#### CO01

COMBINED LIVER AND PERITONEAL RESECTION WITH HIPEC FOR METASTATIC COLORECTAL CANCER: RESULTS OF A WORLDWIDE ANALYSIS OF 570 PATIENTS FROM THE PERITONEAL SURFACE ONCOLOGY GROUP INTERNATIONAL (PSOGI)

R. Lo Dico<sup>1</sup>, M. Faron<sup>1</sup>, D. Goere<sup>1</sup>, O. Glehen<sup>1</sup>, Y. Yonemura<sup>2</sup>, M. Pocard<sup>1</sup>, W. Ceelen<sup>3</sup>, A. Sardi<sup>4</sup>, D. Baratti<sup>5</sup>, G. Liberale<sup>3</sup>, A. Kartheuser<sup>3</sup>, I. De Hingh<sup>6</sup>, P. Sammartino<sup>5</sup>, P. Sugarbaker<sup>4</sup>, B. Moran<sup>7</sup>, M. Robella<sup>5</sup>, M. Hubner<sup>8</sup>, M. Limbert<sup>9</sup>, L. Sideris<sup>10</sup>, D. Morris<sup>11</sup>, P. Psogi Group<sup>4</sup>

<sup>1</sup>(France), <sup>2</sup>(Japan), <sup>3</sup>(Belgium), <sup>4</sup>(United States), <sup>5</sup>(Italy), <sup>6</sup>(Netherlands), <sup>7</sup>(United Kingdom), <sup>8</sup>(Switzerland), <sup>9</sup>(Portugal), <sup>10</sup>(Canada), <sup>11</sup>(Australia)

# **Objectives**

Aggressive surgical approaches combining liver resection (LR), peritoneal cytoreduction (CRS), and hyperthermic intraperitoneal chemotherapy (HIPEC) with curative intent for patients with synchronous peritoneal (PM) and liver metastases (LM) of colorectal cancer (CRC) remains controversial. The aim of this retrospective multicenter study from PSOGI centers was to assess morbidity, disease free survival (DFS), and overall survival (OS) of such patients treated by combining LR and CRS followed by HIPEC.

#### **Methods**

Data from patients undergoing complete LR with CRS and HIPEC with curative intent performed in 34 centers worldwide were retrospectively analyzed.

### Results

Between 1991 and 2016, 576 patients were enrolled. Simultaneous LR with CRS was performed in 457 patients, while, 93 had a two-step surgery (69 had LR prior to CRS, 24 had CRS prior to LR). Mean follow-up was 24 months. Median DFS and OS for the whole cohort were 20.4 [95%CI: 18.8–21.8] and 54.6 [95%CI: 49.7–66.3] months, respectively. The 1-, 3-, and 5-year DFS rates were 78.6%, 23.9%, and 10.2%. The 1-, 3-, and 5-year OS rates were 95.9%, 70.7%, and 46.1%, respectively. Patients undergoing simultaneous surgery had a median DFS and OS of 19.4 [95%CI: 17.5–20.8] and 52.4 [95%CI: 47.6–63] months, respectively. Patients undergoing a two-steps surgery had a median DFS and OS of 27.6 [95%CI: 23.5–38.2, p = 0.085] and 91.9 [95%CI: 46.3–NA] months if LR was performed before CRS, and 17.1 [95%CI: 15.5–37.9] and 54.9 [95%CI: 41.7–NA] months if CRS was performed before LR. Peritoneal carcinomatosis index was identified as an independent prognostic factor for both OS and DFS (aHR 1.05; 95%CI 1.03–1.07, p > 0.0001 and aHR 1.01; 95%CI 1–1.03, p = 0.077, respectively). Postoperative major morbidity occurred in 33% of patients, 32% after simultaneous surgery and 36.6% after two-steps surgery. Postoperative mortality rate was 5.5%, 2.8% for simultaneous surgery and 5.4% for two-steps surgery (5.8% for LR prior to CRS and 4.2% for CRS prior to LR).

### Conclusion

This multicenter study is the largest confirming the feasibility of combined LR with CRS and HIPEC in select patients with LM and PM of CRC, resulting in a 55-month median OS with acceptable morbidity.

#### **CO02**

MECHANISM AND TREATMENT STRATEGY FOR PERITONEAL RECURRENCE AFTER CURATIVE GASTRIC CANCER SURGERY

S. Murata<sup>1</sup>, K. Takebayashi<sup>2</sup>, T. Yamaguchi<sup>2</sup>, S. Kaida<sup>2</sup>, H. Kodama<sup>2</sup>, H. Iida<sup>2</sup>, K. Naomi<sup>2</sup>, H. Maehira<sup>2</sup>, H. Mori<sup>2</sup>, T. Shimizu<sup>2</sup>, E. Mekata<sup>3</sup>, Y. Daigo<sup>4</sup>, M. Tani<sup>2</sup>

<sup>1</sup>Cancer Center, Shiga University of Medical Science Hospital. Department of Surgery, Shiga University of Medical Science - Otsu (Japan), <sup>2</sup>Department of Surgery, Shiga University of Medical Science - Otsu (Japan), <sup>3</sup>Department of Comprehensive Surgery, Shiga University of Medical Science - Otsu (Japan), <sup>4</sup>Cancer Center, Shiga University of Medical Science Hospital - Otsu (Japan)

# **Objectives**

We recently showed that cancer cells, with proliferative and tumorigenic potential, can spill into the peritoneal cavity during curative (R0) gastric cancer (GC) surgery, which is associated with peritoneal recurrence (PM). To elucidate the pathophysiology of PM, the relationship between spilled cancer cells and cancer stem cells was evaluated. Furthermore, to identify a therapeutic strategy for PM, the prognostic impact of hyperthermic intraperitoneal chemotherapy (HIPEC) following GC surgery with spillage of cancer cells was evaluated.

#### **Methods**

Patients with advanced GC (≥pT2 [MP]) who underwent R0 gastrectomy between 2010 and 2015 were retrospectively examined. Ninety-three consecutive patients with negative results in peritoneal cytology and cancer cell culture (CCC [¬]) following peritoneal washing (PW) before GC surgery were included. Spilled cancer cells in PW after GC surgery (PW-Post) were examined to identify any CD44-positive cancer stem-like cells associated with cancer metastasis. Based on the PW-Post CCC results, associations between HIPEC and recurrence-free survival (RFS), or overall survival (OS) were evaluated. HIPEC was performed following GC surgery using CDDP, MMC, and 5-FU in 5 L saline maintained at 42°C for 30 min.

# Results

Spilled cancer cells included CD44+ cancer stem-like cells. In 93 patients 47 showed PW-Post positive CCC (CCC [+]) and 46 PW-Post CCC ( $^-$ ). No clinicopathological difference was observed between the two cohorts. Multivariate logistic regression analysis indicated that PW-Post CCC ( $^+$ ) was an independent risk factor for the recurrence after surgery (Odds: 61.1, P = 0.005). Among patients with PW-Post CCC ( $^+$ ) (n = 46), the 5-year peritoneal RFS, hepatic RFS, and lymph node RFS rates were 94.7%, 100%, and 84.7%, respectively, in patients who received HIPEC (n = 25), and 65.3%, 54.4%, and 78.3%, respectively, in those who did not (n = 22) (P = 0.012, P = 0.013, and P = 0.33, respectively). Among patients with PW-Post CCC ( $^-$ ) (n = 46), none developed recurrence, regardless of whether they received HIPEC (n = 28) or not (n = 18).

### Conclusion

The results show that PW-Post CCC, including cancer stem-like cells, is a promising predictive biomarker for recurrence after R0 GC surgery. Adjuvant HIPEC performed with R0 GC surgery showed preventive effects on peritoneal and hepatic recurrence and survival benefits for patients with PW-Post CCC (+).

### **CO03**

EFFECT OF POSTOPERATIVE MORBIDITY ON SURVIVAL AFTER CYTOREDUCTIVE SURGERY (CRS) WITH HEATED INTRAPERITONEAL CHEMOTHERAPY (HIPEC) FOR PERITONEAL METASTASIS IN A SERIES OF 734 CASES

## C. Eveno, R. Schiavone, M. Pocard, M.J. Caballero, E. Gayat

**Lariboisiere Hospital - Paris (France)** 

# **Objectives**

Major morbidity (MM) after cytoreductive surgery with heated intraperitoneal chemotherapy (CRS/HIPEC) is associated with worsening of disabilities and length of the hospital stay. This study aimed to identify MM prognostic factors and to measure its impact on oncological outcomes.

#### Methods

A post-hoc analysis of a prospective cohort of 734 patients with peritoneal metastasis (PM) from 2006 to 2015 was undertaken. Five hundred and two patients who had complete CRS and HIPEC for PM were included.

### Results

Major morbidity was identified in 31% (156/502) of CRS/HIPEC procedures, including 67 hemorrhagic complication (13.3%), 87 anastomotic leaks (17.4%), 121 reoperation (24.1%), and 65 pulmonary complication (12.9%). The multivariate predictors of MM were American Society of Anesthesiologists (ASA) score (ASA 3 vs. 1-2, 0R 95%CI: 3.58 [1.54–8.34]), origin of PM colorectal adenocarcinoma vs. other, OR 95%CI: 1.62 [1.06–2.48]), type of HIPEC drug (oxaliplatin vs. other, OR 95%CI: 2.85 [1.28–6.32]), number of anastomosis (no vs. at least 1, HR 95%CI: 1.85 [1.19–2.88]), blood transfusion (OR 95%CI: 1.84 [1.05–3.23]), and length of surgery longer than the median value (OR 95%CI: 1.88 [1.22–2.91]). The in-hospital mortality rate for the entire cohort was 1.7% (9/502). Rate of adjuvant chemotherapy after CRS/HIPEC was comparable between the two groups (70.3% vs. 72.4%, p = 0.64). The median duration of follow-up was 18 months. OS and DFS at 3 years was 83% (74% in the MM group vs. 87.5% in the non-MM group) and 44% respectively (32% in the MM group vs. 50% in the non-MM group). After adjustment for main confounders factors, MM was independently associated was worst OS and DFS (Hazard ratio and 95% confidence interval at 3.48 [1.90; 6.35] and 1.91 [1.43; 2.57], respectively).

### Conclusion

Major morbidity after CRS/HIPEC for peritoneal metastasis is a source of significant reoperation and longer hospital and intensive care unit stay; with a decrease in overall survival and disease free survival even after complete CRS. Preoperative ASA score, number of anastomoses, colorectal origin of PM, HIPEC with oxaliplatin, blood transfusion, and length of surgery are independent predictors of MM for CRS/HIPEC patients.

#### **CO04**

MUTATIONS OF RAS/RAF-PROTO-ONCOGENES IMPAIR SURVIVAL AFTER CYTOREDUCTIVE SURGERY & HIPEC FOR PERITONEAL METASTASIS OF COLORECTAL ORIGIN

L. Roth<sup>1</sup>, M. Schneider<sup>1</sup>, J. Eden<sup>2</sup>, B. Pache<sup>3</sup>, F. Laminger<sup>4</sup>, V. Lopez-Lopez<sup>5</sup>, T. Steffen<sup>2</sup>, M. Hübner<sup>3</sup>, F. Kober<sup>4</sup>, S. Roka<sup>4</sup>, P. Cascales Campo<sup>6</sup>, A. Gupta<sup>1</sup>, A. Siebenhüner<sup>7</sup>, G. Passot<sup>8</sup>, V. Kepenekian<sup>8</sup>, P. Gertsch<sup>1</sup>, O. Glehen<sup>8</sup>, K. Lehmann<sup>1</sup>

<sup>1</sup>Department of Surgery, University Hospital of Zurich - Zurich (Switzerland), <sup>2</sup>Department of Surgery, Cantonal Hospital of St. Gallen - St. Gallen (Switzerland), <sup>3</sup>Department of Surgery, Lausanne University Hospital (CHUV) - Lausanne (Switzerland), <sup>4</sup>Department of Surgery, Center for Peritoneal Carcinomatosis, Hanusch-Krankenhaus - Vienna (Austria), <sup>5</sup>Department of Surgery, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB - Murcia (Spain), <sup>6</sup>Department of Surgery, Hospital Clínico University Hospital of Zurich - Zurich (Switzerland), <sup>8</sup>Department of Digestive Surgery & Surgical Oncology, Université Hospital Lyon - Lyon (France)

### **Objectives**

Adequate selection of patients with peritoneal metastasis (PM) for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) remains critical for successful long-term outcomes. Factors reflecting tumor biology are currently poorly represented in the selection process. The prognostic relevance of Ras/Raf mutations for in patients with PM remains unclear.

# **Methods**

Survival data of patients with colorectal PM operated in 6 European tertiary centers were retrospectively collected and predictive factors for survival identified by Cox regression analyses. A simple point-based risk score was developed to allow patient selection and classification.

### Results

Data of 524 patients with a median age of 59 years and a median peritoneal cancer index of 7 (IQR: 3–12) were collected. A complete resection was possible in 505 patients, overall morbidity and 90-day mortality were 50.9% and 2.1% respectively. PCI (HR: 1.08), N1 stage (HR: 2.15), N2 stage (HR: 2.57), G3 stage (HR: 1.80) as well as K-Ras (HR: 1.46) and B-Raf (HR: 3.97) mutations were found to significantly impair survival after CRS/HIPEC on multivariate analyses. Mutations of Ras/Raf impaired survival independently of treatment with anti-EGFR treatment. Consequently, a simple point-based risk-score termed BIOSCOPE (BIOlogical Score of Colorectal PEritoneal metastasis) based on PCI, N-, G- and Ras/Raf status was developed, which showed good discrimination (AUC = 0.720), calibration (p = 0.821) and allowed categorization of patients into 4 groups with strongly divergent survival outcomes.

### Conclusion

Ras/Raf mutations impair survival after CRS/HIPEC. The novel BIOSCOPE score reflects tumor biology, adequately stratifies patient long-term outcomes, and improves patient assessment and selection.

#### **CO05**

PHARMACOKINETIC STUDIES OF INTRAPERITONEAL NANOPARTICLES IN PATIENTS WITH PERITONEAL METASTASES SHOW EPIC AS THE OPTIMAL METHODOLOGY FOR PERIOPERATIVE ADMINISTRATION

## P. Sugarbaker, O. Stuart

Program in Peritoneal Surface Malignancies, Washington Cancer Institute - Washington, DC (United States)

## **Objectives**

Peritoneal surfaces are a common site for the dissemination of gastrointestinal and gynecologic malignancy. Recently, new benefits in the management of peritoneal metastases have been reported using peritonectomy procedures combined with perioperative intraperitoneal chemotherapy. Unfortunately, current perioperative chemotherapy regimens fail to maintain the complete clearing of cancer nodules that is consistently possible using cytoreductive surgery with peritonectomy procedures. More effective perioperative chemotherapy is needed.

#### Methods

The nanoparticle pegylated liposomal doxorubicin (PLD) was instilled directly into the peritoneal space in peritoneal metastases patients following maximal efforts of cytoreductive surgery to resect abdominal and pelvic disease. Samples of blood, peritoneal fluid, tissue from normal peritoneal surfaces, mesenteric lymph nodes, and cancer nodules were obtained at regular intervals and pharmacokinetic parameters calculated. Pharmacokinetics were determined intraoperatively during hyperthermic intraperitoneal chemotherapy (HIPEC) conditions and early postoperative (EPIC) at normothermic conditions. All patients were monitored for adverse events using standardized assessments.

#### Results

The retention of PLD within the peritoneal space over a 90-minute HIPEC was only approximately 20%. At 180 minutes of HIPEC, approximately 40% of the drug was retained within tissue. The median area under the curve ratio of peritoneal fluid concentration times time as compared to plasma concentration times was over 1000 and increased with dose escalation from 50 to 100 mg/m². When PLD was instilled for EPIC, the area under the curve ratios were very similar to the HIPEC but retention of drug within the peritoneal space with access to cancer nodules was maintained a full 48 hours with 100% drug retention. Adverse events were tabulated and found to be absent. No evidence of peritoneal dysfunction from sclerosis was evident with a 1 year of follow-up.

### Conclusion

The nanoparticle PLD is slowly absorbed into the intraperitoneal tissues and not appropriate for HIPEC. EPIC is the preferred methodology for administration.