40 Years of Peritoneal Metastases
Prevention and Treatment:
A History

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No disclosures
Part 1 – Evolution of HIPEC

- 1970 to present: Augmentation of cancer chemotherapy by heat (IJH)
- 1978: Pharmacologic principles of IP drug delivery
- 1980: IP cancer control by heat
- 1980: The first HIPEC
- 1984-1990: Japanese development of HIPEC
- 1991: HIPEC returns to Europe and USA
Part 2 – Evolution of CRS/EPIC

- 1985: CRC RCT with EPIC
- 1987: PMP treated with CRS and EPIC
- 1995: Peritoneectomy procedures
- 1995: Prognostic indicators for appendiceal and colorectal cancer
- 1999: Success with LM and PM from CRC
Part 3 – CRS and IP chemotherapy established/refined

- 2000: EVOCAPE 1, The French effort begins
- 2001: Quality of life studies
- 2003: Dutch RCT with HIPEC
- 2004: Multi-institutional study
- 2006: The learning curve
- 2008: High risk groups
- 2009: HIPEC oxaliplatin
- 2016: Swedish CRC RCT with EPIC
- 2017: Revised NCCN Guidelines
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 demonstration of a pharmacologic advantage of intraperitoneal chemotherapy administration)
Robert L. Dedrick
Bethesda, MD
Pharmacokinetics of 3 different types of 5-fluorouracil administration

Speyer et al., 1980
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.
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
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
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)
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
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 prophylactic treatment for peritoneal metastasis after gastric cancer surgery in humans.

(First HIPEC in an animal model)
Shigemasa Koga
Yonago, Japan
### Table 2

**Survival data after CHPP**

<table>
<thead>
<tr>
<th>Hyperthermic treatment with or without MMC</th>
<th>Time (days) after inoculation</th>
<th>Mean survival time (days)</th>
<th>No. of survivors at 60 days</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (37.0°)</td>
<td>1 (n = 5)</td>
<td>14.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 7)</td>
<td>17.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10 (n = 4)</td>
<td>16.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group 2 (41.5°)</td>
<td>1 (n = 9)</td>
<td>19.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 8)</td>
<td>18.6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10 (n = 7)</td>
<td>&gt;24.3</td>
<td>1</td>
<td>14.3</td>
</tr>
<tr>
<td>Group 3 (42.5°)</td>
<td>1 (n = 8)</td>
<td>&gt;51.5</td>
<td>2</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 4)</td>
<td>&gt;14.8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4 (41.5° + MMC, 1 mg/kg)</td>
<td>1 (n = 7)</td>
<td>&gt;98.9</td>
<td>2</td>
<td>28.6</td>
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<tr>
<td></td>
<td>5 (n = 10)</td>
<td>&gt;56.3</td>
<td>2</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>10 (n = 10)</td>
<td>&gt;102.8</td>
<td>4</td>
<td>40.0</td>
</tr>
<tr>
<td>Group 5 (MMC, 1 mg/kg)</td>
<td>1 (n = 5)</td>
<td>&gt;19.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 (n = 5)</td>
<td>&gt;18.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10 (n = 5)</td>
<td>&gt;18.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control group (tumor cell inoculation only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Significant difference from Group 2 ($p < 0.05$; $\chi^2$ test).
Prospective, Randomized Trial of Intravenous Versus Intraperitoneal 5-fluorouracil in Patients with Advanced Primary Colon or Rectal Cancer


**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


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)
HYPERTHERMIC PERITONEAL PERFUSION FOR GASTRIC CANCER

Survival rate (%)

Postoperative months

CHPP-M group

Control group

83.0%

67.3%

Koga 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, developed in France)*
Francois Gilly
Lyon, France
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
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 – tumor histology, PCI, CC score, PS score)
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)*
Dominique Elias
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.

(Multi-institutional French 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)
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 )
Randomization
105 patients

Standard treatment
51 patients
  Started chemotherapy
  44 patients

Experimental arm
54 patients
  Treated by HIPEC
  49 patients
    Started adjuvant therapy
    33 patients

\[ p = 0.032, \text{ logrank test, two-sided} \]

Zoetmulder et al., 2003
Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy for the Management of Peritoneal Carcinomatosis from Colorectal Cancer: A Multi-Institutional Study
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)*
## Mortality and morbidity of patients undergoing surgery

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

Moran, 2006
Results of Systematic Second-Look Surgery in Patients at High Risk of Developing Colorectal Peritoneal Carcinomatosis
Dominique Elias, Diane Goere, Daniela Di Pietrantonio, Valerie Boige, David Malka, Niaz Kohneh-Shahri, Clarisse Dromain, Michel Ducreux
Institut Gustave Roussy, Villejuif, France

Abstract: The aim of this prospective study was to analyze the impact of second-look surgery in an attempt to treat peritoneal carcinomatosis (PC) at an early stage in a series of patients at high risk of developing PC from colorectal cancer. From 1999 to 2006, 29 patients without any sign of recurrence on imaging studies underwent second-look surgery 13 months after resection of the primary tumor. Patients were selected according to primary tumor-associated criteria: resected minimal synchronous macroscopic PC (n=16), synchronous ovarian metastases (n=4), perforated primary tumor (n=9). Performing second-look surgery at 1 year in selected patients at high risk of developing PC allowed the early detection and treatment of PC in 55% of cases.
Complete Cytoreductive Surgery Plus Intraperitoneal Chemohyperthermia with Oxaliplatin for Peritoneal Carcinomatosis of Colorectal Origin

Dominique Elias, Jeremie H. Lefevre, Julie Chevalier, Antoine Brouquet, Frederic Marchal, Jean-Marc Classe, Gwenael Ferron, Jean-Marc Guilloit, Pierre Meeus, Diane Goere, Julia Bonastre
Institut Gustave Roussy, Villejuif, France
J Clin Oncol, 2008

Abstract: To compare the long-term survival of patients with isolated and resectable peritoneal carcinomatosis (PC) in comparable groups of patients treated with systemic chemotherapy containing oxaliplatin or irinotecan or by cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC). 48 patients were retrospectively included in the standard group and were compared with 48 patients who had undergone HIPEC and were evaluated prospectively. Two-year and 5-year overall survival rates were 81% and 51% for the HIPEC group, respectively, and 65% and 13% for the standard group, respectively. Median survival was 23.9 months in the standard group vs. 62.7 months in the HIPEC group (p<0.05, log-rank test).
Fig 1. Overall survival of group receiving cytoreductive surgery, hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic treatment versus those receiving standard treatment.
Cytoreductive Surgery and Intraperitoneal Chemotherapy versus Systemic Chemotherapy for Colorectal Peritoneal Metastases: A Randomised Trial

Uppsala University, Uppsala, Sweden

Eur J Cancer, 2016

Abstract: This study (the Swedish peritoneal study) compares cytoreductive surgery and intraperitoneal chemotherapy (surgery arm) with systemic chemotherapy (chemotherapy arm). 48 eligible patients (24/arm) were included in the study. Two-year OS was 54% in the surgery arm and 38% in the chemotherapy arm (p=0.04). After 5 years, 8 versus 1 patient were alive, respectively (p=0.02). Median OS was 25 months versus 18 months, respectively (p=0.04). Grade III-IV morbidity was seen in 42% and 50% of the patients, respectively. No mortalities.
Fig. 2. Overall survival after cytoreductive surgery combined with intraperitoneal chemotherapy compared to systemic chemotherapy only in peritoneal metastases of colorectal origin, $p = 0.04$. 
### Proactive Colorectal Protocols

- **ProphyloCHIP: CRS and HIPEC with Second-Look Surgery** (Diane Goere, MD, PhD; Paris, France)
- **COLOPEC ± Adjuvant HIPEC for Primary Colon Cancer** (Pieter Tanis, MD, PhD; Amsterdam, The Netherlands)
- **PROMENADE: Prophylactic HIPEC for Primary Colon Cancer** (Paolo Sammartino, MD, PhD; Rome, Italy)
- **Prophylactic: HIPEC for cT4 Colon Cancer** (Alvaro Arjona-Sanchez, MD, PhD; Cordoba, Spain)

### Colorectal Treatment Protocols

- **PRODIGE 7 ± Adjuvant HIPEC for Peritoneal Metastases from Colon Cancer** (Francois Quenet, MD; Montpelier, France)
- **ICARuS EPIC FUDR versus HIPEC After Optimal Cytoreductive Surgery (CRS) for Neoplasms of the Appendix, Colon or Rectum with Isolated Peritoneal Metastasis** (Garrett M. Nash, MD, MPH; New York City, NY, USA)
- **Surgery and Oxaliplatin or Mitomycin C in Treating Patients with Tumors of the Appendix** (Edward A. Levine, MD; Winston-Salem, NC, USA)
- **Cytoreduction and Intraperitoneal Chemotherapy versus Systemic Chemotherapy in Colorectal Peritoneal Carcinomatosis** (Peter H. Cashin, MD, PhD; Uppsala, Sweden)
- **COMBATAC: Combined Anticancer Treatment of Advanced Colon Cancer** (Pompiliu Piso, MD, PhD; Regensburg, Germany)
- **NIPOX Adjuvant Intraperitoneal Oxaliplatin for Colorectal Cancer with Peritoneal Metastases** (Francois Quenet, MD; Montpelier, France)
- **Mitomycin C vs. melphalan** (Mazin Al-Kasspooles, MD; Kansas City)
### Ovarian Cancer Protocols

- **CRS and HIPEC in Recurrent Ovarian Cancer** (John D. Spiliotis, MD, PhD; Athens, Greece)
- **HIPEC with Carboplatin for Recurrent Ovarian Cancer, Phase II** (Dennis S. Chi, MD; New York City, NY, USA)
- **CHIPOR CRS with or without HIPEC for Relapsed Ovarian Cancer** (Jean-Marc Classe, MD, PhD; Nantes, France)
- **CHORINE CRS with or without HIPEC Upfront for Primary Ovarian Cancer** (Luca Ansaloni, MD; Bergamo, Italy)
- **HORSE CRS with or without HIPEC in Ovarian Cancer Recurrence** (Anna Fagotti, MD, PhD; Rome, Italy)
- **Secondary Debulking Surgery +/- Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer** (Willemien van Driel, MD, PhD; Amsterdam, The Netherlands)
- **Outcomes in CRS/HIPEC as Initial Treatment of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer** (Teresa Diaz-Montes, MD; Baltimore, MD, USA)
- **HIPEC in Primary Ovarian Cancer, NCC Korea** (Sang Yoon Park, MD, PhD; Seoul, Korea)

### Gastric Cancer Protocols

- **GastriCHIP Gastrectomy ± HIPEC as Adjuvant for Primary Gastric Cancer** (Olivier Glehen, MD, PhD; Lyon, France)
- **GASTRIPEC Cytoreductive Surgery (CRS) with/without HIPEC in Gastric Cancer with Peritoneal Carcinomatosis** (Beate Rau, MD, PhD; Berlin, Germany)
- **Phoenix GC Neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) for GC with Peritoneal Metastases** (Hironori Ishigami, MD; Tokyo, Japan)
International and national multi-institutional registries

- **International Registry on Peritoneal Mesothelioma** (Shigeki Kusamura, MD, PhD; Milan, Italy)
- **Big RENAPE including Rare Diseases Treated with CRS and HIPEC** (Diane Goere, MD, PhD; Paris, France)
- **Repeat Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Colorectal Cancer Patients (PSOGI Collaboration)** (Nayef Alzahrani, MD; Sydney, Australia)
- **Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastases from Small Bowel Adenocarcinoma: Multi-institutional Experience** (Yang Liu, MD; Beijing, China)
- **German Registry** (Pompiliu Piso, MD, PhD; Regensburg, Germany)
- **Dutch Registry** (Vic Verwaal, MD, PhD; Aarhus, Denmark)
- **Indian HIPEC Registry: A Registry for Indian Patients with Peritoneal Surface Malignancies** (Aditi Bhatt, MD, Mch; Bangalore, India)
- **Brazilian and South American HIPEC Registry** (Claudio Quadros, MD; Salvador, Bahia, Brazil)
SUMMARY OF PSOGI BIENNIAL CONGRESSES:

1998 – Basingstoke (20 participants)

2000 – Royal College of Surgeons Millenium Masterclass, London (30 participants)

2002 – Basingstoke (50 participants)

2004 – Madrid (250 participants) (Special Issue of EJSO)

2006 – Uppsala (450 participants)

2008 – Milan – Delphi Method Consensus Conference (450 participants) (Special Issue of JSO)

2010 – Lyon (450 participants) (Special Issue of The Cancer Journal)

2012 – Berlin (600 participants) (Spectacular dance party)

2014 – Amsterdam (500 participants)


2018 – Paris, 9-11 September 2018, Maison de la Chimie, France

2020 – Beijing, China
Peritoneal Metastases

The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. The panel recognizes the need for (additional) randomized clinical trials that will address the risks and benefits associated with each of these modalities.
Conclusions:

1. A new treatment option has been established 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
Conclusions:

3. Integration of medical oncologist, colorectal surgeon and gynecologic surgeon into these oncologic efforts is the challenge for the latter half of the 2010s.

4. Clinical trials, registries, and national cooperative groups sustain these efforts.
SAVE THE DATE

11th International Workshop
ON PERITONEAL SURFACE MALIGNANCY
SEPTEMBER 9-11, 2018
Maison de la Chimie, Paris France

LOCAL ORGANISING COMMITTEE
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