### CO11

PROGNOSTIC VALUE OF PERITONEAL GRADING REGRESSION SCORE (PRGS) IN PERITONEAL METASTASIS: AN EXPLORATORY ANALYSIS ON REGISTRY DATA

W. Solass<sup>1</sup>, F. Kurtz<sup>2</sup>, F. Struller<sup>2</sup>, A. Staebler<sup>1</sup>, H. Bösmüller<sup>1</sup>, A. Königsrainer<sup>3</sup>, F. Fend<sup>1</sup>

<sup>1</sup>Institute of Pathology and Neuropathology, University of Tübingen, Germany - Tübingen (Germany), <sup>2</sup>National Center for Pleura and Peritoneum, University of Tübingen, Germany - Tübingen (Germany), <sup>3</sup>Department of General and Transplant Surgery, University of Tübingen, Germany - Tübingen (Germany)

# **Objectives**

Laparoscopic peritoneal biopsies are increasingly used to evaluate therapy response of peritoneal metastases (PM) under palliative chemotherapy. A group of European pathologists has proposed a new 4-tied Peritoneal Regression Grading Score (PRGS) to determine histological regression of PM. Study aim is to examine a possible prognostic significance of PRGS.

## Methods

Registry study. Prospective cohort of 126 laparoscopies in 49 patients with histologically proven PM: Gastric (n = 22); CRC/appendiceal (n = 17); HBP (n = 8); ovarian/tubal (n = 5); PMP (n = 3), MPM (n = 2); others (n = 2) treated with various regimen of SC. 4 biopsies taken from all abdominal quadrants. Analysis by an independent pathologist. Mean PRGS calculated from all available biopsies. An increasing PRGS was considered a POD, a decreasing PRGS an OTR. This study was not powered. Survival statistics with Kaplan-Meyer, multivariate analysis with log-rank.

# Results

Out of 35 patients (71%) eligible for histological response assessment ( $\geq$ 2 laparoscopies), 24 (68.5%) had an objective response. Median survival was 9.51 months (CI 95% 0.45–18.6) in POD vs. not achieved after a 12.5 months in OTR patients. Univariate analysis showed a prognostic trend of PRGS for overall survival (p = 0.08). In the multivariate analysis, only bidirectional chemotherapy (p = 0.04), PCI (p = 0.009), Karnofsky index (p = .003) and number of previous chemotherapy lines (p = 0.001) had independent significance.

### Conclusion

This is the first evidence suggesting a prognostic value for PRGS in PM. This pilot data has to be considered exploratory and should now be confirmed in adequately powered studies.

#### CO12

STANDARDIZATION OF CLASSIFICATION OF PMP DOES NOT WARRANT STANDARDIZATION OF INTERPRETATION: IDENTIFYING THE PROBLEM AREAS

P. Dartigues<sup>1</sup>, L. Van Velthuysen<sup>2</sup>, N. Carr<sup>3</sup>, F. Bibeau<sup>4</sup>, R. Bradley<sup>5</sup>, K. Geisinger<sup>5</sup>, X. Gui<sup>6</sup>, S. Isaac<sup>7</sup>, J. Misdraji<sup>8</sup>, R. Pai<sup>9</sup>, J. Shia<sup>10</sup>, M. Taggart<sup>11</sup>, R. Yantiss<sup>12</sup>

<sup>1</sup>Gustave Roussy Institute - Villejuif (France), <sup>2</sup>Erasmus MC - Rotterdam (Netherlands), <sup>3</sup>Peritoneal Malignancy Institute - Basingstoke (United Kingdom), <sup>4</sup>Caen University Hospital - Caen (France), <sup>5</sup>Wake Forest University Baptist Medical Center - Winston Salem (United States), <sup>6</sup>Foothills Medical Centre - Calgary (Canada), <sup>7</sup>Lyon University Hospital - Lyon (France), <sup>8</sup>Massachusetts General Hospital - Boston (United States), <sup>9</sup>UPMC Presbyterian Hospital - Pittsburgh (United States), <sup>10</sup>Memorial Sloan Kettering Cancer Center - New York (United States), <sup>11</sup>University of Texas MD Anderson Cancer Center - Houston (United States), <sup>12</sup>NewYork-Presbyterian/Weill Cornell Medicine - New York (United States)

## **Objectives**

Recently a consensus for classification of pseudomyxoma peritonei (PMP) was published after a modified Delphi process. This classification standardizes nomenclature and recognizes three categories of PMP: low-grade (i.e. DPAM), high-grade (i.e PMCA) and high-grade with signet ring cells. To explore the robustness of this scheme and its limits thirteen pathologists of the Peritoneal Surface Oncology Group International (PSOGI), as well as a reference group of 16 additional pathologists were asked to classify PMP cases using this three-tiered system.

## **Methods**

Each pathologist from the PSOGI was asked to submit a typical example of each category, as well as 2 dubious cases. Representative micrographs of these cases were then circulated among the 13 PSOGI pathologists in 2 rounds and among the 16 reference pathologists\* in a third round.

\* Reference pathologists are: Averous-Lang G, Chakrabarti B, Fuste V, Lu Y, Mery E, Mustajab A, Poizat F, Rodriguez P, Schaeffer D, Sebastien A, Snaebjornsson P, Sobin L, Sundersing S, Svrcek M, Valmary-Degano S and Zhou Q.

#### Results

The PSOGI pathologists recognized a consensus diagnosis in 35/46 (76%) cases (unanimous in 12/46 (26%)) in the first round. In the second round the PSOGI pathologists were unanimous on 26 of these 35 consensus cases. 16 (46%) of these 35 consensus cases were also unanimously classified by the reference panel with consensus diagnosis in another 8 (42%) cases.

Problematic issues included a lack of consensus with respect to tumor grade in 9 (26%) cases and challenges in determining whether signet ring cells represented high-grade disease or a degenerative phenomenon in 4 (11%) cases.

# Conclusion

An international group of 19 pathologist recognizes the recently published three categories of the consensus classification for PMP, however not all signet ring cell lesions can easily be categorized and high versus low-grade categorization can be difficult. When dealing with PMP one should be aware of these caveats. Further investigation should be aimed at standardizing criteria to improve accuracy when dealing with cases within these problematic areas.

#### **CO13**

PROGNOSTIC IMPACT OF PRIMARY SIDE AND RAS/RAF MUTATIONS ON SURGICALLY TREATED PERITONEAL METASTASES FROM COLORECTAL CANCER

D. Baratti, S. Kusamura, F. Perrone, M. Niger, F. Pietrantonio, M. Guaglio, M. Di Bartolomeo, M. Deraco

Fondazione IRCCS Istituto Nazionale Tumori - Milano (Italy)

## **Objectives**

Selecting patients with colo-rectal cancer peritoneal metastases (CRC-PM) for cytoreductive surgery and hyperthermic intraperitonel chemotherapy (CRS/HIPEC) has always been a concern. A better understanding of biological features has the potential to improve prognostic stratification, but the impact of primary side and KRAS/NRAS/BRAF mutations is still unclear in this setting.

#### **Methods**

We reviewed a prospective database of 121 CRC-PM patients undergoing perioperative systemic chemotherapy (sCT) and CRS/HIPEC (n = 64), or CRS alone (n = 57). Preoperative sCT was given to 54 patients, postoperative sCT to 34, and both to 33. Extensive mutational analysis of KRAS (exons 2, 3 and 4), BRAF (exons 15), NRAS (exons 2, 3 and 4) and PIK3CA (exons 9 and 20) was performed by PCR. In 44 patients, Ion Torrent next-generation sequencing technology was used to characterize 50 gene's hotspot regions.

## Results

KRAS was mutated in 62/121 patients (50.8%), NRAS in 5/117 (4.3%), BRAF in 7/117 (6.0%), PIK3CA in 11/52 (21.2%), TP53 in 22/44 (50.0%), APC in 13/44 (29.5%), SMAD4 in 9/44 (20.5%), and FBXW7 in 4/44 (9.1%). KRAS mutations were located in codon 12 and 13 of exon 2 in 40 (64.6%) and 15 (24.2%) patients, in exon 3 and 4 in 4 (6.4%) and 3 (4.8%) patients, respectively. Primary tumor was right-sided in 68 patients (56.2%) and left-sided in 53 (43.8%). Right-sided primaries were associated with mutated K-RAS (P = 0.006). Median follow-up was 26.6 months, and median survival 28.2 months. No operative death occurred. Right-sided primary (hazard rate [HR] 1.61; 95% confidence interval [CI] 1.08–2.38; P = 0.021) and B-RAF mutations (HR 2.35; 95%CI 1.05–5.26; P = 0.038) independently correlated with poorer survival even after adjustment for completeness of surgical cytoreduction, and peritoneal cancer index. Microsatellite instability-high (MSI-H) correlated with reduced survival, but only at univariate analysis (0.041). There was a trend toward poorer survival for patients having postoperative vs. preoperative (P = 0.076) sCT or both (P = 0.020) s-CT.

# Conclusion

In the present series of CRC-PM, mutation profile was similar to other CRC stages. B-RAF mutations, right-sided primary and possibly MSI-H are adverse prognostic factors that may be used for treatment allocation. A benefit from preoperative sCT was suggested.

#### CO14

NODAL STAGE AND RAS-MUTATIONS PREDICT PERITONEAL RECURRENCE AFTER CRS/HIPEC IN COLORECTAL CANCER PATIENTS

E. Breuer<sup>1</sup>, M.A. Schneider<sup>1</sup>, J. Eden<sup>2</sup>, B. Pache<sup>3</sup>, T. Steffen<sup>2</sup>, M. Hübner<sup>3</sup>, L. Roth<sup>1</sup>, A. Gupta<sup>1</sup>, V. Kepenekian<sup>4</sup>, L. Villeneuve<sup>4</sup>, P. Gertsch<sup>1</sup>, O. Glehen<sup>4</sup>, K. Lehmann<sup>1</sup>

<sup>1</sup>Department of Surgery & Transplantation, 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 Digestive Surgery & Surgical Oncology, Université Hospital Lyon - Lyon (France)

# **Objectives**

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) improve overall survival in patients with peritoneal metastasis (PM) from colorectal cancer. Disease recurrence can occur at multiple sites, e.g. in the peritoneum or in the lung or liver and affects a majority of patients. Current evidence regarding recurrence patterns is scarce, and no data is available about risk factors predicting localization of disease relapse.

#### **Methods**

A cohort of n = 468 patients with colorectal PM, operated 1991–2017 in four different European centers was retrospectively analyzed. Survival data and predictive factors for recurrence sites were analyzed with SPSS version 22, by Cox regression analysis and multivariate regression analysis.

## Results

After a median follow-up time of 22 months, n = 336 (71.8%) patients showed disease recurrence, presenting as solitary distant metastases in 105 (22.4%), and locoregional disease in n = 194 (41.5%) patients. Locoregional disease relapse is associated with a significantly worse outcome compared to patients with distant recurrence in liver or lung only (33 vs. 43 months, HR 1.63, p = 0.005). Multivariate regression analysis identified positive nodal stage (OR 3.56, p = 0.020) and RAS-mutations (OR 4.22, p = 0.001) as predictive factors for peritoneal recurrence after CRS/HIPEC.

# Conclusion

Nodal stage of the primary tumor and presence of *RAS*-mutations predict peritoneal recurrence after CRS/HIPEC, associated with impaired outcome.

#### **CO15**

INTEGRATIVE ANALYSIS OF TRANSCRIPTOMIC AND PROTEOMIC PROFILES OF ASCITES PROVIDES INSIGHT INTO EPITHELIAL-MESENCHYMAL-TRANSITION PHENOTYPE INDUCED BY PARACRINE SIGNALLING IN COLORECTAL PERITONEAL CARCINOMATOSIS

J. Hendrikson<sup>1</sup>, W.H. Ng<sup>1</sup>, X. Qiu<sup>1</sup>, J.W.S. Tan<sup>1</sup>, N.B. Shannon<sup>1</sup>, C.S. Chia<sup>1</sup>, G.H.C. Tan<sup>1</sup>, W. Tse<sup>2</sup>, S.K. Sze<sup>2</sup>, K.C. Soo<sup>1</sup>, O.L. Kon<sup>1</sup>, C.A.J. Ong<sup>1</sup>, M.C.C. Teo<sup>1</sup>

<sup>1</sup>National Cancer Centre Singapore - Singapore (Singapore), <sup>2</sup>Nanyang Technological University - Singapore (Singapore)

# **Objectives**

To elucidate the role of soluble factors present in ascites that influence tumour progression in colorectal peritoneal carcinomatosis (PC).

#### **Methods**

Malignant ascites and benign ascites were collected intra-operatively from patients with colorectal PC (n = 3), gastric PC (n = 1), ovarian PC (n = 1) and benign serous cystadenofibroma (n = 1). Cell-free ascites was fractionated to obtain exosome-depleted ascites. Mass spectrometry of soluble components in ascites coupled with gene expression profiling of ascites treated cells was performed to identify upstream mediators, activated downstream signalling pathways and secretome involved in the pathogenesis of colorectal PC.

## Results

Proteomic analysis identified 466 proteins that were specific to colorectal PC ascites compared to malignant ascites from other histological subtypes and benign ascites. Gene set enrichment analysis of the proteome using Gene Ontology (GO) biological processes and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways revealed significant enrichment of proteins involved in cytoskeleton remodelling, angiogenesis and inflammation. Out of the proteins that are involved in cytoskeleton remodelling, TGFB1 and TIMP1, well-known inducers of Epithelial-Mesenchymal-Transition (EMT), were found in high abundance. Supporting this result, gene expression profiling of ascites treated cells revealed upregulation of EMT signalling pathway (Normalised enrichment score = 1.44 (p < 0.001)). qPCR verification of EMT markers on ascites treated cells confirmed upregulation of transcription factors such as TWIST1 and SNAI2 as well as mesenchymal markers such as VIM and FN1.

## Conclusion

Integrative analyses combining proteomics and transcriptomics offer insights into understanding the mechanism of tumour progression and metastasis through identifying pathways implicated across multiple platforms. Using this method, we have successfully characterised proteins and genes involved in ascites-induced EMT process, which could potentially be used in biomarker investigations and novel therapeutic strategy development for colorectal PC.

### **CO16**

# HOW MANY TISSUE BLOCKS ARE NEEDED TO RELIABLY DIAGNOSE ACELLULAR MUCIN IN THE PERITONEAL CAVITY? A PILOT STUDY

M. Al-Azzawi, B. Moran, T. Cecil, F. Mohamed, S. Dayal, N. Carr

Basingstoke and North Hampshire Hospital - Basingstoke (United Kingdom)

# **Objectives**

In some patients with clinical evidence of pseudomyxoma peritonei, only acellular mucin is found in the peritoneal cavity on histopathological examination and these patients may have a better prognosis. Currently there are no guidelines for how many blocks are needed to classify the mucin as acellular with confidence.

#### **Methods**

The study was done in a high-volume tertiary centre for peritoneal malignancies. All specimens were obtained at the time of cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC) for mucinous appendiceal neoplasia associated with spread of mucin beyond the right lower quadrant of the abdomen. Tissue samples from the formalin-fixed specimens were submitted for histology in accordance with routine practice. Cases in which the histopathology reported that the intra-abdominal mucin was acellular were prospectively identified over a 6-month period, and additional tissue blocks were then taken from the specimen to include either all residual visible intra-abdominal mucin or a maximum of 30 blocks. All sections were reviewed by a senior pathologist.

#### Results

Five patients were identified. The primary lesion was a low grade appendiceal mucinous neoplasm (LAMN) in each case. 30 extra blocks were taken in four cases and 26 extra blocks in one. All showed acellular mucin; none of them revealed any neoplastic epithelial cells.

### Conclusion

Taking up to 30 additional blocks of mucinous material did not change the diagnosis of acellular mucin in this pilot study. Extending the study to include more patients is planned.