UPDATE ON DIGESTIVE RARE CANCERS

Peritoneal Mesothelioma
Pseudomyxoma Peritonei
Serous Papillary Peritoneal Carcinoma

Marcello Deraco M.D.
Director Peritoneal Surface Malignancies Unit
### Common Features:
- Rare neoplasms;
- Peritoneal dissemination;
- Treated with Cytoreductive Surgery and Hyperthermic Intra Peritoneal Chemotherapy (HIPEC)

### Differences:
- Histology;
- PM and PMP: Chemosensitivity Low
- SPPC: Chemosensitivity High
The Concept of Cytoreductive Surgery with Peritoneectomy Procedures

- Means a complete removal of all macroscopic tumor in the peritoneal cavity;
- It could require Peritoneectomy Procedures eventually associated with intestinal and/or organ resection.

<table>
<thead>
<tr>
<th>Abdominal regions</th>
<th>Peritonections</th>
<th>Visceral resections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper</td>
<td>Right sub-phrenic peritonectomy, Glisson’s capsule dissection</td>
<td>Splenectomy, appendectomy, right colectomy</td>
</tr>
<tr>
<td>Left upper</td>
<td>Left sub-phrenic peritonectomy</td>
<td>Gastric antrectomy, cholecystectomy</td>
</tr>
<tr>
<td>Antero-lateral</td>
<td>Stripping of paracolic gutters, Greater omentectomy</td>
<td>Sigmoidectomy, hysterectomy, bilateral adnexectomy</td>
</tr>
<tr>
<td>Sub-hepatic</td>
<td>Lesser omentectomy, stripping of the omental bursa</td>
<td>Total gastrectomy</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Pelvic peritonectomy</td>
<td></td>
</tr>
</tbody>
</table>
Marcello Deraco: Peritoneal Mesothelioma and Serous Papillary Peritoneal Carcinoma
Result after CRS HIPEC
Surgical Technique of Parietal and Visceral Peritonectomy for Peritoneal Surface Malignancies

MARCELLO DERACO, MD,* DARIO BARATTI, MD, SHIGEKI KUSAMURA, MD, PhD, BARBARA LATERZA, MD, AND MARIA ROSARIA BALESTRA, MD
Department of Surgery, National Cancer Institute of Milan, Milan, Italy

Mesenterectomy: the 6° Peritonectomy Procedure
Intraperitoneal Administration

**Rationale:**
- High Chemotherapeutic Drug Concentration (P/P Ratio Area Under Curve):
- Direct effect of heat on Tumor;
- Sinergistic effect of heat and chemotherapy

**HIPEC (Hyperthermic Intra Peritoneal Chemotherapy)**

**DRUGS:**
- MMC: 25+25 mg > PMP
- CDDP 40mg/l + DX 15 mg/l > PM & SPPC

**Temperature:** 42.5 °

**Mean flow:** 700ml/min;

**Duration:** 60-90 min
PERITONEAL MESOTHELIOMA
**Imaging**: Provide adequate information on peritoneal extent and metastases

**Tumor Markers**: Moderate increasing of CA125 and Mesothelin;

**Pathology**:
- ✓ Percutaneous Ascite Collection for Citology: Frequently Inadequate;
- ✓ Percutaneous Biopsy: Provide adequate tissue in most cases;
- ✓ Laparoscopy: Provide adequate tissue in almost all cases, disease extent and resectability evaluation.

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Marcello Deraco: Peritoneal Mesothelioma and Serous Papillary Peritoneal Carcinoma
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Mesothelin binds CA125
The complex may, play a role in the tumor progression and dissemination in the peritoneal cavity
**Imaging:** Provide adequate information on peritoneal extent and metastases

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**CA125:**
- Baseline diagnostic sensitivity: 53.3%;
- Statistical Significant correlation with Grade and PCI;
- Significant correlation of baseline with outcomes


<table>
<thead>
<tr>
<th></th>
<th>Mesothelin</th>
<th>Osteopontin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPM</td>
<td>7.77</td>
<td>7.31</td>
</tr>
<tr>
<td>Controls</td>
<td>3.47</td>
<td>8.65</td>
</tr>
</tbody>
</table>

Mean, ng/dl

Marcello Deraco: Peritoneal Mesothelioma and Serous Papillary Peritoneal Carcinoma
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<table>
<thead>
<tr>
<th>Lesion size score</th>
<th>cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSS-0</td>
<td>No detectable</td>
</tr>
<tr>
<td>LSS-1</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>LSS-2</td>
<td>0-5-5</td>
</tr>
<tr>
<td>LSS-3</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>
Positive Markers:
• Calretinin: tight junction-associated protein
• Cytokeratin 5/6: intermediate-sized basic keratins
• WT-1: tumor suppressor gene
• Podoplanin: transmembrane mucoprotein
• Thrombomodulin: surface glycoprotein involved in the regulation of intravascular coagulation.

Negative Markers:
• Claudin 4, TTF-1, CEA
**Immunohistochemical Evaluation of Minichromosome Maintenance Protein 7 (MCM7), Topoisomerase IIα, and Ki-67 in Diffuse Malignant Peritoneal Mesothelioma Patients Using Tissue Microarray**

Marcello Deraco, MD, Antonello Cabras, MD, Dario Baratti, MD, and Shigeki Kusamura, MD, PhD

1Peritoneal Surface Malignancy Program, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; 2Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy.

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**Peritoneal Mesothelioma: Biology**

- **High MIB-1**
- **Low MIB-1**

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**Ann Surg Oncol**

DOI 10.1245/s10434-015-4498-z

Marcello Deraco: Peritoneal Mesothelioma and Serous Papillary Peritoneal Carcinoma
LOCALISED

- Benign
  - adenomatoid tumour
  - localized fibrous
- Malignant

DIFFUSE

- Borderline
  - multicystic
  - papillary well-differentiated
- Malignant
  - epithelial
  - biphasic (mixed)
  - sarcomatous

Local Excision
Histology: Typical morphology of Epithelial Malignant Mesothelioma with Tubulo-Papillary and Solid pattern with focal SRC surrounded by a fibrous connective tissue capsule.

Clinical presentation: tumor mass with limited peritoneal involvement.
LOCALISED

- Benign
  - adenomatoid tumour
  - localized fibrous
- Malignant

DIFFUSE

- Borderline
  - multicystic
  - papillary well-differentiated
- Malignant
  - epithelial
  - biphasic (mixed)
  - sarcomatous
Multicistic Peritoneal Mesothelioma (MCPM):
- Reproductive age women
- No apparent correlation to asbestos exposure
- Recurrence rates up to 50% after surgical excision
- Potential transformation into a malignant process

Well Differentiated Peritoneal Mesothelioma
- Natural history enigmatic
- Potential transformation into a malignant process
- Mortality possible

Acta Cytol 2003; 46:517
Gynecoł Oncol 2005; 98: 161
Multicystic mesothelioma: Operative and long-term outcomes with cytoreductive surgery and hyperthermic intra peritoneal chemotherapy

Eran Nizri a, b, Dario Baratti a, Marcello Guaglio a, Snita Sinukumar c, Antonello Cabras d, Shigeki Kusamura a, 1, Marcello Deraco a, 1

19 patients Treated with CRS HIPEC
Median of follow-up of 69 months (4-220)
Females: n = 17 (89%)
Mean age: 42
PCI: 15.5 ± 9.9
Major complications: n= 3 (15%)
No perioperative mortality
All patients alive

Recurrence: 4 patient (21%).

p = 0.03
Well differentiated papillary peritoneal mesothelioma treated by cytoreduction and hyperthermic intraperitoneal chemotherapy—the experience of the PSOGI registry

Marcello Deraco a,*, Eran Nizri a, Olivier Glehen c, Dario Baratti a, Jean-Jacques Tuch d, Jean-Marc Bereder e, Vahan Kepenekian c, Shigeki Kusamura a, Diane Goere f

- 45 patients (33/12-m/f)
- CRS HIPEC:38/ CRS:6
- Median follow: 46 months
- Median age: 44 yrs
- Median PCI: 9
- Major complications: 11 (24%)
- Mortality: 1 (2%)
- Prior chemotherapy: 8 (18%)
- Post chemotherapy: 2 (4.5%)

![Graph A](image1.png)
OS: Median: 53.2±17.8
Preoperative CT (8 pts)

![Graph B](image2.png)
RFS: Median: 62.9±11.6
High PCI: Median=9

![Graph C](image3.png)
Median follow: 46 months
Median PCI: Median=9

p<0.001
p<0.05
p<0.01
LOCALISED

- Benign
  - adenomatoid tumour
  - localized fibrous
- Malignant

DIFFUSE

- Borderline
  - multicystic
  - papillary well-differentiated
- Malignant
  - epithelial
  - biphasic (mixed)
  - sarcomatous

CRS HIPEC ± sCT
### Table 4. Histologic Subtypes and Patterns of Malignant Mesothelioma

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid mesothelioma</td>
<td>81%</td>
</tr>
<tr>
<td>Tubulopapillary</td>
<td></td>
</tr>
<tr>
<td>Micropapillary</td>
<td></td>
</tr>
<tr>
<td>Trabecular</td>
<td></td>
</tr>
<tr>
<td>Acinar</td>
<td></td>
</tr>
<tr>
<td>Adenomatoid</td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td></td>
</tr>
<tr>
<td>Deciduoid</td>
<td></td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td></td>
</tr>
<tr>
<td>Signet ring cell</td>
<td></td>
</tr>
<tr>
<td>Small cell</td>
<td></td>
</tr>
<tr>
<td>Rhabdoid</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid mesothelioma</td>
<td>6%</td>
</tr>
<tr>
<td>Conventional, spindle cell</td>
<td></td>
</tr>
<tr>
<td>Desmoplastic</td>
<td></td>
</tr>
<tr>
<td>Heterologous differentiation (osteosarcomatos, chondrosarcomatos, etc)</td>
<td></td>
</tr>
<tr>
<td>Lymphohistiocytoid (may also be classified as epithelioid)</td>
<td></td>
</tr>
<tr>
<td>Biphasic/mixed</td>
<td></td>
</tr>
</tbody>
</table>

*Subtype must be given in the diagnosis, but histologic pattern, epithelioid or sarcomatoid, may be described in a comment or microscopic description.*
Clinical Pictures for DMPM

- Metastatic DMPM
- Disease confined to the peritoneum and not fit for major abdominal surgery
- Recurrence after CRS HIPEC

Systemic Chemotherapy: Platin + Premetrexed/ Gemcitabine

- Patients with DMPM confined to the peritoneum fit for major abdominal surgery,

CRS-HIPEC ± Systemic Chemotherapy (↑Ki67, ↑PCI, N+, CC1)  
sCT: Platin + Premetrexed/ Gemcitabine
Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: A Systematic Review and Meta-analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of studies</th>
<th>Mortality rate</th>
<th>Expected 1-year survival (%)</th>
<th>Expected 5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort</td>
<td>20</td>
<td>0.17 (0, 0.39)</td>
<td>84 (68–100)</td>
<td>42 (14–100)</td>
</tr>
<tr>
<td>EPIC used</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>0.16 (0, 0.44)</td>
<td>85 (64–100)</td>
<td>45 (11–100)</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>0.19 (0, 0.55)</td>
<td>83 (58–100)</td>
<td>39 (6–100)</td>
</tr>
<tr>
<td>Chemotherapy agents used</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin-C only</td>
<td>1</td>
<td>0.24</td>
<td>78</td>
<td>30</td>
</tr>
<tr>
<td>Cisplatin only</td>
<td>3</td>
<td>0.14</td>
<td>87</td>
<td>49</td>
</tr>
<tr>
<td>Doxorubicin + cisplatin</td>
<td>3</td>
<td>0.23</td>
<td>79</td>
<td>32</td>
</tr>
<tr>
<td>Docetaxel + cisplatin</td>
<td>1</td>
<td>0.35</td>
<td>70</td>
<td>17</td>
</tr>
<tr>
<td>Drug combinations including</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>doxorubicin, mitomycin-C, cisplatin</td>
<td>11</td>
<td>0.16</td>
<td>85</td>
<td>45</td>
</tr>
<tr>
<td>Number of patients in a study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>17</td>
<td>0.20</td>
<td>82</td>
<td>37</td>
</tr>
<tr>
<td>&gt;100</td>
<td>3</td>
<td>0.15</td>
<td>86</td>
<td>47</td>
</tr>
<tr>
<td>Median PCI score reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;19</td>
<td>4</td>
<td>0.16</td>
<td>85</td>
<td>45</td>
</tr>
<tr>
<td>&gt;19</td>
<td>16</td>
<td>0.17</td>
<td>84</td>
<td>42</td>
</tr>
<tr>
<td>Median no. of patients undergoing complete cytoreduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 %</td>
<td>6</td>
<td>0.18</td>
<td>84</td>
<td>41</td>
</tr>
<tr>
<td>≥50 %</td>
<td>14</td>
<td>0.16</td>
<td>85</td>
<td>45</td>
</tr>
</tbody>
</table>
The Role of Ki-67 and Pre-cytoreduction Parameters in Selecting Diffuse Malignant Peritoneal Mesothelioma (DMPM) Patients for Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Shigeki Kusamura, MD, PhD¹, Pilar Adriana Torres Mesa, MD¹,², Antonello Cabras, MD³, Dario Baratti, MD¹, and Marcello Deraco, MD¹

Peritoneal Mesothelioma: Patient Selection

Conditional inference tree model. Preoperative risk stratification score (PreRSS)

Node 1
Ki67
P<0.001

≤9%

>9%

Node 3
PCI
P=0.002

Node 2 (n=67)

Node 4 (n=15)

Node 5 (n=32)

Median OS: 86.6 mts

Median OS: 63.2 mts

Median OS: 10.3 months

0.0 20 40 60 80 100 120
0.0 20 40 60 80 100 120
0.0 20 40 60 80 100 120

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DMPM Int. Registry:
• Total: 1165 pts CRS/HIPEC
• Procedures with CC-0/1: 484 (41.5%)
  ✓ Epithelioid: 450 (93%)
  ✓ Biphasic: 34 (7%)

Predictors of Survival Multivariate analysis:
• Peritoneal Cancer Index (PCI; p = 0.03),
• CC-score: (p=0.004)
Median Survival of CC2: 4.3 months

Biphasic DMPM should not be considered as an absolute contraindication for CRS HIPEC if limited PCI and Complete Cytoreduction

Response demonstrated on BAP1-mutant NCI-H2452 cells treated with olaparib in combination with cisplatin; Thus, this combined therapy might be effective for up to 2/3 of patients suffering from MPM

Response of MPM cell lines and lung fibroblasts to treatment with pemetrexed, cisplatin and olaparib;

Cell culture experiments:
- The control lung fibroblast cell line (MRC-5)
- MPM cell lines: MSTO-211H, NCI-H2052 and BAP1-mutant NCI-H2452 were used for the
Loss of *BAP1* as a candidate predictive biomarker for immunotheraphy of mesothelioma

Marc Ladanyi, Francisco Sanchez Vega and Marjorie Zauderer

➢ BAP1 loss in PeM is associated with a more inflamed tumor microenvironment;

➢ This condition could be useful as a predictive marker of responsiveness to immune checkpoint inhibitors (ICIs).
PSEUDOMYXOMA PERITONEI
<table>
<thead>
<tr>
<th>Primary Neoplas</th>
<th>Type of invasion</th>
<th>Cytology</th>
<th>WHO Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMN</td>
<td>Pushing</td>
<td>Low Grade</td>
<td>G1</td>
</tr>
<tr>
<td>Low grade appendiceal mucinous neoplasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMN</td>
<td>Pushing</td>
<td>High Grade</td>
<td>G2</td>
</tr>
<tr>
<td>High grade appendiceal mucinous neoplasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>Infiltrative</td>
<td>Any Grade</td>
<td>G2</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma with signet ring cells</td>
<td>Infiltrative</td>
<td>Signet ring cells in mucin pools or infiltrating tissue</td>
<td>G3</td>
</tr>
</tbody>
</table>
HAMN

Not Perforated

Perforated

Not Perforated

Perforated

Not Perforated

Perforated

CRS HIPEC + Right-Hemi-Colectomy

Right-Hemi-Colectomy?

Acellular Mucin

Tumor Cells & Mucin

Appendectomy

CRS HIPEC

MACA

Not Perforated

Perforated

Right-Hemi-Colectomy

CRS HIPEC + Right-Hemi-Colectomy

Appendectomy

CRS HIPEC

Marcello Deraco: Pseudomyxoma Peritonei
# Pathology of Appendix Neoplasms Causing PMP

## TNM 8

<table>
<thead>
<tr>
<th>pT classification</th>
<th>pT1</th>
<th>pTis (LAMN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour invades submucosa (HAMN and adenocarcinoma only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour invades muscularis propria (HAMN and adenocarcinoma only)</td>
<td>pT2</td>
<td></td>
</tr>
<tr>
<td>Tumour invades subserosa or mesoappendix (includes acellular mucin)</td>
<td>pT3</td>
<td></td>
</tr>
<tr>
<td>Tumour perforates visceral peritoneum, including cells and/or mucin on the serosa</td>
<td>pT4a</td>
<td></td>
</tr>
</tbody>
</table>

## pM classification

<table>
<thead>
<tr>
<th>pM classification</th>
<th>pM1a</th>
<th>pM1b</th>
<th>pM1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraperitoneal acellular mucin only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal metastasis with mucinous epithelium *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-peritoneal metastasis (implies haematogenous or distant lymphatic spread)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* includes ovary
## CLINICAL SIGNIFICANCE

<table>
<thead>
<tr>
<th>Primary Neoplasm</th>
<th>WHO Grade</th>
<th>If confined to appendix:</th>
<th>If evidence of appendiceal rupture or extra-appendiceal spread:</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMN</td>
<td>G1</td>
<td>Risk of pseudomyxoma minimal</td>
<td>Risk of pseudomyxoma about 3% if acellular mucin or about 30% if cellular</td>
</tr>
<tr>
<td>HAMN (scanty data)</td>
<td>G2</td>
<td>Probably similar to LAMN</td>
<td>Peritoneal disease probably more likely to be high grade</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>G2</td>
<td>Pseudomyxoma, lymphatic and haematogenous metastases possible</td>
<td>Peritoneal disease likely to be high grade</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma with signet ring cells</td>
<td>G3</td>
<td>Pseudomyxoma, lymphatic and haematogenous metastases likely</td>
<td>Prognosis is worse than mucinous adenocarcinoma without signet ring cells</td>
</tr>
</tbody>
</table>
Clinical Surveillance After Macroscopically Complete Surgery for Low-Grade Appendiceal Mucinous Neoplasms (LAMN) with or Without Limited Peritoneal Spread: Long-Term Results in a Prospective Series

Marcello Guaglio, MD¹, Snita Sinukumar, MD¹,², Shigeki Kusamura, MD, PhD³, Massimo Milione, MD³, Filippo Pietrantonio, MD⁴, Luigi Battaglia, MD¹, Stefano Guadagni, MD⁵, Dario Baratti, MD¹, and Marcello Deraco, MD¹

Total patients: 41
Median follow-up: months (range) 51.1 (9.3–162)
Appendix wall perforation: 21 (51.2%)
Extra-appendiceal dissemination: 24 (56.3%)
Recurrence: 2 (4.9%)

5-year RFS of 95.2%
- Acellular Mucin;
- **Low-grade** mucinous carcinoma peritonei G1
  OR
- Disseminated peritoneal adenomucinosis (DPAM)
- **High-grade** mucinous carcinoma peritonei G2
  OR
- Peritoneal mucinous carcinomatosis (PMCA)
- **High-grade** mucinous carcinoma peritonei **with signet ring cells** G3
  OR
- Peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)

Marcello Deraco: PM-PMP-SPPC
Current Status & Urgent Needs

PROGNOSTIC INDICATOR FAILURE

Median OS: 210 months in low grade

~ 15-20% of relapses/deaths within 24 months
~ 40-50% of relapses/deaths within 48 months

The current PSOGI pathological classification is insufficient to identify poor prognostic subsets

IMPROVE KNOWLEDGE IN PMP BIOLOGY

DEVELOP PROGNOSTIC SCORES

IDENTIFY “DRUGGABLE” TARGETS

OPTIMIZE THERAPIES

Marcello Deraco: The Future

K. Govaerts et al. / European Journal of Surgical Oncology 44 (2018) 1371e1377
45 patients with PMP treated with CRS HIPEC;

- Evaluable fresh tumor samples;

- Next-Generations Sequencing (NGS) of 50 gene’s hotspot regions;

- Using the Ion Torrent Personal Genome Machine platform (Life Technologies).

KRAS mutations: 72%

GNAS mutations: 52%,

\[ P = 0.006 \text{ Univariate} \quad P = 0.012 \text{ Multivariate} \]

\[ P = 0.011 \text{ Univariate NS Multivariate} \]
Oncogenes mutation

KRAS

GNAS

NF-κB, COX2, EGF, IL6, GMCSF, IKK2/b?

Inflammation

ISH miRNA, Nanostring-NGS

Mucin production

• GPCR
• PI3K-AKT
• MAPK?

PMP: Optimizing Treatment by Exploring the Connections between Onogene Mutations and Inflammation

Marcello Deraco: The Future
PMP: Optimizing Treatment by Exploring the Connections between Onogene Mutations and Inflammation

IMMUNOSUPPRESSIVE ENVIRONMENT IN PMP

➢ 40 FFPE PMPs were investigated by IHC for: CD8, GM-CSF, A2AR, CD39, CD73, p65.
➢ Expression was scored as: negative; 1 (<25% of cells); 2 (26-50%), 3 (51-75%) and 4 (>76%).

CONCLUSION:
➢ Expression of GM-CSF and CD39/CD73-adenosine-A2AR axis in PMP may modulate the activity of immune cells by limiting their capacity to evoke anti-tumor responses;
➢ A2AR expression was equally distributed among GNAS mutated (12/28=43%) and GNAS wild type (16/28=57%) PMPs:
➢ A2AR axis may be a potential therapeutic targets, particularly in GNAS wild type PMPs
Pseudomyxoma Peritonei (PMP):
Building a European Multicentric Cohort to Accelerate New Therapeutic Perspectives

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Building a well curated multi-omic / clinical database of PMP for sharing with the scientific community;

Creating a virtual platform for new biomarker selection and validation to transfer the new knowledge to the clinical scenario;

Generating patient derived organoid (PDO);

Developing and testing new drugs «ex vivo» by the 3D cellular models.
SEROUS PAPILLARY PERITONEAL CARCINOMA
**Morphological features:**
- Papillary growth pattern
- Poor differentiated structure - typical cells with large nuclei and prominent nucleoli
- Calcifications (also called psammoma bodies).

**IHC:**
- CA-125(+), Vimentin(+), CD15(+), CK7(+), S-100(+), ER(±), PR(±), PAX8(+) and claudin-4(+)
- CK20(−), CEA(−).
There are 3 proposed origins for extrauterine HG-SPC:

- Ovarian surface epithelium;
- Fallopian tube mucosa.

80-90% (*high grade serous carcinoma of tubo-ovarian origin* HGSC-TO)

- Peritoneum

10-20% (*Serous Papillary Peritoneal Carcinoma* SPPC);
Relevant Differences EOC/SPPC

IMAGING

EXPLORATIVE LAPAROTOMY

SURGICAL SPECIMEN

Serous Papillary Ovarian Cancer (SPOC)

Serous Papillary Peritoneal Carcinoma (SPPC)
Clinical Evidence Supporting SPPC as Primary Neoplasm

- Often underestimated and misdiagnosed;
- Median age of 55–65 average 3–7 years older;
- Abnormally elevated serum CA125 level >70–90% of patients;
- Similar lymphnodal metastases (20–70%) and visceral or extraperitoneal spread (<5%);
- Late diagnosis, high recurrence rate and higher mortality;
- No validated specific treatment is available to date;
- Lower-volume pelvic disease (normal Ovaries and Fallopian Tubes) with predominance of a diffuse micronodular spread in the peritoneum.

G. Pentheroudakis, Critical Reviews in Oncology/Hematology 75 (2010) 27–42
### SPPC: Literature Data

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cases</th>
<th>Grade</th>
<th>Stage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Debulking surgery</th>
<th>Chemo regimen</th>
<th>MOS&lt;sup&gt;b&lt;/sup&gt; (months)</th>
<th>PFS (months)</th>
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<td>1 2 3</td>
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<td>2 5 3</td>
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<td>29</td>
<td>Platinum</td>
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</table>

NA not available, CP cisplatin/cyclophosphamide, TP cisplatin/paclitaxel, TC carboplatin/paclitaxel, CAP cisplatin/doxorubicin/cyclophosphamide

<sup>a</sup>The majority of cases

<sup>b</sup>Median overall survival
• Median OS = NR
• 5 year OS = 64.5%
• Median PFS = 32.9 months
• 5 year PFS = 33.2%
• Morbidity = 50%
• Surgical Morbidity = 18%
• No Mortality.
Primary peritoneal serous carcinoma treated by cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. A multi-institutional study of 36 patients

N. Bakrin a,*, F.N. Gilly a, D. Baratti b, J.M. Bereder c, F. Quenet d, G. Lorimier e, F. Mohamed f, D. Elias g, O. Glehen a
Association Française de Chirurgie

PATIENTS AND METHODS:
• Patients: 36;
• 9 institutions;
• 39 procedures CRS HIPEC.

RESULTS:
• Morbidity: 20.6%;
• Mortality: 5.6%;
• 5 years OS: 57.4%;
• Median overall survival: not reached;
• Median disease-free survival: 16.7 months;
• PCI (p=0.03) univariate analysis.
CONCLUSION
Rare Peritoneal Surface Malignancies needs a complex management;

Patient should be evaluated at a peritoneal malignancy specialty centre by a MDT;

CRS and HIPEC should be offered as first option on PM and PMP;

NACT followed by CRS HIPEC should be offered to SPPC patients;

Ongoing studies aims to optimize biological knowledges and new treatments.
Peritoneal Surface Malignancies: MDT

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Medical Oncologists:
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- Filippo Pietrantonio
- Maria Di Bartolomeo

Pathologists:
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- Antonello Cabras
- Federica Perrone

Biologists:
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- Federica Perrone
- Annunziata Gloghini
- Emanuela Gariboldi
- Francesca Bianchi