of colorectal origin in 118 cases, of pancreatic origin in 58 cases, of unknown origin in 43 cases, and of miscellaneous origins in 26 cases. Mean and median overall survival periods were 6.0 and 3.1 months, respectively. Survival rates were mainly affected by the initial PC stage (9.8 months for Stage I versus 3.7 months for Stage IV). The presence of ascites was associated with poor survival of patients with gastric or pancreatic carcinoma.

(Prospective study of the natural history of peritoneal metastases)

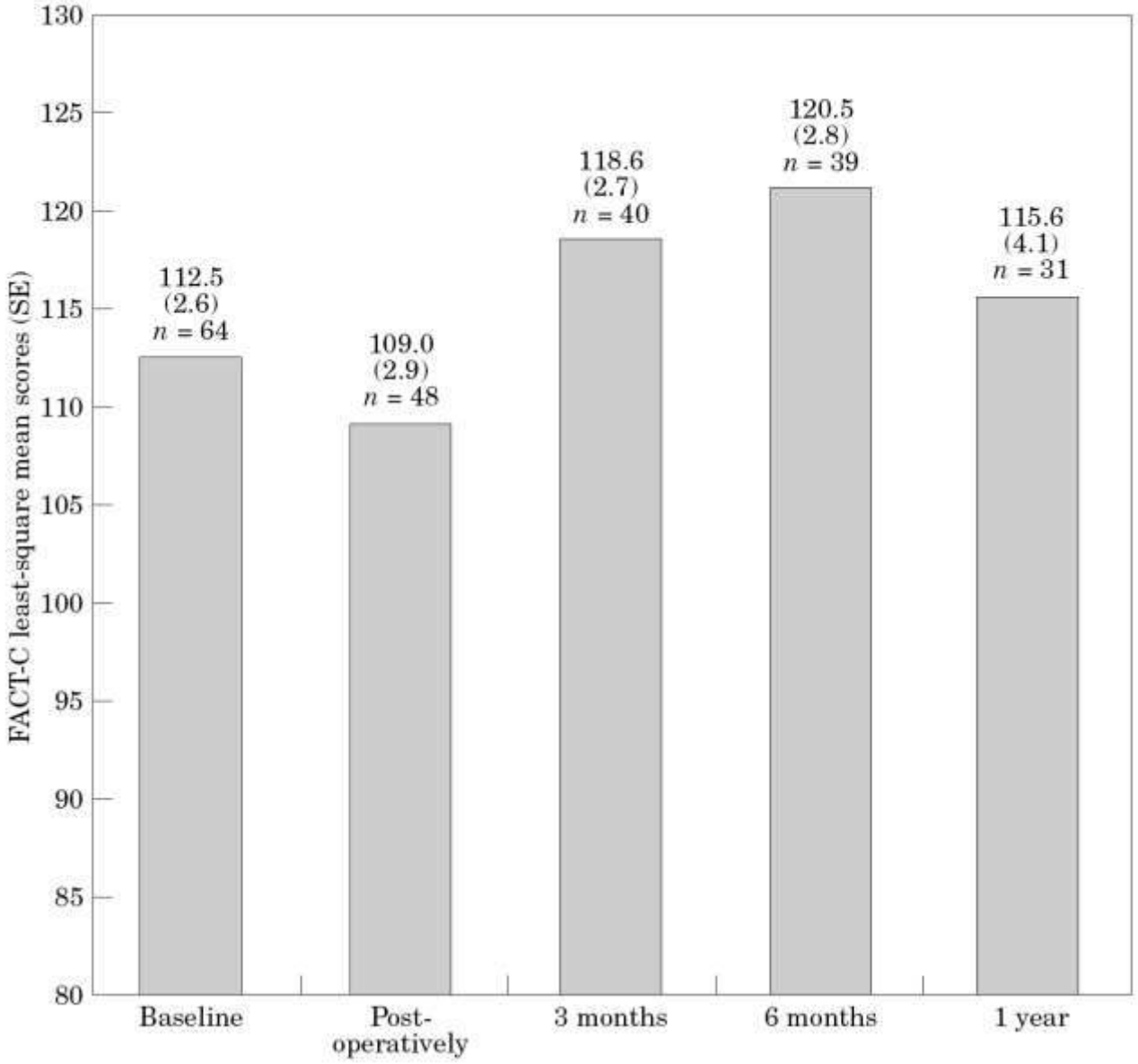
Quality of Life After Intraperitoneal Hyperthermic Chemotherapy (IPHC) for Peritoneal Carcinomatosis

RP McQuellon, BW Loggie, RA Fleming, GB Russell, AB Lehman, TD Rambo
Wake Forest University School of Medicine, Winston-Salem, NC
Eur J Surg Oncol, 2001

Abstract: This study assessed the functional status and quality of life (QOL) of patients with disseminated peritoneal cancer (DPC) before and after cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy (IPHC). There was a significant overall effect on the physical (P=0.0025), emotional (P<0.0001) and functional well-being (P=0.0044) subscales and the FACT-C (P=0.0076). Physical and functional well-being scores decreased at post-surgery follow-up and increased relative to baseline at 3, 6 and 12 months. Cytoreductive surgery followed by IPHC was well tolerated. Most patients returned to baseline or better levels of functioning within 3 months post-treatment.

(First study reporting quality of life after CRS and HIPEC)

Brian W. Loggie
Omaha, NE



Functional assessment of cancer therapy (FACT-C) at five time points.

Loggie et al., 2001

Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients with Peritoneal Carcinomatosis of Colorectal Cancer

Vic J. Verwaal, Serge van Ruth, Eelco de Bree, Gooike W. van Slooten, Harm van Tinteren, Henk Boot, Frans A. N. Zoetmulder

Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam

J Clin Oncol, 2003

Abstract: Between February 1998 and August 2001, 105 patients were randomly assigned to receive either standard treatment consisting of systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery, or experimental therapy consisting of aggressive cytoreduction with HIPEC, followed by the same systemic chemotherapy regime. The primary end point was survival. After a median follow-up period of 21.6 months, the median survival was 12.6 months in the standard therapy arm and 22.3 months in the experimental therapy arm (log-rank test, P=.032). The treatment-related mortality in the aggressive therapy group was 8%.

(First and only successful RCT for treatment of colon cancer peritoneal metastases)

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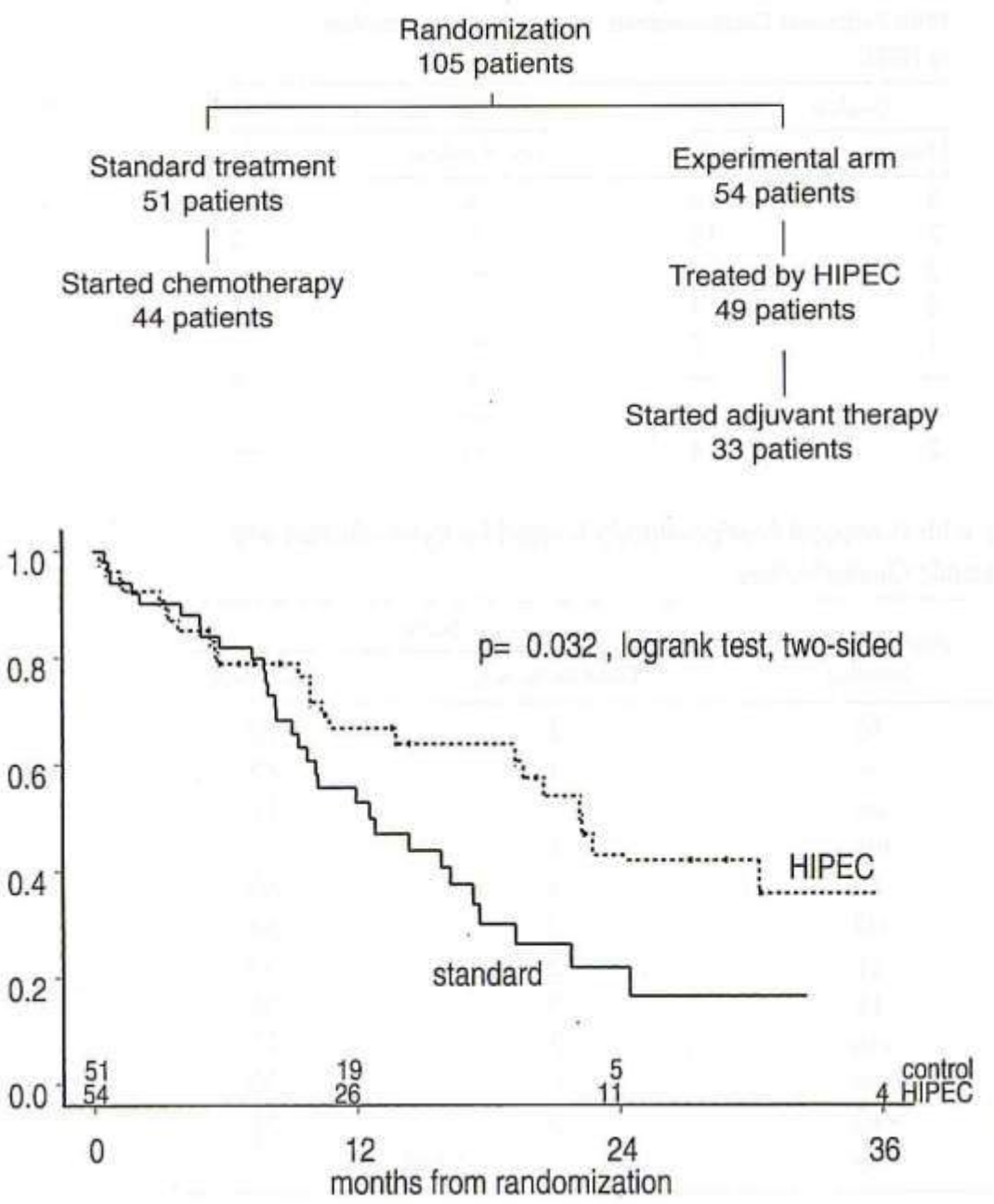

Zoetmulder et al., 2003

Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy for the Management of Peritoneal Carcinomatosis from Colorectal Cancer: A Multi-Institutional Study

O. Glehen, F. Kwiatkowski, P.H. Sugarbaker, D. Elias, E.A. Levine, M. De Simone, R. Barone, Y. Yonemura, F. Cavaliere, F. Quenet, M. Gutman, A.A.K. Tentes, G. Lorimier, J.L. Bernard, J.M. Bereder, J. Porcheron, A. Gomez-Portilla, P. Shen, M. Deraco, and P. Rat

J Clin Oncol, 2004

Abstract: A retrospective multicenter study was performed to evaluate the international experience with this combined treatment and to identify the principal prognostic indicators. PC from appendiceal origin was excluded. The study included 506 patients from 28 institutions operated between May 1987 and December 2002. The morbidity and mortality rates were 22.9% and 4%, respectively. Patients in whom cytoreductive surgery was complete had a median survival of 32.4 months, compared with 8.4 months for patients in whom complete cytoreductive surgery was not possible (P<.001). Positive independent prognostic indicators by multivariate analysis were complete cytoreduction, treatment by a second procedure, limited extent of PC, age less than 65 years, and use of adjuvant chemotherapy. The use of neoadjuvant chemotherapy, lymph node involvement, presence of liver metastasis, and poor histologic differentiation were negative independent prognostic indicators.

(First multi-institutional report of CRS and HIPEC to treat colon cancer peritoneal metastases)

Olivier Glehen
Lyon, France

Decision-making and Technical Factors Account for the Learning Curve in Complex Surgery

Brendan J. Moran, Pseudomyxoma Peritonei Centre, Basingstoke, Hampshire, UK

J Public Health, July 2006

Abstract: The general public, the legal profession, patients and relatives expect best practice and have difficulty with the concept of a learning curve in surgical interventions. However, it is improbable that technical and innovative skills can be developed, or optimized, without some aspects of learning by experience and indeed 'risk taking'. In total, 100 of 242 (41%) patients referred underwent a laparotomy. The 100 were divided into three numerically equal groups of 33, 33 and 34 cases, and the proportions undergoing surgery, mortality and major morbidity rates for the three groups were analysed. A mechanism to reduce the surgical learning curve is suggested involving teamwork, and at least two experienced surgeons involved in all major surgical interventions. Decision-making and technical factors account for the learning curve in complex surgery.

(First description of Learning Curve in CRS and HIPEC)

Brendan Moran
Basingstoke, UK

Mortality and morbidity of patients undergoing surgery

	Total referred	*Number undergoing laparotomy (%)*	*Mortality number (%)*	*Number of re-operation for bleeding (%)*	*Anastomotic leakage number (%)*
Group 1	54	33 (61)	6/33 (18)	5 (15)	4 (12)
Group 2	96	33 (34)	1/33 (3)	1 (3)	1 (3)
Group 3	92	34 (37)	1/34 (3)	0 (0)	0 (0)

Moran, 2006

Conclusions:

1. A new treatment option exists for selected patients with peritoneal metastases from gastrointestinal cancer and peritoneal mesothelioma.
2. New management strategies to achieve success include:
   - Intraperitoneal administration of cancer chemotherapy
   - Augmenting chemotherapy response with heat
   - Use of chemotherapy in the perioperative period
   - Utilization of peritonectomy procedures and visceral resections to downstage disease
   - Selection of patients using prognostic indicators
   - Integrating systemic chemotherapy into the peritoneal metastases treatment package

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Conclusions:

3. Pharmacologic, surgical and technologic advances have progressed since 1978 and are now continuing 3 decades later.
4. Integration of medical oncologist, colorectal surgeon and gynecologic surgeon into these oncologic efforts is the challenge for the latter half of the 2010s.

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